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Potential of algae-derived bioactive molecules for cure of SARS-CoV-2

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Abstract

The exploration for various effective antiviral agents is pressing issue regarding the histrionic circumstances of the global COVID pandemic, a blowout of SARS-CoV-2 virus disease. Actual antiviral remedies are not existing at present and the agreed remedy available for COVID somewhat has not been well recognized yet. In these circumstances, there is a need of more consideration which should be given to the exploration for all possible antiviral agents existing in nature. Though, the algae (marine/fresh water) are one of the richest reservoirs of bioactive complexes yet they are sporadically been studied as antiviral agents. In past, the bioactive compounds of algal origin have demonstrated remarkable *in vitro* antiviral activity against the HIV and HCV. The present article recapitulates the antiviral possessions of algae or their extracts that have been studied in several *in vitro*/*in vivo* animal system-based studies, with the aim that the vast algal diversity should get the due attentions related to the deterrence of SARS-CoV-2.

1. Introduction

Typical construction of viruses and their intricate life cycle have made compulsory to discover effective treatments against them. In spite of various all-inclusive research attempts to determine appropriate immunization approaches against viral infections in recent past, still control of many viruses, *viz*., human immuno-deficiency virus (HIV-AIDS), hepatitis C virus (HCV), papillomavirus and dengue virus (DENV) is an immense challenge in front of scientific community (Buck *et al*., 2006; Murrell *et al*., 2011; Loutfy *et al*., 2013; Lazarus *et al*., 2014).

The development of vaccine to counter viruses, *viz*., HIV and HCV was up to now evidenced to be an unfinished task, consequently there is no certain serum available to combat viral infections, such as including herpesviruses (HSV-1 and HSV-2), human papilloma viruses (HPVs) and most respiratory-tract viruses. The elevating resistance in viruses against various drugs available has always been a stern obstruction in the prevention and treatment of such viral infections (Li *et al*., 2012). However, with improving knowledge base of viral propagation, in its life cycle now, many studies are now noticeable regarding the findings of novel antiviral drugs (De Clercq, 2002). However, regardless of little bit success, still the control on most of the viruses is not attained.

The huge and intricate aquatic bionetwork has given the biosphere of the aquatic system a range of algal diversity from microalgae to oversize algal forms have inspired note worthy financial awareness as, fertilizer, food, agar, source of iodine, and potash, *etc*. (Yasuhara-Bell and Lu, 2010). The usefulness of algal forms as food have been known well in ancient times by countless refinement in human beings and their cultural practices worldwide. Then, algal biotechnology has started in the middle of the 20th century which is now developing extensively (Mendes *et al*., 2003). Especially, the microalgae and blue green algae have given massive forecasts in several industries, such as food, pharmaceuticals and cosmetics because of their potential biosubstances. It has been estimated that around 9% of biomedical compounds have been derived from various algal forms, especially, marine algae (Jha and Zi-rong, 2004). These marine algal forms can manufacture chlorophyll, amino acids, polysaccharides, fatty acids, acetogenins, vitamins, xanthophylls, and some halogenated compounds during their metabolic activities (Moghadamtousi *et al*., 2014). Beside these, several studies have showed the significant antiviral possessions in various isolated compounds of algal origin (Mayer and Hamann, 2005) that suggests these algal forms as the influential reservoirs of natural antiviral compounds. Though, algal forms are somewhat underexploited as plant resources, current researches have recognized many algae as a rich cache of bioactive compounds having therapeutic value, including antiviral, antitumor, anticancer and antioxidant properties.

This appraisal recapitulates the antiviral activities biomolecules of algal origin that can be used against the COVID pandemic.

2. Antiviral biomolecules derived from algae

2.1 Polysaccharides

It was found that polysaccharides obtained from marine algae had inhibitory activity against influenza virus B. The polysaccharides of marine algae origin, especially, the Rhodophyceae forms were then assessed against HIV-1 and HSV (Gerber *et al*., 1958). Subsequently, several researches have revealed that polysaccharides of algae-driven have antiviral properties (Table 1). Likewise, marine

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microalgal forms, *viz*., *Cochlodidium polykrikoides* (Figure 1c) and *Porphyridium* sp. (Figure 1a) were found to have sulphated exopolysaccharides which had the capability to interact with the enveloped viruses, *viz*., HIV and HSV, averting them to infect the host cells (Amaro *et al*., 2011) and also showed worthy antiviral action against HSV (type 1 and 2) *in vitro* and *in vivo* in animal system (Huleihel *et al*., 2001). The antiviral possessions of the polysaccharides obtained from *Porphyridium* sp. was noted which was due to the adjoining add-on of HSV-1 particles to this polysaccharide (Batiniæ and Robey, 1992). A diatom, *Navicula* sp. (Figure 1b), is another example from which an extracellular sulphated polysaccharide naviculan was produced. This sulphated polysaccharide contains rhamnose, xylose, galactose, fucose, sulfate, and mannose that were stated to have antiviral consequence on HSV. Naviculan was found to hinders the influenza virus particles from entering the host cells at the early stages of infection (Lee *et al*., 2010). Blue green algae also contain vigorous antiviral compounds, for instance, *Arthrospira platensis* (Figure 2c) consists of exopolysaccharides which showed antiviral activity against koi herpes virus (KHV) (Reichert *et al*., 2017). The extract of *Spirulina platensis* (Figure 2d) is identified to have calcium spirulan (Ca-SP), a form of sulphated polysaccharide. This Ca-SP contains ribose, galactose, mannose, fructose, and rhamnose which are known to interrupt the replication process of both enveloped (Influenza A, HIV) and non-enveloped (polio, HSV) forms of viruses (Takebe *et al*., 2013).

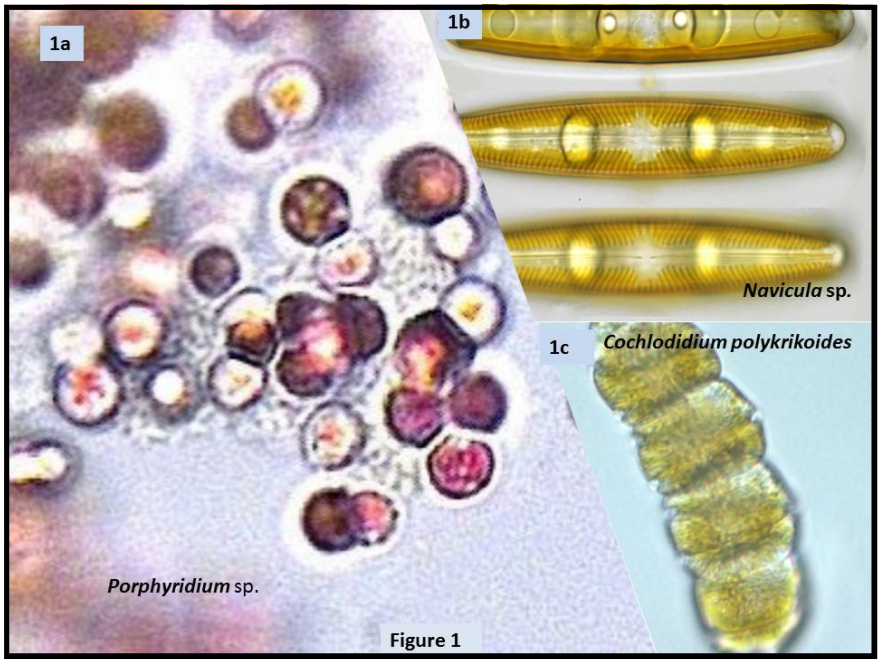


Figure 1

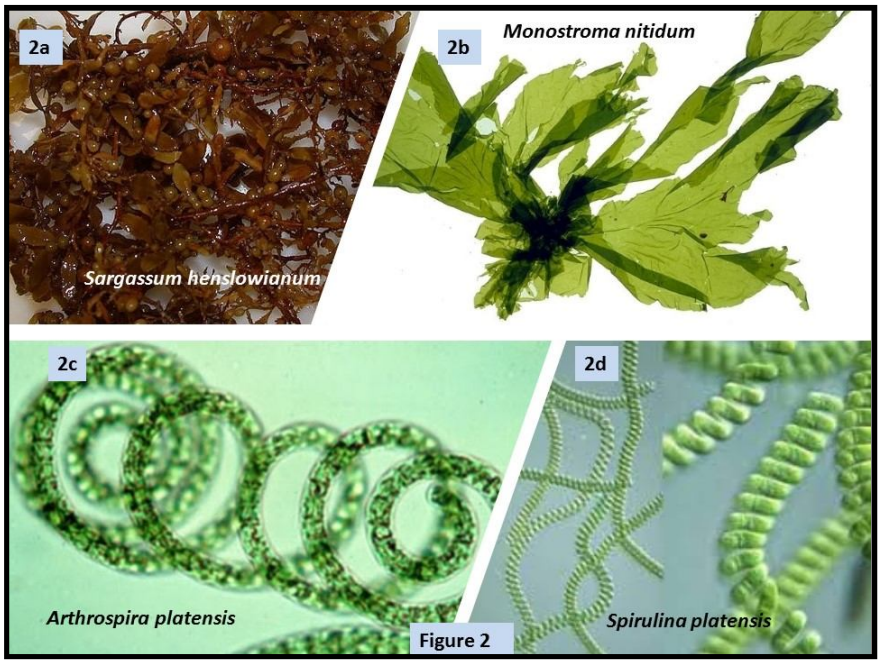


Figure 2

According to several crude *in vitro*/*in vivo* experiments, it has been demonstrated that sulphated polysaccharides of algal origin can activate both the cellular and/or humoral responses to strengthen the immunity (de Paniagua-Michel *et al*., 2014). Recently, to fucoidans from brown algae (*Sargassum henslowianum*; Figure 2d) have been purified and characterized and designated as SHAP-1 and SHAP-2, both showed considerable antagonistic activity against the HSV-1 and HSV-2 strains of herpes simplex virus (Sun *et al*., 2019). Their IC_{50} value was estimated around 0.89 (SHAP-1) and 0.82 µg ml^{-1} (SHAP-2) to counter HSV-1 strain (Sun *et al*., 2019). However, in case of HSV-2, the IC_{50} values were reported low (0.48 µg ml^{-1}). Correspondingly, time-based experiments discovered the more effective anti-HSV activities were attained when fucoidans (Figure 8e) were supplemented in the contagion phase, thus portentous their utility at the initial phases of viral contamination. Moreover, the adsorption and infiltration assays verified the involvement of fucoidans in disruptionof HSV binding to the host cell. Therefore, fucoidans have potential to inhibit the initial adsorption stage of HSV-2 viruses and proved its clinical claims. Similarly, a green macroalgae *Monostroma nitidum* (Figure 2b) also produces a sulphated polysaccharide which was isolated and acknowledged as sulphated glucuronorhamnan (water-soluble) named as MWS (Wang *et al*., 2020). This MWS exhibited broad-spectrum antiviral activity and found effective *in vitro* against a strain of human pathogenic enterovirus (EV71). It was pragmatic that MWS was not lethal to the experimental animal cell lines and confirmed as a broad-spectrum antiviral agent, particularly against EV71 under well-defined *in vitro* conditions. It was reported that MWS hinders the contagion of EV71.

Likewise, the SPs attained from algal species like *Ulva clathrata* (Figure 3b) and *Cladosiphon okamuranus* (Figure 3d) were showed noteworthy *in vitro* antiviral activity in case of new castle virus (Aguilar-Briseño *et al*., 2015). Other algae, *viz*., *Sargassum* sp. (Figure 2a; 3c), *Ulva pertusa*, *Grateloupia filicina* (Figure 3a) also reported as the potential source of SPs that are effective *in vivo* and *in vitro* conditions against the avian influenza virus (Kwon *et al*., 2017).

Curiously, recently the potential of SPs obtained from red alga (*Porphyridium* sp.) reported as a possible healing agent to fight the COVID-19 (Ramakanth *et al*., 2021). Since, the SPs of *Porphyridium* sp. were found effective against a range of viruses, *viz*., varicella zoster virus (Huleihel *et al*., 2001; Chelsea *et al*., 2020), vaccinia virus hepatitis B virus (Schillie *et al*., 2018), HSV (Huheihel *et al*., 2002), and retroviruses (Zheng *et al*., 2020). Hence, this red alga holds enormously promising in the progress to manufacture an immunizing composition against SARS-CoV-2 too. Paul *et al*. (2020) also reported the active inhibition of SARS-CoV-2 by fucoidans found in *Saccharina japonica* (Figure 4c) during *in vitro* study. The SPs were found highly branched and categorized as RPI-27 and RPI-28 and found inhibitory to SARS-CoV-2 by interfering with the binding ability of viral S protein. Further, the RPI-27 was found better in comparison to the popular anti-COVID drug remdesivir.

Thus, the examples suggest the prospect of employing algal components either alone or in blend with other antiviral agents as a hopeful healing approach against the infection of SARS-CoV-2 (Paul *et al*., 2020).

2.2 Proteins

Various species of algae are known to produce antiviral proteins. Lectins are the most common of them which are basically carbohydrate-binding proteins (glycoproteins). These proteins can confer with carbohydrates and carbohydrate moieties of the glycoconjugates. In the recent past, diverse lectins that have anti-HIV action by conferring sturdily with moieties of carbohydrate on the glycosylated envelope of HIV have been identified (Huskens and Schols, 2012) (Table 2).

The envelope of HIV displays anessential mannose-rich glycoprotein (gp120) on its surface to bind to facilitate the binding to the cellular receptor CD4 of the target cells (Tiwari *et al*., 2009). Further, *Scenedesmus obliquus* (Figure 4b) hydrolysates, *viz*., Sd, Sd1 and Sd2 possess a sturdy antiviral activity against Coxsackie virus B (Afify *et al*., 2018).

2.2.1 Potential of lectins

Macroalgae have plenty of carbohydrate-binding proteins, *e.g*., lectins, which have high specificity towards the sugar groups of viral glycoproteins. Therefore, lectins have become widely used in numerous pharmacological and remedial applications (Breitenbach Barroso Coelho *et al*., 2018). In various viral infection pathways, the Mannose-binding lectins (MBL) are the majorly studied protein (Auriti *et al*., 2017) and it was reported that the self-organization of viruses during their replication cycle is interrupted by MBL (Gupta and Gupta, 2021). Later, these proteins have also been shown to be a possible therapy against Ebola virus (Michelow *et al*., 2011).

Lectins derived from red algae were first highlighted when Griffithsin was revealed by Watson and Waaland (1983) in *Griffithsia* sp. (Figure 4a). Consequently, it has been studied extensively for various uses (Mori *et al*., 2004). As antiviral agent it has been found to have high specificity for mannose residues present in viral glycoproteins and remarkable antiviral potential was reported in case of HIV1 (Lusvarghi *et al*., 2016), hepatitis C (Meuleman *et al*., 2011) and the SARS-CoV glycoprotein (Zumla *et al*., 2016). Recently, the anti-MERS CoV activity of Griffithsin was also reported, where the lectins inhibited virus invasion while conferring insignificant cellular noxiousness. The curbing consequence of Griffithsin on the binding stage during virus contamination was also investigated (Millet *et al*., 2016).

Furthermore, several other similar attempts have demonstrated the *in vivo* antiviral activity of this Griffiths into counter the replication of Herpes simplex virus 2 (Nixon *et al*., 2013), Japanese encephalitis virus (Ishag *et al*., 2013), and human papilloma virus (Levendosky *et al*., 2015). For example, the effect of an anti-HIV Griffithsin-containing microbicide on the rectal microbiome in *Rhesus macaques* (Girard *et al*., 2018). It was observed that the 0.1% Griffiths in gel had no adverse effects on the proteome or microbiome of the rectal mucosa. Earlier, O'Keefe *et al*. (2010) testified 100 per cent survival of model mice infected with a high dose of SARS-CoV-2 when a 10 dose of Griffithsin was administered.

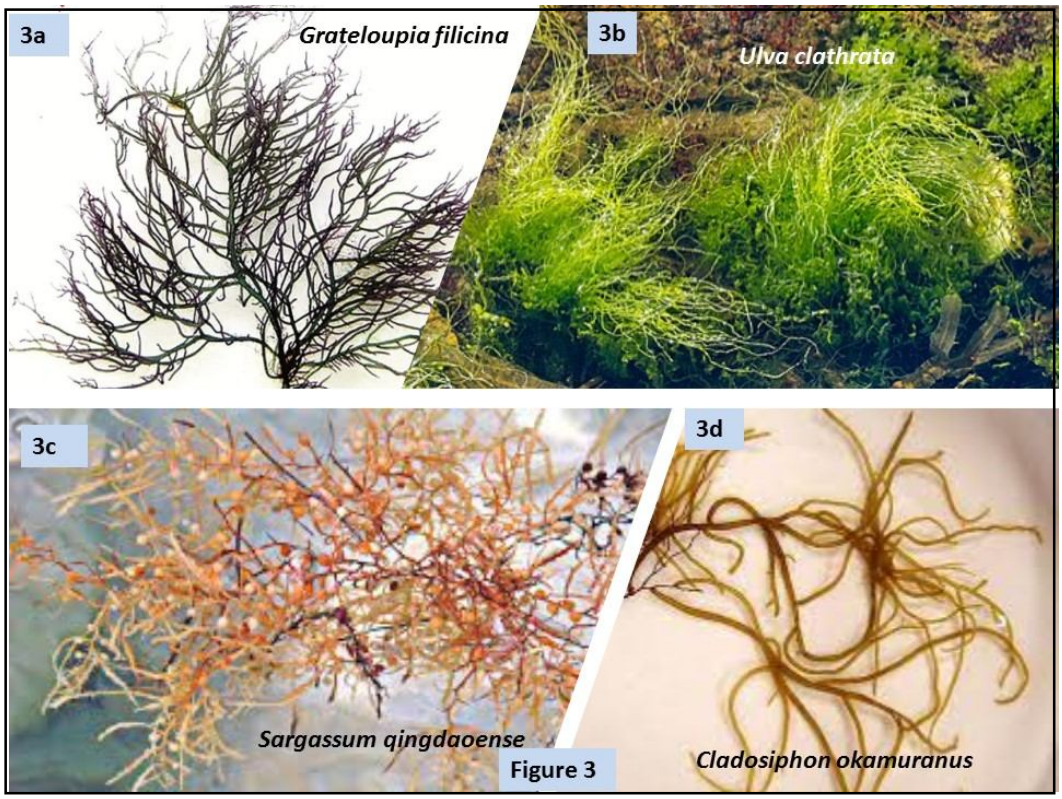


Figure 3

Table 1: Algal proteins with antiviral properties (Ahmadi *et al.*, 2015)

Algal group	Antiviral proteins and source species	Target viruses
Red algae	Carrageenan ($C_{23}H_{23}FN_4O_7Zn$) (*Gigartina skottsbergii*; Figures 5a; 8d)	Influenza virus, DENV, HSV-1, HSV-2, HPV, HRV, HIV
	Galactan ($C_6H_{10}O_5$)n (*Callophyllis variegata*; Figures 5c; 8b)	HSV-1, HSV-2, HIV-1, HIV-2, DENV, HAV
	Sea algae extract (*Schizymenia pacifica*; Figure 5c)	HIV, AMV, RMLV
Brown algae	Alginate ($C_6H_8O_6$)n (Figure 8f) (*Laminaria* spp.; Figure 6a)	HIV, IAV, HBV
	Sulfated polymannuroguluronate (Ulva sp.; Figure 8a)	HIV
	Fucan ($C_6H_9O_3SO_3$)n (*Adenocytis utricularis*; Figure 6b)	HSV-1, HSV-2, HCMV, VSV, Sindbis virus, HIV-1
	Laminaran ($C_6H_{10}O_5$)x (*Fucus vesiculosus*; Figures 6c; 8c)	HIV
Diatom	Naviculan (*Navicula directa*) (Figure 1b)	HSV-1, HSV-2
Microalga	A1 and A2 (*Cochlodidium polykrikoides*; Figure 1c)	Influenza A and B viruses, RSV-A, RSV-B, parainfluenza-2
Blue-green alga	Calcium spirulan (*Arthrospira* platensis; Fig.2c)	HSV-1, measles, mumps, influenza, polio, Coxsackie, HIV-1, HCMV
Blue-green alga	Nostaflan (*Nostoc flagelliforme*)	HSV-1, HSV-2, influenza A virus, human cytomegalovirus

2.3 Lipids

Though, the lipids derived from algae lesser antiviral activity compared to algal polysaccharides and proteins yet the lipid compounds (sulfolipids and glycolipids) such as sulfo-quinovosyl-diacyl-glycerol (SQDG) and mono-galactosyl-diacyl-glycerides (MGDG) exhibited antiviral potential. Gustafson *et al.* (1989) noticed the anti-HIV activity in SQDG which was isolated from *Phormidium tenue* and *Lyngby alagerheimii*. *Spirulina's* methanol extract (IC_{50} value of 25.1 µg ml^{-1}) was also reported to have antiviral activity against HIV-1 (Zalah *et al.*, 2002; Yim *et al.*, 2004; Li *et al.*, 2008) (Table 2).

2.4 Pigments

There is a huge diversity in algal pigments and these algal pigments also showed appreciable bioactivity against viruses. For instance, photosynthetic pigments of *Dunaliella primolecta* have confirmed anti-HSV activity (Ohta *et al*., 1998). Likewise, a diatom (*Haslea ostrearia*) which produces a water-soluble fraction (blue pigment) containing marennine (IC_{50} value: 4 µg ml^{-1}), was reported to constrain HSV-1 replication *in vitro*. Moreover, this component extended the progress of syncytia caused by HIV-1 in MT2 cells (Kamat *et al*., 1992; Shih *et al*., 2003). Cyanophycean and red algae contain phycobiliproteins as their key photosynthetic pigments that have pharmaceutical importance as the natural coloring agent. The two most acknowledged phycobiliproteins are phycoerythrin and phycocyanin have been isolated from *Arthrospira* and *Porphyridium*, respectively, supposed to have antiviral potential and can be used in future as antiviral agents (Table 2).

Phycocyanobilins (PCBs) found in some cyanobacteria and red algae as light-capturing pigments are also extensively investigated in the recent past for their antioxidant, antiviral and inhibitory NADPH oxidase activities (Hirata *et al*., 2000; McCarty, 2007; Ramakrishnan, 2013; Guedes *et al*., 2019). Recently, regarding their antiviral role, Pendyala and Patras (2020) conferred the probable use of phycocyanobilins of *Spirulina* spp. as potential inhibitors of SARS-CoV2 contagion by affecting its binding ability to the host cell. The base of this was an *in silico* study (*via* COVID-19 docking server) of these bioactive compounds found in *Spirulina* spp.

Remarkably, the PCB verified a better binding to targeted enzymes the well-known antiviral drugs such as remdesivir, lopinavir and nelfinavir. Thus, the finding emphasized, the noteworthy probable of PCB as antiviral agent. Moreover, the cleansed allophycocyanin attained from *Spirulina platensis* (Figure 2d) has been confirmed substantial inhibitory activity against enterovirus 71 (Singh *et al*., 2020). Similarly, outcomes of an *in silico* study established that the PCB found in *Arthrospira* sp. could be used as an effective antiviral against SARS-CoV-2 (Petit *et al*., 2020). Recently, it was reported by Nikhra (2020) the likelihood to employ phycocyanobilin holding cyanobacteria (*Spirulina* sp.) to control the infections of RNA viruses.

The extract of PCB proved a considerable decline in the existence of zoonotic RNA viruses by elevating the host immune responsive type 1 interferon (Nikhra, 2020). Henceforth, it is expected that PCB of microalgal origin may reveal significant action in contradiction of SARS-CoV-2 (Zhou *et al*., 2020; Cascella *et al*., 2020). However, there is an acute need of further research regarding *in vivo* studies to recognize the specificity of PCBs for the progress in therapeutic approaches to counter the human pathogenic viruses, together with SARS-CoV-2.

3. Antiviral properties of algae

Immunization is the most effective method against the viral ailments, but some viruses are some what unaffected during immunization; for instance, immunization against active herpetic infections were found unaffected (Naesens and Clercq, 2001), and it was found to generate side effects like allergic responses due to resistance mutation in virus in case of the long-term conduct. Some algal extracts were tested for their antiviral effects on different viruses, including herpes (Serkedjieva, 2004) that showed the effectiveness of brown algae as antiviral agents.

Many brown algae have also been evaluated for their antiviral potential and rousing results have been obtained but the immuno-suppressive nature of these compound is a major concern to finalize their roles as antiviral agents (Munro *et al*., 1987).

Table 2: Algal protein, lipids and pigments with antiviral properties (Intan *et al*., 2018)

Algal group	Antiviral lectins and source species	Target viruses
Cyanobacteria	cyanovirin-N (*Nostoc ellipsosporum*; Figure 7e)	HIV
	scytovirin (*Scytonema varium*; Figure 7c)	
	cyanovirin-N (*Nostoc ellipsosporum*)	
	Agglutinin (*Oscillatoria agardhii*; Figure 7a)	
	Antiviral lipids and source species	
Cyanobacteria	sulfoquinovosyldiacylglycerides (SQDG)	HIV
	[*Spirulina* spp., *Lyngbya lagerheimii* (Figure 7b)	
	and *Phormidium tenue*]	
	monogalactosyl-diacylglycerides (MGDG), galactosyl	
	diacylglycerides (DGDG) (*Phormidium tenue*)	HIV
	Antiviral pigments and source species	
Cyanobacteria	chlorophyll analogues (pheophorbide-like substances)(*Geitlerinema* sp.; Figure 7d)	HSV
	Marennine, the blue pigment (*Haslea ostrearia)*	HSV-1
	Phycocyanin (*Arthrospira* sp.) and phycoerythrin (*Porphyridium* sp.)	HSV
	allophyco-cyanin [*Spirulina* (*Arthrospira*) *platensis*]	Enterovirus 71

Figure 4

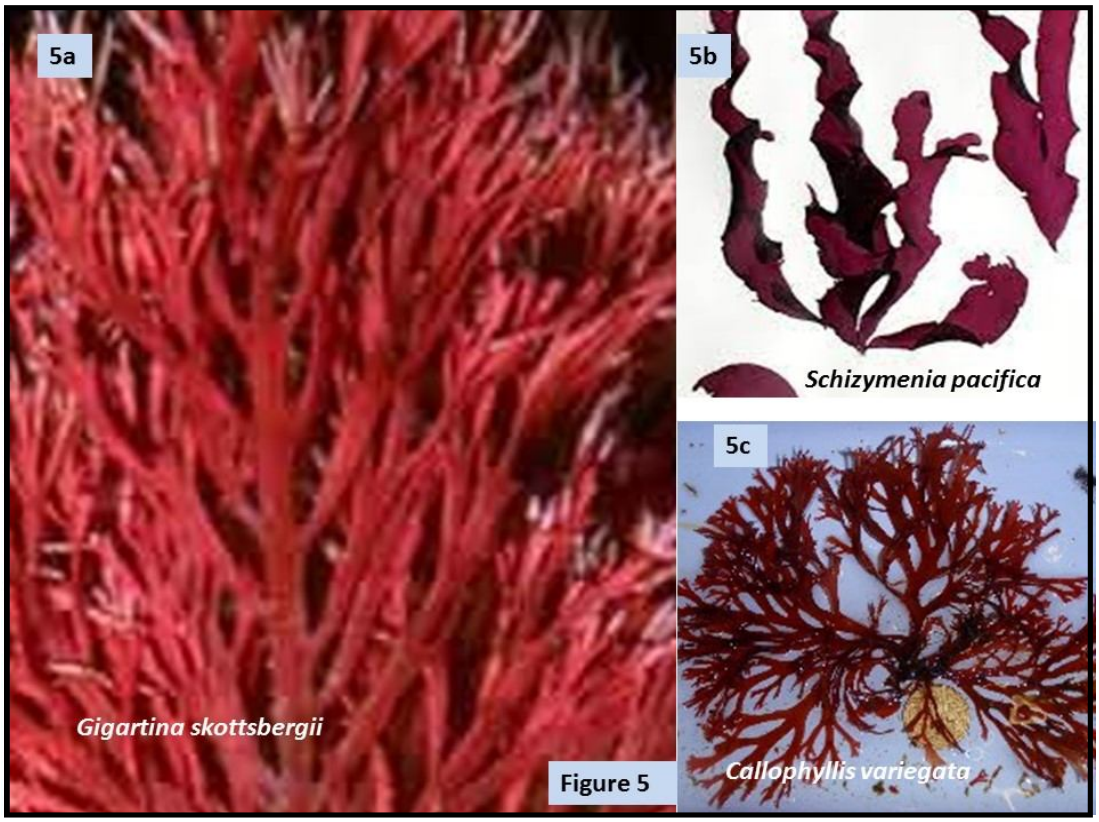


Figure 5

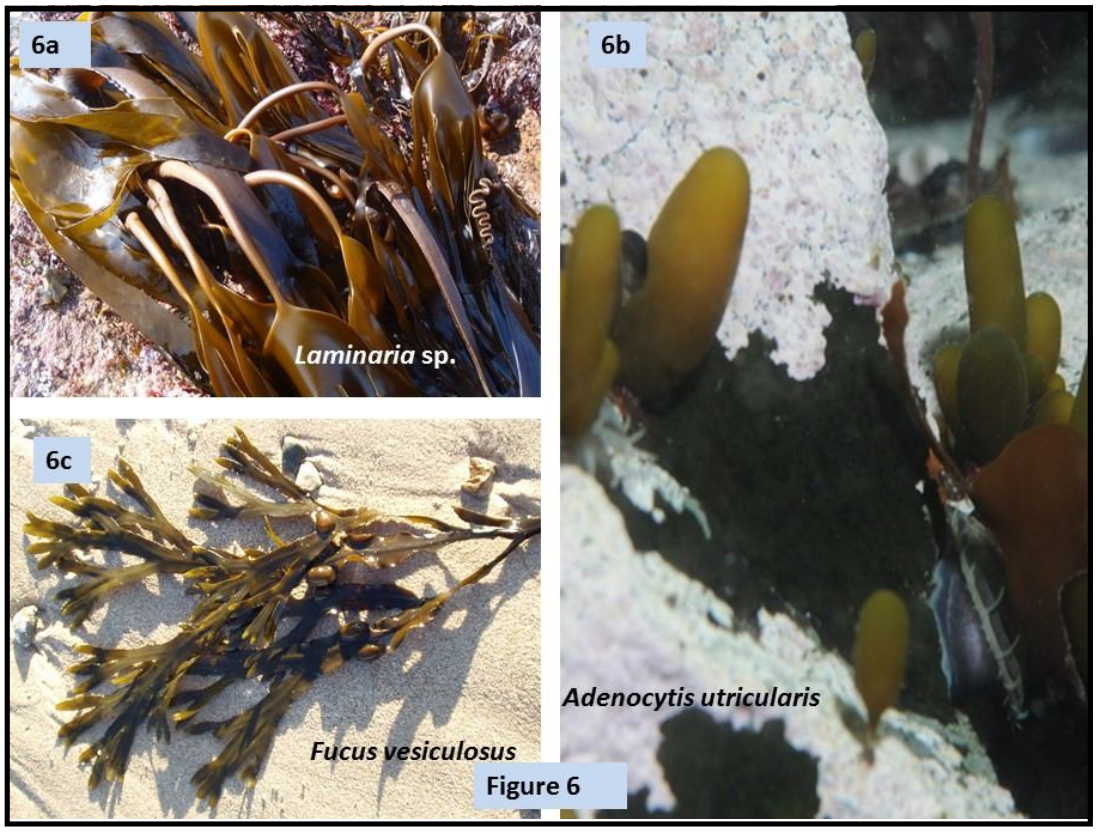


Figure 6

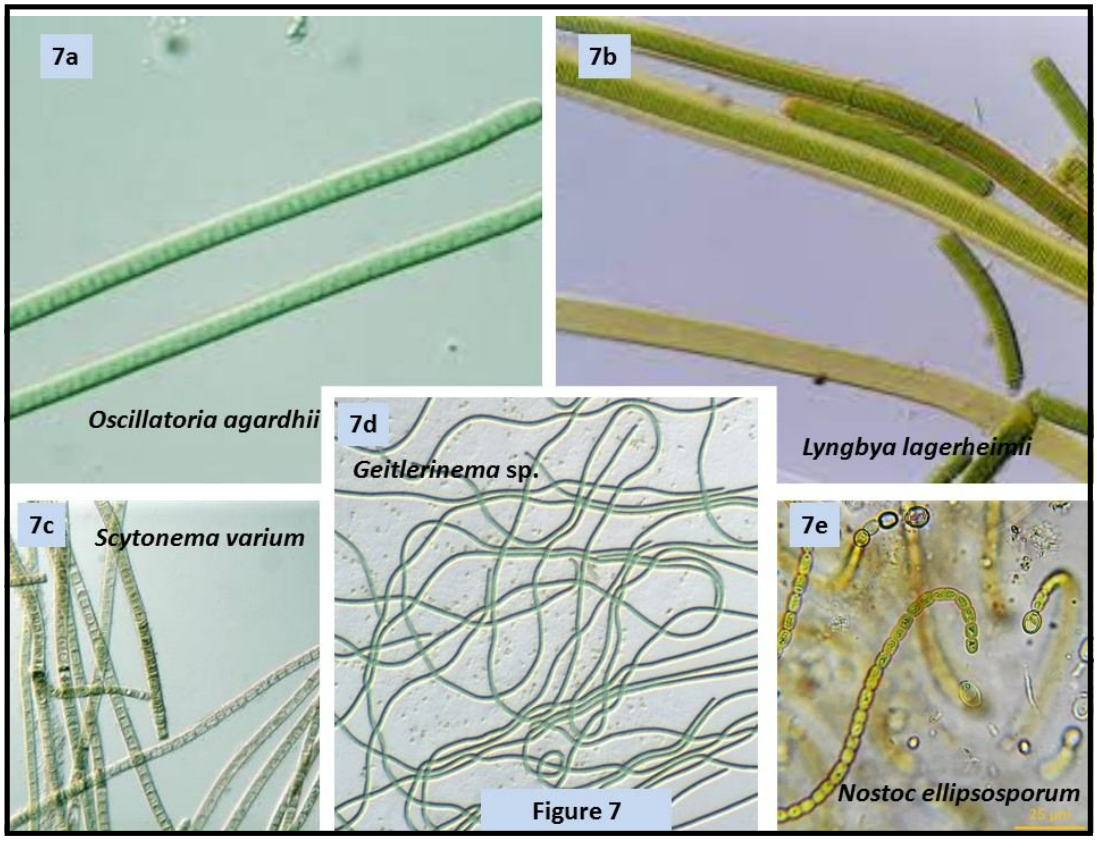
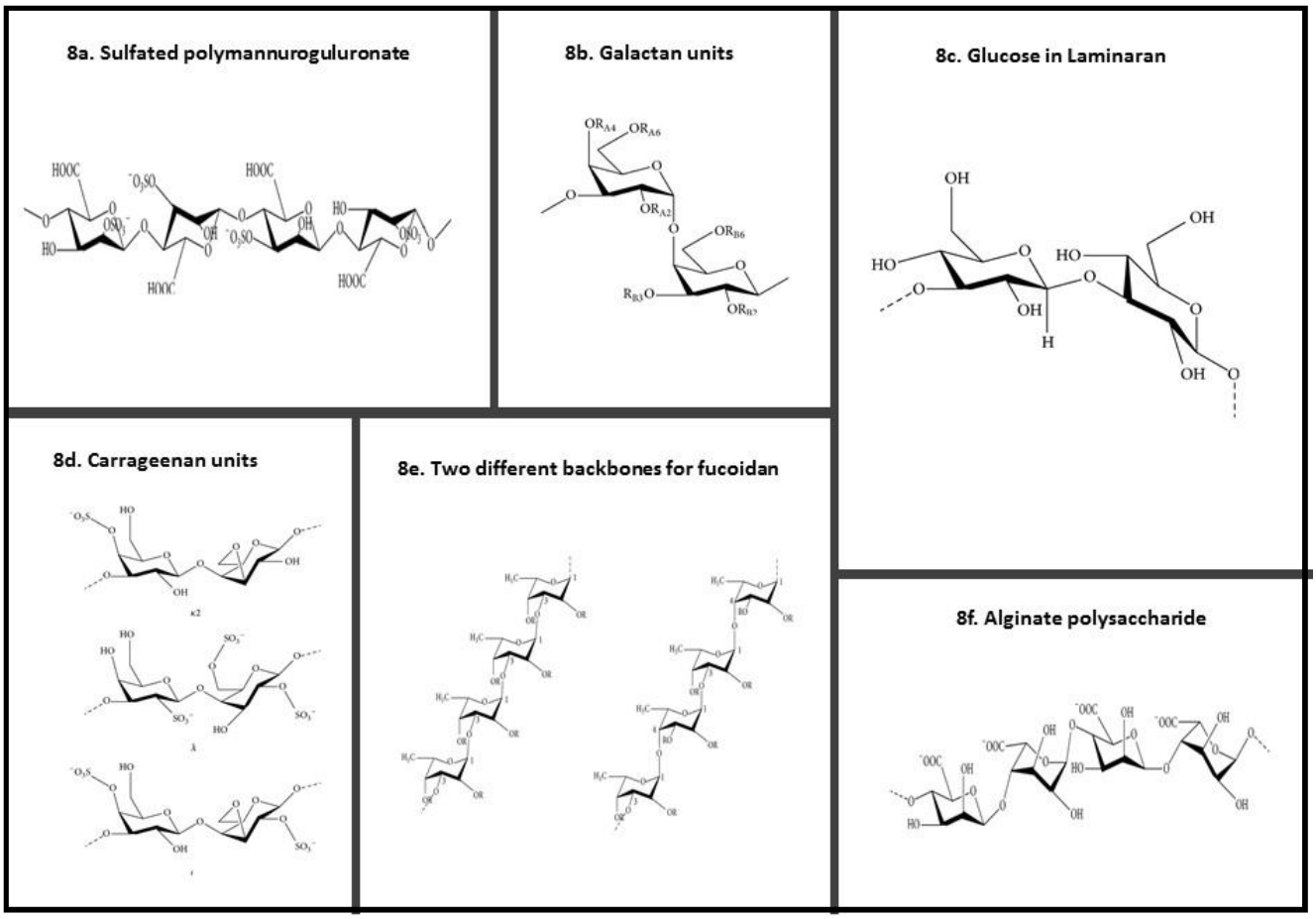


Figure 7



Figures 8a-8f: Chemical structures of algal derived significant compounds of antiviral nature (Ahmadi *et al*., 2015).

3.1 Use of algae against SARS-CoV-2 virus

Considering the alarming situation of the continued COVID-19 pandemic, more and more efforts are required to develop and formulate green remedy alternatives in the form of easily available algal resources to address viral diseases. The SARS-CoV-2, a positive single strand RNA virus from beta corona virus family contains diverse spike proteins along with non-structural (3-chymotrypsin-like protease, helicase, papain-like protease, and RNA-based RNA polymerase), and other proteins (Yeo *et al*., 2020; Li and De Clercq, 2020). Among all components of this virus, especially, the spike glycoprotein has been taken into consideration, as it plays the decisive role in infection by reacting with the host's receptors (Li and De Clercq, 2020). Since, the glycoprotein is essential for the access of virus into the host cells, therefore, numerous current researches are targeted in this structural protein to combat the viral infection (Zumla *et al*., 2016).

Based on past researchers, it is obvious that till date the use of algal diversity for their biologically active compounds are basically restricted to HIV and HSV, however, the antiviral action is appreciable in case of these viruses. Since, the biologically active compound obtained from various algae have shown good antagonist activity in the binding of enveloped viruses to the host cell, and to slow down the replication of virus genome in the affected cells of the host. Both these properties of algal compounds are encouraging to use these algae against the tarnished SARS-CoV-2 virus.

4. Discussion

Hitherto, algal forms represent a huge reservoir of antiviral compounds where the novel antiviral compounds can be found after serious explorations. Thus, there is a great need of unceasing research determination to get new algal derived bioactive compounds. Microalgal and cyanobacterial forms can serve the humanity by producing pharmaceutically useful and low-cost manufacture systems to generate natural vaccines, particularly for developing countries. As evident in the well-known genetic transformation attempt in *Chlamydomonas reinhardtii* which permitted the making of antigens against malaria and cholera (Jones *et al*., 2012; Gregory *et al*., 2013). The biosynthesis of silver nanoparticles (AgNPs) by microalgae or Cyanophyta could epitomize a new arena of research (Merin *et al*., 2010), if the nanotechnologies will able to validate the nonappearance of risks related with the well-being and ecological impacts.

Several biological activities, together with the unique antiviral effect, have been recognized from different algae akin to angiosperms (Mehrotra, 2020) and bryophytes (Alam, 2021). The extracted molecules from diverse algal species have evidently proved this potential of various algae. Though, the findings are mainly restricted to *in vitro* experiments, yet attempts are being made *in vivo*. Several

studies have been done in recent past to elucidate and promote the use of algal diversity in the pharmaceutical industry, especially as effective antiviral agents. Hence, there is a great scope and opportunities to the researchers to explore this aspect of both fresh water and marine algae. The marine algae are categorically varied, high yielding, bioactive, and chemically distinctive leads a great hope for discovering new anticancer drugs. The seaweeds contain polyphenols and sulphated polysaccharides are rich in the clinically effective chemical component. Since algae proved to be the imperative source of vitamins, antioxidants, minerals and natural dyes, the combination of the whole biomass in food and feed could be used to provide color, enhance dietary value and increase texture or confrontation to the oxidation process. While a combination of various species of seaweeds or incorporation with other traditional food opens many likelihoods.

5. Conclusion

There has been a significant upsurge that discloses the antiviral activity of several algal metabolites like sulphated polysaccharides, lectins and phycocyanobilins. In the recent past, it has been reported that these algal-derived compounds confer significant action to counter a varied range of RNA and DNA viruses, including the influenza virus, the potential cause of respiratory infections. As conferred, the bioactive molecules of algal origin could assist in the formulations a novel therapy to block the spread and impact of SARS-CoV-2. Considering the acute necessity for the development of formulations against SARS-CoV-2. The available diversity and essential farming of selective algal colonies with plenty of medicinal values needs to be explored and improved by the latest technology to combat SARS-CoV-2 virus disease.

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Authors' contribution

AA conceptualized the review topic and finalized the manuscript. FB and KP collected the relevant material and prepared the first draft. All the authors have finally read the manuscript and approved.

Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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