Potential of algal metabolites for the development of broad-spectrum antiviral therapeutics: Possible implications in COVID-19 therapy

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Covid-19 pandemic severely affected human health worldwide. Till October 19, 2020, total confirmed patients of COVID-19 are 39,944,882, whereas 1,111,998 people died across the globe. Till to date, we do not have any specific medicine and/or vaccine to treat COVID-19; however, research is still going on at war footing. So far vaccine development is concerned, here it is noteworthy that till now three major variants (named A, B, and C) of severe acute respiratory syndrome-coronavirus2 (SARS-CoV-2) have been recognized. Increased mutational rate and formation of new viral variants may increase the attrition rate of vaccines and/or candidate chemotherapies. Herbal remedies are chemical cocktails, thus open another avenue for effective antiviral therapeutics development. In fact, India is a large country, which is densely populated, but the overall severity of COVID-19 per million populations is lesser than any other country of the world. One of the major reasons for the aforesaid difference is the use of herbal remedies by the Government of India as a preventive measure for COVID-19. Therefore, the present review focuses on the epidemiology and molecular pathogenesis of COVID-19 and explores algal metabolites for their antiviral properties.

KEYWORDS
algal metabolites, antiviral, COVID-19, HIV, HSV, SARS-CoV-2

1 INTRODUCTION

Expeditious global transmission of coronavirus disease 2019 (COVID-19), apparently induced by a novel coronavirus (SARS-CoV-2), has entailed the scientists worldwide to discover efficient antiviral drugs and/or vaccines on urgent basis. Researchers around the world are working on a war footing for the development of effective therapeutics to prevention and treatment of SARS-CoV-2. Due to the distinctive framework and intricate life cycle of viral pathogens, the invention of a definite therapeutic antiviral agent is a major challenge, which needs huge investment of time and money. Although, substantial research has been done for the advancement of vaccines and treatment of various viral infections, in spite of that, infection from viral pathogens such as AIDS-HIV retrovirus, Coronavirus, Hepatitis C virus, Dengue virus, etc. are still devastating the considerable population of the world. Conventionally, a virus is a distinctive pathogen that is unable to replicate without a host cell and mostly dependent upon the host for its survival and propagation. Thus, it is difficult to design and produce effective treatment methodologies to inhibit viral entry and propagation into host cells specifically without exerting any adverse effects to the host. Further, mutations in the viral genome make the vaccine ineffective. Usually, infection and/or replication processes have been shared by enveloped as well as non-enveloped viruses and generally proceeds as follows: Attachment and invasion into the target cells; viral mRNA transcription; viral genome replication, and maturity and liberation of viral progeny (Kitazato, Wang, &
Kobayashi, 2007). Henceforth, this review shed light on the molecular pathogenesis of SARS-CoV-2 and exploration of algal metabolites based antiviral therapeutic modalities.

1.1 | Epidemiology and viral pathogenesis of SARS-CoV-2

COVID-19 is a type of pneumonia induced by severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) (X. Li, Geng, Peng, Meng, & Lu, 2020). As per the dashboard of WHO as on October 19, 2020, the total confirmed cases of COVID-19 are 39,944,882, whereas the total deaths are 1,111,998 throughout the world (https://covid19.who.int/). It is also important that this is the third outbreak of extremely pathogenic coronavirus in the human population within the last two decades, as earlier epidemics were marked with severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) in the present century. However, it is imperative to mention that the SARS-CoV and MERS-CoV were restricted to a few countries, but the spreading potential of SARS-CoV-2 is so high that almost all the countries of the world are affected by this infection.

1.1.1 | Viral structure and genome of SARS-CoV-2

Corona viruses belong to the family of coronaviridae having characteristics of enveloped, positive-sense, single-stranded RNA viruses having genome size of 26–32 kb (Bukhari et al., 2018; de Groot, Cowley, Enjuanes, et al., 2012). Viral particles are decorated with approximately 20 nm surface projections known as “spikes” and under electron micrographs, these particles look-alike of the solar corona, thus known as coronaviruses. Four coronavirus genera (α, β, γ, and δ) have been discovered till now in which two human coronavirus genera have been identified including α (HCoV-229E and NL63), and β (MERS-CoV, SARS-CoV, HCoV-OC43, and HCoV-HKU1) (Perlman & Netland, 2009). Eruption of SARS-CoV-2 human infection was first reported in late December 2019 in Wuhan, China and within a few months, it became pandemic. This novel β coronavirus shown 88% sequence identity with SARS-like bat-corona virus SL-CoVZC45 and bat-SL-CoVZXC21, while it was showing a 50% sequence identity with MERS-CoV (Lu et al., 2020), therefore, International Virus Classification Commission named it as SARS-CoV-2.

1.1.2 | Genome structure and function

Phylogenetic tree analysis of SARS-like coronaviruses, MERS-CoV and SARS-CoV revealed that the complete genome sequence is mainly divided into two ORFs out of which ORF1a/b encompass two-third of the genome and mainly translated into two large polypeptides pp1a and pp1ab. These polypeptides further processed into 16 non-structural proteins (nsp1-nsp16) participate in viral replicate transcriptase complex (Fehr & Perlman, 2015). Interestingly, these proteins serve to rearrange membranes originating from the Golgi complex and rough endoplasmic reticulum into double-membrane vesicles where replication and transcription of virus occurs, so that virus can escape from the cellular immune mechanism that degrades the double-stranded form of RNA intermediates during the process of replication (Fehr & Perlman, 2015; Knoops et al., 2008).

The other third one of the genetic makeup contains other ORFs, which mainly encode for major structural proteins including nucleocapsid (N), membrane (M) proteins, spike (S), and envelope along with the various accessory proteins exhibiting unknown function. Angiotensin-converting enzyme 2 (ACE2) receptor is suggested to be the mediator of the invasion of SARS-CoV-2 into the susceptible cells (W. Li et al., 2003; Masters, 2006).

1.1.3 | Mechanism of corona virus entry and replication

The entry of SARS-CoV-2 into the host cell initiated by the binding of spike protein to the ACE2 receptors of the host cells followed by the fusion of viral and host cell membranes (Simmons et al., 2004; De Wit et al., 2016). At this point, priming of spike protein at S2’ position by transmembrane protease serine 2 (TMPRSS2) and furin protease enzymes takes place which is mediating membrane fusion and viral infectivity. TMPRSS2 and furin enzymes expressed by the host cells of various organs including lungs, small intestine, and liver (Walls et al., 2020). Role of clathrin-dependent and independent endocytosis in mediating the viral entry was also reported for SARS-CoV (Kuba, Imai, Ohno-Nakanishi, & Penninger, 2010; H. Wang et al., 2008).

Viral entry is followed by releasing the RNA genome in the cytoplasm and then process of replication and transcription occurs. Translated proteins then inserted into the membranes of ER or Golgi, through which nucleocapsid formed by combining the RNA genome and capsid proteins. Endoplasmic reticulum-Golgi intermediate compartment (ERGIC) is germinated out of viral particles. Fusion of virion containing vesicles with the plasma membrane resultant releases the viral particles from the cells.

1.2 | Immunological aspect of COVID-19 pathogenesis

This aspect is still poorly understood in case of SARS-CoV-2, however, importantly, the clinical manifestations of the COVID-19 are quite similar with the symptoms of SARS-CoV and MERS-CoV that include dyspnea, fatigue, fever, myalgia, cough, radiographic evidence of pneumonia and normal or decreased leukocyte counts (Peiris, Guan, & Yuen, 2004). Therefore, the knowledge of immunological studies of SARS and MERS coronavirus provide important clues to understand the immunological mechanisms of COVID-19 pathogenesis.
Specific immunity against the virus starts with the entry into the host cells where viral antigen processing takes place which is followed by displaying the antigenic peptides by antigen-presenting cells (APCs). Human leukocyte antigen presentation (HLA) or major histocompatibility complex (MHC) is responsible for presentation of antigenic peptides. The complex of viral antigenic peptides and the MHC class I and MHC class II molecules are presented, respectively to the CD8+ and CD4+ T-cells, by the APCs. These displayed antigenic peptides are then contemplated by the cytotoxic T lymphocytes (CTLs) which are specific to the certain virus. In the case of SARS-CoV, MHC-1 molecules and MHC-2 molecules are involved subsequently in the antigen presentation (Wieczorek et al., 2017). Here, it is noteworthy that the dendritic cells play an essential role in viral pathogenesis as they link innate and adaptive immunity. In the case of SARS-CoV and MERS-CoV pathogenesis, dendritic cells were found to be involved in antigen presentation and they are thought to be the potential candidate to present antigen in SARS-CoV-2 (Lau, Peiris, & Law, 2012). It is crucial to understand the role of dendritic cells in antigen presentation, as antigen presentation is an initial signal to trigger a downstream cascade of signal transduction, which ultimately elicits the immune response, as well as the underlying immunopathology.

Epitope mapping of MHC class I and II, an important step toward vaccine development has been intensively pursued in the scenario of SARS-CoV-2 (Sarkar, Ullah, Tuz, Afrin, & Araf, 2020). These analyses showed that various alleles of HLA can be characterized into protection alleles (HLA-Cw1502, HLA-DR0301, HLA-B*0201), whereas HLA-B*4601, HLA-B*0703, HLA-DRB1*1202, and HLA-Cw*0801 were correlated to the susceptibility of SARS-CoV (Y. M. A. Chen et al., 2006, Keicho et al., 2009; S. F. Wang et al., 2011).

### 1.2.1 | Humoral immune response

Humoral immune response is mainly mediated by neutralizing antibodies specifically bind to the antigen. In this process, T-helper cells participate in co-activation signalling through which differentiation of B cells into plasma cells and synthesis of specific antibodies take place.

Several studies related to SARS-CoV infection depict the conventional pattern of production of IgM and IgG antibodies. These studies have shown that the SARS-specific IgM antibody disintegrates at the end of 12 weeks, whereas the IgG antibody was found to be everlasting; especially antibodies specific to S and N proteins (G. Li, Chen & Xu, 2003; De Wit et al., 2016). For the knowledge of structural and envelope proteins of SARS-CoV, both B and T cell epitopes are being mapped extensively (Channappanavar, Zhao, & Perlman, 2014). The structural location of the B cell epitope is important to inhibit viral entry through ACE2 receptor binding, thus to develop neutralizing antibody. B-cell epitopes should be located at the receptor-binding domain (Yu et al., 2007). Importantly, T-cell epitopes are located anywhere in viral protein, as they do not require location-specific epitopes. Recent evidences suggest that Th1 type response is more important to control SARS, MERS Coronaviruses, and also possibly for SARS-CoV-2 (Yong, Ong, Yeap, & Tan, 2019).

### 1.2.2 | Cellular immune response

The mechanism of adaptive immunity is portrayed by cellular immune response, in which cytotoxic T cells kill the infected cells straightaway, whereas T-helper cells participate in the co-activation of both humoral and cellular pathways. Therefore, the cellular immune response is more important for viral clearance by killing of the infected cells than the humoral response. In fact, recent studies suggest that the shortage of T-cells in mice against SARS and MERS Corona virus shown zero viral clearance in infected mice and consistently demonstrates the value of cellular immunity in viral pathogenesis (S. Lee et al., 2012; Yong et al., 2019).

Studies from SARS and MERS coronavirus revealed the presence of CD8+ (TNFα, IFNγ) and CD4+ (IFN, IL-2, and TNFα) memory cells in patients even after 4 years of infection and function in T-cell proliferation and delayed-type hypersensitivity response (Kuri & Weber, 2010).

Out of 23 investigated SARS-recovered patients, 14 have shown the presence of memory T cells, which responded to the S library of SARS-CoV peptide, after 6 years of post-infection (Channappanavar et al., 2014).

Similarly, during MERS-CoV clearance, CD8+ cells were found in the mouse model (Coleman et al., 2017). Interestingly, in SARS-CoV-2 infected individuals, a significant reduction in CD8+ and CD4+ cells was reported in peripheral blood mononuclear cells (PBMCs) which might result in weakened development of memory T cells.

### 1.2.3 | Cytokine storm in SARS-CoV-2 patients

The liberation of large quantity of pro-inflammatory cytokines such as chemokines (CCL2, CCL3, CCL5, CXCL8, CXCL9, CXCL10, etc.) and IFN-α, IFNγ, IL1β, IL-6, IL-12, IL-18, IL-33, TNF-α, TGF-β by immune effector cells in viral infection induced by SARS-CoV-2, results into the condition of lethal unrestrained systemic inflammatory response which broadly defines the “cytokine storm” (Cameron, Bermejo-Martín, Danesh, Muller, & Kelvin, 2008; Channappanavar & Perlman, 2017; Huang et al., 2020; Williams & Chambers, 2014). The acute respiratory distress syndrome (ARDS), a conventional immunophathological event for MERS, SARS, and SARS-2 coronaviruses has been reported as the prime cause of fatality (Huang et al., 2020; Xu et al., 2020). Here, it is noteworthy that the cytokine storm is one of the major causes for ARDS, as it triggers systemic inflammatory immune attack to the multiple organs, thus multiple organ failure leads to the death which was reported in the outbreaks of infections induced by SARS-2, SARS, and MERS coronaviruses (Yao et al., 2020). In fact, the cytokine storm was also observed in the earlier pandemics of coronaviruses including MERS-CoV and SARS-CoV (H. Y. Zheng et al., 2020). Drugs influencing IL-18, IFNγ, and IL-6 have been
established to be adequate for the treatment of cytokine storm syndrome in infections caused by several other viruses and a hypothesis may be drawn that same drug can be implicated so as to reduce the severity of the COVID-19 (Cameron et al., 2007). In COVID-19 treatment, one such IL-6 inhibitor was found suitable to treat a few patients in China (Mehta et al., 2020).

1.2.4 Corona virus immune evasion

To escape from the immune surveillance of the cell SARS-CoV and MERS-CoV instigated the generation of double-membrane vesicles that are deprived of pathogen-associated molecular patterns (PAMPs) which otherwise could be acknowledged by pattern recognition receptors (PRRs). Another approach is to replicate inside these vesicles, so that they can avoid dsRNA recognition machinery otherwise which would have degraded the viral genome after replication (Snijder et al., 2006). Another important evasion mechanism is the hindrance of the interferon (IFN) pathway by MERS-CoV and SARS-CoV infections. In response to viral infection, IFN pathway activation takes place which exerts protective antiviral response, but it was observed that the IFN-1 (IFN-α and IFN-β) pathway was inhibited in SARS-CoV and MERS-CoV infected mice (Channappanavar et al., 2016, 2019). It was elucidated that accessory protein 4α of MERS-CoV inhibits the activation of MD5 that promotes IFN activation through expression of interferon regulatory factors (IRFs) (Niemeier et al., 2013). Also, membrane proteins, ORF4a, ORF4b, and ORF5 of MERS-CoV obstruct the nuclear movement of IRF3 which ultimately inhibits the activation of IFN-β (Yang et al., 2013). As we have discussed that the antigen presentation is an important initial step in order to clear the infection by triggering immunity, but in the event of MERS-CoV, the genes involved in antigen presentation were found to be down-regulated (Menachery et al., 2018).

1.3 Current treatment modalities for COVID-19

RNA-dependent RNA polymerase is an elegant target for RNA viruses to inhibit the viral RNA synthesis. Consistent with this idea remdesivir, which is an adenosine analogue has been evident for its antiviral actions on MERS-CoV and SARS-CoV by using virus-ridden cultured cells (Lo et al., 2017), non-human primate (Lo et al., 2019; de Wit et al., 2020), and mice (Sheahan et al., 2020) models.

In fact, the US health department at Washington also administered remdesivir intravenously to the patient for protection, in response to SARS-CoV-2 (Holshue et al., 2020). Similarly, chloroquine and remdesivir have been reported extensively for SARS-CoV-2 inhibition in vitro (M. Wang et al., 2020), suggesting a possibility to use these drugs in the therapeutic regimen. In fact, 4-hydroxy chloroquine has been used for health workers as a preventive measure for containing the SARS-CoV-2 across the globe. On the basis of knowledge of remdesivir, other nucleoside analogues including, galidesivir, ribavirin, and favipiravir hold promising potential for clinical application against SARS-CoV-2 (De Clercq, 2019; Zumla, Chan, Azhar, Hui, & Yuen, 2016). Chymotrypsin-like and papain-like proteases perform a crucial role in coronaviral replication, proliferation as well as in inhibition of innate immune response, so inhibitors of these enzymes including cinanserin, flavonoids, and diarylethapantoids may be useful for the inhibition of SARS-CoV-2 pathogenesis (L. Chen et al., 2005; Y. Chen, Liu, & Guo, 2020; Jo, Kim, Shin, & Kim, 2020; J. Y. Park et al., 2012).

ACE2 is receptor through which binding of SARS-CoV-2 takes place via S-protein, so blocking this binding may provide another promising option to treat COVID-19 successfully (W. Li et al., 2003).

Recently, plasma therapy also came into the clinical regimen for the severe patients of COVID-19, which is established on the fact that patients who have recently cured from the COVID-19 will have antibodies in their blood and thus the transfusion of these antibodies to the other patients may boost their immune system (Albahrī, Al-obaidi, Zaidan, Albahrī, & Zaidan, 2020). It has also achieved favorable findings in acute SARS-CoV-2 patients. Another straightforward way is to develop a monoclonal antibody in response to SARS-CoV-2 receptor binding domain, like one such antibody is CR3022 which may be an effective therapeutic candidate for COVID-19 (Tian et al., 2020). In order to neutralize SARS-CoV infection, similar antibodies such as CR3014 and m396 have also been reported (Zhang & Liu, 2020). Several other vaccine development strategies for SARS-CoV and MERS-CoV have been investigated in animals such as protein vaccines, recombinant DNA vaccines, live attenuated virus, inactivated virus, viral vectors, and subunit vaccines (Graham, Donaldson, & Baric, 2013), so all of these strategies may be utilized to manufacture vaccines against SARS-CoV-2. However, vaccine production for SARS-CoV-2 using above mentioned approaches are still in progress, but it may take a few more months or years to translate into clinical settings. Besides, some traditional Chinese medicines and herbal products shown to be effective as preventive and curative medicines to treat SARS-CoV-2 (Jiang, Cui, Ni, & Chen, 2020; Lim & Pranata, 2020; Qing, Zhang, Bai, & Luo, 2020).

Similarly, Indian traditional medicines and herbal products including decoction developed by the Ministry of AYUSH which acts as an immune booster proves to be useful against SARS-CoV-2, which is evident by the comparably less number of COVID-19 patients along with the highest recovery rate among the Indian population, as compared to the other countries of the world in per million population (Lakshmi, Shafreen, Priya, & Shumugiah, 2020; Murugan, Pandian, & Jeyakanthan, 2020; Priya & Sujatha, 2020; Rajkumar, 2020). Indian Government recommended various practices together to prevent SARS-CoV-2 pathogenesis including drinking of warm water, daily practice of Yoga and meditation, consumption of spices in cooking including Turmeric, Cumin, Coriander, and Garlic. They also recommended the consumption of an Ayurvedic recipe Chyavanprash 10 g daily. Besides, the Government of India through Ministry of AYUSH also recommended the consumption of decoction or herbal tea (KADHA) made from Raisin, dry Ginger, Black Pepper, Cinnamon, and Basil once or twice daily. Golden milk containing half teaspoon Turmeric powder was also another part of the Government recommendation. Some other practices related to the personal hygiene related to respiration and oral
cavity was also recommended including—gargles with Sesame oil for few minutes, cleansing of nostrils with Sesame or coconut oil, steam inhalation with Caraway seeds or fresh mint leaves; Clove in honey during sore throat or dry cough, etc. (https://www.mohfw.gov.in/pdf/ImmunityBoostingAYUSHAdvisory.pdf).

Here, it is noteworthy that India is a hugely populated country, but least affected in terms of population by various viral epidemics erupted during the last two decades including SARS-CoV, MERS-CoV, Ebola, Zika, H1N1, and now SARS-CoV-2. It seems that the use of herbal medicines, plant products, Ayurvedic medicines, and food habits provided better immunity to the Indian population for such type of viral infections. Several natural compounds derived from the marine environment have also been explored recently by molecular dynamic study and it was postulated that these compounds may be capable of inhibiting the main protease of SARS-CoV2 and thus can aid in the effective management of COVID-19 (Khan et al., 2020). It has also been postulated by many researchers that algae has proven to be an optimistic candidate for efficiently hindering the infection process of the virus at initial or later stages (Gentile et al., 2020). Consistent with this notion, we shed light on the potential of algal metabolites for the prevention and cure of infections due to viral pathogens; especially COVID-19; a disease induced by SARS-CoV-2 (Figure 3).

2 | ANTIVIRAL POTENTIAL OF ALGAE

Number of antiviral drugs has been developed for various viral pathologies, but genetic changes in the viral strains due to mutations make them resistant for the available therapies. Therefore, the production of broad-spectrum antiviral therapeutics is of paramount importance for long-term clinical efficacy of the drugs. Antiviral activities of various microorganism and algae are being reported elsewhere (Irwin, Renzette, Kowalik, & Jensen, 2016; Kelso & Hurt, 2012). An alga being a photosynthetic organism has the potential to channelize the atmospheric CO₂ and sunlight along with water nutrients toward the formation of productive biomass along with the essential bioactive compounds, even in the presence of environmental perturbations (Michalak & Chojnacka, 2015).

Algae are found in aquatic, as well as terrestrial habitat and based on its dimensions, it is broadly classified as microalgae and macroalgae. Microalgae are further classified as cyanobacteria, chlorophyta, rhodophyta, chrysophyta, and phaeophyta, whereas macroalgae comprises of huge aquatic photosynthetic plants such as seaweeds, kelps, etc. Algae have received great attention, all over the world, because of their capabilities to produce numerous high value-added primary as well as secondary, economically viable, and sustainable products along with its phenomenal CO₂ sequestration and wastewater treatment repertoires (Ghosh & Kiran, 2017).

Algal extracts, because of its characteristic composition and industrial applications have acquired a great amount of attention from the researchers. Algal biomass comprises of proteins, carbohydrates, minerals, polyunsaturated fatty acids, oil, fats along with several bioactive compounds including, pigments (carotenoids, chlorophylls, and phycobilin) and antioxidants (vitamins, polyphenols, etc.). Algae are widely consumed in the form of foods and also proved to be an important therapeutic source as they possess antiviral, antibacterial, antifungal, antitumor, anti-inflammatory, and antioxidative properties (Michalak & Chojnacka, 2015; Pooja, 2014). Different metabolic compounds extracted from various species of microalgae, macroalgae, and cyanobacteria are widely found to hamper the replication of several viruses without being toxic to the susceptible cells and therefore they are investigated primarily for their bio-prospecting approach in antiviral research (Abonyi, Adikwu, Esimone, & Ibezim, 2009; Claudio et al., 2018; Silva et al., 2018).

This review focuses on various biochemical constituents of algae (both microalgae and macroalgae), which can be utilized extensively as an antiviral drug for eradicating the viral infections caused by HIV, HSV, HPV, dengue virus (Wittine, Saffitić, Peršurić, & Pavelić, 2019) as well as novel coronavirus (SARS-CoV2). As shown in Table 1, biochemical metabolites of algae such as lipid, protein, pigments, terpenes, phlorotannins, polysaccharides, etc. can be explored and exploited comprehensively, for analyzing their virucidal efficacy against the broad range of viruses (Figure 1). Some of the algal compounds evaluated till now provided positive evidence of being effective antiviral agents both pharmacologically as well as economically and can be used globally on a commercial scale to obliterate the viral pathogen responsible for the pandemic situation all over the world.

2.1 | Polysaccharides

Polysaccharides, otherwise known as glycans, are carbohydrate-derived biopolymers and are one of the most abundant and well-established biochemical constituents of algae. The compositional and structural properties of a polysaccharide vary with the type of algae, environmental and growth conditions, harvesting time and extractions processes, etc. Thus, the diversified constitution and complicity of algal polysaccharide and its derivatives account for their antiviral activity at various stages of viral infection. Past few years witnessed outstanding results of virucidal activity of algal polysaccharides and have endorsed them as a valuable pharmaceutical or biomedical element.

As per the previous literature, a variety of algal polysaccharides including carrageenan, galactan, alginate, fucan and fucoidan, laminaran, naviculan, calcium spirulan, and nostafian, etc. have been shown to exert antiviral activities. The majority of these polysaccharides exhibiting virucidal effects on influenza, herpes simplex, HIV, hepatitis C, corona virus, etc. are the sulfated polysaccharides. It has been reported that because of the existence of sulfate and uronic acid moieties, the structure of sulfated polysaccharides showed congruency to the human glycosaminoglycans (heparan sulfates) and this molecular mimicry inhibits viral entry by binding with the viral glycoproteins. Different methodologies including, interference in the viral binding with the host cells, obliterate protein synthesis and DNA replication, have been reported as the most preferred mechanisms of polysaccharide’s antiviral activity (Jiao et al., 2012; Witvrouw & De Clercq, 1997).
### TABLE 1  Depicting potential algae-derived bioactive metabolites prodigiously combating several targeted viruses

| Biochemical constituents | Major antiviral metabolites | Targeted viruses                                                                 | References                                                                                                                                 |
|--------------------------|----------------------------|----------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|
| Polysaccharide           | Carrageenan                | Dengue virus, Herpes simplex virus, Human papillomavirus, Influenza A virus, Human rhinovirus, Coronavirus, Adenovirus, Paramyxovirus, Orthomyxovirus | Talarico & Damonte, 2007; Paula et al., 2006; Carlucci, Scolaro, & Damonte, 1999; Boulho et al., 2017; Buck et al., 2006; Tang, Chen, & Li, 2013; Graf et al., 2018; Nagle, Gaikwad, Pawar, & Dasgupta, 2020; Grassauer & Prieschl-Grassauer, 2019 |
| Galactan                 | HUMAN IMMUNODEFICIENCY VIRUS, HERPES SIMPLEX VIRUS, PSEUDORABIES VIRUS, HUMAN CYTOMEGALOVIRUS, DENGUE VIRUS | Witvrouw et al., 1994; Matsuhiro et al., 2005; Ohta, Lee, Hayashi, & Hayashi, 2009; J. Lee, Ohta, Hayashi, & Hayashi, 2010; Pujol, Errea, Matulewicz, & Damonte, 1996; Talarico, Duarte, Zibetti, Noseda, & Damonte, 2007 |
| Fucoidan                 | HERPES SIMPLEX VIRUS, HUMAN CYTOMEGALOVIRUS, HUMAN IMMUNODEFICIENCY VIRUS, HUMAN T-CELL LEUKEMIA VIRUS-1, HEPATITIS B VIRUS, HEPATITIS C VIRUS, INFLUENZA A VIRUS, ENTEROVIRUS | K. Hayashi, Nakano, Hashimoto, Kanekiyo, & Hayashi, 2008; Alboofetileh et al., 2019; Sanniyasi, Venkatasubramanian, Anbalagan, Raj, & Gopal, 2019; Ponce et al., 2019; Kuznetsova et al., 2020; Hoshino et al., 1998; Preeprame, Hayashi, Lee, Sankawa, & Hayashi, 2001; W. Wang et al., 2017; Ueno et al., 2019; Krylova et al. (2020) |
| Ulvan                    | INFLUENZA A VIRUS, JAPANESE ENCEPHALITIS VIRUS, FLAVIVIRUS, PARAMYXOVIRIDAE FAMILY, HERPES SIMPLEX VIRUS, VESICULAR STOMATITIS VIRUS | Ivanova et al., 1994; Chiu, Chan, Li, & Wu, 2012; Aguilar-Briseño et al., 2015; Hardouin et al., 2016; Chi et al., 2020 |
| Exopolysaccharide        | INFLUENZA A VIRUS, ORTHOPOXVIRUS, HERPES SIMPLEX VIRUS, VESICULAR STOMATITIS VIRUS, ENCEPHALOMYOCARDITIS VIRUS | W. Zheng, Chen, Cheng, Wang, & Chu, 2006; Radonić et al., 2010; Filomena et al., 2014; Yim et al., 2004 |
| Naviculan                | INFLUENZA VIRUS, HERPES SIMPLEX VIRUS | J. B. Lee et al., 2006 |
| Nostoflan                | INFLUENZA A VIRUS, HERPES SIMPLEX VIRUS, HUMAN CYTOMEGALOVIRUS | Kanekiyo et al., 2005; Kanekiyo, Hayashi, Takenaka, Lee, & Hayashi, 2007 |
| Alginate                 | HEPATITIS C VIRUS, POLIOVIRUS-1, SINDBIS VIRUS, HERPES SIMPLEX VIRUS | Tran et al., 2014 |
| Seaalgal extract (SEA)   | HUMAN IMMUNODEFICIENCY VIRUS, AVIAN MYELOBLASTOSIS VIRUS | Nakashima et al., 1987 |
| Calcium Spirulan         | HUMAN IMMUNODEFICIENCY VIRUS, HERPES SIMPLEX VIRUS, INFLUENZA A VIRUS, HUMAN CYTOMEGALOVIRUS, MUMPS VIRUS, MEASLES VIRUS | Hayashi et al., 1996; Rechter et al., 2006 |
Some sulfated polysaccharides are known to hinder the binding of virus onto the susceptible cells, either by direct interaction with virus or by adhering to specific receptors of the host cells through mimicking the virus associate proteins. The in-vivo inhibitory potential of these metabolites corresponds to their structural diversity which varies as per the monosaccharide composition, different glycosidic linkages, several isomeric forms, number of various substituents along with their position and distribution, etc. It has been reported that the degree of sulfation has a great significance on the virucidal activity of sulfated polysaccharides (Chattopadhyay et al., 2007; Laroy, Contreiras, & Callewaert, 2006; Mandal et al., 2007). Electrostatic interactions between the negatively charged heparan sulfate chains of the host cell surface proteoglycan receptors with the positively charged viral glycoproteins are interfered effectively by the highly charged polysaccharides. It has been observed that the methyl group present on fucoidan interact with the hydrophobic pocket of glycoproteins of herpes simplex virus and distorts the complex viral proteins (Uryu et al., 1992). Similarly, attachment of gp120 glycoprotein present on the envelope of HIV, which binds onto the susceptible cells is also hindered by galactan and sulfated polysaccharides. At higher concentrations, these carbohydrates are known to block the formation of syncytia in virus-infected cells (Witvrouw et al., 1994). Therefore, the structural complexity of the polysaccharide greatly affects the antiviral efficacy of sulfated polysaccharides, both qualitatively as well as quantitatively.

Additionally, Gerber and colleagues were the first to explore the inhibitory effects of algae-derived polysaccharides by developing resistance to influenza B and mumps virus (Gerber, Dutcher, Adams, & Sherman, 1958). Subsequently, a sulfated polysaccharide extracted from Spirulina platensis was identified, which eventually suppresses the proliferation of several enveloped viruses such as herpes simplex virus-1, hepatitis C, influenza A, measles, HIV-1, and mumps virus (Ayehunie, Belay, Baba, & Ruprecht, 1998; K. Hayashi, Hayashi, & Kojima, 1996; Yakoot & Salem, 2012).

### 2.1.1 Carrageenans

Sulfated polysaccharide, carrageenans are one of the central biochemical components derived from some of the red algae genera including,
Eucheuma, Gigartina, Chondrus, Hypnea, and constitutes for about 30 to 75% of dry algal weight. Chemical structure of carrageenans as shown in Figure 2a-c consists of 2 D-galactose, the iterative unit joined via β-1,4 glycosidic bond, which further classifies them into λ (delta), κ (kappa), and ι (iota) carrageenans. Diverse classes of carrageenans exhibit distinguishable inhibitory responses on varied virus infections (McCandless & Craigie, 1979). It was further illustrated by Buck et al. (2006) that carrageenans are capable of inhibiting the viral infection caused by human papillomavirus (HPV) in the initial stage and virucidal efficiency of ι class is more than λ and κ class of carrageenans.

From a structural point of view, lambda carrageenans and its different conformations hinder the interaction of HSV glycoproteins and cell surface heparan sulfate, thus affecting early steps of the infection. Different derivatives of carrageenans can firmly attach to the HSV virions by altering the framework of glycoproteins (gB and gC) present on the surface of HSV in order to inactivate these glycoproteins which are accountable for adsorption of a virus on the vulnerable cell, thus eventually inhibiting the viral replication (Carlucci et al., 1999). Carrageenans are also known to mimic the proteoglycans present on the cell surface, thus inhibited the entry of Dengue virus, whereas they also inhibited the incorporation of the nucleocapsid into the cytoplasm. Direct binding of carrageenan with the glycoprotein E of the Dengue viral membrane was shown to inhibit the viral entry as well as liberation of virions from the endosomes, thus preventing the viral spreading even after the invasion of the virus into the host cells (Talarico & Damonte, 2007).

It was demonstrated in a study that κ carrageenans after an optimal degree of sulphation and acetylation, was the potential candidate for an antiviral activity against influenza virus (Tang et al., 2013). Similarly, antiviral activity of the water-soluble polysaccharide carrageenans from Meristiella gelidium; a red seaweed of Brazilian origin was also observed. Extract from the Meristiella gelidium which was consisting about 88–90% of the iota carrageenan was found to be effective against HSV-2 infections (Paula et al., 2006). Microwave-assisted extraction of iota carrageenan from Solieria chordalis also
confirmed its strong virucidal activity against HSV type 1 with the absence of cytotoxic activity on Vero cell lines (Boulho et al., 2017).

Grassauer and Prieschl-Grassauer (2019) developed a pharmaceutical formulation comprising of iota and kappa carrageenans shown to be potent antiviral against respiratory tract related infections or diseases caused by certain groups of viruses including corona virus, adenovirus, paramyxovirus, and orthomyxovirus (Grassauer & Prieschl-Grassauer, 2019). Another study revealed that the combination of ι carrageenan and xylometazoline HCl worked effectively in the form of nasal spray against human corona virus OC43, human rhinovirus 1a (hRV 1) and human rhinovirus (hRV8) (Graf et al., 2018). It was recently reviewed by Nagle et al. (2020), which the sulfated polysaccharide, carrageenans derived from marine red algae Porphyridium, has an immense potential to be utilized as a protective layer on the sanitary objects along with its antiviral efficacy in the treatment of COVID 19.

2.1.2 | Galactan

It has been demonstrated in the earlier studies that galactan, a sulfated polysaccharide, derived from Aghardhiella tenera, a red seaweed showed an antiviral efficacy in developing resistance to a certain enveloped viruses- HIV and HSV, which is accomplished by obliterating the attachment of the virus to the host cell (Witvrouw et al., 1994). Pujol et al. (1996) illustrated the importance of S1, a sulfated galactan, derived from Pterocladia capillacea for inhibiting the adsorption of viruses such as type 1 and type 2 HSV, pseudo rabies virus and human cytomegalovirus. Similarly, galactan derived from Schizymenia binderi exhibited a peculiar pattern of sulfation, which hinders the interaction of heparin sulfate and herpes simplex virus, thus blocking the invasion of the virus into the host cell along with the suppression of viral replication (Matsumoto et al., 2005).

**FIGURE 2** Chemical structure of polysaccharides (a)–(d), lipid (e) and phlorotannins (f, g) extracted from algae for effective antiviral therapeutics.
Talarico et al. (2007) demonstrated that the algae-derived D, L galactan hybrid C25-3 is an appropriate viral entry inhibitor demonstrated in vitro against the infection caused by dengue virus-2 via restricting the viral binding and subsequently the invasion into the host cells (Talarico et al., 2007). Sulfated and pyruvylated galactan isolated from edible seaweed Codium fragile shown to be effective both in vitro and in vivo through immuno-stimulatory antiviral activity on type 2 herpes simplex virus. It was speculated that these algal galactan activated the macrophages those mediates the inhibition of viral entry and replication processes, thus holding a promising potential as prophylactic agent against HSV-2 infection (J. Lee et al., 2010; Ohta et al., 2009).

2.1.3 | Fucoidan

A high molecular weight sulfated polysaccharide; fucoidan (Figure 2) has been examined widely for its broad range antiviral activity against HIV-1, influenza A, and herpes simplex virus-1. K. Hayashi et al. (2008) isolated fucoidan from Undaria pinnatifida, an eatable brown alga, and examined its effects in vivo on the replication of herpes simplex virus-1 and immune-modulatory activities. They observed stimulation of both innate and adaptive immunity of the along with suppression of viral proliferation by oral consumption of fucoidan. In order to explore treatment and prevention of influenza, W. Wang et al. (2017) shown antiviral activity of fucoidan KW nasal spray by

FIGURE 3 Schematic diagram representing algae as a rich trove of efficacious anti-SARS-CoV drug; potential candidates derived from algae such as sulfated polysaccharides, lectins, terpenes, polyphenols and lipids can be tested for possession of high degree drug-likeness for prevention and treatment of COVID-19 [Colour figure can be viewed at wileyonlinelibrary.com]
targeting viral neuraminidase and cellular EGFR pathways. Another report on the fucoidan isolated from two different brown algae *Dictyota bortayesiana* and *Turbinaria decurrens* has been shown antiviral activity against HIV further consolidating a promising potential of fucoidan for the development of novel anti-viral therapeutics (Sanniyasi et al., 2019).

Acidic polysaccharides such as fucoidan, ascophyllan, alginate, and porphyran derived from brown and red marine algae were further investigated for their inhibitory effects against adsorption, penetration, and replication of HIV-1, hepatitis B and C, and human T-cell leukemia virus-1. It was deduced that these sulfated polysaccharides are acidic due to the existence of sulfate and carboxyl group and exhibited nonspecific initial virucidal efficacy against a broad range of viruses and thus can be utilized as a prophylactic agent against numerous viral infections (Ueno et al., 2019). Viral infection induced by HSV-1 and HSV-2 was highly inhibited by the antiviral activity of galactofucan portion of the fucoids, extracted by cetrimide fractionation from *Scytosiphon lomentaria*, brown seaweed. Effective antiviral activity of galactofucan was observed because of increased sulfation degree and decrease in uronic acid content along with the presence of some varied monosaccharides in trace amount (Ponce et al., 2019). Similar studies were performed to detect the antitherapeutic activity of fucoidan isolated from *Nizamuddinia zanardinii*, a brown alga in response to HSV type 2, and it was found that fucoidan extracted via viscozyme extraction method displayed better selectivity index, as compared to the other extraction methods (Alboofetileh et al., 2019). Fucan sulfate having fucose as main sugar moiety, extracted from *Sargassum horneri*, an edible brown alga was found to be an effective anti-viral agent against HSV-1, human cytomegalovirus and HIV-1. Sulfated polysaccharides were shown to inhibit attachment, invasion, and replication of these viruses (Hoshino et al., 1998; Preeprame et al., 2001).

Recently, Kuznetsova et al. (2020) determined that enzymatic hydrolysis of fucoidan, derived from *Fucus evanescens*, yields purified fucoidans and demonstrated the activation of innate and adaptive immunity and served as an adjuvant in order to augment the production of IgG against hepatitis B virus along with increased cytotoxic capability of natural killer cells. It was further suggested by Krylova et al. (2020) that depolymerization of fucoidan by enzymes, yields derivatives having varying potency of cytotoxic and anti-viral responses against HIV-1, HSV-1, HSV-2, and enterovirus in human MT-4 and Vero cell lines. Eventually, it was deduced that native, as well as enzyme-modified fucoidan both, acts as a promising candidates to inhibit the infectious activity of broad-spectrum RNA or DNA viruses in vitro and in vivo.

### 2.1.4 Ulvan

Ulvan is as water-soluble sulfated polysaccharide isolated from cell walls of Ulvales green seaweeds and constitutes about 8–29% of its dry algal weight based on diverse attributes (Lahaye & Robic, 2007). Polysaccharide isolated from *Ulva lactuca* was found to be an efficient selective inhibitor of influenza virus. The efficiency of polysaccharide’s antiviral activity usually depends upon the viral strain and the cell line used (Ivanova et al., 1994). An interesting study was performed to deduce the antiviral activity of ulvan, in response to infection induced by Japanese encephalitis virus in Vero cells. It was observed that ulvan inhibited the viral invasion via hindering the adsorption stage of infection and also stimulates cytokine production in the infected glial cells, thus can be utilized as a food supplement in order to obviate the viral infections; especially viruses from paramyxoviridae family and flavivirus (Aguilar-Briseno et al., 2015; Chiu et al., 2012).

Ulvan extracted enzymatically from *Ulva* species comprises of a sulfate group, uronic acid, and rhamnose in large amount, whereas due to presence of glucanase and hydrolase activities it also exerts radical scavenging potential that leads to the moderate suppression of HSV-1 (Hardouin et al., 2016). Ulvan and its high molecular weight derivatives were also found to hinder the replication and proliferation of vesicular stomatitis virus with 40.75 and 40.13% inhibition, respectively. The molecular weight of polysaccharide was established to be an important factor influencing the anti-viral activities of the ulvan (Chi et al., 2020).

### 2.1.5 Exopolysaccharides

Exopolysaccharides are the sulfated polysaccharides derived from cyanobacteria and marine algae; they make up the external mucilaginous layer (sheath or capsule) of the algae and is released into the media. p-KG03 is one such algal sulfated exopolysaccharide extracted from marine microalgae such as the KG03 strain of *Gyrodinium impudicum* and *Porphyridium cruentum*. Prolific antiviral activity of p-KG03 in resistance to encephalomyocarditis virus has been reported. Inhibition of viral replication was observed in vitro by p-KG03 (Yim et al., 2004). p-KG03 was also found to be immuno-stimulatory in vivo via increasing the production of macrophages and natural killer cells (Joung, Son, Pyo, & Hong, 2005).

Exopolysaccharide extracted from *Alphanothece halophytica* a cyanobacteria also displayed inhibitory potential to restrict the replication and proliferation of influenza A virus and also regulated the immune system of the host by activating macrophages and thus inducing the release of interleukins and cytokines (W. Zheng et al., 2006). Radonić et al. (2010) determined the antiviral activities of exopolysaccharide and anionic exopolysaccharide TK V3 isolated from red algae *Porphyridium purpureum* and cyanobacteria *Arthrosira platensis*, respectively, against the members of orthopox virus and other enveloped viruses (Radonić et al., 2010). In another study, exopolysaccharide from red algae *P. cruentum* shown to be strongly effective against vesicular stomatitis virus, whereas moderate antiviral effects were observed on HSV-1 and HSV-2 (Filomena et al., 2014).

### 2.1.6 Diverse polysaccharides

Additionally, sulfated polysaccharide, naviculan extracted from a diatom *Navicula directa* displayed a potential antiviral response to...
enveloped viruses such as influenza virus and herpes simplex virus type 1 and type 2 by inhibiting the viral entry and proliferation into the host cells (U. B. Lee et al., 2006). An effective broad range inhibitory potential against enveloped viruses with carbohydrate receptors such as influenza A virus, HSV-1, HSV-2, and cytomegalovirus was exhibited extensively by nostoflan, an acidic polysaccharide derived from *Nostoc flagelliforme*, a terrestrial edible blue-green alga. It was observed that nostoflan induced antiviral activity by altering the binding of virus to the target cells (Kaneikeyo et al., 2005, 2007).

Ahmadi, Zorofchian Moghadamtousi, Abubakar, and Zandi (2015) reviewed that laminaran, a water-soluble polysaccharide which is made up of glucose units produced from 1,3-β-D-glucan and extracted from the kelp, potently prevents the replication and proliferation of HIV via suppressing the viral binding with lymphocytes (Ahmadi et al., 2015). Acidic polysaccharide LJT4 derived from *Laminaria japonica*, brown algae was also found to be an efficient antiviral agent against enterovirus 71. It was explained that LJ04 inhibited enterovirus 71 induced apoptosis, whereas it also induced the expression of IFN-β which resultanty triggered the innate immunity through which transmission of enterovirus 71 was inhibited (Yue et al., 2017).

Microencapsulated alginate was formulated to be an effective protective agent against infection induced by the hepatitis C virus, poliovirus-1, Sindbis virus, and HSV-1, thus can be used as regenerative medicine. Interaction of virus and alginate hydrogel was found to be dependent on the dose as well as the incubation time of the cells (Tran et al., 2014).

Sea algal extract (SEA), a sulfated polysaccharide isolated from *Schizymenia pacifica* red alga is formulated of galactose, sulfonate, and 3, 6-anhydro galactose. It has shown to inhibit reverse transcriptase enzyme of the avian myeloblastosis virus and HIV, thus inhibited the viral replication. It was also suggested that the presence and the degree of sulfation played an essential role in inhibiting the replication as well as reverse transcriptase of pathogenic viruses (Nakashima et al., 1987).

A sulfated polysaccharide along with metal salt make up calcium-spirulan which is composed of calcium, sulfate, rhamnose, mannose, galactose, glucose, galactouronic acid, ribose, fructose, xylose, and glucuronic acid. Calcium spirulan was initially fractionated from cyanobacteria *Spirulina* (Arthrospira platensis) by water extraction method and exhibited an inhibitory effect against replication, penetration, and adsorption of various enveloped viruses such as HIV-1, HSV-1, mumps virus, influenza A virus, measles virus, and human cytomegalovirus. It was further proposed that calcium ion binding with sulfate group was a prerequisite for prolific antiviral efficacy of novel calcium spirulan polysaccharide (T. Hayashi, Hayashi, Maeda, & Kojima, 1996; Rechter et al., 2006).

When monolayer cells of mouse embryo fibroblast were treated with extracts of *Constantinea simplex* and *Farlowia mollis* marine algae, effective inhibition in the replication of vesicular stomatitis virus, HSV-1, HSV-2 and vaccinia virus were observed. It was postulated that a structural polysaccharide which was the potent antiviral ingredient in these algal extracts, hindered viral attachment to the cells by blocking the receptor sites of the cells. Therefore, these active compounds in *Constantinea simplex* and *Farlowia mollis* extracts could serve as potential antiviral agents (Richards et al., 1978). Similar antiviral activity was also exhibited by sulphated polysaccharide, SP-2a, isolated from *Sargassum patens*, a brown alga. SP-2a was determined to be an effective inhibitor of HSV-2 as well as acyclovir-resistant HSV-1 strain (Zhu, Ooi, Chan, & Ang, 2003). In-vitro antiviral activity of sulphated heteropolysaccharides and their fractions derived from *Padina pavonia*, a brown alga, against HSV and hepatitis A virus was also reported. It was concluded that the distribution of sulfate moieties and structural conformations play a vital role in virus-polysaccharide complex formation (Mohamed & Agili, 2013).

In a nutshell, it has been observed that representative polysaccharides extracted from algae specifically differing in chemical structure, molecular weight and degree of sulfation, proved to be effective against viral replication and entry inside the host cell, either by mimicking the human heparins or by stimulating the defense immune system of host cells, which in turn aid in prevention and treatment of viral infections such as HIV, HSV, influenza, coronavirus, etc. Further, it has been observed that in-vivo exploration of the antiviral efficacy of polysaccharides needs to be the pivotal goal of the research for the development of pharmaceutical antiviral drugs to be used clinically at a larger scale.

### 2.2 Protein

Proteins extracted from algae also perform a significant role in obliterating the spread of contagions, especially those induced by viral pathogens. Lectin or glycoproteins being one such significant protein, bind to carbohydrate moiety of the virus in order to inhibit its attachment to the target cells and also to hinder the replication of viral DNA or RNA.

#### 2.2.1 Cyanovirin-N

A well-known 11 kDa antiviral protein, cyanovirin-N is isolated from cyanobacteria *Nostoc ellipsosporum* and proves to be a prolific viral-cidal agent against simian immunodeficiency virus (SIV) and HIV type 1 as well as type 2. It has been explained that cyanovirin-N aborted the cell to cell fusion through which it prevents transmission of HIV in vitro, whereas it also binds with the viral glycoprotein gp120 and alter viral binding with the target cells (Boyd et al., 1997). In another interesting study, cyanovirin-N was found to inhibit strains of influenza A and influenza B viruses. Insights into molecular mechanisms revealed that the viral hemagglutinin was the target binding site of the cyanovirin-N, preferably with oligosaccharide comprised sites (O’Keefe et al., 2003).

Cyanovirin-N was found to be the first biochemical constituent to reduce invasion of Ebola virus strain Zaire into the host cells by interacting with the viral surface envelope glycoproteins (GP 1, 2) both in vitro and in vivo. Besides, Cyanovirin-N also prevented the viral induced cytopathic effects to the host cells (Barrientos et al., 2003).
Helle et al. (2006) demonstrated antiviral effects of cyanovirin-N on hepatitis virus C and it was explained that the binding of cyanovirin-N with the viral envelope glycoprotein E2 that alter the interaction of E2 with the cell surface receptor CD81 which resulted inently inhibited the entry of the virus inside the host cells. They have suggested that cyanovirin-N interacted broadly with the N-linked glycans linked to glycoproteins and inhibited the virus at an early stage of infection (Helle et al., 2006).

Similar antiviral effects of cyanovirin-N, extracted from N. ellipsosporum a blue-green alga were also reported on the HSV-1 through the inhibition of viral entry into the host cells by blocking the membrane fusions (Tiwari et al., 2009).

In silico and experimental data from the study of Woodrum, Maxwell, Bolia, Banu Ozkan, and Ghirlanda (2013) revealed that the cyanovirin-N is an oligomannose or glycan specific multivalent antiviral agent that preferably binds with the glycans or carbohydrate moieties of the viral surface or envelop which is making it a promising algal protein to be utilized for the production of antiviral medications in order to combat several viruses (Woodrum et al., 2013).

### 2.2.2 | Scytovirin

Scytovirin is known for inhibiting the invasion and proliferation of HIV and is being derived from the water extract of Scytonema varium, a terrestrial cyanobacterium. Scytovirin consists of 95 amino acid long single chain protein which interacts preferably with the high mannose oligosaccharides specifically of viral glycoprotein gp120 and gp160, thus exhibit substantial anti-HIV activity (Bokesch et al., 2003). It was further investigated that protein is made up of two alleged domains, SD1 and SD2 which are comprised of 1–48 and 45–95 amino acids, respectively. It has been further emphasized that SD1 was found significantly more active, as compared to the SD2 in exhibiting the anti-HIV activity. Further structural elucidation of scytovirin illustrated that the strength of anti-viral efficacy is depends upon the carbohydrate residues present on the viral surface (Xiong et al., 2006). Scytovirin was also found moderately effective against angola strain of the Marburg virus by inhibiting the viral entry and replication (Garrison et al., 2014).

Scytovirin, cyanovirin-N, and griffithsin are individually found to be efficient inhibitors of mucosal transmission of HIV-C and are thought to be the potent anti-viral drug candidates (Alexandre et al., 2010).

### 2.2.3 | Griffithsin

Griffithsin, lectins derived from red algae exhibited a broad spectrum antiviral activity in vitro and in vivo without being toxic to the host cells. Griffithsin is comprised of 121 amino acids, which is having carbohydrate-binding moieties; especially the mannose-binding lactins binds to the carbohydrate moieties present on the enveloped viruses including MERS-CoV and SARS-CoV, HIV, hepatitis C virus etc. Griffithsin withstand with the wide range of changes in the pH and high temperatures and less toxic to the host cells and because of these properties, it seems to be a promising potential anti-viral drug candidate. O’Keefe et al. (2010) demonstrated the therapeutic response of griffithsin in vitro and in vivo on reduction of mortality by SARS-CoV infection through inhibition of the infection as well as immune-modulation of the host (O’Keefe et al., 2010). Griffithsin substantially inhibits the penetration of the virus into the host cell by suppressing the activity of glycosylated spike protein present on the coronavirus (MERS-CoV and SARS-CoV), thus efficiently obliterating the attachment of the virus to the target cells (Millet et al., 2016).

Many viruses are consisting glycopolypeptides having high mannose glycans on the surface of their viral envelope. High mannose glycans are found to exist in large amount on the surface glycoproteins of HCV and SARS-CoV. However, these high mannose glycans act as a potential target for carbohydrate-binding proteins. Usually, the antiviral efficacy of lectins depends on their mannose-binding ability (Balzarini, 2007). Structural features of griffithsin such as compact domain-swapped dimeric structure, six separate binding sites for monosaccharides, and three identical domains significantly enhance the carbohydrate-binding potential of griffithsin, as compared to other lectins. The causative agent of SARS-CoV, coronavirus comprises a highly glycosylated S spike protein on the surface envelope which binds efficiently to the monosaccharide specific human lectin. Ziółkowska et al. (2006, 2013) speculated the possibility of griffithsin binding to the spike protein of the coronaviruses through which it may inhibit the viral infection. It was observed that multivalent binding sites on griffithsin are the prime reason for their high-affinity binding to individual oligo mannose glycans present on the surface of the enveloped viruses. Griffithsin was found to be capable enough in hindering the replication of the virus and suppressing the cytopathic behavior induced by the virus. Therefore, the antiviral activity of lectin such as griffithsin can be exploited further for the production of efficient, heat and pH tolerable, non-toxic anti-viral therapeutics (Ziółkowska et al., 2006, 2013).

Few recent reports from Moulaei et al. (2010, 2015) emphasized the importance of the orientation of the tandem monomeric repeats of the griffithsin on the native griffithsin resistance strains of HIV and suggested the necessity of the engineering of lactin molecules for the development of the potent anti-viral therapeutics especially for resistant viral strains (Moulaei et al., 2010, 2015).

Trimeric repeats and oxidation resistant properties of Griffithsin were found to efficiently block the formation of syncytia induced by glycoproteins present on Nipah virus. Griffithsin was shown to obliterate viral invasion and inhibition of cell-to-cell transmission of the Nipah virus via blocking the glycosylation of the viral glycoprotein, which is responsible for the formation of syncytia. Thus, griffithsin resistant to oxidation was found to be more effective in inhibiting the Nipah virus and can be used for therapeutic purposes (Lo et al., 2020).

### 2.3 | Lipids

Algae derived lipids specifically sulfolipids and glycolipids, though less evident in comparison to algal polysaccharides and proteins, but too
exhibit inhibitory effect on several enveloped viruses. Gustafson discovered the application of structural sulfolipid, sulfoglycosyldiacylglycerols (SQDG) (Figure 2) extracted via tetrazolium microassay from two cyanobacteria, Phormidium tenue, and Lyngbya lagerheimii, in obliterating the cytopathogenic effect of HIV onto the host cells (Gustafson et al., 1989). In similar studies, a category of diacylated sulfoglycolipids, sulfoglycosyldiacylglycerol lipid isolated from cyanobacteria was reported as an efficacious inhibitor of RNA dependent DNA polymerase enzyme of HIV-1. The magnitude of the enzyme inhibition was affected substantially by the presence of sulfonic acid and by the side chain of the fatty acid ester (Loya et al., 1998).

However, SQDG extracted from alga Caulerpa racemosa and brown seaweed Sargassum vulgare have also shown a strong antiviral activity against both the strains of the herpes simplex virus. Sulfoglycolipid played an essential role in hampering the transmission of herpes simplex virus along with the low cytotoxicity of SQDS to the host cells (Plouguerné et al., 2013; H. Wang et al., 2007). Glycolipid extracted from alga Dilophysfasciola had quite an effective antiviral effect against HSV-1 (El Baroty et al., 2011). Reports suggest that explicit anti-HSV-1 and anti-HSV-2 activity of algal extract was attributed to the inhibitory potential of SQDG isolated from Osmundaria obtusiloba, a Brazilian red alga. Glycoglycerolipids such as monogalactosyldiacylglycerol and digalactosyldiacylglycerol derived from O. obtusiloba were found to stimulate the synergistic effects and thus it was concluded that algal extract containing sulfoglycolipids along with glycoglycerolipids, enhanced the anti-HSV potential of the red algae (De Souza et al., 2012). An octocoral reef, Litophyton arboreum, widely distributed in the Red Sea, consists of various cytotoxic metabolites among which polyhydroxysterols were found to be the most potent for medicinal purposes, whereas certain metabolites also exhibited anti-HIV-1 activity (Ellithey, Lall, Hussein, & Meyer, 2013).

Lipids derived from algal biomass are usually measured in terms of saturated and unsaturated fatty acids and are considered as a source of polysaturated fatty acids or as raw stock for the production of oil. In the context of ongoing coronavirus pandemic, a recent study discussed the preventive aspect of algal oil comprising of linoleic acid, palmitic acid, oleic acid, and stearic acid, against the virulence activity of the virus and it was inferred that the formulation consisting of algal oils can pose a strong inhibitory effect by suppressing the integration of the virus into the host cells (Subhash, Kumar, Sapre, & Dasgupta, 2020).

### 2.4 | Terpenes

Terpenes or terpenoids are significant secondary metabolites, produced by a variety of algal species, particularly brown algae. Structure of terpenoids is assembled from several units of isoprene molecules and based on their structure terpenes are classified into monoterpene (C10), sesquiterpene (C15), diterpene (C20) and so on (Gaysinski, Ortalo-Magne, Thomas, & Culioli, 2015). Diterpene derivative, Halitunal was extracted from marine alga Halimeda tuna and its structural elucidation revealed its capability to inhibit the viral activity of coronavirus A59 in vitro (Koehn et al., 1991). An effective inhibition of the HIV-reverse transcriptase is attributed to the activity of sesquiterpenes; perysonol A and perysonol B, extracted from Peyssonelia sp., which belongs to the class of marine red algae. It was speculated that the terpenoid derivative hampered the binding of HIV-reverse transcriptase to the template primer, which indirectly inhibited the replication of viral pathogen to a great extent (Loya et al., 1995). Pereira et al. (2004) and De Souza Pereira et al. (2005) demonstrated the antiretroviral activity of 2 diterpenes, (6R)-6-acetoxidichotoma-3,14-diene-1,17-dial and (6R)-6-hydroxydichotoma-3,14-diene-1,17-dial. It was deduced that diterpenes were successful in restraining the reverse transcription of HIV genomic RNA by obliterating the activity of RNA dependent DNA polymerase enzyme and consequently hindering the viral replication.

Another study on the extract from brown alga Taonia atomaria containing metabolites like taondiol, styropodiol, sargaoil, isopeitaondiol exhibited high radical scavenging activity (RSA) which could also be used as a powerful antioxidant. This high RSA activity displayed by taondiol and epitaondiol makes them powerful antiviral candidates for pharmaceutical development (Nahas et al., 2007). Anti-herpes activity of diterpenes isolated from Canistrocarpus cervicosis brown seaweed was demonstrated which was accompanied with their minimal cytotoxic activity to the Vero cells in vitro (Vallim et al., 2010). Diterpene (8,10,18-trihydroxy-2,6-dolabelladiene and (6R)-6-hydroxydichotoma-4,14-diene-1,17-dial) extracted from one of the brown macroalgae have also shown to obliterate replication of HSV-1 (Abrantes et al., 2010). Terpenoids such as halogenated sesquiterpenes and meroditerpenes derived from marine red seaweed and green sea weed, respectively were found as effective antiviral curatives against acyclovir resistant strains of HSV-1 and 2 (Soares et al., 2012). Nevertheless, these studies reinforced the role of terpenes and their derivatives derived from several algal species as important biochemical components with the virostatic capabilities.

### 2.5 | Polyphenols

Algal polyphenols also known as phlorotannins are extracted from brown algae and exhibited commendable antiviral activity against viruses of coronaviridae family. 8,8-bieckol and 8,4-dieckol (Figure 2) derivatives of phlorotannin, derived from Ecklonia cava, brown marine alga, rendered paramount inhibitory effects onto the reverse transcriptase and protease activity of HIV-1 (Ahn et al., 2004). 8,4-dieckol was also revealed to hinder the syncytia formation, viral antigen production along with the lytic effects of HIV-1 and was thus reported to be considered as a potent antiviral candidate for further pharmaceutical trials (Karadeniz et al., 2014). Extract of several Mexican seaweeds was found to be enriched with polyphenols and their derivatives. It was demonstrated that polyphenols restricted the adsorption and penetration of Measles virus onto the target cells. Synergistic effects of polyphenols along with the sulfated polysaccharides was suggested to be an effective source of preventive and curative therapeutics the
viral infections caused by the Measles virus (Morán-Santibañez et al., 2018).

Furthermore, a study was conducted to determine the inhibitory activity of nine phlorotannins extracted from E. cava, on SARS-CoV 3CL proteinase necessary for the replication of severe acute respiratory syndrome coronavirus. They concluded that 8 out of 9 phlorotannins were capable to inhibit the activity of proteinase. Surface plasmon resonance and molecular docking simulation studies revealed that phlorotannin dieckol was found to be more potent antiviral agent, as it binds to the 3CL proteinase of SARS-CoV more efficiently. The most potent proteinase inhibitory activity was exhibited by dieckol, which was composed of two eckol groups linked via diphenyl ether. Study on kinetic mechanism of dieckol revealed that dieckol competitively inhibited the SARS-CoV 3CL proteinase. Dieckol was found to be more efficient at blocking the cleavage of proteinase, as compared to the previously reported phenolic compounds derived from plants. Molecular docking was performed to analyze the interaction of dieckol and protein residues present on the ligand-binding site of SARS-CoV. It was observed that dieckol showed the lowest binding energy, as compared to other phlorotannins and hence it was concluded that dieckol forms strong hydrogen bonds with the catalytic groups (dyad) of SARS-CoV 3CL proteinase and possessed the highest association rate (J. Y. Park et al., 2013).

Recently, Gentile et al. (2020) screened marine natural products using molecular docking and hyphenated pharmacophore model to determine the most potential marine product, which can be used comprehensively to hinder the activity of SARS-CoV-2 main protease Mpro, which is a chymotrypsin-like protease. They have demonstrated that phloroglucinol oligomers, phlorotannins extracted from brown algae Sargassum spinuligerum were expected to be the highly potential SARS-CoV-2 inhibitors. Among them, 8,8-Bieckol, 6,6-Bieckol and Dieckol phlorotannins derived from marine brown alga E. cava were recognized and confirmed as one of the most interactive and active inhibitors of the protease (Gentile et al., 2020).

2.6 Multivariable secondary algal metabolites to combat viruses

Apart from algal polysaccharides, proteins, sulfolipids, terpenes, and phlorotannins derived from algae, several other secondary metabolites or other constituents are distinguished as broad spectrum anti-viral agents those are capable to inhibit the viral replication and cell-to-cell transmission and they opened a new avenue for the development of the novel anti-viral therapeutics.

According to a study done by Serkedjieva (2000), Polysiphonia denudate water extract inhibited the replication and proliferation of HSV-1 and HSV-2 (Serkedjieva, 2000). 2,3,6-tribromo-4,5-dihydroxybenzyl methyl ether (TDB); the major component of methanol extract of Symplycocladia latiuscula suppressed wild-type HSV-1, APR HSV-1 (acyclovir and phosphonoacetic acid-resistant HSV-1) and TK HSV-1 (thymidine kinase-deficient HSV-1) (H. J. Park et al., 2005).

Similarly, the water extract from Gracilaria salicornia displayed antiviral activity against HSV-2 by inhibiting the viral replication (Zandi, Salimi, & Sartavi, 2007). The blockage of adsorption and reproduction processes of viruses such as HCV and HIV by hindering the initial stages of the viral life cycle was attributed to the photosynthetic pigment phycobili proteins derived from cyanobacteria, which paved the way for exploring the antiviral effects of algal-derived pigments (Abd El Hamid et al., 2019).

3 FUTURE PROSPECTS OF ALGAL DERIVATIVES-BASED ANTIVIRAL THERAPEUTICS

Presently, COVID-19 crisis evident severe morbidity, mortality, and enormous socio-economic losses. The corona virus SARS-CoV-2 persuades to respiratory illness, which may lead to the death in severe cases. It is also evident from the available literature that SARS-CoV-2 is already having many variants and continuous mutations in the viral genome may further increase the number of viral variants in future, which renders failure to the efforts of the vaccine development.

Scientists from all over the world are working at war footing level to develop vaccines, therapeutic drugs and immune boosters for the prevention and cure of COVID-19, as well as other viral infections including HIV, HSV, dengue etc. Algal metabolites have shown multi-step anti-viral potential start from the binding, entry, and replication of the viruses into the host cells, cell-to-cell transmission and cytotoxic effects without exerting substantial adverse effects to the host cells. Present review shed light on the specific and broad-spectrum anti-viral effects of the algal metabolites even on the drug resistant strains, consistently suggesting a need for further research using algal metabolites on COVID-19. Based on the present literature we strongly believe that algal metabolites may open new avenues to the development of novel therapeutic modalities for not only for COVID-19, but also for the other viral infections prevailing the globe. We conclude that based on the available reports algal metabolites hold promising potential for the development of novel anti-viral therapeutics with cost efficiency, as irrespective to the geographical distribution, algae are easily cultivable in controlled conditions in any part of the world.

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CONFLICT OF INTEREST

There are no conflicts of interest involved with this manuscript.

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