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Exploring the potential of microalgae and cyanobacteria derived antiviral metabolites: Insights from molecular docking studies

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REVIEW ARTICLE

The world has been confronted with many viral outbreaks, epidemics, and pandemics with limited safe antiviral options. There are 219 viral species that have been identified as capable of infecting people. Of them, the yellow fever virus was the first to be identified; yet, every year, three to four new species are still found. The coronavirus disease 2019 (COVID-19) pandemic is exacerbated by the spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus. Animal and human coronavirus infections are typically accompanied by symptoms related to the respiratory and digestive systems. One of the main goals of scientific research is the creation of medications for the prevention and treatment of acute and severe viral infections. Microalgae and cyanobacteria are factories of bioactive phytochemicals with a wide range of biological activities, including antiviral and anti-inflammatory effects. Therefore, special attention has been paid to algal natural compositions such as polysaccharides, alkaloids, lectins, polyphenolic compounds, and pigments, which are extracted from microalgae and cyanobacteria and exhibit antiviral activities. Some studies showed that discovering the inhibitory diagnoses of 23 cyanobacterial compounds against the SARS-CoV-2 that have been well-thought-out as promising drug intents such as cylindrospermopsin, deoxycylindrospermopsin, carrageenan, cryptophycin 52, eucapsitrione, tjipanazole, tolyporphin and apratoxin A. This review deal with the antiviral activities of different microalgal and cyanobacterial metabolites, approaches to enhance their production with different stress conditions and underlined mechanisms or modes of actions by using different docking programs for imagining the 3D structure of a molecule. The molecular docking method is concerned with the optimization of lead molecules, biological pathway assessment, and *de novo* drug design.

Keywords: Antiviral activities, COVID-19, Cyanobacteria, Mechanism of action, Microalgae, Molecular docking

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INTRODUCTION

Viruses are obligatory parasites with genome, DNA or RNA, that is wrapped by a protein capsid. They are either non-enveloped or enveloped with a lipid bilayer (Gorbalenya et al., 2020). In the 21st century, numerous zoonotic viral pathogens have been emerged in humans, like Ebola, Zika, Middle East respiratory

syndrome coronavirus (MERS-CoV), severe acute respiratory syndrome coronavirus (SARS-CoV), influenza, and Nipah virus (Luo & Gao, 2020; Al-Karmalawy et al., 2021). In Egypt, several studies have reported several viruses including rotavirus, astrovirus, and norovirus as etiological pathogens of acute gastroenteritis in children (Rizk et al., 2021). Also, Egypt is one of the highest cumulative numbers of hepatitis C virus (HCV) infection worldwide.

Egypt has been working towards the shared goal of controlling viral hepatitis by 2030, as reported by the World Health Organization (WHO), and has been doing so for the past ten years. A typical change in HCV organization and a decrease in mortality have been brought about by the introduction of direct-acting antivirals (DAAs) and widespread access to therapy. Interferon-free DAA regimens demonstrated significant SVR12 (sustained virologic response) rates in Egyptian patients with ongoing HCV infection, according to a large Egyptian study, which also shown a noticeable decrease in mortality in Egypt. Significant improvements in the haematologic, hepatic, and renal biochemical profiles were associated with them.

The baseline AST (aspartate aminotransferase), liver cirrhosis, and treatment regimen might have an impact on achieving SVR (Naguib et al., 2021). During the winter of 2014–2015, Egypt experienced a remarkable rise in the number of human infections with the highly dangerous avian influenza A(H5N1) virus (WHO, 2015). The spread of viral illnesses creates expenses and negatively affects the social and economic spheres due to insufficiently effective preventative or qualification measures.

Vaccination against viral infection is the optimum prophylactic strategy to control viral diseases. Nevertheless, the impact of vaccination during pandemics or established infections is significantly limited. Meanwhile, effective antivirals represent an alternative therapeutic intervention. Cyanobacteria and microalgae are from the most important natural options for their formation due to their broad-spectrum biological activities such as antiviral activities (Yasuhara-Bell & Lu, 2010; Ahmadi et al., 2015; Singh et al., 2020). Microalgae can produce several types of antiviral compounds including proteins, terpenoids, pigments, steroids, and sulfated polysaccharides. Lectins of cyanobacteria and marine algae have essentially been examined against human immunodeficiency virus (HIV), and some of them revealed antiviral activity against different viruses, including the SARS-CoV, hepatitis C virus (HCV), Marburg virus (MARV), herpes simplex virus (HSV), human influenza virus, and Ebola virus (Huskens & Schols, 2012; Mitchell et al., 2017). Calcium spirulan and phycocyanin, polysaccharides from *Spirulina platensis (Arthrospira Platensis)*, inhibit the replication of many viruses as influenza, mumps, and HIV (Singh et al., 2020) and have NADH oxidase inhibitor with anti-inflammatory properties. Microalgae and Cyanobacteria are potential adjuvant therapies for COVID-19 patients, with *Spirulina* being a promising source for these compounds (Khavari et al., 2021).

A natural chemical storehouse full of beneficial compounds is marine microalgae. Despite their potential applications in biotechnology, many creatures are still genuinely unknown. The antiviral, antibacterial, anti-inflammatory, and anti-cancer properties of extracts from 33 strains (representing 20 dinoflagellates, 4 diatoms, and 9 strains from seven other algal classes) grown under equal conditions were evaluated by Hernández-Urcera et al. (2024). Using the ZF4 cell line, the extracts' antiviral activity against the spring viraemia of carp virus (SVCV) was identified in a few strains.

The main reason microalgae and cyanobacteria are appealing as natural sources of bioactive chemicals is that they exhibit encouraging metabolite production in cultures, which enables the biosynthesis of structurally complicated molecules that are difficult or impossible to synthesize by chemical synthesis.

Large-scale production of these bioactive chemicals in culture is dependent on a number of variables, such as temperature, pH, light intensity, growth phase duration, biomass treatment prior to extraction, and medium components (Varfolomeev & Wasserman (2011).

In this regard, the present review listed the most active components produced from these species together with their mechanisms of action and illustrated the relationship between microalgal species and their antiviral potentialities.

Microalgae and cyanobacteria as source of antiviral compounds

In the last few decades, Human health has been impacted by the unexpected emergence

of several deadly viral infections (Wang et al., 2020). In the last few decades, natural compounds have played a significant role in the hunt for new antiviral medications. According to Goswami et al. (2020), these natural products comprise a variety of active chemicals with a wide spectrum of biological activities. Algae have long been utilized to prevent or treat a variety of illnesses, and many nations continue to use them in their healthcare systems (Xian et al., 2020).

Cyanobacteria and microalgae have excellent opportunities for the extraction of naturally occurring compounds with substantial commercial value in sectors like pharmaceuticals, food, and cosmetics. Because of this, cyanobacteria and microalgae are raw resources with significant added value. HIV, HSV, Ebola, and influenza viruses, are the primary targets of antiviral cyano-metabolites (Mazur-Marzec et al., 2021). Prior research has unequivocally demonstrated that metabolites of cyanobacteria and microalgae can be used as a therapy against different human diseases, such as cancer, diabetes, viral infections, and problems affecting the central nervous system (CNS) (Prabhu et al., 2022).

Pigments

Numerous research have demonstrated the potential applications of microalgal pigments in the biomedical sector, including as phycobiliproteins (allophycocyanin, phycocyanin and phycoerthrin), carotenoids and astaxanthin.

- **Chlorophylls**

Studies carried out by Bouslama et al. (2011), Xodo et al. (2012), Ratnoglik et al. (2014), Perez-Galvez et al. (2017) and Saide et al. (2020) revealed that chlorophylls and pheophorbide pigments exhibited some antiviral activities. It was believed that these pigments may prevent viral adsorption and entry to the host cell.

- **Carotenoids**

Polymerized pigments from isoprene units are called carotenoids. Key carotenoids found in microalgae include beta-carotene, astaxanthin, lutein, zeaxanthin, and lycopene (Barkia et al., 2019). They have both direct and indirect antiviral properties and are employed in various biotechnological domains. Carotenoids, chlorophyll, β-carotene and astaxanthin pigments from *Chlamydomonas reinhardtii, Dunaliella salina* and *Haematococcus pluvialis* microalgae were shown it inhibit many viruses as herpes virus, white spot syndrome virus (WSSV) and COVID-19 reported by Hosikian et al. (2010), Couso et al. (2012), Barkia et al. (2019), Talukdar et al. (2020), Carter et al. (2021) and Ribeiro et al. (2022).

- **Phycobiliproteins**

Other pigments having antiviral properties are phycobiliproteins, which include phycocyanin, allophycocyanin, and phycoerthrin. Allophycocyanin-containing *Spirulina platensis* extracts postponed the EV71 single-stranded RNA virus's in vitro RNA tuning (Ribeiro et al., 2022). Its cold-water extract exhibited antiviral activity against two bacteriophages (MS-2 and ΦX-174) (Garrison et al., 2014) and anti-IAV activity because of the presence of cyanobacterial phycocyanin (CPC), which typically suppresses the expression of inflammatory factors brought on by viruses (Carbone et al., 2021).

By directly interacting with the capsid protein, they provide a virucidal impact (Garrison et al., 2014). This virucidal action hindered viral growth and decreased viral titer. Furthermore, they may have therapeutic assurance for nonenveloped viruses as rhinoviruses, polioviruses, and noroviruses, according to Sami et al. (2021) (Table 1).

Polysaccharides

Polysaccharides (sulfated and acidic) exhibit various biological activities (antioxidant, anticancer, anticoagulant, antiviral and antiproliferative activities), which are complex structures in terms of monosaccharide structure (Nie et al., 2018). In essence, antiviral chemicals derived from microalgae are polysaccharides that have been chosen to be effective against harmful human viruses. Their ability to block the viral stages of the infection and interfere with its adhesion, penetration, or replication may be the cause of their activity (Lalani & Poh, 2020; Claus-Desbonnet, et al., 2022).

- **Sulfated polysaccharides**

The strongest antiviral properties are seen in sulfated polysaccharides. Herpes simplex virus type 1 (HSV-1) and HIV-1 are both susceptible to the antiviral effects of the cyanobacterium *Spirulina platensis* isolated sulfated polysaccharides (Nie et al., 2018).

Table1. Microalgal and cyanobacterial compounds have antiviral activities. (designed by authors)

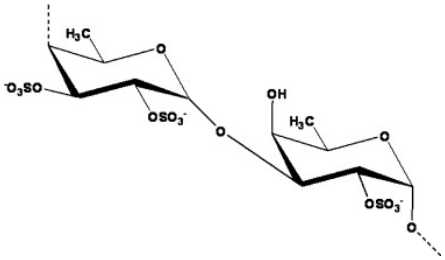
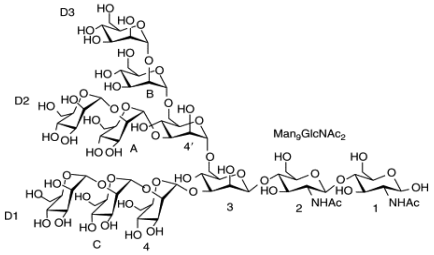
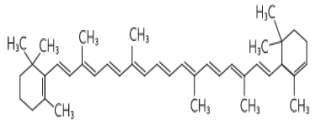
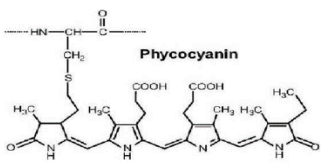
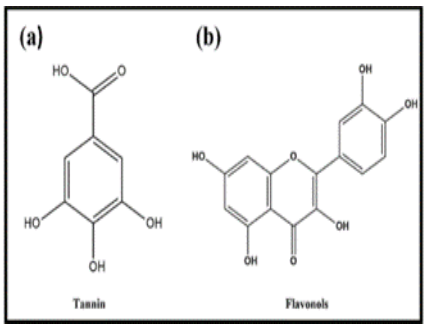
Algae species	Antiviral compounds	Target Viruses	References
Cyanobacteria *Nostoc flagelliforme* *Spirulina platensis* *Arthsospira fusiforme* **Microalgae** *Gyrodinium impudium* *Cochlodinium polykrikoides* *Porphyridium cruentum* *P. aerugineum* *Porphyridium sp* *Chlorella autotrophica* *Navicula directa* *Chlorella pyrenoidosa* *Ellipsoidon sp.* *Rhodella reticulate*	**Polysaccharides** 	(HSV 1, 2), (VZV). HIV1, HIV2, HCMV, MuV, IAV ECTV, VV, MuLV ,HH3, ASFV, VHSV, HIV1, IBV, HPIVs, MuV, IAV, EMCV, VSV, Influenza A virus ASFV Encephalomyocarditis virus	Lee et al. (2006), Sharaf et al. (2010), Schmidt et al. (2011), Gardeva et al. (2009, 2012), Xodo et al. (2012), Kavitha et al. (2016)
Cyanobacteria *Oscillatoria agardhii* *Nostoc ellipsosporum* *Microcystis aeruginosa* *Microcystin viridis* *Scytonema varium* *Nostoc muscorum*	**Lectin** (Agglutinin OAA CV-N Microvirin MVL Scytovirin)  cyanovirin N as a microalgal lectin	HIV1, HIV2 , HSV1, HCV IAV, IBV, ZEBOV	Kehr et al. (2006), Sexton et al. (2006), Zilliges et al. (2008), Sato & Hori (2009), Tiwari et al. (2009), Gao et al. (2010), Huskens et al. (2010), Shahzad-ul-Hussan et al. (2011), Agarwal et al. (2020)
Cyanobacteria *Lyngbya* *Cryptomonads* *Arthrospira maxima (LEAF046) (Spirulina maxima)* *Spirulina platentis* **Microalgae** *Chlorella vulgaris (LEAF749)* *Dunaliella salina (LEAF754)* *Haematococcus pluvialis* *Dunaliella Primolecta*	**Pigments** (Allophycocyanin Phycocyanin carotenoids astaxanthin (xanthophylls) Pheophorbide a)  Beta carotene 	Mayaro virus, EV71 IAV, HSV1 Su-HV1, PRV, Enterovirus 7**1**	Shih et al. (2003), Chen et al. (2016), Ribeiro et al. (2022)

Table 1. Cont.

Algae species	Antiviral compounds	Target Viruses	References
Cyanobacteria *Nostoc linckia* *cyanobacterium Geitlerinema*	bioactive compounds such as high phenolic, flavonoid, and tannin contents  	H5N1, HCV	El-fayoumy et al. (2021)

The marine microalgal diatoms *Navicula directa*, and *Cochlodinium polykrikoides* has three polysaccharides (naviculan, and other two types named A1 and A2) showed antiviral activities against numerous enveloped viruses, for instance HIV-1, HSV-1 or influenza virus type A (IFV-A) (Zheng et al., 2020). The sulfated polysaccharide p-KG03, which was isolated from *Gyrodinium impudicum,* has also been shown to be effective against a number of influenza virus strains and the encephalomyocarditis RNAvirus (EMCV) (Yim et al., 2004), with efficacy on par with some of the medications now on the market (Kim et al., 2011).

Indeed, it has been suggested that the sulfated exopolysaccharides found in some marine microalgae inhibit the initial phase of viral infection (Amaro et al., 2011). Tiny molecules like sulfated polysaccharides present a good challenge in antiviral drug discovery studies because the actual antiviral pharmaceutics are proteins that work at Stage II of the infection. Due to its strong oral cell surface adhesion capacity (Belouzard et al., 2012) and its easy entry through the lung cell surface's ACE2 receptor (stage I of the viral infection) (Jia et al., 2005), the virus is extremely contagious in the context of COVID-19 (Livingston & Bucher, 2020).

- **Acid polysaccharides**

Additionally, microalgal acid polysaccharides containing carboxyl, phosphate, or ester groups demonstrated anti-HSV action. One of the most notable acidic polysaccharides is nostoflan, which is generated by the cyanobacterium *Nostoc flagelliforme.* By reducing gD, a key constituent of the virion envelope glycoprotein, it has strong action against HSV (Kanekiyo et al., 2007; Hayashi, 2008). When administered intranasally to mice models, it also exhibits some actions against IAV in vitro, decreasing the virus output at low dosages (Hayashi, 1996).

The acid polysaccharide that *Chlorella pyrenoidosa* produced in mice somewhat inhibited the vesicular stomatitis virus (VSV), a negative stranded enveloped RNA virus of the Rhabdoviridae family that produces mucosal vesicles and ulcers in the mouths of cattle, horses, and pigs. (Plaza et al., 2009) (Table 1).

Polyphenolic compounds

Polyphenolic compounds with antiviral qualities, including flavonoids, cinnamic acid, gallic acid, benzoic acid, quercetin, and phlorotannins, are produced by microalgae (Lalani & Poh, 2020). Antiviral, antibacterial, anti-inflammatory, and antioxidant qualities are among the many bioactivities displayed by phenoltannins, which are tannin derivatives (Al-Mola, 2009; Gastineau et al., 2012). Phenolglucinol derivative 8, 80-bieckol inhibited HIV-1 protease and recombinant RT activities in vitro (Wijesekara et al., 2010).

Agrawal (2011) states that flavonoids, some of which are derived from microalgae, are potent antivirals. The cyanobacterium *Geitlerinema* sp. strain's methanol extract contained a flavonoid group component that showed potent anti-HCV activity by reducing ATPase activity, which in turn reduced RNA helicase and virus multiplication

(Zaenal et al., 2015, 2016) (Table 1). Marennine is a pigment that is probably polyphenolic in nature and exhibits interesting antiviral properties (Daglia, 2012). Water-soluble marennine is a blue-grey auxiliary pigment produced by the tychopelagic diatom *Haslea ostrearia* during blooms (Mouget et al., 2005). Its exact mode of action is unknown, but Olicard et al. (2005) found that it has strong antiviral properties against HSV and HIV; its action is not clear in detail.

Lectins

Non-immunoglobulin proteins called lectins can bind saccharides without changing the structures of particular glycosyl ligands (Mitchell et al., 2017). All of the antiviral microalgal lectins that have anti-HIV activity come from cyanobacteria and work by stopping the microorganisms from entering the cells by obstructing their ability to connect with the cell membrane (Nie et al., 2018). Cyanobacteria produced five lectins that are the most studied such as Microvirin, Agglutinin OAA, Cyanovirin-N, Microcystis Viridis Lectin (MVL), and Scytovirin.

Agglutinin OAA, which exhibits anti-HIV1 and anti-HIV 2 activity in vitro as well as significant mitogenic activity, is one of the several lectins produced by *Oscillatoria agardhii* to sustain blooms on the surfaces of lakes and ponds (Nie et al., 2018).

Nostoc ellipsosporum was used to extract cyanovirin-N (CV- N) (Nie et al., 2018). According to numerous research, CV-N contains anti-influenza A-B viruses (IAV, IBV) and prevents three viruses from penetrating human ocular cells: the hepatitis C virus (HCV), ZEBOV, and herpes simplex virus (HSV) (Nie et al., 2018). Additionally, it has suppressed a number of laboratory strains of HIV. It prevents the virus from attaching to host cells by irreversibly impasseing viral glycoprotein 120 (Prabhu et al., 2022).

Under conditions of iron and light stress, *Microcystis aeruginosa* PCC7806 produces more microvirin (Zilliges et al., 2008). It helps prevent the establishment of syncytium by having strong anti-HIV action. The PCC7806 strain of *Microcystis viridis* is the source of Microcystis Viridis Lectin (MVL) (Yamaguchi et al., 1999). This lectin shows anti-HCV action and a strong affinity for the HCV E1E2 glycoprotein, according to Kachko et al. (2013).

Using an aqueous solvent, scytovirin was extracted from the *Scytonema varium* (Bokesch et al., 2003) and N-terminal residue of the scytovirin domain 1 (SD1) interacts with HIV1 in vitro (Takebe et al., 2013; Wood , 2013). According to Breitenbach et al. (2018), Western blot investigation also verified the existence of this lectin against ZEBOV and HCV. In particular, Garrison et al. (2014) showed that the lectin's presence reduced mortality in 9 BALB/c mice infected with ZEBOV and that its activity had some effects when the lectin was given one day before the infection and one day after the infection. Scytovirin inhibits the Marburg virus, SARS-CoV, Zaire ebolavirus, and HIV (Li et al., 2008). It binds with the mannose-rich oligosaccharides of glycoproteins.

Nostoc muscorum generated two types of lectins that operate in distinct ways (N/O-glycan and Mannose-binding). N/O-glycan specific lectin derived from *Nostoc muscorum* displays its antiviral effects during the HSV-1 entry phase, whereas Mannose-binding lectin notably reduced HSV-1 activity following entry (Saad et al., 2022) (Table1).

Effect of abiotic stress conditions on the enhancment of algal antiviral compounds

Physical factors

- **Light**

When comparing continuous high light intensity exposure to the control condition, cyanobacteria and microalgae generate a greater amount of exopolysaccharides. *Cyanothece sp*. generated exopolysaccharide (EPS) as a result of ongoing culture illumination at 86.0µE/m^2/s (Costa et al., 2021). Ge et al. (2014) indicated that the highest light intensity (80µE/m^2/s) promoted the production of exopolysaccharide and capsular polysaccharide in *Nostoc sp.* In comparable fractions, heightened protein levels of EPS were often triggered by intense continuous illumination. When examined with atomic force microscopy, the surface structure of EPS appeared as round clusters, strands, and webs. Greater light intensities were employed to identify the long chains. Consequently, light intensity influenced the type and production of EPS.

The red light enhances the production of exopolysaccharides and capsular polysaccharides in *Nostoc flagelliform* (Costa et al., 2021). Additionally, elevated UV-radiation levels enhance carotenoid concentrations in certain Bacillariophyceae (Rech et al., 2005).

• **Temperature**

Low temperatures enhance the production of pigments in *Chlamydomonas reinhardtii.* Temperatures ranging from 10 to 20°C stimulated the accumulation of carotenoids and chlorophyll in *Chlamydomonas reinhardtii.* A temperature of 15°C resulted in the greatest accumulation of carotenoids and chlorophyll, being 2 times and 1.3 times greater than at 25°C, respectively (Potijun et al., 2021).

The ideal temperature for exopolysaccharide production varies based on the cultivated microalgal strain (Lakatos et al., 2019). The production of exopolysaccharides in *Anabaena sp.* increased by approximately 4–5 times when the temperature was altered from 30–35 to 40–45°C in cultured conditions (Costa et al., 2021). Yu et al. (2010) discovered that when *Nostoc flageliforme* was grown in BG-11 medium, the synthesis of exopolysaccharides increased at 25°C, yielding 228.56mg/L. Another research indicated that *Spirulina sp.* had an accumulation of exopolysaccharides at 9.5g/L. Ideal temperature conditions (33–35°C) and light intensity promoted greater productivity of exopolysaccharides (Jesus et al., 2018).

Chemical factors

• **Salinity stress**

Salinity stress can modify the metabolic pathways of affected organism(s), resulting in either the enhancement or production of biologically active compounds. Shalaby et al. (2010) demonstrated that an increase in salt concentration enhanced the production of both phycocyanin and phycoerythrin pigments in *Spirulina platensis*. The antiviral properties of algal extracts (from water or phosphate buffer of salt-stressed cultures) against HSV-1 (a DNA virus) were notably higher (98.0%) compared to those against HAV-MBB, an RNA virus (60.0%), possibly due to the presence of sulfated polysaccharides and tannins in the *S. platensis* extracts.

The salt stress from sodium chloride (NaCl 0.3–0.7mol/L) increased the exopolysaccharides (EPS) accumulation by 63% in *Microcoleus vagiantus* (Chen et al., 2006). Additionally, the synthesis of exopolysaccharides by *Cyanothece sp*. increases when the microalga is grown in elevated salinity (70g/L) (Chi et al., 2007). The production of exopolysaccharides in *Chlorella sp.* increased between 3 to 30 times due to the rise in salinity from freshwater (0.1%) to seawater (3.5%) (Vo et al., 2020). Sheng & Yu (2006) found that the buildup of EPS generated by *Rhodopseudomona sacidophila* rose in high NaCl concentrations. Additionally, Ozturk & Aslim (2010) demonstrated that the quantity and composition of EPS in three *Synechocystis* species were significantly influenced by the NaCl concentration in the growth medium.

• **Nitrogen and sulfur concentrations**

El-Fayoumy et al. (2021) indicated that growing *Nostoc linckia* under nitrogen and sulfur stress conditions enhanced the total phycobiliprotein content by five times. Additionally, nitrogen reduction notably increased the highest levels of phenolic and flavonoid compounds. *N. linckia* extract exhibits antiviral properties against the H5N1 virus, showing inhibition rates of 50% and 63.6% at concentrations of 7µg/mL and 28µg/mL of nitrogen (N) and sulfur (S), respectively, with cytotoxicity below 7µg/µL.

Lupi et al. (1994) grew *Botryococcus braunii* UC58 using various nitrogen sources (nitrate, ammonium, and urea), revealing that elevated levels of exopolysaccharides (EPS) were present when nitrate served as the nitrogen source. The occurrence of sodium nitrate ($NaNO_3$) in *Cyanothece sp*. CCY 0110, the cultivation environment significantly improved the production of polysaccharides when compared to a condition lacking $NaNO_3$ (Mota et al., 2013). Although *Nostoc sp.* BTA97 and *Anabaena* species. BTA990 generated 1.58 and 1.29mg/mL of exopolysaccharides, respectively, when no combined nitrogen source was present (Tiwari et al., 2015). Han et al. (2014) grew *Nostoc flagelliform* using four different nitrogen sources (urea, $NaNO_3$, NH_4Cl, and arginine). Urea enhanced biomass production by 66% and boosted exopolysaccharide accumulation by 217.3%. Research has demonstrated that the nitrogen/phosphorus (N/P) ratio can enhance the production of exopolysaccharides by microalgae (Khattar et al., 2010; Jindal et al., 2011; Villay et al., 2013; Razaghi et al., 2014; Chentir et al., 2017). Soanen et al. (2016) observed that the N/P ratio influenced the exopolysaccharide content generated by the microalga *Porphyridium cruentum.* Additionally, it was found that raising the N/P ratio decreased biomolecule accumulation.

• **Carbon sources**

Arthrospira platensis ($0.30gL^{-1}$) has been studied for polysaccharide production in

mixotrophic cultures (Li et al., 2020). *Chlorella* species. exopolysaccharide accumulation can be stimulated in ($0.03gL^{-1}$) by utilizing glucose and sucrose as carbon sources (Vo et al., 2020). Given the elevated price of organic carbon sources like sodium acetate, glycerol, sucrose, and glucose, industrial sugarcane waste molasses syrup can be employed to enhance microalgae growth in mixotrophic cultivation. Crude molasses is provided as a raw glucose material and is utilized only after hydrolysis pretreatment (Ma et al., 2017).

- **Nanometals**

In recent times, the significance of nanomaterials has risen substantially (Wang et al., 2017). They serve to enhance biomass and the amount of valuable substances generated by cellular metabolism (Ozkaleli & Erdem, 2018). Xiong & Xu (2022) found that TiO_2 and reduced graphene oxide titanium dioxide nanoparticles showed significant phycocyanin content accumulation under visible light conditions in *Arthrospira (Spirulina) platensis* (FACHB-314) cells, with phycocyanin levels reaching 80.3mg/g and a peak production of 97.16mg/L in rGO-TiO_2 nanoparticles cultures. In contrast, TiO_2 nanoparticles cultures produced 55.7mg/g and 81.88mg/L, while the control culture yielded 75.5mg/g and 81.86mg/L. The control exhibited antiviral properties against viruses like Mayaro virus, EV71IAV, HSV1, Su-HV1, PRV, and Enterovirus 71 (Shih et al., 2003; Chen et al., 2016; Ribeiro et al., 2022).

Additionally, various carbon-based nanomaterials (CNMs) like carbon nanosheets (CNS) have demonstrated the significance of microalgae as energy-efficient bio-nano factories, thanks to their enhanced productivity, nutrient availability, and resilience to abiotic stress. These elements play a crucial role in advancing bio-stimulant products for pharmaceutical, nutraceutical, bioenergy, and environmental uses (Agarwal et al., 2022).

Mode of action of microalgal antiviral compounds

As shown in Figure 1, the primary stages at which the biologically active antiviral molecule can disrupt the viral replication cycle within the host cell include attachment to the infected cells, active replication within the cell, or a direct cell-free viricidal action. Present antiviral treatments target various stages of viral infection, including the adsorption and entry into host cells, the uncoating and replication of nucleic acids, as well as the assembly and release of viruses (Mazur-Marzec et al., 2021). Various metabolites from microalgae and cyanobacteria possess significant potential to block virus attachment to host cells, as well as to impede virus replication, inhibit reverse transcriptase, halt protease activity, prevent syncytia formation, avoid apoptosis, lessen histopathological effects, and enhance interleukin-1β (IL-1β), tumor necrosis factor-1α (TNF-1α), MCP-1, MIP-1, IP-10, and COX-2.46-60 (Prabhu et al., 2022). As illustrated in Table 2 and Figure 2, the metabolites were extracted from different species of microalgae and cyanobacteria.

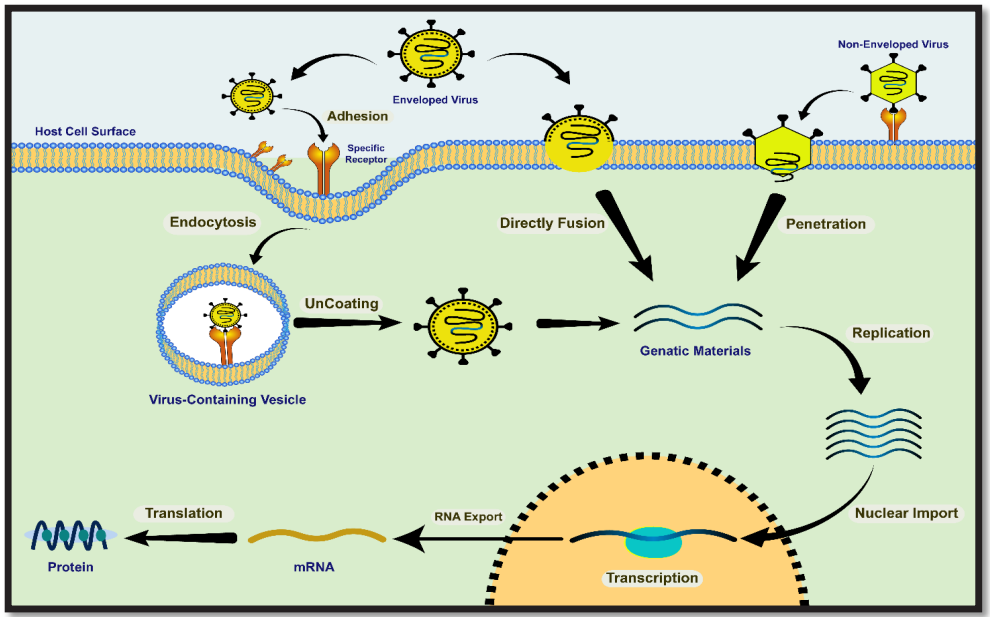


Figure 1. Main stages of viral infection to the host cell (This figure is designed by authors)

Table 2. Action potential of microalgal and cyanobacterial antiviral compounds

Microalgal antiviral components	Mechanism of action	viruses	Ref.
Polysaccharides	- Interaction between the positively charged and negative charge on polysaccharides - Preventing a late step during the virus replication cycle. - Inhibition of cytopathic effect	Herpes simplex viruses types 1 and 2 (HSV 1, 2) and Varicella zoster virus (VZV).	Lee et al. (2006), Sharaf et al. (2010), Schmidt et al. (2011), Gardeva et al. (2009, 2012), Xodo et al. (2012), Kavitha et al. (2016)
Lectins	-Lectins interact directly with the high-glycan structure of viral envelope glycoproteins	HIV1, HSV1, HCV,IAV, IBV	Kehr et al. (2006), Sexton et al. (2006), Zilliges et al. (2008), Sato & Hori (2009), Tiwari et al. (2009), Gao et al. (2010), Huskens et al. (2010), Shahzad-ul-Hussan et al. (2011), Agarwal et al. (2020)
Pigments	- Inhibition of cytopathic effect - Delay in synthesis of viral RNA - Bonds to virus cell receptors, effects post-entry steps - Inhibition of plaque formation and down regulation of gene and protein expression - Delay of viral RNA synthesis in vitro - Down regulation of expression of inflammatory factors	HSV1, Su-HV1, PRV, Enterovirus 71, EV71 IAV	Shih et al. (2003), Chen et al. (2016), Ribeiro et al. (2022)
Polyphenolic compounds	- Virus as a percentage of inhibition was50% and63.6%	H5N1	El-fayoumy et al. (2021)
Secondary metabolites	- Petroleum ether and water algal extracts exhibited high antiviral activity (99.9%<) and the mode of action of extracts was not correlated with virus replication but with its adsorption process. - Spirulina methanol extracts inhibited LMP1, EBNA ,and ZEBRA proteins from the lytic cycle of the EBV virus.	H5N1, EBV	El-fayoumy et al. (2021), Shalaby & Shanab (2021), Ribeiro et al. (2022)

Adhesion to host cell

The initial phase of viral infection involves the attachment of the invading viral particle to the host cell receptor. For enveloped virions, adsorption is usually aided by a particular glycoprotein in the virus envelope, like the hemagglutinin glycoprotein of the influenza virus (Cosset & Lavillette, 2011). In non-enveloped viruses, attachment can be facilitated by one protein, like the adenovirus fibre protein, or through a multiprotein complex, as seen in poliovirus (Suomalainen & Greber, 2013). SARS-CoV-2 belongs to the coronavirus family and consists of three structural proteins: membrane protein, envelope protein, and spike protein (S), which is a glycoprotein crucial for the virus's binding to the host cell (Li, 2016).

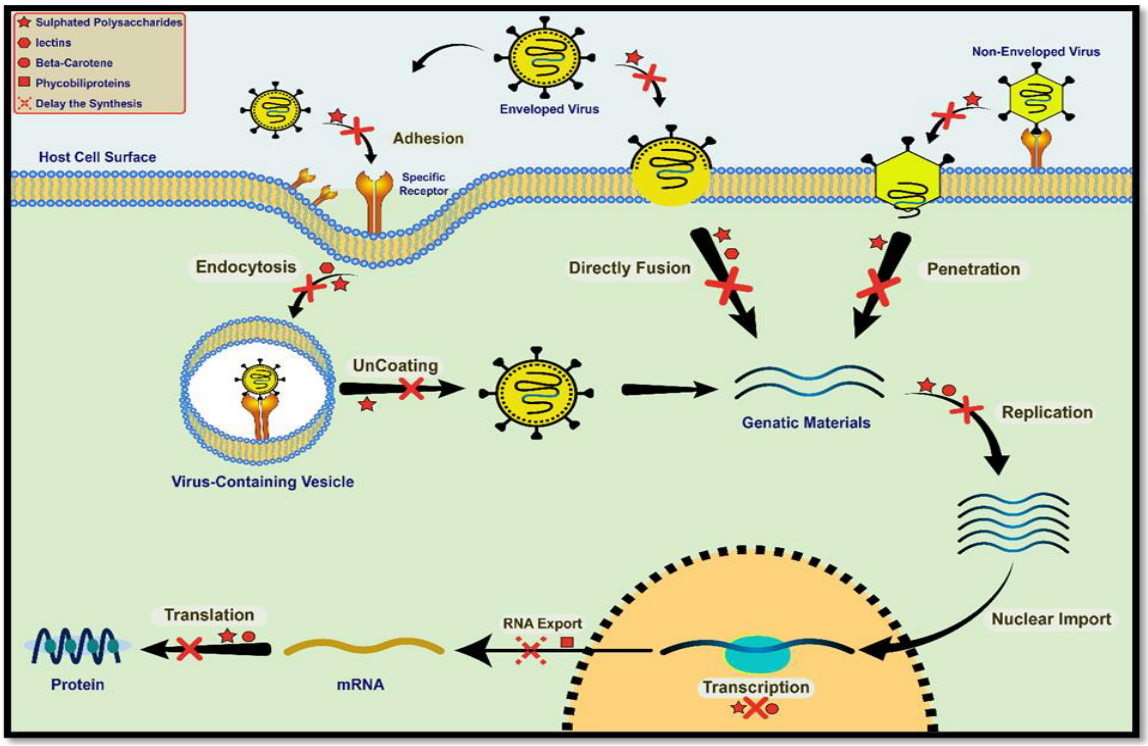


Figure 2. Antiviral mechanism of the bioactive compounds from microalgae and cyanobacteria [this figure is designed by authors]

Sulfated polysaccharides demonstrate significant antiviral effectiveness against enveloped viruses. Their engagement with the positively charged areas of the virus's glycoprotein envelope leads to a non-reversible complex, attributed to the negative charge of the sulfonate group (Carbone et al., 2021). Numerous factors, such as the level of sulphation, molecular weight, the allocation of sulphate within the structure and stereochemistry, the influence of counter cations, and the interaction between hydrophobic and hydrogen bonds, are associated with the functionality of sulfated polysaccharides (Neyts et al., 1992; Lüscher-Mattli, 2000; Lee et al., 2006; Harden et al., 2009), as depicted in Figure 2.

Host cell invasion

Penetration refers to the method by which the virus obtains entry into the cytoplasm. Some viruses, such as HIV-1, merge their envelopes directly with the plasma membrane of cells. After undergoing endocytosis, various enveloped viruses—such as influenza viruses—merge their envelopes with the membrane of the endocytic vesicle. A hydrophobic fusion peptide, which facilitates membrane fusion and releases the viral nucleocapsid into the cytoplasm, is illustrated by a conformational change in a viral membrane protein during both processes (Plemper, 2011). In contrast to enclosed viruses, the penetration mechanisms of non-enveloped viruses are not as thoroughly defined. Non-enveloped viruses experience conformational alterations that expose a hydrophobic region or an alternative upon interacting with the cell membrane or endocytic vesicles.

Lectins inhibit the entry of microbes into cells by obstructing their interaction directly with the high-glycan structure of virally enveloped glycoproteins, which prevents fusion with the glycan structure of human cell membrane glycoproteins (Botos & Wlodawer, 2003), as illustrated in Figure 2.

Replication and virus particles releasing

In order for the replication cycle to operate, viral genes need to be translated into mRNA and transcribed following the invasion of the host cell. The type of nucleic acid (DNA or RNA), and whether it is single-stranded (ss) or double-stranded (ds), is among the fragile characteristics of a virus genome (Knipe et al., 2013). Most human DNA viruses possess dsDNA, which replicates their genomes within the nucleus and transcribes their protein-coding

genes utilizing cellular RNA polymerase.

To generate a DNA provirus from their RNA genomes, RNA viruses produce RNA-dependent DNA polymerase, commonly referred to as reverse transcriptase. RNA viruses replicate through a DNA intermediary. Virion assembly requires many moving parts and significant interaction with cellular machinery for processing and transporting proteins (Knipe et al., 2013). Most DNA viruses begin their assembly in the nucleus, whereas most RNA viruses assemble in the cytoplasm. When infected cells burst, non-enveloped virions are usually released. To form an envelope around enveloped virions, it is essential to first assemble a capsid containing the genome, followed by the budding off of the suitable cellular membrane. The emerging virion is subsequently transported in a vesicle to the plasma membrane, where it merges with the membrane for release from the cell (Pellett et al., 2014).

As illustrated in Figure 2, sulfated polysaccharides can impair enzymes related to viral replication and relevant targets in host cells, in addition to halting the internalization process and initial viral replication (Chen et al., 2020). Li et al. (2016) state that beta-carotene reduces the levels of cytokines and nitric oxide. It additionally inhibits the generation of the jak/stat pathway gene and protein when the pseudorabies virus (PRV), an Alphaherpes virus responsible for neurological issues in mice, is present. Owing to its negative charge, sulfoquino vosyldiacyglycerol obstructs the negative charge of DNA phosphodiester bonds through interaction with the positive charge of DNA polymerase. Phycobiliproteins are additional substances that possess antiviral characteristics. The in vitro RNA synthesis of Enterovirus 71 (EV71), a single-stranded RNA virus from the Piconaviridae family responsible for neurological and cardiovascular diseases, was inhibited by *Spirulina platenis* preparations that include allophycocyanin (APC) (Shih et al., 2003).

Direct cell-free viricidal effect

The minimal cytotoxic effects and strong viricidal properties of certain microalgae metabolites highlight their potential effectiveness against viruses, significantly contributing to the creation of nutraceuticals for human and animal ailments. Michelon et al. (2021) described that extracts of microalgae using hexane, dichloromethane, and methanol (cultivated in a pilot-scale bioreactor supplied with swine wastewater as the growth medium) were evaluated for their virucidal activity against HSV-1 and HAdV-5. All microalgae extracts reduced the infectious capacity of HSV-1 by 100%. The extracts of microalgae in methanol and dichloromethane showed the lowest level of inhibition (3.125µg mL^{-1}). Utilizing microalgae extract from hexane and methanol, virucidal tests against HAdV-5 demonstrated a reduction in the virus's infectious ability by 70% across all concentrations (3.125, 6.25, 12.5, 25.0, 50.0, and 100.0µg mL^{-1}) at 37°C. At this temperature, the microalgae extract from dichloromethane diminished HAdV-5's infectious capability by 50–80% at a concentration of 12.5µg $mL^{-1.}$ In general, the results indicate that microalgae could be an important biomass source for feedstock in researching different viricidal agents.

Moreover, Hayashi et al. (2022) showed the antiviral effectiveness of monogalactosyl diacylglyceride (MGDG), which was extracted from the microalga *Coccomyxa sp.* KJ, in opposition to the human norovirus surrogates, feline calicivirus (FCV) and murine norovirus (MNV). In a manner that depends on both dose and time, MGDG showed virucidal effects against the two viruses; following 60min of incubation, MGDG at 100µg/mL reduced MNV and FCV infection to nearly 10%. In animal trials with MNV infection, the intraoral injection of MGDG (1mg/day) demonstrated a therapeutic effect by inhibiting viral shedding in the faeces and producing elevated neutralizing antibody titers in both sera and faces. Administering MGDG orally to immunocompromised mice receiving 5-fluorouracil led to elevated neutralizing antibody levels in their sera and a quicker end to viral shedding compared to the control mice who were given distilled water. Consequently, MGDG could offer a new preventive and treatment alternative for norovirus infection.

Molecular docking method

The molecular docking approach involves optimizing primary molecule(s), evaluating biological pathways, and designing drugs. Molecular docking refers to the proper

positioning of a ligand molecule on a receptor molecule to form a stable compound (Moitessier et al., 2008). Docking is mainly utilized in the realm of pharmaceuticals, playing a crucial part in drug design and drug discovery. It reduced the overall free energy of the system. There are three types of docking (Mohanty & Mohanty, 2023): Rigid docking, flexible-rigid docking, and flexible docking (based on the flexibility of the interacting molecules, receptor, and ligand). To discover potential inhibitors of the SARS-CoV-2 druggable target human angiotensin converting enzyme (ACE2), critical for the virus's binding and penetration into the host cell, Sahu et al. (2023) employed molecular docking. The receptor-binding domain (RBD) of ACE2 can be obstructed to prevent the virus from infiltrating the partition. The ACE2 protein, scytonemins, mycosporine-like amino acids, and various other photoprotective compounds underwent a molecular docking study employing AutoDock technologies, as illustrated in Figure 3.

Additionally, Fellizar et al. (2023) indicated that seven compounds from cyanobacteria inhibit the entry of SARS-CoV-2 into host cells and its replication, as shown by their computational studies. They were recognized as leading in silico antagonistic metabolites due to their affinity for binding to the SARS-CoV-2 spike RBD (receptor-binding domains) for ACE2 (angiotensin-converting enzyme 2) and GRP78 (glucose-regulated protein 78); as well as the nsps, 3CLPRO (3-chymotrypsin-like protease), PLPRO (papain-like protease), and RdRp (RNA-dependent RNA-polymerase). The multi-targeting cyanobacterial substances cyclic peptide scytonemin, cytotoxin cryptophycin, and an indole alkaloid tjipanazole A2 could serve as models for developing anti-COVID-19 medications due to their strong binding affinities and favorable pharmacokinetic properties illustrated in Figure 4.

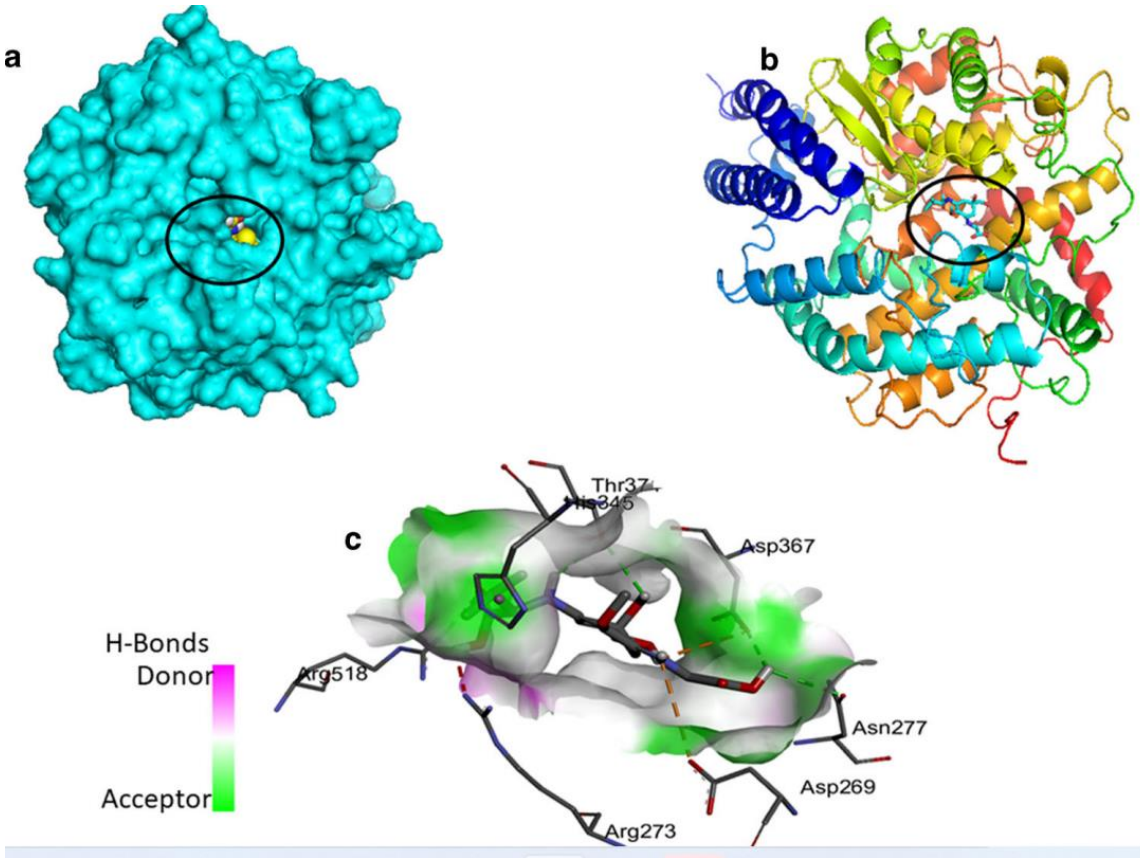


Figure 3. Molecular docking for a the reaction between mycosporine– glycine–valine with chain A of ACE2 receptor protein, cyan surface, b Docked complex map built in PyMol, c 3-Dimensional contact map based on hydrogen bond donor and acceptor characteristics of amino acid residue built in Biovia Discovery Studio (Sahu et al., 2023)

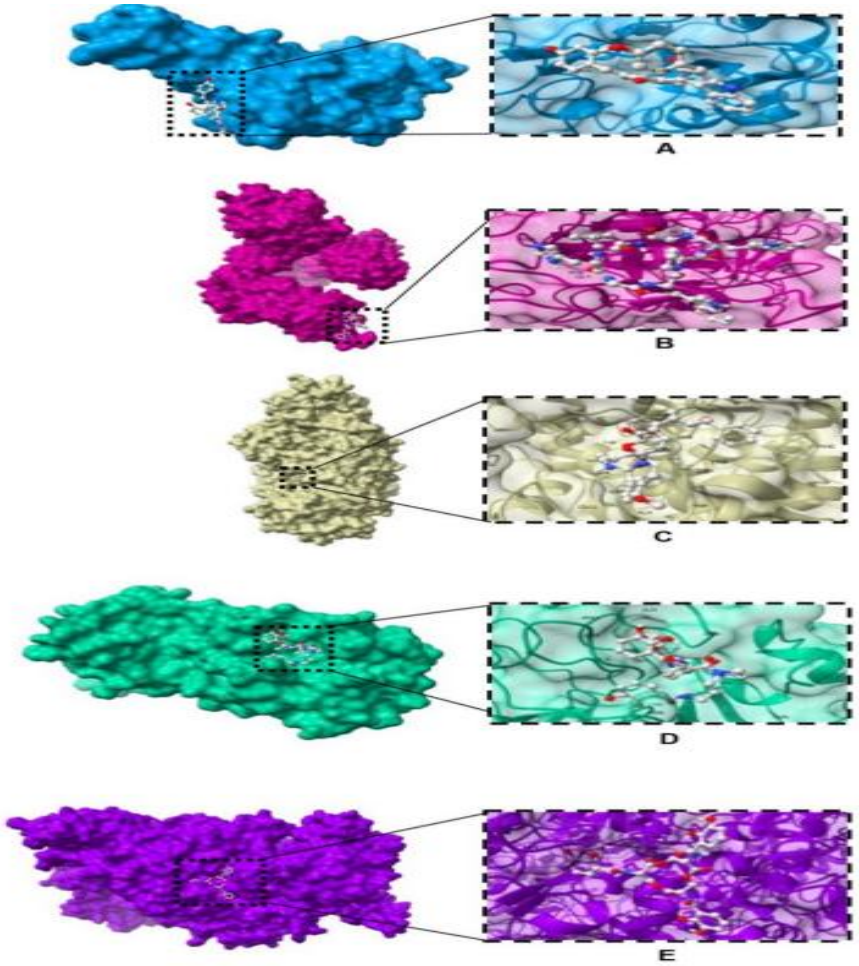


Figure 4. 3-Dimensional representation of the interaction of [A] Scytonemin (1) in the binding site of Spike RBD ACE2; [B] Agardhipeptin A (3) in the binding site of Spike RBD GRP78; [C] Cryptophycin (5) in the binding site of RdRp; [D] Vibriobactin (7) in the binding site of 3CLPRO; and [E] Enterobactin (2) in the binding site of PL PRO (Fellizar et al., 2023).

CONCLUSION AND FUTURE PERSPECTIVES

The production of antiviral compounds by microalgae and cyanobacteria showcases a multifaceted antiviral ability that encompasses virus attachment, intercellular spread, replication within host cells, and cytopathic effects while minimizing damage to the host cells. As a result, these antivirals sourced from algae have the potential to be significant clinical tools, improving treatment approaches for prevalent viral infections and new mutant pandemics. To completely clarify chemical structures, assess bioactivity profiles, and understand mechanisms of antiviral action, the pharmaceutical industry, academia, and clinicians need to collaborate, despite the promising antiviral effects of microalgal and cyanobacterial metabolites observed *in vitro* and in animal studies. This will promote the progress of these molecules to meet unfulfilled clinical requirements globally.

With continual mutations in the SARS-CoV-2 viral genome, which may result in more aggressive variants and difficulties in vaccine creation, further pharmacological research on the suggested microalgal and cyanobacterial compounds is crucial in combating the coronavirus. The records of target binding sites and inhibitory mechanisms will aid in comprehending antiviral functions in humans and pave the path for applicable disease remedies. Molecular docking serves as an essential resource for upcoming medicinal chemists in uncovering innovative drug designs and development methodologies by revealing new uses for existing medications and utilizing newly discovered drugs to combat illnesses. Nonetheless, there are challenges and constraints in docking techniques,

since forecasted docking outcomes might not consistently be accurate. Currently available force fields might not accommodate all types of atoms, and the majority of docking software only recognizes biomolecules, like DNA, RNA, proteins, and enzymes, as receptors without adequate differentiation. Moreover, the quantity of atoms and the rotations of a molecule are frequently limited.

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