REVIEW

Cyanobacterial metabolites as novel drug candidates in corona viral therapies: A review

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Abstract

Most of the medical and nonmedical research labs, all around the world, are racing against time to produce an effective vaccine or an antiviral medicine for coronavirus disease 2019 (COVID-19). Conventional medicines and novel nano-materials including chemical and herbal-based compounds are all into positive trials toward coronaviruses and other pandemic infections. Among them, natural immune boosters have attracted physicians because of their longevity and reliability for fewer side effects. This is a review article with a detailed picture of an unexplored antiviral source with maximum potency in curing viral infections. Cyanobacteriae have been known for centuries and are rich in secondary metabolites of proteins, biopeptides, and poly-saccharides for prominent antiviral action against chest infections. But de-tailed exploratory research is required to purify, scale-up, and commercialize the pharmacologically active agents from these drug reserves.

KEYWORDS

antiviral drugs, coronavirus, covid-19, cyanobacteria

1 | INTRODUCTION

Coronavirus belongs to the family of *Coronaviridae* and the subfamily of Coronavirinae.[1] It constitutes the largest viral family, which affect the respiratory and digestive systems of animals and humans.[2-4] At first, due to transmission within avian and mammalian hosts, the viruses were referred to as epizoonotic.[5] Nearly, six strains of coronaviruses have been identified by previous research findings.[6,7] Among the six strains, four strains of coronaviruses are circulating with common mucous on humans and the other two strains are popular, such as Severe Acute Respiratory Syndrome (SARS-CoV) and Middle Eastern Respiratory Syndrome (MERS-CoV). In the last two decades, the SARS-CoV and MERS-CoV have infected more than 251 million people around the globe, reaching a mortality ratio of 34.4% and 9.6%, respectively.[8,9] SARS-CoV infection can also cause severe pneumonia.

In this scenario, the novel coronavirus 2019 (COVID-19) is circulating as a pandemic disease around the world. This disease is caused by the novel coronavirus: SARS-CoV-2. This virus outbreak threatens the population with its high mortality rate. Those affected initially suffered from the symptoms of fever, dry cough, and tiredness (initial stage). In the intermediate stage, those affected suffered from the symptoms of pain, sore throat, diarrhea, conjunctivitis, headache, loss of taste or smell, rashes, and discoloration of the skin on the fingers or toes. Eventually, those who were in the terminal stages were noted with symptoms of shortness of breath or shortness of breath and chest pain.[10] The signs of this virus are precisely depicted in Figure 1. Hence, the antiviral drugs are
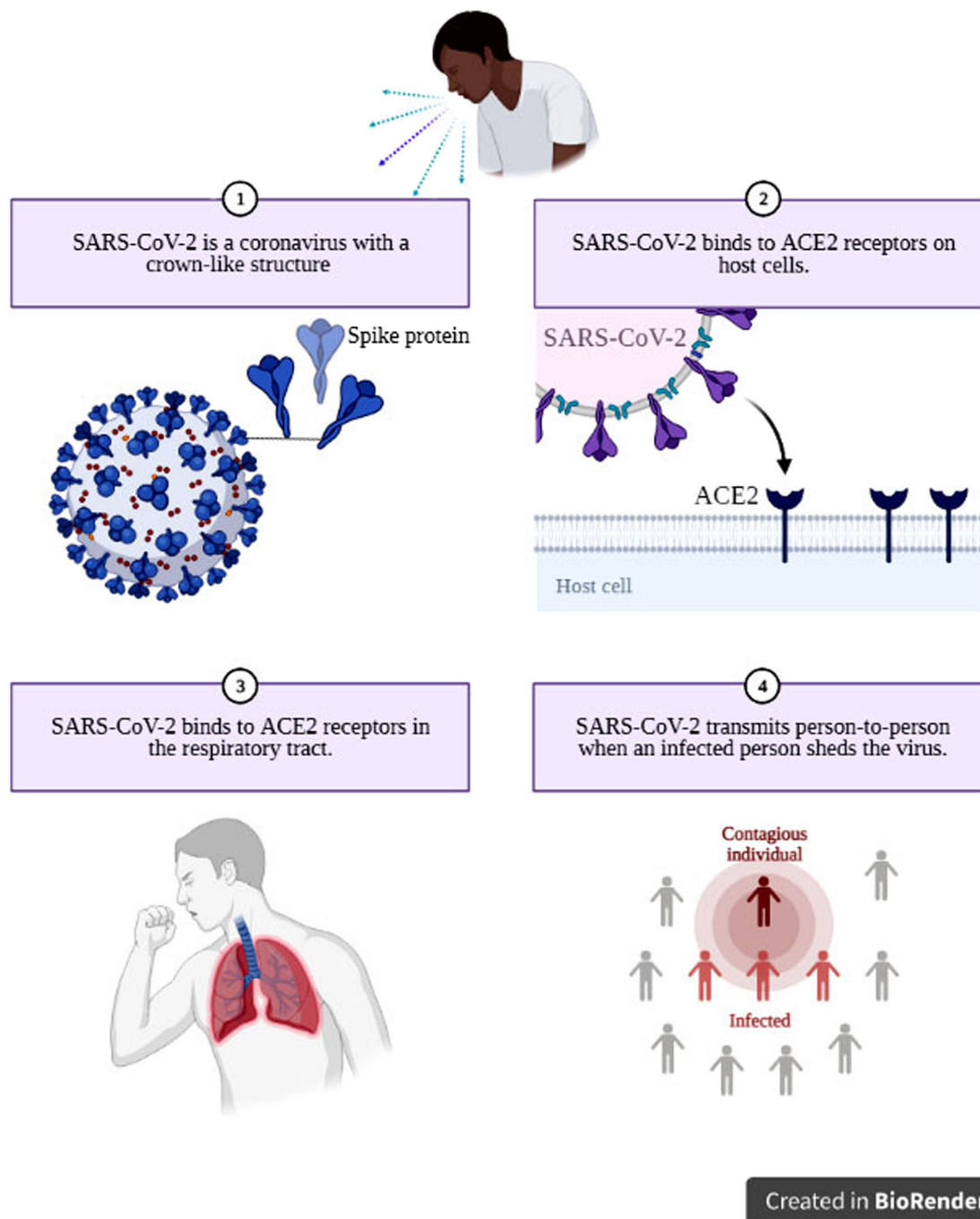
FIGURE 1 Transmission and symptoms of SARS-CoV-2 (Source gathered from Adobe stock). SARS-CoV, severe acute respiratory syndrome

urgently needed for the treatment of affected individuals, which can reduce or block the mortality ratio of human races. At present, World Health Organization (WHO) reported that there is no significant vaccine or antiviral drug available to alleviate and prevent the novel virus COVID-19 especially delta variant. People were typically infected with the delta variant coronavirus, even after vaccinations. Therefore, an exploration is being experimented to identify novel antiviral candidates supported by the statements of existing research articles.[11] As cyanobacteria exhibit antiviral effects, this review proposes that cyanobacterial phytochemicals have a greater potential for treating viral diseases. Previous studies have clearly revealed that cyanobacteria and their metabolites are a possible medication for a wide range of human health issues including cancer, diabetes, central nervous system (CNS), viral infections, and so on.

2 | STRUCTURE AND SEQUENCES OF CORONA VIRUSES

SARS-CoV-2 belongs to the family of corona virus, which is wrapped with positive RNA strain within. The viral genome of SARS-CoV-2 is embedded into a capsule assembled by nucleocapsid protein and it is enclosed in an envelope. The coronavirus consists of three structural proteins such as membrane protein, envelope protein, and spike protein (S): a glycoprotein that plays the key role in the attachment of the virus to the host cell.[12] The name "Corona" (crown-like structure) originated from the stretching of S protein on its surface. The ectodomain of spike (S) glycoprotein exists as a trimeric organization. Each Monomer consists of two subunits. The subunits are categorized into S1 and S2. S1 pertains to the recognition of host cell receptor, which constitutes a couple of major domains namely N-terminal domain (S1-NTD) and C-terminal domain (S1-CTD) (Figure 2 as created in biorender.com). S2 pertains to the mechanism of membrane fusion.[12] To identify the sequence similarity of reported virus strains, some sequences of SARS-CoV-2 were compared with the developing countries including China, the United States, and India, and are shown in Figure S1. As shown in the phylogenetic tree, the proteins were subjected to a network pharmacological approach by Cytoscape, which offers a possible target for the mutated strains of SARS-CoV-2. It reveals 104 target nodes and 1020 edges with a clustering coefficient of 0.715. The Pprotein-Pprotein Iinteraction (PPI) enrichment obtained p-value is < 1.0e−16 (Figure S2). Based on the observation that the mutated viruses have become more prevalent in the population, a SARS-CoV-2 mutation has been detected that was thought to have created a more "aggressive" strain of the virus.[13] Limited numbers of viruses will migrate to new environments during a pandemic and cause new localized epidemics, which would then intensify exponentially. Among them, the biggest protein encoded by the coronavirus (CoV) genome is Nsp3. Multidomain nonstructural protein 3 (Nsp3) is a key component of the complex for replication/transcription. In the viral life cycle, Nsp3 plays several roles.[14] Hence, the sequence of Nsp3 was subjected to PPI by using a string database. This approach is represented by 61 target nodes and 497 edges with a clustering coefficient of 0.656. The PPI enrichment produced a p-value of < 1.0e−16 (Figure 3).

3 | MORTALITY AND SPREAD OF SARS-CoV-2

In Asia, the first SARS *Coronavirus* was noticed in February 2003 and it's outspread very expeditiously affected the populations. World widely, more than 21.9 million
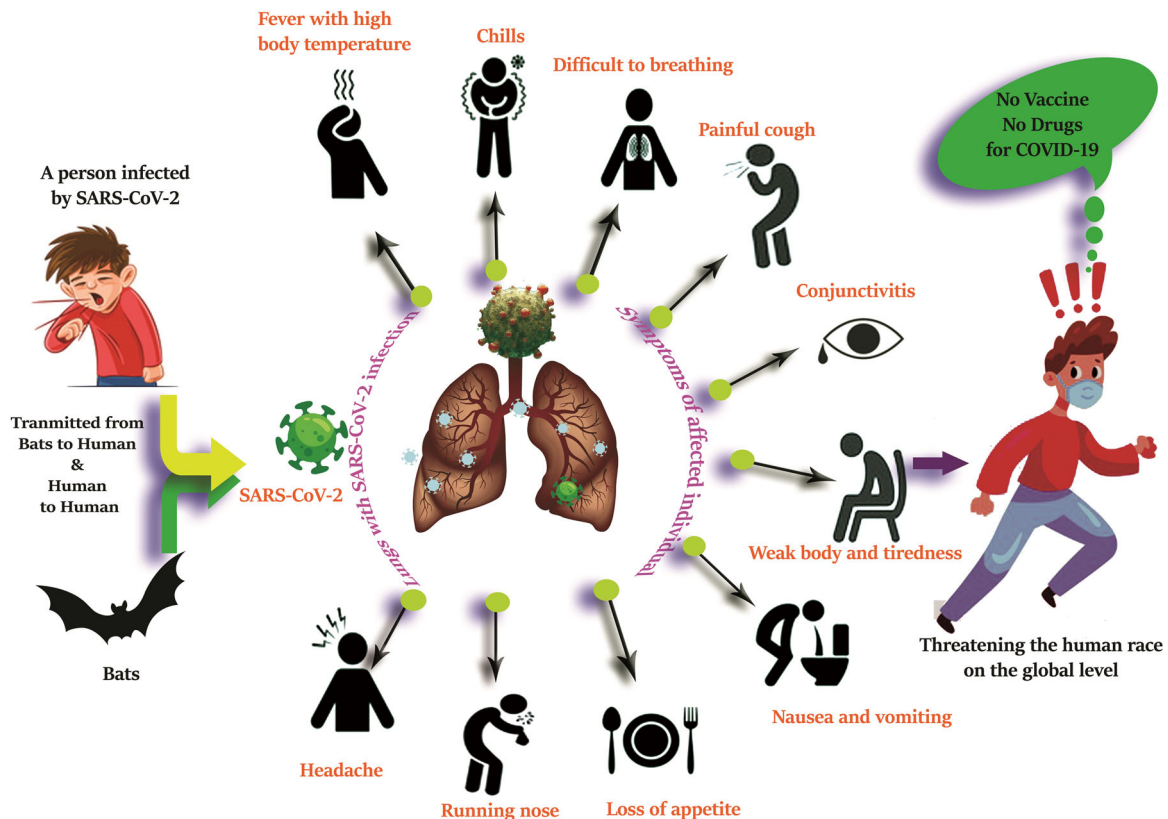
FIGURE 2 Transmission and attachment of SARS-CoV-2 onto host cell receptors, created in biorender.com. SARS-CoV, severe acute respiratory syndrome
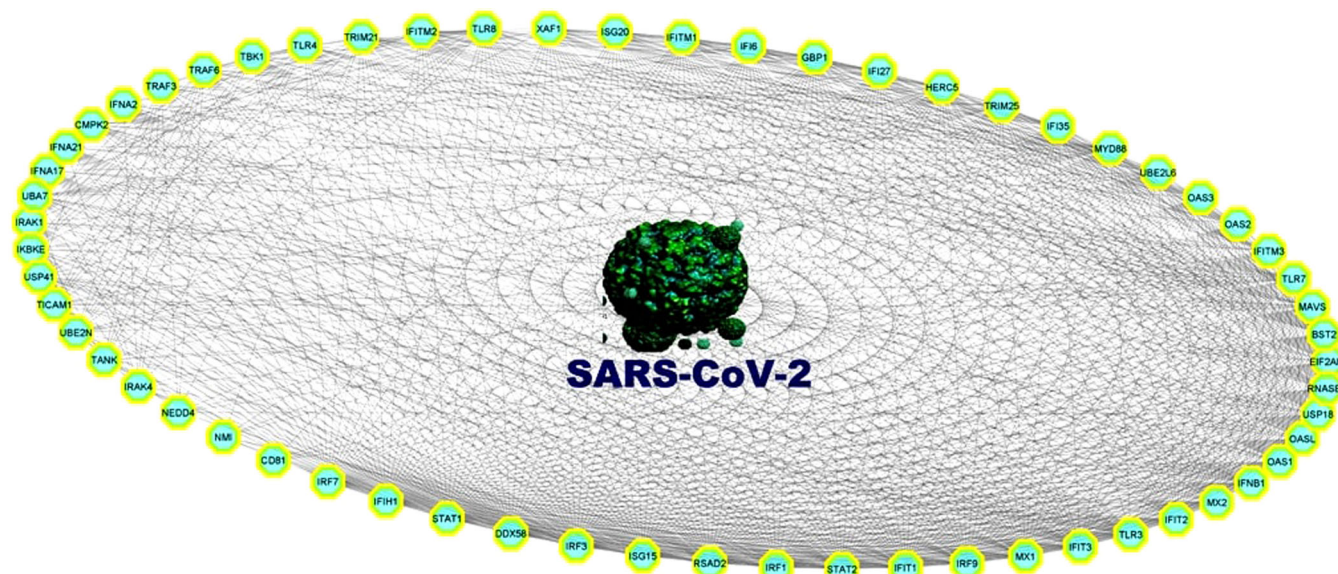
FIGURE 3 Pharmacology network that represents the putative target against Nsp3 *coronavirus*

people were affected and 45.5 million people have lost their lives.[15] Similar to SARS, the novel coronavirus: SARS-CoV-2 was manifested firstly in China in the month of December 2019. The COVID-19 is chasing relentlessly the human race at the global level, which affects drastically the world public health, economic progress, and social stability. As per the recent scenario, it becomes a major challenge for human races universally.[16,17] In October 2021, trillions of people were infected with the novel coronavirus (COVID-19) and more than 0.57 million people died. Especially, In India, more than 3.39 million people were infected and 0.45 million people died from this viral infection. Globally, India is positioned second in the infection cases of novel viruses. SARS-CoV-1, SARS-CoV-2, and MERS-CoV have been linked with widespread epidemic SARS in 2002–2003, MERS in 2012–2020, and an ongoing 2019–2021 COVID-19 pandemic.[9,18] SARS-CoV-2 and other coronaviruses have not yet been evaluated with regard to infectivity and dosage in the event of a human infestation.[1,5] A dose–response model proposed for SARS-CoV-1 reported that 50% of people exposed would develop the disease if exposed to 280 plaque-forming units of the virus.[19]

4 | PHARMACEUTICAL SECTORS AND THEIR CONTRIBUTIONS IN VACCINE DEVELOPMENT

SARS-CoV-2 has been outspread in over 200 countries and regions around the globe, which causes a severe threat to public health.[20] Woefully, it is quite circulating with no proper drugs clinically authorized. In India, the vaccines such as Covaxin (Bharat Biotech) and COVISHIELD™ (manufactured by Serum Institute of India Pvt Ltd) are injected to improve immunity against the novel virus. However, specific vaccine research against the Delta variant coronavirus is also being underway in many laboratories around the world. At present, Curevac's mRNA-based vaccine is remaining in the preclinical phase. The University of Queensland, Bayer College of Medicine, ExpresS2ion and Scicual Clover Biopharmaceutical are working together for vaccine development by utilizing S-glycoprotein as an antigen. Likewise, Applied DNA Sciences and Inovio are trying to develop DNA vaccine. Whereas, the Serum Institute of India is attempting to discover a live alleviate vaccine candidate against SARS-CoV-2.[21] At recent times, the drugs ritonavir, lopinavir, azvudine, ribavirin, favipiravir, and remdesivir are even being used as an alternate treatment for the affected individuals of SARS viruses.[20,22–24] These drugs were previously approved by the US Food and Drug Administration (FDA) for other diseases, but these are currently also used to alleviate the novel virus. The drugs chloroquine (CQ) and hydroxychloroquine (HCQ) are initially recommended for the treatment of rheumatoid arthritis, lupus, and porphyria cutanea tarda (PCT); but later it was also recommended for the viral disease malaria. Similarly, Auranofin is recommended for the treatment of rheumatoid arthritis but is currently recommended for this novel coronavirus. Treatment of CQ and HCQ medication has resulted in better relief for people with COVID-19.[23,25,26] Nevertheless, the role of CQ and HCQ in COVID-19 is still unclear while inventing new drugs or evaluating obsolete drugs would be a most expensive and time-consuming clinical process. Consequently, the need for computer-aided investigations has become inevitable both in the development of new therapeutic drugs and

in the investigation of the possible use of discovered drugs. By using computer-aided investigations, we can save ourselves the expense of cost-effectiveness and time. It can be seen that this technique is in sharp contrast to the earlier work of Ghaleb et al.[27]

5 | CURRENT STATE ANTIVIRAL DRUGS AND THE URGENT NEED FOR CYANOBACTERIAL METABOLITES AS ANTIVIRAL AGENTS

Around the world, the crude extracts and secondary metabolites of cyanobacteria have been identified as remedies for many human health complications, which are used as anticancer, antiviral, antimicrobial, and so on. These pharmacological properties have been identified by a variety of approaches including in silico, in vitro, and in vivo methods. Over the past half-century, the lack of vaccines and drugs against some viral infections, including the human immunodeficiency virus (HIV) and hepatitis C virus (HCV), has put a huge strain on the world's population. Until now, there is no specific drug candidate for certain viral infections especially respiratory tract infectious viruses such as Herpes Simplex Viruses (HSV-1 and HSV-2), SARS-CoV, and MERS-CoV. For this, the United Nations Millennium Development (UNMD) has been supporting financially for the past 16 years to decrease the pathogenic diseases infection ratios in low-income countries.[28] Furthermore, marketed antiviral drug candidates are inducing adverse effects when used to treat persons infected by such viruses. This circumstance pushes researchers to look for new antiviral possibilities from natural sources.[29] Hence, researchers adopt a wide range of strategies to directly collect compounds from cyanobacteria and find novel antiviral candidates. The secondary metabolites of cyanobacteria are being extracted by using various solvents viz water, methanol, and ethanol for the past two decades to identify novel antiviral candidates. Previous explorations have revealed the different proportions of antivirals in the aspects of pharmacology, depending on the fields of research and applications.[29–35] Consistent with this statement, Lau et al.[30] reported that cyanobacteria strains exhibit potential viral inhibitory activities for HIV and the avian myeloblastosis virus through their reverse transcriptase activity.

6 | ANTIVIRAL POTENTIAL OF CYANOBACTERIA AND ITS METABOLITES

Algae can be found in fresh and marine water, which are categorized into macro and microalgae. The majority of the macroalgae are found in marine environments and few are in freshwater. Among them, cyanobacteria are recognized as a prominent natural manufacturer of primary and secondary metabolites such as proteins, lipids, alkaloids, flavonoids, and so on. These constitute a therapeutic role against diseases in human beings.[36] The strains of cyanobacteria have been studied since ancient times because of their secondary metabolites with therapeutic potential.[37–39] In Figure S3, we have displayed some bioactive secondary metabolites of cyanobacteria as stated in the previous research reports. For the past two decades, all the focus has been on cyanobacteria to find the new antiviral drug candidates for a wide variety of viral infections, including the coronavirus.[40,41] For instance, the algae and cyanobacteria produce the natural proteins known as lectin, which hold promising antiviral potential for HIV, SARS coronavirus, and Zaire Ebola virus.[42] To prove this, the antiviral activity has experimented with HIV and HSV; the lectin has revealed significant inhibitory capacity against both of these viral organisms.[43,44] Mimouni et al.[45] have reported on algae and their corresponding generic properties on immuno-stimulatory, antioxidant, and antiviral nature. Furthermore, cyanobacterial metabolites such as cyanovirin-N, phycobiliprotein, calcium spirulan, allophycocyanin, nostoflan, dolastatin3, ichthyopeptins A/B, microvirin, allophycocyanin, and lipoproteins have a broad potential to prevent the penetration of viruses into the body epithelial urogenital or virustatic, virucidal, prevent virus adhesion to host cells, virus replication inhibitor, anti-RT, protease inhibition, anti-syncytia formation, antiapoptosis, reduced histopathology, up-regulation of interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), (IL)–8, MCP-1, MIP-1, MIP-1, IP-10, and COX-2.[46–60] Table 1 reveals that the metabolites were isolated from the different cyanobacterial species.

6.1 | Polysaccharides of cyanobacteria as antiviral agents

To acquire the antiviral active ingredients, the cyanobacteria are the decisive repository. Consistent with the above statement, Reichert et al.[36] used the polysaccharides of Arthrospira platensis as a supernatant to investigate the antiviral potential for the Koi Herpes Virus (KHV). It has actively inhibited the viral replication at concentrations of fractions between 18 and 36 μg/ml; where, the operation mode of the cyanobacterial molecules tends to impede the attachment of KHV. This also contains the compound calcium spirulan (Ca-SP), known as polysaccharides.[50] It has been revealed that cyanobacterial polysaccharides contain efficient antiviral activities on both enveloped and nonenveloped viruses such as HIV-1, HSV-1, Human CytoMegalo Virus (HCMV), influenza A, coxsackie virus, measles, polio, and mumps. It probably occurs by inhibiting the viral entry into host cells.[29,50] Certain

TABLE 1 Diverse biological functions of cyanobacterial metabolites as antiviral agents

Metabolites	Species	Viruses	Mode of study	Mode of action	Reported literature
Lectins	*Nostoc ellipsosporum* [1]	HSV-2, HVP	*In vitro*; TZM-bl	Prevent the entrance of viruses into the body via Urogenital epithelia	[45, 46]
Cyanovirin-N	*Nostoc ellipsosporum*	HIV	*In vitro* (PBL, MAC)	Virustatic	[47]
Phycobiliprotein	*Spirulina platensis*	MS-2 ΦX-174	*In vitro* (*E. coli*)	Virucidal	[48]
Calcium spirulan	*Arthrospira platensis*	HSV-1, CTMV, MeV, MuV, IAV, HIV-1	*In vitro* (Vero, MDCK, HeLa, HEL, MT-4) *In vitro* (Vero)	Prevent virus adhesion to host cells	[49, 50]
Allophycocyanin	*Arthrospiraplatensis*	Enterovirus-71 (EV71)	*In vitro* (Vero, humanrhabdomyosarcoma)	Prevent virus adhesion to host cells	[51]
Arthrospira crude extracts	*Arthrospira platensis*	HSV-1	*In vitro* (Vero)	Prevent virus adhesion to host cells	[52]
Nostoflan	*Nostoc flagelliforme*	HSV-1	*In vitro* (Vero)	Prevent the virus adhesion to host cells	[53]
Dolastatin 3	*Lyngbya majuscula*	HIV-1	Enzymeassay	Anti-HIV-1 integrase (inhibit the viral replication cycle)	[54]
Cyanobacterialextracts	Nostoc, Phormidium, Oscillatoria, Chroococcus, Schizothrix, Aphanocapsa, Synechococcus, Aphanothece, Xenococcus	AMVHIV-1	Enzymeassay	Anti-RT (inhibit the viral replication cycle)	[55]
Ichthyopeptins A/B	*Microcystis ichthyoblabe*	IAV	*In vitro* (MDCK)	Protease inhibition (inhibit viral processing after replication)	[36]
Cyanovirin-N	*Nostoc ellipsosporum*	HIV-1	*In vitro* (CD4 + HeLa)	Anti-syncytia formation (Inhibit the viral release)	[47]
Cyanovirin-N	Not reported	HIV-1	*In vitro* (TZM-bl)	Anti-syncytia formation (Inhibit the viral release)	[40]
Scytovirin	*Scytonema varium*	EVD	*In vivo*	Inhibit the virus penetration to the host cell	[56]
Microvirin	*Microcystis aeruginosa*	HIV-1	*In vitro* (CD4 + T-cells)	Anti-syncytia formation (Inhibit the viral release)	[57]
Lipoprotein	*Arthrospira platensis*	IAV	*In vivo* (murine)	Decreased histopathology	[58]
Lipoprotein	*Arthrospira platensis*	(H1N1)	*In vitro* (THP-1)	Upregulate IL-1β, TNF-α, (IL)–8, MCP-1, MIP-1, MIP-1, IP-10, COX-2	[59, 60]

Abbreviations: COX-2, Cyclooxygenase-2; EVD, Ebola virus disease; HIV, human immunodeficiency virus; HSV, Herpes Simplex Viruses; HVP, Human papillomavirus; IAV, Influenza A virus; IL-1β, interleukin-1β; IL-8, Interleukin 8; IP-10, Interferon gamma-induced protein 10; MCP-1, Monocyte, hemoattractant Protein-1, MIP-1, Macrophage inflammatory protein-1; TNF-α, tumor necrosis factor-α.

findings have not revealed the proof for virucidal action, but have confirmed that the viral infection has been blocked by the avoidance of virion adsorption and penetration of host cells. In accordance with the preceding report, the polysaccharides of *Spirulina maxima* were subjected to hot water extract treatment to determine the antiviral activity against HSV-2 and HSV-1 infections; where the concentrations of 69 and 333 µg/ml have revealed moderate IC50 values on it. According to Hernandez-Corona et al.[61] the hot water extraction of *s. maxima* has revealed effective inhibitory potential in the tested viruses, including HSV-2 infection, pseudorabies virus (PRV), HCMV, and HSV-1; whereas, it was registered that the 50% effective inhibitory doses (ED50) for each virus were found to be 0.069, 0.103, 0.142, and 0.333 µg/ml, respectively.

Worldwide, the Influenza viruses are circulating as seasonal epidemics which mainly affect respiratory tracts. Sometimes, they cause serious health complications such as pneumonia, pulmonary disease, and cardiac disease. However, only a few cyanobacterial exopolysaccharides have shown prophylactic and therapeutic effects against infections with influenza and pneumonia viruses; therefore, such cyanobacterial polysaccharides should be subjected to clinical trials for further pharmacological research to find a new drug for these viral diseases. Nostoflan is an acidic polysaccharide extracted from the *Nostoc flagelliforms* and it has antiviral capability against viruses that employ carbohydrates as cellular receptors.[62] A study published in 1997 reported that calcium spirulina was collected from the hot water extracts of *Spirulina platensis* and it also had antiviral effects against HSV-1, HIV-1, and HSP-1. It prevents viral entry into host cells and the development of syncytium even while administered at lower doses.[61] It has also been shown to have antiviral activity against enveloped viruses, most notably to influenza A virus (IAV).[29,54] Similarly, the cyanobacterium *Aphanothece halophytica* consisted of a large amount of sulfated exopolysaccharide, which is made up of arabinose, rhamnose, fucose, mannose, glucose, galactose, glucuronic, and sulfuric acids. Zheng et al.[63] studied the effect of this exopolysaccharide on the influenza virus A FM (H1N1)-induced mice. It was an effective therapeutic candidate in pneumonia-induced mice, and it also inhibited the decline of immunocompetence in mice. According to previous findings, this review proposes that it has potent antiviral ability against HSV-1, HSV-2, human cytomegalovirus, and IAV; moreover, it also inhibits the initial stage of viral infection, particularly the virus binding and internalization developments.[54]

6.2 | Proteins of cyanobacteria as antiviral agents

Similar to polysaccharides, proteins also have the ability to inhibit the replication of viruses (Figure S4). The lectins have been identified and are isolated from the diverse cyanobacterial species as shown in Table 1. Lectins are proteins that bind to carbohydrates or glycoproteins that are capable of attaching directly to glycol conjugate carbohydrates or carbohydrate moieties.[57] They also have powerful viral replication suppression potential when used topically as microbicides.

6.3 | Virucidal and virustatic potentials of proteins

Virion particles in their free state are attacked by virucidal substances, which destabilize their surface integrity or invade the capsid to damage their genome.[64,65] Virustatic substances attach to the cell surface of virions and keep them in slack, preventing them from attaching with cell receptors and infecting cells. Some cyanobacterial metabolites have revealed virucidal or virustatic effects when they pass through the body's vasculature as shown in Table 1. These substances, which do not enter the body's cells as toxic material and slow down the replication of viral progression, are used as an ideal drug for viruses.[65] According to a recent review, cyanobacterial metabolites may be consumed orally, thus, reducing the necessity for physicians to treat viral diseases.[66] According to a recent review, cyanobacterial metabolites can be taken orally and reduce the need for doctors to treat viral diseases.

6.4 | Cyanovirin-N

Cyanovirin-N is a 101 amino acid protein with a molecular weight of 11 kDa that binds to HIV glycoprotein 120 (gp120) with high affinity. Also, in *in vitro* research, it has suppressed several HIV laboratory strains and primary isolates with LC50 values < 5 nmol/L. Most importantly, it binds to viral glycoprotein120 in an irreversible way, preventing viral adherence to target cells. Significant denaturing agents were unable to breakdown the complex of cyanovirin-N gp120, thus, they have a strong virustatic impact on HIV virions.[48] Another study discovered that cyanovirin-N from *Nostoc ellipsosporum* has effectively reduced HIV infection in rhesus macaques by 63%–85%. It has consistently inactivated HIV virions with minimal cytotoxicity in *in vitro* research.[57]

6.5 | Scytovirin

Scytovirin is a 95-amino acid compound that acts as a possible inhibitor of HIV, Zaire ebolavirus, Marburg virus, and SARS-CoV viruses.[46,67] When administered to ebola virus-infected mice (30 mg/kg per day) every 6 h, it led to the survival of 9 mice out of 10. It binds with

great affinity to the envelope with glycoprotein's mannose-rich oligosaccharides, also inhibiting penetration into target cells.[56] It has been isolated from the *Scytonema varium* using aqueous solvent.[67] Also, Sato et al.[68] reported that the protein agglutinin was found in the cyanobacterium *Oscillatoria agardhii*. Also, a patent by O'keefe et al.[69] stated that scytovirin is a novel drug to treat high mannose-enveloped viruses infection, especially HCV.

6.6 | Phycobilinproteins

Phycobiliproteins are water-soluble proteins that are essential photosynthetic accessory pigments in cyanobacteria. In 2019, researchers carried out an *in vitro* experiment to explore the antiviral activity of *Arthrospira platensis* extract against two bacteriophages, MS-2 and ΦX-174. MS-2 is a single-stranded RNA virus that is widely used as a model for human poliovirus, hepatitis A virus, and enterovirus. The ΦX-174 is a single-stranded DNA virus used as a model for hepatitis B virus, HCV, and HIV. According to their findings, *Arthrospira platensis* extracts containing Phycobiliproteins have revealed a significant virucidal impact on both phages by altering the shape of viral capsids and inhibiting integration into *Escherichia coli*.[49] As with many other viruses investigated previously, neither of the phages examined in this experiment has a lipid envelope. As a result, it appears that the phycobiliproteins are directly interacting with the protein capsid to produce virucidal action. This virucidal action suppressed viral development and decreased viral titer. Thus, according to a recent review, phycobiliproteins may have therapeutic assurance for nonenveloped viruses such as rhinoviruses, polioviruses, and noroviruses.[70]

6.7 | Microvirin

It has a molecular mass of 14.3 kDa and is 33% identical to cyanovirin.[71] A recent research reported that the lectin microvirin (MVN) isolated from the *Microcystis aeruginosa* prevented syncytia formation between HIV-1-infected T-cells and virus-free CD4 + T-cells in *in vitro*. Although chronic infection leads to the development of a viral mutation, its mutation is suppressed by other lectins. Notably, the cytotoxicity of microvirin was >50-fold lower than that of cyanovirin-N.[57]

6.8 | Lipids of cyanobacteria and its antiviral potential

Similar to polysaccharides and lipids, the lipids of cyanobacteria also possess antiviral properties. Structurally,

the lipids are classified as sulfoquinovosyl diacylglycerides (SQDGs), monogalactosyl diacylglycerides (MGDGs), digalactosyl diacylglycerides (DGDGs), but they resemble the sulfolipids and glycolipids. Gustafson et al.[72] reported that the lipids SQDGs of *Lyngbya lagerheimii* and *Phormidium tenue* have higher HIV inhibitory potential. In 1993, Shirahashi et al.[73] have documented that the lipids MGDGs and DGDGs of *Phormidium tenue* revealed stronger inhibitory activities for Epstein-Barr virus than the lipids SQDGs. It has exhibited its potential during the tumor-promoting stage of the Epstein-Barr virus. In 1998, Loya et al.[74] has reported that anti-HIV properties have been expressed by *Scytonema* sp due to the lipophilic extract containing SQDGs. In 2009, Chirasuwan et al.[75] reported that the methanolic extracts of *spirulina* expressed inhibitory activities on HSV-1 with IC50 values 25.1 µg/ml. Kamat et al.[76] suggested that the antiviral potential was due to the presence of SQDG containing fatty acids such as palmitic and linoleic acid. The present review proposes that certain cyanobacterial fatty acids also have some antiviral effects.

7 | COMPUTER-AIDED DRUG DESIGN (CADD)

In the midst of the current epidemic, pharmaceutical firms are battling to develop novel antiviral treatments for SARS-CoV-2. The CADD is useful for discovering potential viral blockers for such virus-related issues without wasting time and money.[77] CADD is considered as a solitary rational drug design method, which contributes a key role in the development of drug discovery. This is a hopeful branch of bioinformatics where a computer system with the ability to reflect human reasoning is used to identify precise drug efficiency. To improve the quality of patient care, electronic medical records which are incorporated with patient-specific genomic information are used. Despite all the data, there is no precise drug recommended for COVID-19, yet. This dry lab approach helps to search for new therapeutic methods during the emergency of the current pandemic situation, which will offer suitable care and treatment of affected individuals.

7.1 | Sitemap generation

Before grid generation and molecular docking, the drug-binding pocket (sitemap) is required for molecular docking. The active drug-binding pocket is encompassed by many residues, which leads to the contact between the ligand and the target molecule. The active site in the protein cannot be found without this step. At the end of this phase, it would display the active ligand-binding cavities along with the site scores and binding cavity volume. Ultimately, the site with a larger volume

was taken for grid generation.[78] The current review proposes that binding pocket analysis is important in the molecular docking approach.

7.2 | Grid generation

It has been used to lock the ligand docking site in the protein molecule. The prepared ligands are docked with a target molecule to get docking parameters with the help of grid-based ligand docking tools. The binding cavity was shown in crystal structure around the ligand. The default grid volume was generated by the glide grid module. At the centroid of the target site, the docking study revealed the grid generation. The grid box is generated with the coordination of X: Y: Z. At this stage, the crude score values and geometrical filters were weeded out unlikely.[79]

7.3 | Molecular docking

It is frequently used to estimate the recognized geometry complex of a protein and ligand.[80] In virtual screening analysis, the docking method is often cast-off in combination with energy and scoring functions for visualizing the interaction of ligand. The ultimate goal of fine docking is to find the discrepancy between lot sorts of accurate and false solutions. However, the docking method entails determining the optimal kinetic performance of the enzymes as well as maximal ligand binding. Both the empirical and theoretical boundaries are to be considered for the free energy of ligand binding. This review reveals that the empirical fact also shows a significant trend of slighter assistance per atom as the ligand's virtual molecular mass raises. Furthermore, the docking predictions are assisted to find the drug potential of ligand molecules. This strategy is to demonstrate convenient routes when there is not much information on specific interactions between both the ligand atoms and the protein concerned.

7.4 | Ligand-based CADD

It is being used to find the contacts of ligand methoxyl, hydroxyl, and other contacts with the target residues. The computer-based drug design endorsed product binding affinities, physicochemical characteristics, glide energy, score, and so on. In this phase, the process is extremely more successful than the structure-based approaches.[81] The procedure is focused on the biological properties of ligand molecules. In addition, the ligand-based drug design is an important strategy to find an accurate inhibitor (ligand) against the target.[82]

7.5 | Absorption, description, metabolism, and excretion analysis (ADME)

A physicochemical indicator is used for the early phase of drug development to seek the essential variables that affect the biological processes. There have been some important physicochemical properties that are being computed such as permeability, solubility, lipophilicity, integrity, and stability by the process of ADME. The multiple endpoints regarding the potentially harmful effects that had an impact on drug reliability and adverse drug reactions were not predicted at the initial stage of drug development. Since the beginning of the drug discovery through the in-silico approach, the ADME has been used for the prediction of accurate pharmacokinetic properties of a molecule.[83]

8 | CONCLUSIONS

Effective antiviral candidates for SARS-CoV-2 are essential to reduce disease severity, viral load, and transmission, so they can also be used to prevent the coronavirus epidemic outbreak. To reduce the complications and break the chain of SARS-CoV and MERS-CoV, several studies are being conducted to find new drugs and vaccines. So far, the number of infected cases and mortality has been increasing rapidly. In this context, the potential secondary metabolites obtained from different cyanobacterial species would serve to refine a therapeutic model against the common viral infections and novel mutant pandemics of today and tomorrow. CADD is becoming very important to determine the virion's physical properties and affinities of drug molecules, which could also help experimental/clinical scientists identify successful inhibitors using *in vitro* approaches. A multitude of possible enzymes and signaling pathways that are specific for SARS-CoV-2 are established with the help of advanced technology. However, there are only a few hurdles in the development of drugs for the SARS-CoV-2 Delta variant. The main hurdles are the availability of effective drug candidates and funds to conduct research as well. Nowadays, the important drug discovery strategy in pharmacy, particularly virus research, has come under pressure. Even then, there is still no specific treatment. Currently, FDA-approved, repurposed drugs such as CQ and HCQ are being used as an alternative therapy for SARS-CoV-2-infected people. However, much more pharmacological studies of the proposed cyanobacterial molecules are needed against the coronavirus.

all authors have helped to complete the paper. P.K Praseetha (PKP) has drawn the diagrams.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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