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REVIEW

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Cyanobacteria and their metabolites - can they be helpful in the fight against pathogenic microbes?

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Abstract

Natural ecosystems are a rich source of compounds that can be considered as drugs to combat viral and bacterial infections. Cyanobacteria play a key role in the search for these compounds. These microorganisms, besides their well-known cytotoxicity to humans, are also a rich reservoir of metabolites with antiviral and antibacterial activities. These compounds are extremely diverse in their chemical structures. Moreover, recent reports have shown that Cyanobacteria can be used as platforms for the synthesis of antibacterial molecules such as gold and silver nanoparticles. In this review, we summarize and discuss recent reports on antiviral significance of these metabolites against the most relevant viruses, such as Human Immunodeficiency Virus (HIV), Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), Herpes Simplex Virus (HSV), and Influenza Virus. We also focus on the effects of cyanobacterial metabolites against Gram-positive bacteria, including *Staphylococcus aureus*, as well as Gram-negative bacteria, including those from the ESKAPE group of pathogens. It is outlined what future research on the isolation of cyanobacterial metabolites should focus on to improve the effectiveness of this process and lead to the commercialization of widely available drugs for the pharmaceutical market.

Keywords Cyanobacteria , Antibacterial activity, Antiviral activity

Introduction

The danger caused by viruses was seen during the COVID-19 pandemic. The latest epidemic showed that current treatments for viral infections are ineffective and new drugs are highly desirable. As of January 2023, there were 671 million cases of SARS-CoV-2-associated illnesses worldwide, 6.71 million of which ended in death [1].

Another global disease that humanity has been facing since the 1990s is acquired immunodeficiency syndrome (AIDS), caused by the human immunodeficiency virus (HIV). According to World Health Organization (WHO) data, at the moment, about 37 million people worldwide are infected with this virus [2]. The main method of treatment is based on the use of antiretroviral drugs which leads to a reduction in mortality, morbidity, and improvement in the lives of infected patients. However, this therapy is not widely available, and treatment costs are high [3]. Therefore, novel alternatives are being sought in the treatment of HIV.

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A global problem is also the rapid increase in the number of bacterial strains resistant to all known antibiotics. Increasingly, scientists around the world are asking whether humanity can be considered to have returned to the pre-antibiotic era? Definitely, one can agree that the drugs currently available on the market are no longer effective against all bacteria. The problem of antibiotic resistance has been recognized by WHO as one of the top ten global threats to humanity [4]. Available data shows that each year more than 1.27 million people worldwide die from infections caused by drug-resistant bacteria [5]. Therefore, alternatives to antibiotics are considered in this battle against bacteria. Among them, the most promising appear to be bacteriophages, probiotics, plant-derived substances, antibacterial proteins, and compounds produced by Cyanobacteria [6].

Cyanobacteria is a remarkable group of Gram-negative bacteria which played an important role in the evolution of the early life forms on Earth. These microorganisms globally colonize a variety of ecosystems, such as soils, freshwater and oceans, as well as extreme environments [7]. Cyanobacteria are the only group of prokaryotic organisms capable of undergoing oxygenic photosynthesis, therefore they are believed to have been responsible for oxygenating the atmosphere and oceans for 2.4 billion years [8]. These bacteria adsorb solar energy with a significantly high efficiency (3–9%), which supports the fixation of huge amounts of nitrogen and inorganic carbon [9]. The ubiquity of Cyanobacteria in the biosphere with access to light, is due to multiplicity of biosynthetic pathways, phylogenetic diversity and potential to produce a variety of compounds that protect them from potential competitors [7, 10].

Due to the chemical diversity of compounds produced by Cyanobacteria, complex and diverse pathways are involved in their synthesis, depending on the produced substance [11]. Most of these biomolecules are largely synthesized by polyketide synthase (PKS), non-ribosomal polypeptide synthetase (NRPS), and the integration of these two pathways (PKS-NRPS). In addition, these compounds can undergo chemical modifications such as halogenations, methylations, and oxidations [12]. Moreover, some compounds can be synthesized by ribosomes and then be post-translationally modified (peptides synthesized by ribosomes and post-translationally modified (RiPP)) [13].

In recent years, it has been shown that compounds produced by Cyanobacteria can be potential alternatives to antibiotics in combating viral infections, as well as to antibacterial drugs.

Among the groups of compounds synthesized by Cyanobacteria with antimicrobial activity there are polyketides, alkaloids, peptides, terpenes, lipids and polyphenols [11]. Each of these groups of compounds has a specific mechanism of action, interfering with the metabolism of the pathogenic bacterium. The main mechanisms of action of these molecules are: (i) inhibition of efflux pump (e.g., alkaloids); (ii) inhibition of translation by preventing the binding of tRNA to mRNA (e.g., polyketides); (iii) negative regulation of DNA replication and transcription by inhibiting appropriate polymerases (e.g. alkaloids); (iv) destabilization of the bacterial cell wall and disrupting the electron transport chain (e.g., peptides and lipids); (v) inhibition of quorum sensing (e.g., polyketides, alkaloids and lipids) [14]. The mechanisms of antimicrobial actions of compounds produced by Cyanobacteria have been discussed in detail by Kar et al. [14].

The groups of compounds produced by Cyanobacteria with antiviral activity include proteins, carbohydrates, sulfoglycolipids, polyketide, alkaloids, lipids and polyphenols [11]. So far, the identified mechanisms of action of metabolites with antiviral potential are as follows: (i) inhibition of viral protein binding to the host cell; (ii) inhibition of viral replication; (iii) binding to host cell receptors preventing further infection [14].

Therefore, the aim of this review was to summarize and discuss previous reports on the antiviral and antibacterial activities of Cyanobacteria and their metabolites. Moreover, the latest cutting-edge molecular biology techniques using Cyanobacteria to synthesize bactericidal agents are presented.

Antiviral properties of cyanobacterial metabolites

Among the metabolites of Cyanobacteria the antiviral activities have so far been confirmed for lectins, pigments, depsipeptides and carbohydrates. These compounds were effective against HIV, SARS-CoV-2, coxsackie B3 virus, rotavirus, HSV-1, influenza viruses types A and B, and others [15, 16]. The most commonly isolated Cyanobacteria with antiviral potential are lectins that show inhibitory specificity against glycoproteins [17]. Prominent among them are *Oscillatoria agardhii* agglutinin homolog (OAAH) proteins, cyanovirin-N, microvirin, or scytovirin [11].

Another group of compounds with antiviral activity are pigments. Special attention should be paid to C-Phycocyanin. This compound, is water-soluble and is a component of the photosynthetic apparatus of Cyanobacteria [18]. Its antiviral properties are particularly effective against Retroviruses, as it causes inhibition of reverse transcription and, consequently, replication of these viruses [19].

Depsipeptides are another group of agents that exhibit antiviral activity. These compounds are cyclic nonribosomal peptides, that have at least one of the amide bonds

replaced by an ester bond [20]. So far known depsipeptides with antiviral activity can attach to viral glycoproteins or cell receptors, preventing viral entry into the host [14].

A specific example of carbohydrates with antiviral activity is calcium spirulan, which causes inhibition of viral replication at very early stages, i.e. adsorption to the receptor and penetration into the interior of the eukaryotic cell [21]. However, it was noted that its antiviral mechanism of action applies to enveloped viruses [22].

Below, we summarize and discuss previous reports on the antiviral properties of Cyanobacteria and their metabolites in more detail.

Human Immunodeficiency Virus (HIV)

Human Immunodeficiency Virus (HIV) is a species of lentivirus transmitted through body fluids and secretions. The virus attacks host cells by attaching to CD4 receptors and then to one of the two major core chemokine receptors, CCR5 or CXCR4, leading to the destruction of T lymphocytes, during replication [2]. As mentioned above, failure to treat infection with this virus leads to Acquired Immune Deficiency Syndrome (AIDS) [2].

Numerous reports have presented the potential of cyanobacterial metabolites as candidates for HIV treatment. Here we present some of them, published recently.

Lectins

Oscillatoria agardhii agglutinin homolog (OAAH) proteins belong to the lectin family and was first isolated from *Oscillatoria agardhii* strain NIES-204 [23]. These compounds exhibit a broad spectrum of activity against HIV [24]. Férir et al. showed that these proteins inhibit: (i) viral replication, (ii) syncytium formation between virus-infected and uninfected T cells, and (iii) virus uptake and translocation to target CD4+T cells. Importantly, the authors showed that these proteins have their unique recognition motif on gp120 glycans. This was a significant discovery because other lectins with anti-HIV potential recognize the reducing or non-reducing end mannoses of Man-8/9. Moreover, these compounds have also been observed to act synergistically with other compounds showing anti-HIV potential, including *Hippeastrum hybrid* agglutinin and griffithsin [23].

Another lectin showing anti-HIV activity is Microvirin, isolated from the *Microcystis aeruginosa* PCC7806. This compound inhibits the formation of syncytium between HIV-1-infected T cells and uninfected CD4(+) T cells, and moreover inhibits one of the primary pathways of virus infection, i.e. binding of DC-SIGN-mediated viral transmission to CD4+T cells. Importantly, compared to and other lectins, this compound showed no cytotoxic effects in MT-4 cells and BMC, and no mitogenic activity [25].

Pigments

C-Phycocyanin, isolated from *Spirulina* sp., can also be considered as a potential drug against HIV infection. Jadaun et al., by using a luciferase gene assay in TZM-bl cells, showed that the compound inhibited HIV-1 replication by 50% at concentrations of 85—174 µg/mL, depending on the strain used. This phenomenon was due to the inhibition of HIV-1 reverse transcriptase and protease. Moreover, the authors showed that C-Phycocyanin reduced the amount of ROS that encourage viral replication by modulating cellular pathways and covalent changes in viral elements [19].

SARS-CoV-2

The SARS-CoV-2 virus belongs to Coronaviridae, a family of positive-sense single-stranded RNA (ssRNA) viruses [26]. The main problem in the control of this virus is the frequency of its recombination which leads to the emergence of strains with an increased transmission rate, as well as resistance to available drugs and vaccines [27]. According to available data, potential drugs against SARS-CoV-2 should affect its cysteine proteases (Mpro/3CLpro and PLpro), the spike (S) glycoprotein or RNA-dependent RNA polymerase (RdRp) [28, 29].

Depsipeptides

Among the anti-SARS-CoV-2 compounds produced by Cyanobacteria, cyanopeptolines should be highlighted. Konkel et al., isolated 15 cyanopeptolines from *Nostoc edaphicum* strain CCNP1411 that inhibit SARS-CoV-2 infection. CP978, the Arg-containing structural variant, showed the greatest antiviral potential. This compound inhibited viral infection at a low IC_{50} (80 ng/mL), through direct binding to the S protein of coronavirus. Importantly, this compound was shown to effectively inhibit the development of 3 different SARS-CoV-2 variants, i.e. Alpha, Omicron and Delta [28].

Another compound showing anti-SARS-CoV-2 potential is gallinamide A. This product is a modified depsipeptide that is produced by *Schizothrix* sp. and *Symploca* sp. [30, 31]. The compound is a potent inhibitor of many cysteine proteases, including, cathepsin L (CatL), essential for cell infection by SARS-CoV-2 [32]. Ashhurst et al., showed that gallinamide A and its analogues interacted directly with cathepsin L in cells to inhibit virus infection. At the same time, the compound inhibited the virus most potently in VeroE6 cells at EC_{50} of 28 nM, while its analogues were most effective in human A549/ACE2 cells at 310 nM. Moreover, the combined use of gallinamide A with nafamostat mesylate (an inhibitor of the TMPRSS2

protein that mediates virus entry into the cell) caused synergistic inhibition of virus [33].

Lectins

Cyanovirin-N is a lectin isolated from *Nostoc ellipsosporum*. Naidoo et al. demonstrated that this compound showed the highest binding energy with the spike protein, the main protease (Mpro) and the papainlike protease (PLpro) of SARS-CoV-2, so that it could be considered as a potential drug in studies against SARS-CoV-2 [34]. Importantly, these results were confirmed experimentally in vitro and in vivo by Muñoz-Basagoiti et al. Indeed, they demonstrated that cyanovirin-N can bind to the S protein of coronavirus, inhibiting infection [35]. On the other hand, Sahu et al. conducted analyses of target inhibitors against human angiotensin-converting enzyme (ACE2) which is crucial in the adsorption and entry of the virus into the cell. Based on molecular docking and studies on other metabolite properties, shinorine and mycosporine-glycine-valine were estimated to have the highest binding energy to the receptor, and could be considered for use against SARS-CoV-2 [36].

Genomic analysis of 7 new Amazonian Cyanobacteria by Siqueira et al. revealed the presence of cyanovirin-N homologs in *Nostoc* sp. CACIAM 19 and *Tolypothrix* sp. CACIAM 22, which have antiviral properties. In addition, when studying *Alkalinema* sp., the authors identified CACIAM 70d, a putative antiviral lectin, with binding sites predicted for sialic acid and N-acetylglucosamine [37].

Herpes Simplex Virus 1

Herpes Simplex Virus 1 (HSV-1) is an enveloped DNA virus that causes gingivitis and stomatitis. It turns out that worldwide up to 50-90% of people are seropositive for this virus [38]. Infection with HSV-1 can lead also to encephalitis or blindness. This virus is particularly dangerous for organ transplant recipients, as well as immunocompromised individuals. It is this virus that plays a key role in increasing immune complications in patients with Acquired Immune Deficiency Syndrome (AIDS). One of the peculiarities of HSV-1 is its ability to cause latent infection which leads to dormancy in the host [39]. The mechanism of action of existing therapies against HSV-1 is based on the use of guanine nucleoside analogues, however, strains resistant to this type of treatment have been reported [40]. Moreover, these drugs are not effective for the virus in its latent state, which leads to relapse [38]. Therefore, it is important to look for drugs that will effectively eliminate the virus.

Lectins

One of the compounds with an anti-HSV-1 character are lectins. These protein are produced by many species of mammals, plants, fungus, protists, as well as bacteria, and it is responsible for binding carbohydrates in a reversible manner [15]. Saad et al. characterized a newly identified lectin, isolated from *Oscillatoria acuminate*. The authors showed that this compound has anti-HSV-1 activity, causing neutralization of virions and inhibition of their replication in Vero cells, with IC_{50} values of about 90 ng/mL and about 130 ng/mL, respectively. A plausible explanation for this phenomenon could be that lectin caused increased viral uptake by immune cells or activation of the complement pathway, leading to virolysis. However, the exact mechanism of this process has not been investigated [41].

Interestingly, another lectin with anti-HSV-1 activity was characterized by El-Fakharany et al. The authors identified a lectin, derived from the newly isolated cyanobacterium *Lyngabya confervoides* MK012409, which exhibited antiviral activity with an IC_{50} value of 167 ng/mL. The authors suggested that the lectin can directly interact with HSV-1 virions, thereby inhibiting their entry into cells [42]. Moreover, lectins isolated by Saad et al. and El-Fakharany et al. showed anticancer potential against human breast cancer cells (MCF-7 cells) [41, 42].

Carbohydrates

Another compound showing anti-HSV-1 activity is calcium spirulan, isolated from *Spirulina platensis* by Mader et al. Indeed, the authors demonstrated that this compound inhibited infection of Vero cells by HSV-1 at an IC_{50} value of 0.05–0.5 μg/mL, and this was comparable in efficacy to a commonly used drug, acyclovir. Moreover, it has also been demonstrated that the compound revealed antiviral potential against Kaposi's sarcoma-associated herpesvirus (HHV-8) [43].

Influenza A virus

According to WHO, Influenza A virus is one of the main etiological agents causing acute respiratory infections, leading to 650,000 deaths every year [44]. A particular danger associated with influenza is its ability to rapidly mutate, resulting in the development of strains that are not susceptible to vaccines or available drugs, or even appearance of strains capable of causing epidemics [45]. Currently, the main group of drugs used to combat the influenza virus are inhibitors of neuraminidase, a protein involved in the release and spread of progeny virions, in completing the virus replication cycle inside cells [46].

Cyanobacterial extracts

Silva et al. examined a number of extracts from Cyanobacteria isolated from marine and freshwater biomass in Brazil. The authors showed that 7 extracts caused an 80% inhibition of influenza A virus replication. In addition, they showed that extracts from the cyanobacterium *Leptolyngbya* sp. inhibited neuraminidase activity at an IC_{50} below 210 µg/mL [45]. However, in order to consider those results in the light of application purposes, it would be necessary to analyse the composition of such extracts and isolate the active compounds.

Lectins

One of the anti-influenza A virus compounds is that mentioned as anti-SARS-CoV-2 virus agent, Cyanovirin-N. This compound might be also a promising candidate to combat the influenza virus, however, due to its high cytotoxicity and immunogenicity, it could not be used in medicine [47]. Therefore, Wu et al., synthesized PEGylated linkered Cyanovirin-N (PEG20k-LCVN). The use of such a compound at a concentration of 12.5 µM effectively inhibited the proliferation of the H3N2 influenza virus in chicken embryos, and in addition, its use in a mouse model, at a concentration of 2.0 mg/kg/day, doubled the survival rate of mice and reduced pathological changes in the animals' lungs [47].

Other viruses

Coxsackieviruses B (CVB) are non-motile, single-stranded RNA viruses that are commonly found worldwide and cause a range of mild diseases such as rashes in humans, but also acute and chronic diseases such as type 1 diabetes, cardiomyopathy and severe neonatal diseases [48]. Rotavirus (RV) infection, on the other hand, leads to severe, dehydrating gastroenteritis in children under the age of 5 years, causing up to 200.000 yearly deaths [49]. Deyab et al. studied the impact of 5 cyanobacterial isolates: *Arthrospira platensis*, *Leptolyngbya boryana, Leptolyngbya* sp., *Oscillatoria* sp., and *Nostoc punctiforme*, isolated from Egypt, againt CVB and RV. It was shown that the tested extracts exhibited strong antiviral activities against CVB, with the greatest effect observed for a *L. boryana* extract (a decrease in virus titer by 5.75 $\log_{10}$ $TCID_{50}$/0.1 mL), while a *A. platensis* extract had the strongest effect on RV (decrease in virus titer by 5.75 $\log_{10}$ $TCID_{50}$/0.1 mL). According to the authors, the likely action of the above extracts was to bind to the capsids of viruses, preventing them from binding to the receptor on the host cell surface [50].

Another pathogen with global reach is Hepatitis C virus (HCV). This hepatotropic RNA virus causes acute and chronic hepatitis which can lead to hepatic cirrhosis, decompensated liver disease, and hepatocellular carcinoma [51]. Despite advances in the fight against this virus, it is estimated that more than 58 million people worldwide are infected with the virus, with more than 1.5 million new cases each year [52]. Therefore, new drugs to combat HCV are constantly being researched. Min et al. showed that one such compound could be the previously mentioned microvirin. In addition to using the monomer of this compound, the study used its recombinant forms, i.e. di-, tri- and tetra-mers, to test their potential to combat HCV in human hepatoma-derived (HuH-7.5.1) cell lines. On the basis of the studies on production of the NS3 protease, one of the key proteases for HCV, the authors showed that all the microvirin forms effectively neutralized the virus (94-100% efficiency), with the trimer and tetramer forms being the most effective (100% efficacy) at the concentration of 650 ng/mL [53].

Ebola virus is a strong pathogen that can cause local epidemics. The Ebola virus disease (EVD) is a severe illness manifested by fever, gastrointestinal symptoms and multiple organ dysfunction syndrome [54]. The disease is characterized by a high mortality rate. According to 2015 data, 26,277 cases of the disease were reported in West Africa, including 10,899 deaths [55]. It turns out that currently there is no drug against EVD approved by relevant regulatory authorities. Consequently, numerous studies are underway to identify a potential drug against the Ebola virus [54]. One such compound may be scytovirin, a lectin first isolated from *Scytonema varium* strain HG-24-1 and tested as anti-HIV agent [56]. The compound is related to mannose-rich oligosaccharides with a high affinity to the envelope glycoprotein of many viruses, including Ebola virus. Garrison et al. showed that scytovirin interacts specifically with the mucin-rich protein domain of Zaire Ebola virus, leading to inhibition of replication of this virus at EC_{50} = 50 nM, but was also effective against the related Marburg virus. Subcutaneous administration of scytovirin to mice at a dose of 30 mg/kg/day was shown to increase mouse survival by 90% [57].

It is also worth highlighting the epidemiological significance of Chikungunya virus (CHIKV). This is an alpha virus causing a febrile illness known as Chikungunya fever, characterized by myofascial pain, fever and maculopapular rash [58]. Given the ability of the vectors of this virus, which are the *Aedes albopictus* and *Aedes aegypti* mosquitoes, to adapt perfectly to environmental changes and spread effectively across continents, CHIKV should be considered as a potential source of epidemiological threat with global reach [59]. Therapeutics that could be used to combat this disease are debromoaplysiatoxin and 3-methoxydebromoaplysiatoxin, isolated from a cyanobacterium *Trichodesmium erythraeum*. In an *in vitro* experiment with SJCRH30 rhabdomysarcoma cell

lines, these compounds were shown to effectively inhibit CHIVK growth in post-infected cells at EC_{50} values between 1.3 and 2.7 μM. In addition, antiviral efficiency tests, performed before infection, excluded the effect of the compounds at the stage of virus entry into the cells. Therefore, the mechanism of action of these compounds is believed to be the inhibition of viral replication [60].

Antibacterial properties of cyanobacterial metabolites

Besides direct antibacterial activity, Cyanobacteria can be used to synthesize nanoparticles with antibacterial activity. Among the compounds showing the greatest antibacterial potential are peptides, macrolides, fatty acids and alkaloids. Particularly noteworthy are cyanopeptides which have a variety of structures; however, they are mainly cyclic peptides [61]. The mechanisms of actions of metabolites with antibacterial potentials, identified to date are as follows: (i) inhibition of the quorum sensing system which plays an important role in virulence and biofilm formation; (ii) disruption of the cell membrane; (iii) disruption of bacterial metabolic pathways; (iv) interference with DNA, RNA and protein synthesis in the bacterial cell [14]. Here, we summarize the importance of the antibacterial properties of produced by Cyanobacteria and their metabolites.

Gram-positive *bacteria*

In 2017, WHO published a list of pathogens most dangerous to humans and requiring the development of new treatments. Bacteria were classified into three categories of antibiotic resistance: critical, high, and medium [62]. Among them there are Gram-positive pathogens such as *Staphylococcus aureus*, *Enterococcus faecium* and *Streptococcus pneumoniae*.

Staphylococcal infections

The compound showing antibacterial activity is bacteriocin B135CC, isolated from the terrestrial cyanobacterium *Chroococcidiopsis cubana*. This peptide is particularly effective against staphylococcal infections. Indeed, it was shown to completely inhibit the growth of *Staphylococcus auricularis* at a concentration of 6.25 μg/mL, while its use at a concentration of 5 μg/mL inhibited the growth of the bacteria by 80%, compared to the control group (untreated bacteria). This peptide showed the highest activity against *Staphylococcus* spp., as 10-20-times higher concentrations had to be used to inhibit the growth of other bacteria, like *Micrococcus luteus*, *Mycobacterium phlei*, *Pseudomonas fluorescens*. Therefore, it can be considered as a potential agent in the control of drug-resistant *Staphylococcus* species, including methicillin-resistant *S. aureus* (MRSA). Importantly, the compound does not induce cytotoxicity against mouse neural crest-derived cell line (N2a) even at a concentration of 150 μg/mL [63]. The explanation for such a strong inhibitory effect of bacteriocin may be its specificity for a particular bacterial species. The mechanism of action of bacteriocins differs from commonly used antibiotics. Therefore, their effectiveness can be high even against strains resistant to other antibiotics. For example, lisostaphin is a bacteriocin that is a peptidoglycan hydrolase that specifically binds to *S. aureus* cells due to its C-terminal sequence targeting the cell wall. However, it should be noted that the mechanism of the targeted action of bacteriocin B135CC may explain such potent activity against *S. aureus*, but has not yet been confirmed [63, 64].

Other compounds that are worth noting for their potential in eradicating MRSA are carbamidocyclophanes. These compounds, have been isolated from Vietnamese cyanobacterium *Nostoc* sp. CAVN2 and are able to effectively inhibit MRSA growth at very low concentrations, i.e. MIC of 0.1–1.0 μM. Moreover, it was emphasized that such strong antibacterial activity is due to the presence of one or two carbamoyl groups in the structure of these compounds [65].

Examples of the most promising compounds isolated from Cyanobacteria with anti-staphylococcal activity are presented in Table 1.

Functional metal nanoparticles have a strong bactericidal effect. Recently, Cyanobacteria have been increasingly used to synthesize these compounds. These microorganisms have C-phycocyanin, C-phycoerythrin, and R-phycoerythrin pigments in their cells, which are able to synthesize metal nanoparticles and stabilize them [77]. A variety of molecules are also involved in the process, including peptides, enzymes, carboxylic acids, aldehydes and ketones. These compounds contribute to the reduction of metal ions, but can also stabilize nanoparticles and prevent their agglomeration [78]. Moreover, it has also been shown that the presence of amino, sulfate or carboxyl groups in cyanobacterial proteins improves the bioreduction process of nanoparticles [79]. Namely, amino groups can donate electrons to metal ions, facilitating their reduction to metallic nanoparticles, while carboxyl groups are involved in electron transfer processes crucial for the reduction of metal ions. Moreover, these groups are then capable of stabilizing them and preventing their agglomeration. On the other hand, sulfate groups, although they do not directly regulate the reduction of metal ions, create an acidic pH environment that facilitates ion reduction by other cyanobacterial molecules. Moreover, these groups are negatively charged and can adsorb on the surface of nanoparticles, providing a repulsive force that prevents nanoparticle aggregation

Table 1 The metabolites of *Cyanobacteria* showing anti-staphylococcal activity

Name of metabolite	Target	Source	Effective concentration	Reference
12-epi-hapalindole E isonitrile	*S. aureus*	*Fischerella* sp.	ND	[66]
Aeruginazole DA1497		*Microcystis aeruginosa*	25 µg/disk (zone of inhibition 7 mm)	[67, 68]
Anaephene B		*VPG 16–59 (Oscillatoriales)*	MIC value 6.1 µg/mL	[69]
Hapalindole T		*Fischerella* sp.	MIC value 0.25 µg/mL	[70]
Kawaguchipeptins A & B		*Microcystis aeruginosa NIES-88*	MIC value 1 µg/mL	[71]
Laxaphycin A		Unidentified cyanobacterium	MIC value 125 µg/mL	[72]
Malyngolide		*Lyngbya majuscula*	ND	[73]
Crossbyanol B	*S. aureus* (MRSA)	*Leptolyngbya crossbyana*	MIC value 2.0 – 3.9 µg/mL	[74]
Comnostins A-E	*S. epidermidis*	*Nostoc commune*	MICs values 4–32 ppm	[75]
Diterpenoid noscomin		*Nostoc commune EAWAG 122b*	MIC value 8 ppm	[76]

ND not determined

[79–81]. Moreover, some cyanopeptides have been shown to possess hydrolytic activity, which enables ion reduction and nanoparticle coating [77]. Cyanopeptides can also affect the biological properties of nanoparticles including antibacterial properties and cytotoxicity. Cyanopeptides can increase the biocompatibility of nanoparticles, making them safer for medical applications. Silver compounds are widely used in wound care due to their antimicrobial properties, but high concentrations of silver are toxic to mammalian cells. A cyanopeptide which binds silver and releases the small amounts necessary to fight bacterial infection, has been shown to reduce the problem of silver toxicity to fibroblasts [82]. In addition, an important aspect affected by cyanopeptides is the enhancement of antibacterial activity. This is significantly influenced by the small size of the nanoparticles and their high surface-to-volume ratio [83]. They can bind to the surface of nanoparticles, facilitating targeted delivery or increasing interaction with bacterial membranes, thereby improving their enhanced antimicrobial activity [84]. The biosynthesis of nanoparticles is definitely more ecological method, shortens the synthesis time, and also reduces energy consumption and high synthesis costs [77]. Moreover, this process allows obtaining particles of the same shape and size [85]. One of the most frequently synthesized nanoparticles using Cyanobacteria and having antibacterial properties are gold (AuNP) and silver (AgNP) nanoparticles [86].

Sunganya et al. used *Spirulina platensis* to synthesize gold nanoparticles. As a result of the reduction of gold ions Au^{3+} to Au^{0} by a cyanobacterial protein, the formation of functional AuNP particles was reported. Moreover, the antibacterial activity of the nanoparticles obtained in this way was tested against *S. aureus*. It was observed that at a concentration of 150 µg/mL, the number of bacteria (CFU) was reduced by more than 80%, while increasing the AuNP concentration to 200 µg/mL reduced the number of bacteria by 99%. In addition, using transmission electron microscopy, the authors showed that silver nanoparticles caused a change in the shape of bacteria, as well as damage to the cytoplasmic membrane [84].

In another work, Younis et al. used *Phormidium* sp. as a bioreactor to synthesize silver nanoparticles. A schematic presentation of the experiment is shown in Fig. 1. The reduction of Ag^{+} ions to Ag^{0} by Cyanobacteria resulted in the formation of functional AgNP nanoparticles. Subsequently, the synthesized particles, at a concentration of 20 µg/mL, were shown to effectively inhibit the growth of MRSA (inhibition zone 20 mm), and combining them with 0.5% chloramphenicol increased the zone of inhibition to 28 mm. Moreover, in in vivo experiments, employing a rat model of skin infections caused by MRSA, it was shown that the application of AgNPs (at concentrations of 10, 30 and 50 µg/mL) led to a significant decrease in bacterial counts, wound healing, as well as a decrease in serum levels of the pro-inflammatory cytokines IL-6 and IFN-γ [87].

Moreover, Cyanobacteria can be used as a platform to synthesize antibacterial compounds. Astaxanthin is a natural carotenoid that inhibits bacterial growth and also inhibits bacterial biofilm formation, particularly by

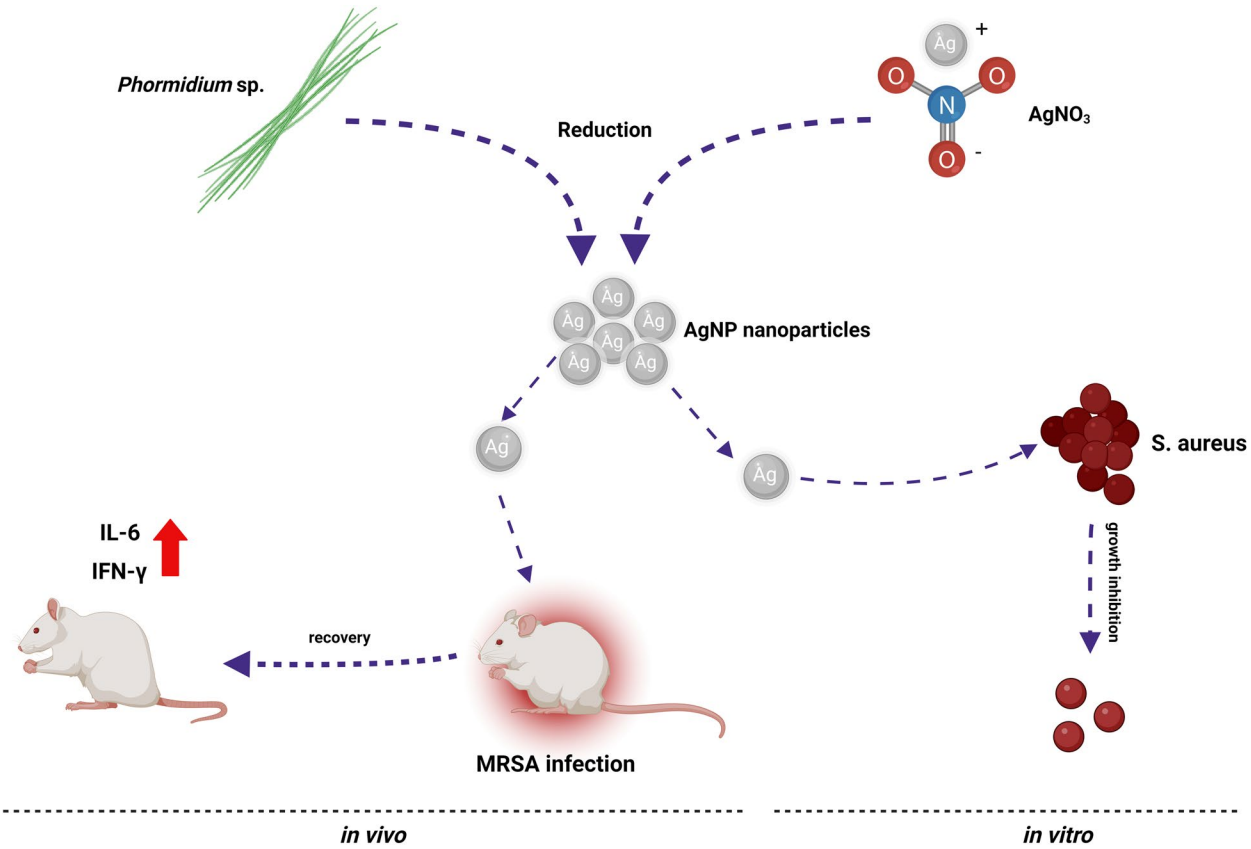

Fig. 1 Synthesis of silver nanoparticles with anti-staphylococcal potential using *Phormidium* sp. as a bioreactor (based on results summarized and discussed by Younis et al. [87])

MRSA, as well as by *Staphylococcus epidermidis* [88]. Diao et al. used *Synechocystis* sp. PCC 6803 and constructed an efficient biosynthetic pathway for this compound. Indeed, they found that such a system could efficiently synthesize more than 29.6 mg/g of astaxanthin, which was the highest result reported in the literature [89].

Other Gram-positive bacteria

Rajabpour et al. studied the effects of four extracts from *Fischerella* sp., *Nostoc* sp., *Calothrix* sp., and *Spirulina* sp. on the survival of *Streptococcus pneumoniae*. The authors observed antibacterial effects of the Cyanobacteria as early as at 18 h post treatment, with inhibition growth zones of 15.1 mm, 13.9 mm, 13.9 mm, and 8 mm, respectively. However, it should be noted that compounds responsible for the antibacterial effect have not been isolated, nor is the mechanism of this phenomenon known [90].

Interestingly, cyanobacterial extracts may have immunomodulatory effects in addition to their antibacterial activities. *Phormidium papyraceum* extract showed a broad antibacterial spectrum against Gram-positive bacteria such as *Bacillus cereus*, *Bacillus subtilis* and *S. aureus*, resulting in zones of inhibition of 17 mm, 16.5 mm, and 10.9 mm, respectively. Moreover, the extract also affected the immunophenotype of human leukocytes. Particular changes were observed in CD4+ T cells, where the activation levels of CD4+CD152+ T cells and TCD4+CD25+ regulatory cells were significantly increased. In addition, elevated efficiencies of synthesis of two pro-inflammatory interleukins, IL-2 and IL-6, were noted in cells treated with the extract. Analysis of the chemical profile of the extract using LC-ESI-MS/MS identified 112 putative compounds. It is presumed that the antibacterial activity of the extract was due to the presence of diversonol, thorularhodin, tanicolide, oligomycin C, and azithromycin, while betulin or azithromycin were perhaps responsible for the immunomodulatory activities [91].

Undoubtedly, the antibacterial properties of alginate, an extracellular polymer extracted from the newly isolated *Synechocystis algini* MNE ON864447, are also noteworthy. This compound acted at concentrations of 2.5–10 mg/mL on a wide range of Gram-positive and Gram-negative bacteria, with the most effective

inhibition of *Streptococcus mutans* growth (zone of inhibition 21.5–34 mm) [92].

Examples of other compounds showing antibacterial activities against Gram-positive bacteria are shown in Table 2.

Gram-negative *bacteria*

The inappropriate use and overuse of antibiotics in medicine and veterinary medicine has led to the rapid emergence of multidrug-resistant strains of bacteria, accounting for about 15.5% of all hospital-acquired infections worldwide. According to WHO and the U.S. Centers for Disease Control and Prevention (CDC), infections with these pathogens generate healthcare costs of $4.7 billion in the U.S., and $1.5 billion in Europe [100, 101]. The Infectious Diseases Society of America (IDSA) has classified six bacterial species as particularly dangerous due to their potential multidrug resistance mechanisms and pathogenicity. These pathogens, known as ESKAPE (consisting of *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Enterobacter* spp.), are particularly dangerous to children and the elderly, and immunocompromised individuals [102].

Cyanobacterial metabolites are able to inhibit the growth of Gram-negative bacteria, including *Pseudomonas aeruginosa*. One of the mechanisms playing a key role in regulating the pathogenesis of *P. aeruginosa* is the so-called quorum-sensing (QS) system [103]. This mechanism involves intercellular communication, in which extracellular molecules are produced, accumulating as the density of the bacterial cells increases. The expression of many *P. aeruginosa* virulence genes, including those encoding pyrocyanin and elastase, is activated by QS [104]. Therefore, QS pathways may be molecular targets for potential antibacterial compounds [105].

Liang et al. isolated a newly identified metabolite, called Doscadenamide A, from *Moorea bouillonii.* The authors showed that this compound has structural similarities with the QS signalling molecule and at a concentration of 10 µM is able to effectively interfere with the QS of *P. aeruginosa* in a LasR-dependent manner. The mechanism of action of this compound is to artificially regulate the production of virulence factors when fewer bacterial cells are present, which stimulates the host immune system to remove the pathogen [106].

Another metabolite that disrupts the QS system is pitinoic acid A, a metabolite isolated from *Lyngbya* sp. This compound effectively reduces transcript levels of genes involved in pyrocyanin biosynthesis at concentrations of 10 µM and 1 mM. Moreover, the chlorinated ester of this metabolite (pitinoic acid B), at a concentration of 100 µM, was shown to prevent the induction of the expression genes encoding pro-inflammatory cytokines TNF-α and IL-6 in LPS-induced THP-1 macrophages [107].

Benderadiene and lyngbyoic acid, isolated from *Lyngbya* sp., are examples of cyclopropane-containing metabolites. These compounds inhibit QS-regulated gene expression at IC_{50} of 20.4 µM for lyngbyoic acid and IC_{50}

Table 2 Metabolites of Cyanobacteria showing activity against some Gram-positive bacteria

Name of metabolite	Target	Source	Effective concentration	Reference
Carbamidocyclophane F	*Mycobacterium tuberculosis*	*Nostoc* sp. *UIC 10274*	MIC value 0.8 µM	[93]
Lyngbic acid		*Moorea producens*	MIC value 12.5 µg/mL	[94]
Pitipeptolide F		*Lyngbya majuscula*	ND	[95]
Scytoscalarol		*Scytonema* sp. (UTEX 1163)	MIC value 110 µM	[96]
Bromoanaindolone	*B. cereus*	*Anabaena constricta*	MIC value 128 µg/mL	[97]
Isomalyngamide A		*Padina* sp. *and Ulva* sp.	MIC value 7.8 µg/mL	[72]
Tiahuramide C	*M. luteus*	*Lyngbya majuscula*	MIC value 17 µM	[98]
Malyngolide	*Streptococcus pyogenes* *B. subtilis*	*Lyngbya majuscula*	ND	[73]
Cybastacine B	*Enterococcus* spp.	*Nostoc* sp.	MIC value ≤ 4 µg/mL	[99]
	Tsukamurella pulmonis		MIC value ≤ 2 µg/mL	

ND not determined

of 89.9 µM for benderadiene. Indeed, these metabolites were shown to be deposited within the ligand-binding domain of LasR in a similar way to the native autoinducer. Moreover, lyngbyoic acid, at concentrations above 500 µM, is able to inhibit biofilm synthesis, another important factor in *P. aeruginosa* pathogenesis [108].

Examples of other compounds produced by Cyanobacteria and showing antibacterial activities against Gram-negative bacteria are shown in Table 3.

The future of cyanobacterial metabolites

Without a doubt, Cyanobacteria are a source of compounds that may in the future be used in the treatment of diseases caused by bacteria and viruses. In recent years, there has been a significant increase in the interest in the medical use of cyanobacterial metabolites. This translates into the number of publications related to this topic. After entering the phrase "Cyanobacteria antibacterial activity" in the PubMed database (https://pubmed.ncbi.nlm.nih.gov; last accession 21/02/2024), one could see 932 records, while when we search for information on the antiviral properties of these metabolites, the database contained 301 results.

In addition to Cyanobacteria, yeast, plants, fungi and Actinomycetes are also used in green synthesis [77]. However, compared to other organisms, the use of Cyanobacteria as bioreactors to produce compounds with antibacterial potential has several key advantages. It should be noted that Cyanobacteria produce a wide spectrum of metabolites, showing antibacterial activity. Such an ability is a consequence of their development of mechanisms and adaptations for survival in the extreme ecosystems they inhabit [114]. Importantly, these compounds are extremely diverse in chemical structure. This natural diversity can be used to discover new antimicrobial agents [13]. Moreover, the method of biosynthesizing compounds using Cyanobacteria is considered eco-friendly. These bacteria, as photosynthetic microorganisms, are able to convert CO_2 into valuable metabolites, and are also capable of eliminating heavy metal ions from the surrounding environment [11]. An indisputable advantage of using Cyanobacteria to synthesize antibacterial agents is their rapid growth rate, compared to higher organisms, which facilitates the production of large biomass in a short time. In addition, Cyanobacteria can grow in simple, low-cost media, such as saline water, industrial wastewater or freshwater, which can further reduce the cost of biosynthesizing such compounds [21]. Cyanobacteria also have considerable plasticity and genetic variability, making many strains easy to transform, which may influence the optimization of the efficiency of synthesis of antimicrobial compounds [115].

However, it should be taken into account that some of the published results of studies on antimicrobial effects of cyanobacterial compounds are subject to certain weaknesses. When searching for potential drugs, a number of factors must be taken into account that can affect the effectiveness of the process. Figure 2 shows the most important factors affecting the efficiency of the extraction process of cyanobacterial metabolites with antimicrobial and antiviral potential. The first challenges arise already at the stage of laboratory work. This is because the activities of cyanobacterial compounds and extracts depend on the strain of Cyanobacteria, the target pathogens, as well as the method of preparing extracts and isolating specific compounds. At the same time, it should be noted that the antibacterial activity of extracts is generally higher against Gram-positive bacteria relative to Gram-negative species [116]. Therefore, in the process

Table 3 Antibacterial activities of cyanobacterial metabolites against Gram-negative bacteria

Name of metabolite	Target	Source	Effective concentration	Reference
Peptide SP-1	*E. coli*	*Spirulina platensis*	MIC value 8 mg/mL	[109]
Cyanobacterial peptide (sequence KLENCNYAVELGK)		*Limnospira maxima*	ND (inhibition zone 27 mm)	[110]
Crude extract	*P. aeruginosa*	*Oscillatoria* sp.	100 mg/mL (zone of inhibition 15.4 mm)	[111]
Portoamide	*Pseudoalteromonas atlantica*	*Phormidium* sp.	6.5 µM (inhibition of 21.5%)	[112]
20-nor-3α-acetoxyabieta-5,7,9,11,13-pentaene	*Salmonella typhi*	*Microcoleus lacustris*	MIC value 46.2 µg/mL	[113]
Tiahuramide C	*Aeromonas salmonicida*	*Lyngbya majuscula*	MIC value 6.7 µM	[98]
12-epi-hapalindole E	*Proteus mirabilis*	*Fischerella* sp.	MIC value 23 µM	[66]

ND not determined

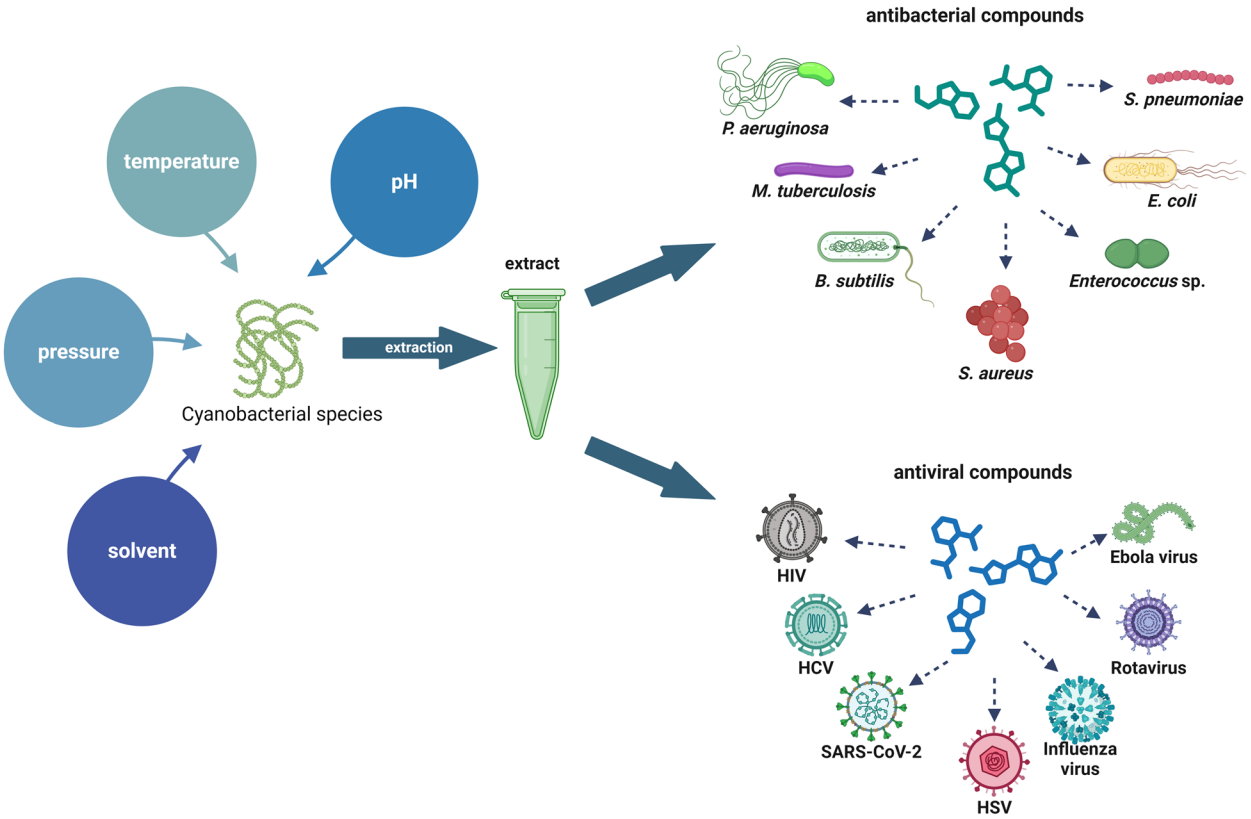

Fig. 2 Physicochemical factors affecting the efficiency of extraction of cyanobacterial compounds with antiviral and antibacterial potential

of identifying new cyanobacterial metabolites, basic research is so important. Such basic studies should help to optimize cyanobacterial culture methods, as well as to increase the efficiency of extraction of metabolites from these microorganisms.

The effectiveness of the anti-microbial action of extracts can vary due to the isolation method used. The whole procedure begins with culturing Cyanobacteria in the appropriate medium. During the cultivation process, the values of physicochemical parameters such as light intensity, temperature, access to CO_2, and access to inorganic components should be optimized. Then, biomass can be extracted from the supernatant, containing compounds whose antibacterial activity is verified by in vitro tests such as agar diffusion test or well plate test [117].

The process begins with drying the cyanobacterial biomass, and for this purpose lyophilization is most often used to avoid possible degradation of compounds that are not heat-resistant [117]. According to Strieth et al., the most commonly used extraction method is solid–liquid extraction, which involves immersing the dried biomass in an extraction solvent [117]. Other extraction methods used are microwave or sonic-assisted extraction and Soxhlet extraction. The first of these methods disrupts the cells, leading to high extraction efficiency [117, 118]. The second allows continuous contact between the matrix and the solvent, which is passed through boiling and condensation, with the sample being collected in the hot solvent [119]. Extraction of active compounds can also be carried out from the supernatant of cyanobacterial cultures. Liquid–liquid or solid-phase extraction (SPE) using resins are employed for this purpose [117]. Other extraction methods used are pressurized liquid extraction (PLE), supercritical fluid extraction (SFE), solvent microextraction (SME) [117, 120, 121].

The efficiency of metabolite synthesis depends on the cyanobacterial culture temperature used, which can be problematic from a laboratory perspective. Indeed, Assunção et al., showed that the synthesis of not all metabolites is positively correlated with the optimal bacterial growth temperature. Those authors showed that the greatest increase in *Synechocystis salina* biomass, as well as most metabolites, was obtained at 25 °C, while the increase in levels of phycoerythrin and antioxidants was most effective at lower temperatures, i.e. 15 °C and 15–19 °C, respectively [122]. Mohanty et al., on the other hand, showed that the use of different temperatures (25, 28, 33 and 38 °C) in the culture of *Hapalosiphon* sp.

affects its metabolome, but does not negatively affect the growth rate of these Cyanobacteria. In response to the effect of temperature, they identified an increase in the mass of many secondary metabolites associated with the biosynthesis of carotenoids, terpenoids and quinones, polyketide sugar units or monobactams [123].

The most commonly used solvents are organic compounds, such as methanol, acetone, ether, and chloroform–methanol, with methanol and ethyl acetate appearing to be the most effective solvents. However, the choice of solvent for extraction depends on the properties of the target compound and should always be optimized [124–126]. Thus, it was showed that the application of crude extract of *Oscillatoria* sp. worked most effectively against *S. aureus* at a concentration of 100 mg/mL, with an inhibition zone area of 14.1 mm. At the same time, it was indicated that the use of methanolic extract showed antibacterial activity against this pathogen at a concentration of 0.2 mg/mL, with an inhibition zone of 12 mm [111, 127]. On the other hand, Ostensvik et al. compared antibacterial activities of aqueous and methanolic extracts of five different Cyanobacteria. The experiments showed that the methanolic extracts exhibited significantly more pronounced zones of inhibition than the aqueous extracts, for *Escherichia coli*, *Aeromonas hydrophila*, *B. cereus* and *B. subtilis* [128].

Another factor that may affect the extraction efficiency is the use of appropriate pressure in the pressurized liquid extraction technique [129]. Indeed, it has been shown that techniques of cell disruption operating by high pressure allow high extraction efficiency and can be used on an industrial scale [130]. Marzorati et al. showed that pressures up to 300 Ba are necessary for efficient extraction of bioactive cyanobacterial compounds [131], while Imbimbo et al., on the other hand, optimized a method for metabolite extraction at 350 Ba [132].

One of the main problems of research on the antibacterial effects of cyanobacterial metabolites is the indeterminacy of the role of single metabolites from the extracts, on bacterial viability. Many reports have examined the effects of extracts, while their antibacterial effects might be due to the synergistic action of several or even more than a dozen compounds. For example, Gutiérrez-del-Río et al. isolated 4 esters of (mono-, di- or tri)chlorinated lauric acid and lactic acid, from a methanolic extract of *Sphaerospermopsis* sp. Those authors showed that the isolated compounds inhibited the growth of *S. aureus* at concentrations of 2.7–6.0 mM, however, the effect was not as significant as that of the extract. A plausible explanation for this phenomenon could be the presence of other antibacterial compounds in the extract, such as palmitic acid and glycerolipids, which acted together with chlorosphaerolactylates [133]. Here, attention should also be given to the techniques used to determine the antibacterial potential of extracts and metabolites. The most common methods used for this purpose are the agar diffusion and microdilution assay. The techniques used should be inexpensive and rapid, and should have high sensitivity and reproducibility [117]. However, many factors must be taken into account, so that the results obtained are not affected by error, for example, the optimized amount of extract used, as well as the concentration of antibacterial compounds in the crude extract [117]. Therefore, further research should focus on identifying individual active metabolites in the extracts, as well as developing microbiological tests that reliably and reproducibly prove their antimicrobial potential [134].

Another weakness of the studies conducted with Cyanobacteria is the failure to define the molecular mechanisms of action of different metabolites. The mechanism of action of any therapeutic allows one to know its molecular interaction with a biological target, resulting in a physiological response [135]. Therefore, future studies should clearly define such mechanisms of actions of the active compounds, which will allow understanding and exploiting the kinetics of binding, and designing and discovery of new molecules that can show a greater antibacterial and antiviral effects [136]. Today, this target screening is facilitated by application of advanced in silico methods [36, 137]. Moreover, knowledge of a mechanism of action is essential for regulatory approval and successful pharmaceutical application [136].

However, it should be remembered that the safety of antibacterial and antiviral agents synthesized by Cyanobacteria cannot be guaranteed. Before using such compounds, a comprehensive analysis of their toxicity, potential interactions with other drugs, and an assessment of possible environmental effects should be conducted. In fact, it has been shown that some antibacterial agents synthesized by Cyanobacteria can interact with cells of the immune system, and can also be toxic to eukaryotic cells [115]. Moreover, the purity of the obtained compounds should be investigated, so as to exclude potential contamination with heavy metals, toxins, as well as substances that may be immunogenic [77].

The very process of commercializing and regulating the use of cyanobacterial metabolites can be problematic. In order for a drug to be registered for medical use, it must undergo a series of in vitro and in vivo tests using various animal models, as well as preclinical and clinical studies, and then it must be approved by the relevant regulatory body. Therefore, in order to increase the chances of commercialization of drug-like compounds, a number of pharmacokinetic properties of such a compound known as LADME (Liberation-Absorption-Distribution-Metabolism-Excretion) should be thoroughly understood

Table 4 Summary of studies on the antiviral and antibacterial properties of Cyanobacteria and their metabolites against the most significant pathogens

No	Target	Compound	Class of compound	Source	Effect	Reference
1	SARS-CoV-2	CP978	cyanopeptolin	*N. edaphicum*	Inhibition of viral infection by binding to coronavirus S protein	[28]
2		Gallinamide A	depsipeptide	*Schizothrix* sp.	Direct interaction with cathepsin L inhibits virus entry	[33]
3		Cyanovirin-N	lectin	*N. ellipsosporum*	Inhibition of viral infection by binding to coronavirus S protein	[34, 35]
4		mycosporine–glycine–valine and shinorine	mycosporine-like amino acids	Molecular analysis	Inhibition of human angiotensin-converting enzyme (ACE2)	[36]
5		ND	putative antiviral lectin	*Alkalinema* sp. CACIAM 70d	Inhibition of infection by sialic acid and N-acetyl-glucosamine	[37]
6	HSV-1	oscillatorial lectin	lectin	*O. acuminate*	Neutralization of virions and inhibition of their replication	[41]
7		lyngabyal lectin		*L. confervoides*	Directly interaction with HSV-1 virions, leading to the inhibiting of entry into cells	[42]
8		calcium spirulanate	polysaccharide	*S.platensis*	Inhibition of infection at an IC_{50} value of 0.05–0.5 µg/mL	[43]
9	Influenza A virus	extract	ND	*Leptolyngbya* sp	Inhibition of neuraminidase activity	[45]
10		PEG20k-L Cyanovirin-N	modified lectin	Molecular construct	a) Inhibition of the H3N2 influenza virus proliferation b) Increasing the survival rate of mice	[47]
11	HIV	Oscillatoria agardhii agglutinin homolog (OAAH) proteins	lectin	*O. agardhii*	Inhibition of virus replication	[23]
12		microvirin	lectin	*M. aeruginosa* PCC7806	Inhibition of the formation of syncytium between HIV-1-infected T cells and uninfected CD4(+) T cells	[25]
13		C-Phycocyanin	protein-bound pigment	*Synechococcus* sp. PCC7002	Inhibition of HIV-1 reverse transcriptase and protease	[19]
14	Coxsackievirus B	extracts	ND	*L. boryana*	Inhibition of binding to the receptor on the host cell surface	[50]
15	Rotavirus			*A. platensis*		
16	HCV	microvirin and di-, tri- and tetramers	lectin	*M. aeruginosa* and molecular constructs	Effective neutralization of the virus (94–100% efficiency)	[53]
17	Ebola virus	scytovirin	lectin	*S. varium*	a) Interaction with mucin-rich protein domain of virus and inhibition of virus replication b) Increasing of mouse survival by 90%	[57]
18	Chikungunya virus	debromoaplysiatoxin & 3-methoxydebromoaplysiatoxin	macrolide	*T. erythraeum*	Inhibition of CHIVK virus growth at EC50 values of 1.3 and 2.7 µM, respectively	[60]

Table 4 (continued)

No	Target	Compound	Class of compound	Source	Effect	Reference
19	*S. auricularis*	bacteriocin B135CC	peptide	*C. cubana*	Completly inhibition of bacterial growth at concentration 6.25 µg/mL	[63]
20	*S. aureus* (MRSA)	carbamidocyclophanes	[7.7] paracyclophanes	*Nostoc* sp. CAVN2	Inhibition of MRSA growth at MIC 0.1–1.0 µM	[65]
21	*S. aureus*	gold nanoparticles	synthesized nanoparticles	*S. platensis*	Synthesis of gold nanoparticles, inhibiting bacteria growth by 99% in concentration 200 µg/mL	[84]
22	*S. aureus* (MRSA)	silver nanoparticles	synthesized nanoparticles	*Phormidium* sp.	Synthesis of silver nanoparticles, inhibiting bacteria growth in concentration 20 µg/mL (inhibition zone20 mm)	[87]
23	*S. epidermidis*	astaxanthin	carotenoid	*Synechocystis* sp. PCC 6803	Inhibition of bacterial growth and biofilm formation	[89]
24	*S.pneumoniae*	extracts	ND	*Fischerella* sp., *Nostoc* sp., *Calothrix* sp. & *Spirulina* sp.	Inhibition of bacterial growth (inhibition growth zones 15.1 mm, 13.9 mm, 13.9 mm and 8 mm, respectively)	[90]
25	*B. cereus*, *B. subtilis* & *S. aureus*	extract	ND	*P. papyraceum*	a) Inhibition of bacterial growth (inhibition growth zones 17 mm, 16.5 mm and 10.9 mm, respectively) b) Increasing of CD4 + CD152 + T cells and TCD4 + CD25 + regulatory cells counts, and elevated levels of IL-2 & IL-6	[91]
26	*S. mutans*	alginate	extracellular polymer	*S.algini* MNE ON864447	Inhibition of bacterial growth (inhibition growth zone 21.5–34 mm, depending on concentration)	[92]
27	*P. aeruginosa*	doscadenamide A	non-homoserine lactone	*M. bouillonii*	a) Effective interference with QS *P. aeruginosa* b) stimulation of the host immune system to eradication bacteria	[106]
28		pitinoic acid A	lipid	*Lyngbya* sp.	Inhibition of gene transcription involved in biosynthesis of virulence factor	[107]
29		pitinoic acid B			Induction of the expression of pro-inflammatory cytokines TNF-α and IL-6 in macrophages	

Table 4 (continued)

No	Target	Compound	Class of compound	Source	Effect	Reference
30	*P. aeruginosa*	Benderadiene	ester derivative of lyngbyoic acid	*Lyngbya* sp.	Inhibition of QS-regulated gene expression at IC_{50} of 89.9 µM	[108]
31		lyngbyoic acid	fatty acid		a) Inhibition of QS-regulated gene expression at IC_{50} of 20.4 µM b) Inhibition of biofilm synthesis at concentrations above 500 µM	

ND not determined

[138]. According to available data, it appears that only a few cyanobacterial compounds showing antibacterial or antiviral activity have entered clinical trials, but to date, none of them have been approved for use by the Food and Drug Administration [14].

Conclusions

This review summarizes previous reports regarding the antibacterial and antiviral potential of Cyanobacteria and their metabolites. In Table 4, we summarize all literature reports included in this work. Without a doubt, Cyanobacteria are a source of metabolites that can be used in the future as drugs to combat the most dangerous viral and bacterial infections. However, in order for these compounds to be used in pharmacy and medicine, further research should focus on optimizing their syntheses, as well as improving their stabilities, understanding the molecular mechanisms of actions of these compounds, and determining the potential adverse effects of the use of the identified biologically active molecules.

Abbreviations

AIDS	Acquired Immunodeficiency Syndrome
ACE2	Against human angiotensin-converting enzyme 2
AgNP	Silver nanoparticles
AuNP	Gold nanoparticles
CDC	U.S. Center for Disease Control and Prevention
CFU	Colony-forming unit
CHIKV	Chikungunya virus
CVB	Coxsackieviruses B
DC-SIGN	Dendritic cell-specific ICAM-3 grabbing non-integrin
EC_{50}	Half maximal effective concentration
EVD	Ebola virus disease
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
HSV-1	Herpes Simplex Virus 1
IC_{50}	Half maximal inhibitory concentration
LC–ESI–MS/MS	Liquid Chromatography Electrospray Ionization Tandem Mass Spectrometric
IDSA	Infectious Diseases Society of America
MIC	Minimum inhibitory concentration
Mpro	Main Protease of SARS-CoV-2
MRSA	Methicillin-resistant *S. aureus*
N2a	Neural crest-derived cell line
OAAH	Oscillatoria agardhii agglutinin homolog
PEG20k-LCVN	PEGylated linkered Cyanovirin-N
PLpro	Papainlike protease of SARS-CoV-2
RdRp	RNA-dependent RNA polymerase
ROS	Reactive oxygen species
RV	Rotavirus
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
ssRNA	Single-stranded RNA
QS system	Quorum-sensing system
WHO	World Health Organization

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Authors' contributions

ŁG conceived the manuscript, wrote the initial and final drafts of the manuscript, conducted the bibliographic research on the antiviral and antibacterial properties of metabolites, prepared the figures. KW & MŻ conducted initial bibliographic research on the antibacterial properties of metabolites. MK & MZ conducted initial bibliographic research on the antiviral properties of metabolites. ER, ZC, LG & KP provided critical comments and revised the manuscript. HMM led and supervised the project and revised the manuscript. GW provided critical comments, revised the manuscript and contributed to writing the final version. All the authors read and approved the final version of the manuscript.

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Availability of data and materials

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

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Competing interests

The authors declare no competing interests.

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