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REVIEW

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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 therapies 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 dash board 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 replicase 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, Ohto-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 resultantly released 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 and HLA-A* 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, Ho, & 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-2patients

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-Martin, Danesh, Muller, & Kelvin, 2008; Channappanavar & Perlman, 2017; Huang et al., 2020; Williams & Chambers, 2014). The acute respiratory distress syndrome (ARDS), a conventional immunopathological 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 one 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-I (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 4a of MERS-CoV inhibits the activation of MDA5 which promotes IFN activation through expression of interferon regulatory factors (IRFs) (Niemeyer 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 diarylheptanoids 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 (Albahri, Al-obaidi, Zaidan, Albahri, & 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, & Shunmugiah, 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 CO_2 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 CO_2 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 food 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, Saftić, 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 complicacy 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 nostaflan, 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

(Continues)

TABLE 1 (Continued)

Biochemical constituents	Major antiviral metabolites	Targeted viruses	References
Protein	Cyanovirin-N	Human immunodeficiency virus, Simian immunodeficiency virus, Influenza A virus, Influenza B virus, Hepatitis C virus, Herpes simplex virus, Ebola virus	Boyd et al., 1997; O'Keefe et al., 2003; Helle et al., 2006; Tiwari, Shukla, & Shukla, 2009; Barrientos et al., 2003
	Scytovirin	Human immunodeficiency virus, Ebola virus, Marburg virus	Bokesch et al., 2003; Xiong, O'Keefe, Byrd, & McMahon, 2006; Alexandre et al., 2010; Garrison et al., 2014
	Griffithsin	Human immunodeficiency virus, Japanese encephalitis virus, Coronavirus (SARS-CoV & MERS-CoV), Hepatitis C virus, Nipah virus	Moulaei et al., 2010, 2015; O'Keefe et al., 2010; Millet et al., 2016; Balzarini, 2007; Ziółkowska et al., 2006, 2013; Lo et al., 2020
Lipid	Sulfo-quinovosyl-diacylglycerols (SQDG)	Herpes simplex virus, Human immunodeficiency virus	Gustafson et al., 1989; Plouguerné et al., 2013; H. Wang et al., 2007; El Baroty, El-Baz, Ibtisam, et al., 2011; Souza et al., 2012
Terpene	Diterpenes	Coronavirus – A59, Human immunodeficiency virus, Herpes simplex virus	Koehn, Sarath, Neil, & Cross, 1991; Pereira et al.,2004; Pereira et al., 2005; Vallim et al., 2010; Abrantes et al., 2010
	Sesquiterpenes	Herpes simplex virus, Human immunodeficiency virus	Soares et al., 2012; Loya, Bakhanashvili, Kashman, & Hizi, 1995
Polyphenols (phlorotannins)	Dieckol; 8,8′-bieckol	Human immunodeficiency virus, SARS-coronavirus, Measles virus	Ahn et al., 2004; Karadeniz, Kang, Park, Park, & Kim, 2014; J. Y. Park et al., 2013; Gentile et al., 2020; Morán-Santibañez et al., 2018

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, Contreras, & 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, Admas, & 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,

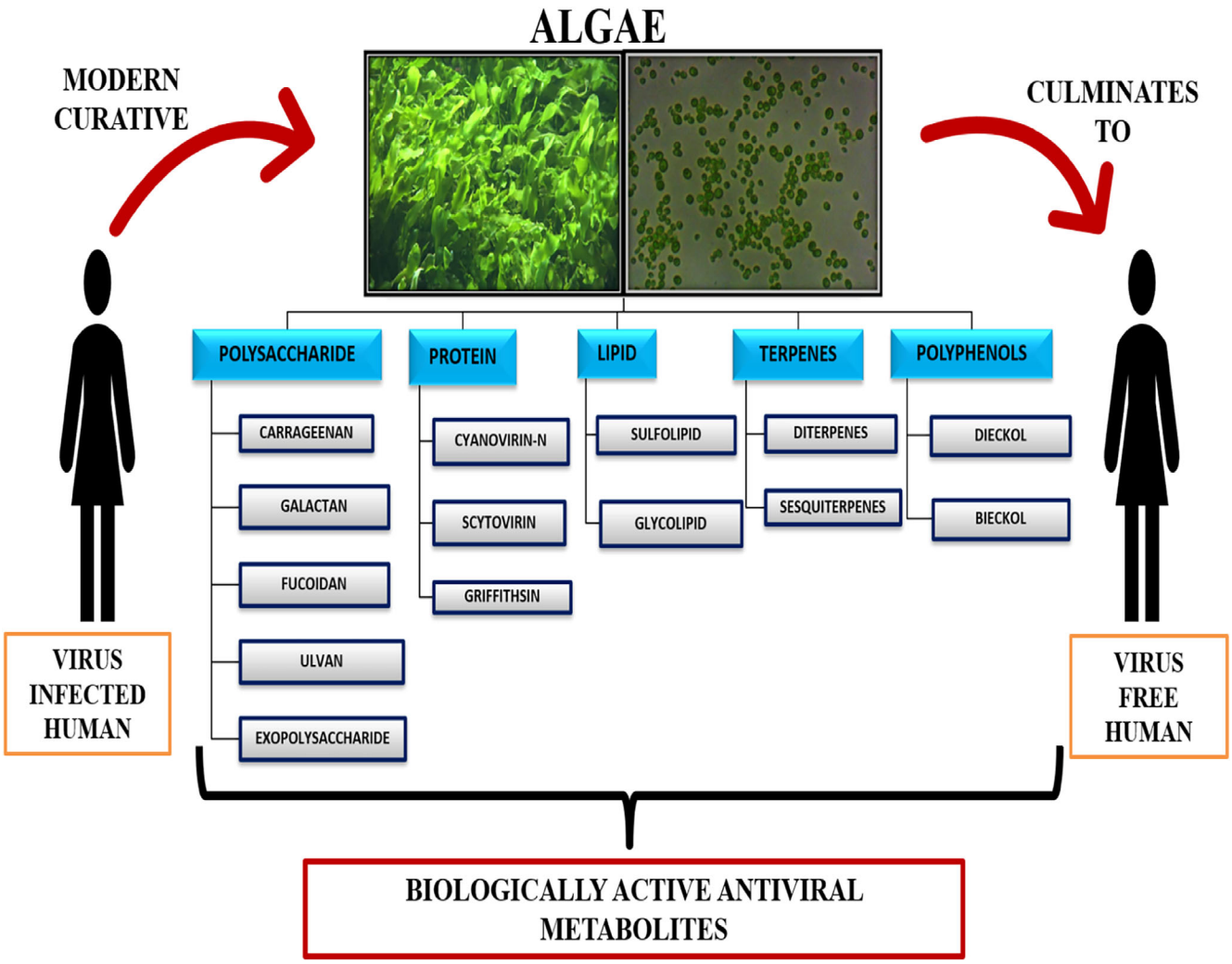

FIGURE 1 Illustrating fundamental algae-derived bioactive components beneficial in the treatment and prevention of infection induced by viral pathogens [Colour figure can be viewed at wileyonlinelibrary.com]

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, paramyxo virus, and orthomyxo virus (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 (Matsuhiro et al., 2005).

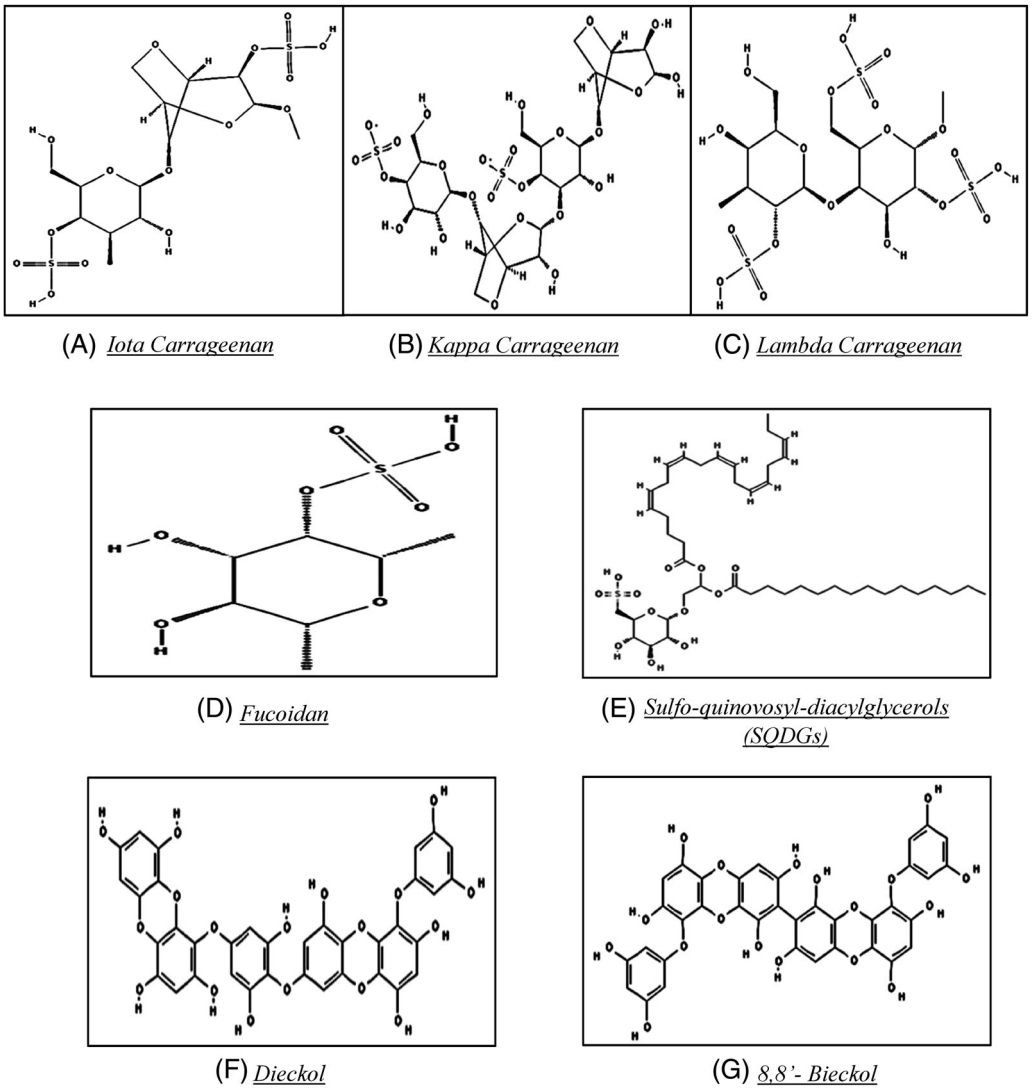

FIGURE 2 Chemical structure of polysaccharides (a)–(d), lipid (e) and phlorotannins (f, g) extracted from algae for effective antiviral therapeutics

Talarico et al. (2007) demonstrated that the algae-derived D, L galactan hybrid C2S-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

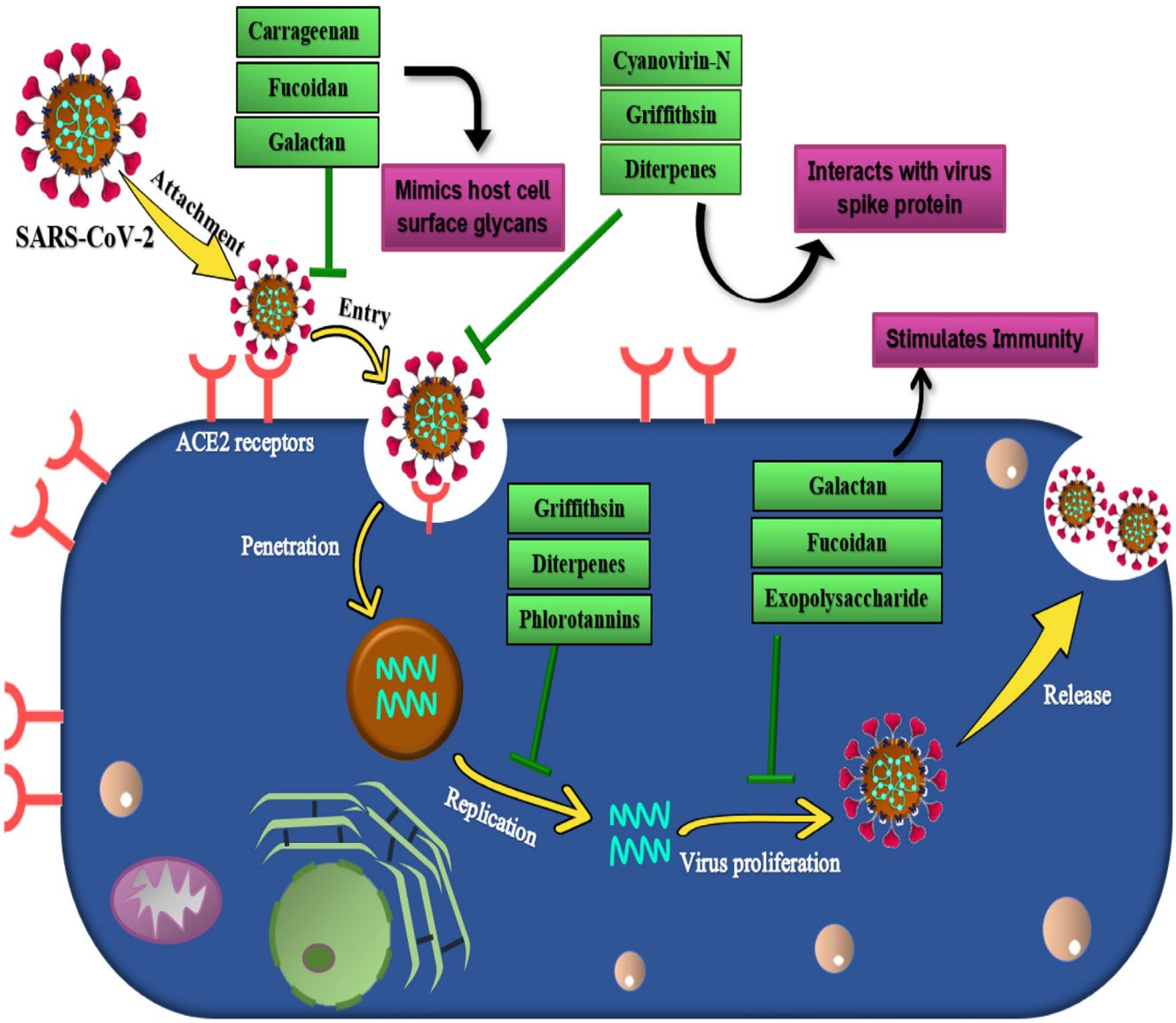

FIGURE 3 Schematic diagram representing algae as a rich trove of efficacious anti-SARS-CoV drug; potential candidates derived from algae such as sulfated polysaccharides, lectins, terpenes, polyphenols and lipids can be tested for possession of high degree drug-likeness for prevention and treatment of 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 bartayesiana 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 non-specific 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 fucoidans, 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 antiherptic 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-Briseño 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 *Arthrospira 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 (J. 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 (Kanekiyo 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 LJ04 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 resultantly 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 anti-herpes 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 virucidal 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 resultantly 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 glycoproteins 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 the 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 obliterated 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, sulfoquinovosyldiacylglycerols (SQDG) (Figure2) extracted via tetrazolium microassay from two cyanobacteria, *Phormidium tenue*, and *Lyngbya lagerhemii*, in obliterating the cytopathogenic effect of HIV onto the host cells (Gustafson et al., 1989). In similar studies, a category of diacylated sulfoglycolipids, sulfoquinovosylpranosyl 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 arboretum* 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 polyunsaturated 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 monoterpenes (C_{10}), sesquiterpenes (C_{15}), diterpenes (C_{20}) and so on (Gaysinski, Ortalo-Magne, Thomas, & Culioli, 2015). Diterpene derivative, Halitunal was extracted from marine algae *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; peyssonol A and peyssonol 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, stypodiol, sargaol, isoepitaondiol 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 cervicornis* 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 M^{pro}, 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 | Multivarious 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 *Symphyocladia 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 cytopathic 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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REFERENCES

Abd El Hamid, M. I., Abd El Fatah, W. M., El Morsi, A. A., Draz, M. S., Kallakuri, S., Bungau, S. G., … Hafez, E. E. (2019). Anti-HIV / HCV activity of cyanobacterial phycobiliproteins by a new standardized method using bacteriophage surrogates. *Revista de Chimie*, *70*, 3115–3122.

Abonyi, D. O., Adikwu, M. U., Esimone, C. O., & Ibezim, E. C. (2009). Plants as sources of antiviral agents. *African Journal of Biotechnology*, *8*, 3989–3994.

Abrantes, J. L., Barbosa, J., Cavalcanti, D., Pereira, R. C., Frederico Fontes, C. L., Teixeira, V. L., … Paixão, I. C. P. (2010). the effects of the diterpenes isolated from the Brazilian brown algae Dictyota pfaffii and Dictyota menstrualis against the herpes simplex type-1 replicative cycle. *Planta Medica*, *7*, 339–344.

Aguilar-Briseño, J. A., Cruz-Suarez, L. E., Sassi, J. F., Ricque-Marie, D., Zapata-Benavides, P., Mendoza-Gamboa, E., … Trejo-Avila, L. (2015). Sulphated polysaccharides from Ulva clathrata and Cladosiphon okamuranus seaweeds both inhibit viral attachment/entry and cell-cell fusion, in NDV infection. *Marine Drugs*, *13*, 697–712.

Ahmadi, A., Zorofchian Moghadamtousi, S., Abubakar, S., & Zandi, K. (2015). Antiviral potential of algae polysaccharides isolated from marine sources: A review. *BioMed Research International*, *2015*, 825203.

Ahn, M. J., Yoon, K. D., Min, S. Y., Lee, J. S., Kim, J. H., Kim, T. G., … Kim, J. (2004). Inhibition of HIV-1 reverse transcriptase and protease by phlorotannins from the brown alga Ecklonia cava. *Biological and Pharmaceutical Bulletin*, *27*, 544–547.

Albahri, O. S., Al-obaidi, J. R., Zaidan, A. A., Albahri, A. S., & Zaidan, B. B. (2020). Helping doctors hasten COVID-19 treatment: Towards a rescue framework for the transfusion of best convalescent plasma to the most critical patients based on biological requirements via ml and novel MCDM methods. *Computer Methods and Programs in Biomedicine*, *196*, 105617.

Alboofetileh, M., Rezaei, M., Tabarsa, M., Rittà, M., Donalisio, M., Mariatti, F., … Cravotto, G. (2019). Effect of different non-conventional extraction methods on the antibacterial and antiviral activity of fucoidans extracted from Nizamuddinia zanardinii. *International Journal of Biological Macromolecules*, *124*, 131–137.

Alexandre, K. B., Gray, E. S., Lambson, B. E., Moore, P. L., Choge, I. A., Mlisana, K., … Morris, L. (2010). Mannose-rich glycosylation patterns on HIV-1 subtype C gp120 and sensitivity to the lectins, Griffithsin, Cyanovirin-N and Scytovirin. *Virology*, *402*, 187–196.

Ayehunie, S., Belay, A., Baba, T. W., & Ruprecht, R. M. (1998). Inhibition of HIV-1 replication by an aqueous extract of Spirulina platensis (Arthrospira platensis). *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology*, *18*, 7–12.

Balzarini, J. (2007). Targeting the glycans of glycoproteins: A novel paradigm for antiviral therapy. *Nature Reviews Microbiology*, *5*, 583–597.

Barrientos, L. G., O'Keefe, B. R., Bray, M., Sanchez, A., Gronenborn, A. M., & Boyd, M. R. (2003). Cyanovirin-N binds to the viral surface glycoprotein, GP1,2 and inhibits infectivity of Ebola virus. *Antiviral Research*, *58*, 47–56.

Bokesch, H. R., O'Keefe, B. R., McKee, T. C., Pannell, L. K., Patterson, G. M. L., Gardella, R. S., … Boyd, M. R. (2003). A potent novel anti-HIV protein from the cultured cyanobacterium Scytonema varium. *Biochemistry*, *42*, 2578–2584.

Boulho, R., Marty, C., Freile-Pelegrín, Y., Robledo, D., Bourgougnon, N., & Bedoux, G. (2017). Antiherpetic (HSV-1) activity of carrageenans from the red seaweed *Solieria chordalis* (Rhodophyta, Gigartinales) extracted by microwave-assisted extraction (MAE). *Journal of Applied Phycology*, *29*, 2219–2228.

Boyd, M. R., Gustafson, K. R., McMahon, J. B., Shoemaker, R. H., O'Keefe, B. R., Mori, T., … Henderson, L. E. (1997). Discovery of cyanovirin-N, a novel human immunodeficiency virus- inactivating protein that binds viral surface envelope glycoprotein gp120: Potential applications to microbicide development. *Antimicrobial Agents and Chemotherapy*, *41*, 1521–1530.

Buck, C. B., Thompson, C. D., Roberts, J. N., Müller, M., Lowy, D. R., & Schiller, J. T. (2006). Carrageenan is a potent inhibitor of papillomavirus infection. *PLoS Pathogens*, *2*, e69.

Bukhari, K., Mulley, G., Gulyaeva, A. A., Zhao, L., Shu, G., Jiang, J., & Neuman, B. W. (2018). Description and initial characterization of metatranscriptomic nidovirus-like genomes from the proposed new family Abyssoviridae, and from a sister group to the *Coronavirinae*, the proposed genus Alphaletovirus. *Virology*, *524*, 160–171.

Cameron, M. J., Bermejo-Martin, J. F., Danesh, A., Muller, M. P., & Kelvin, D. J. (2008). Human immunopathogenesis of severe acute respiratory syndrome (SARS). *Virus Research*, *133*, 13–19.

Cameron, M. J., Ran, L., Xu, L., Danesh, A., Bermejo-Martin, J. F., Cameron, C. M., … Kelvin, D. J. (2007). Interferon-mediated immunopathological events are associated with atypical innate and adaptive immune responses in patients with severe acute respiratory syndrome. *Journal of Virology*, *81*, 8692–8706.

Carlucci, M. J., Scolaro, L. A., & Damonte, E. B. (1999). Inhibitory action of natural carrageenans on herpes simplex virus infection of mouse astrocytes. *Chemotherapy*, *45*, 429–436.

Channappanavar, R., Fehr, A. R., Vijay, R., Mack, M., Zhao, J., Meyerholz, D. K., & Perlman, S. (2016). Dysregulated type I interferon and inflammatory monocyte-macrophage responses cause lethal pneumonia in SARS-CoV-infected mice. *Cell Host & Microbe*, *19*, 181–193.

Channappanavar, R., Fehr, A. R., Zheng, J., Wohlford-Lenane, C., Abrahante, J. E., Mack, M., … Perlman, S. (2019). IFN-I response timing relative to virus replication determines MERS coronavirus infection outcomes. *Journal of Clinical Investigation*, *129*, 3625–3639.

Channappanavar, R., & Perlman, S. (2017). Pathogenic human coronavirus infections: Causes and consequences of cytokine storm and immunopathology. *Seminars in Immunopathology*, *39*, 529–539.

Channappanavar, R., Zhao, J., & Perlman, S. (2014). T cell-mediated immune response to respiratory coronaviruses. *Immunologic Research*, *59*, 118–128.

Chattopadhyay, K., Mateu, C. G., Mandal, P., Pujol, C. A., Damonte, E. B., & Ray, B. (2007). Galactan sulfate of Grateloupia indica: Isolation, structural features and antiviral activity. *Phytochemistry*, *68*, 1428–1435.

Chen, L., Gui, C., Luo, X., Yang, Q., Günther, S., Scandella, E., … Jiang, H. (2005). Cinanserin is an inhibitor of the 3C-like proteinase of severe acute respiratory syndrome coronavirus and strongly reduces virus replication in vitro. *Journal of Virology*, *79*, 7095–7103.

Chen, Y., Liu, Q., & Guo, D. (2020). Emerging coronaviruses: Genome structure, replication, and pathogenesis. *Journal of Medical Virology*, *92*, 418–423.

Chen, Y. M. A., Liang, S. Y., Shih, Y. P., Chen, C. Y., Lee, Y. M., Chang, L., … Chu, D. C. (2006). Epidemiological and genetic correlates of severe acute respiratory syndrome coronavirus infection in the hospital with the highest nosocomial infection rate in Taiwan in 2003. *Journal of Clinical Microbiology*, *44*, 359–365.

Chi, Y., Zhang, M., Wang, X., Fu, X., Guan, H., & Wang, P. (2020). Ulvan lyase assisted structural characterization of ulvan from Ulva pertusa and its antiviral activity against vesicular stomatitis virus. *International Journal of Biological Macromolecules*, *157*, 75–82.

Chiu, Y. H., Chan, Y. L., Li, T. L., & Wu, C. J. (2012). Inhibition of Japanese encephalitis virus infection by the sulfated polysaccharide extracts from *Ulva lactuca*. *Marine Biotechnology*, *14*, 468–478.

Claudio, C. C. S., de SB, C., Caio, C. R. N., Amorim, L. C., de MC, R., Ratcliffe, N. A., … de Palmer Paixao Izabel, C. N. (2018). Antiviral effect of the seaweed Osmundaria obtusiloba against the Zika virus. *Journal of Medicinal Plants Research*, *12*, 387–395.

Coleman, C., Sisk, J., Halasz, G., Zhong, J., Beck, S. E., Matthews, K. L., … Frieman, M. B. (2017). CD8+ T cells and macrophages regulate pathogenesis in a mouse model of Middle East respiratory syndrome. *Journal of Virology*, *91*, e01825–e01816.

De Clercq, E. (2019). New nucleoside analogues for the treatment of hemorrhagic fever virus infections. *Chemistry - An Asian Journal*, *14*, 3962–3968.

de Groot, R. J., Cowley, J. A., Enjuanes, L., Faaberg, K. S., Perlman, S., Rottier, P. J., … Gorbalenya, A. E. (2012). *Virus taxonomy. The 9th Report of the International Committe on Taxonomy of Viruses*. San Diego, CA: Academic Press.

De Souza, L. M., Sassaki, G. L., Romanos, M. T. V., & Barreto-Bergter, E. (2012). Structural characterization and anti-HSV-1 and HSV-2 activity of glycolipids from the marine algae Osmundaria obtusiloba isolated from Southeastern Brazilian coast. *Marine Drugs*, *10*, 918–931.

De Souza Pereira, H., Leão-Ferreira, L. R., Moussatché, N., Teixeira, V. L., Cavalcanti, D. N., da Costa, L. J., … Frugulhetti, I. C. (2005). Effects of diterpenes isolated from the Brazilian marine alga Dictyota menstrualis on HIV-1 reverse transcriptase. *Planta Medica*, *71*, 1019–1024.

de Wit, E., Feldmann, F., Cronin, J., Jordan, R., Okumura, A., Thomas, T., … Feldmann, H. (2020). Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection. *Proceedings of the National Academy of Sciences of the United States of America*, *117*, 6771–6776.

De Wit, E., Van Doremalen, N., Falzarano, D., & Munster, V. J. (2016). SARS and MERS: Recent insights into emerging coronaviruses. *Nature Reviews Microbiology*, *14*, 523–534.

El Baroty, G. S., El-Baz, F. K., Abd-Elmoein, A., El-Baky, H. H. A., Ali, M. M., & Ibrahim, A. E. (2011). Evaluation of glycolipids of some Egyptian marine algae as a source of bioactive substances. *Electronic Journal of Environmental, Agricultural and Food Chemistry*, *10*, 2114–2128.

Ellithey, M. S., Lall, N., Hussein, A. A., & Meyer, D. (2013). Cytotoxic, cytostatic and HIV-1 PR inhibitory activities of the soft coral litophyton arboreum. *Marine Drugs*, *11*, 4917–4936.

Fehr, A. R., & Perlman, S. (2015). Coronaviruses: An overview of their replication and pathogenesis. In H. Maier E. Bickerton & P. Britton, (Eds.), *Coronaviruses. Methods in molecular biology*, (Vol. 1282, pp. 1–23). New York, NY: Humana Press.

Filomena, M., Raposo, D. J., Maria, A., Bernardo, M., Manuel, R., & Costa, S. (2014). Influence of sulphate on the composition and antibacterial and antiviral properties of the exopolysaccharide from *Porphyridium cruentum*. *Life Sciences*, *101*, 56–63.

Garrison, A. R., Giomarelli, B. G., Lear-Rooney, C. M., Saucedo, C. J., Yellayi, S., Krumpe, L. R. H., … O'Keefe, B. R. (2014). The cyanobacterial lectin scytovirin displays potent in vitro and in vivo activity against Zaire Ebola virus. *Antiviral Research*, *112*, 1–7.

Gaysinski, M., Ortalo-Magne, A., Thomas, O. P., & Culioli, G. (2015). Extraction, purification, and NMR analysis of terpenes from brown algae. In D. B. Stengel & S. Connan, (Eds.), *Natural products from marine algae:Methods and protocols* (Vol. 1308, pp. 207–223). New York, NY: Humana Press.

Gentile, D., Patamia, V., Scala, A., Sciortino, M. T., Piperno, A., & Rescifina, A. (2020). Putative inhibitors of SARS-CoV-2 main protease from a library of marine natural products: A virtual screening and molecular modeling study. *Marine Drugs*, *18*, 225.

Gerber, P., Dutcher, J., Admas, E., & Sherman, J. (1958). Protective effect of seaweed extracts for chicken embryos infected with influenza B or mumps virus. *Proceedings of the Society for Experimental Biology and Medicine*, *6*, 590–593.

Ghosh, A., & Kiran, B. (2017). Carbon concentration in algae: Reducing $CO_2$from exhaust gas. *Trends in Biotechnology*, *35*, 806–808.

Graf, C., Bernkop-Schnürch, A., Egyed, A., Koller, C., Prieschl-Grassauer, E., & Morokutti-Kurz, M. (2018). Development of a nasal spray containing xylometazoline hydrochloride and iota-carrageenan for the symptomatic relief of nasal congestion caused by rhinitis and sinusitis. *International Journal of General Medicine*, *11*, 275–283.

Graham, R. L., Donaldson, E. F., & Baric, R. S. (2013). A decade after SARS: Strategies for controlling emerging coronaviruses. *Nature Reviews Microbiology*, *11*, 836–848.

Grassauer, A., & Prieschl-Grassauer, E., Marinomed Biotech, A. G. (2019). Antiviral Composition comprising a sulfated Polysaccharide. *U.S. Patent No*. 10,342,820. Washington, DC: U.S. Patent and Trademark Office.

Gustafson, K. R., Cardellina, J. H., Fuller, R. W., Weislow, O. S., Kiser, R. F., Snader, K. M., … Boyd, M. R. (1989). AIDS-antiviral sulfolipids from cyanobacteria (blue-green algae). *Journal of the National Cancer Institute*, *81*, 1254–1258.

Hardouin, K., Bedoux, G., Burlot, A. S., Donnay-Moreno, C., Bergé, J. P., Nyvall-Collén, P., & Bourgougnon, N. (2016). Enzyme-assisted extraction (EAE) for the production of antiviral and antioxidant extracts from the green seaweed Ulva armoricana (Ulvales, Ulvophyceae). *Algal Research*, *16*, 233–239.

Hayashi, K., Hayashi, T., & Kojima, I. (1996). A natural sulfated polysaccharide, calcium spirulan, isolated from Spirulina platensis: in vitro and ex vivo evaluation of anti-herpes simplex virus and anti-human immunodeficiency virus activities. *AIDS Research and Human Retroviruses*, *12*, 1463–1471.

Hayashi, K., Nakano, T., Hashimoto, M., Kanekiyo, K., & Hayashi, T. (2008). Defensive effects of a fucoidan from brown alga Undaria pinnatifida against herpes simplex virus infection. *International Immunopharmacology*, *8*, 109–116.

Hayashi, T., Hayashi, K., Maeda, M., & Kojima, I. (1996). Calcium spirulan, an inhibitor of enveloped virus replication, from a blue-green alga Spirulina platensis. *Journal of Natural Products*, *59*, 83–87.

Helle, F., Wychowski, C., Vu-Dac, N., Gustafson, K. R., Voisset, C., & Dubuisson, J. (2006). Cyanovirin-N inhibits hepatitis C virus entry by binding to envelope protein glycans. *Journal of Biological Chemistry*, *281*, 25177–25183.

Holshue, M. L., DeBolt, C., Lindquist, S., Lofy, K. H., Wiesman, J., Bruce, H., … Washington State 2019-nCoV Case Investigation Team. (2020). First case of 2019 novel coronavirus in the United States. *New England Journal of Medicine*, *382*, 929–936.

Hoshino, T., Hayashi, T., Hayashi, K., Hamada, J., Lee, J. B., & Sankawa, U. (1998). An antivirally active sulfated polysaccharide from Sargassum horneri (TURNER) C. AGARDH. *Biological and Pharmaceutical Bulletin*, *21*, 730–734.

Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., … Cao, B. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet*, *395*, 497–506.

Irwin, K. K., Renzette, N., Kowalik, T. F., & Jensen, J. D. (2016). Antiviral drug resistance as an adaptive process. *Virus Evolution*, *2*, vew014.

Ivanova, V., Rouseva, R., Kolarova, M., Serkedjieva, J., Rachev, R., & Manolova, N. (1994). Isolation of a polysaccharide with antiviral effect from *Ulva lactuca*. *Preparative Biochemistry*, *24*, 83–97.

Jiang, S., Cui, Q., Ni, B., & Chen, Y. (2020). Databases for facilitating mechanistic investigations of traditional Chinese medicines against COVID-19. *Pharmacological Research*, *159*, 104989.

Jiao, G., Yu, G., Wang, W., Zhao, X., Zhang, J., & Ewart, S. H. (2012). Properties of polysaccharides in several seaweeds from Atlantic Canada and their potential anti-influenza viral activities. *Journal of Ocean University of China*, *11*, 205–212.

Jo, S., Kim, S., Shin, D. H., & Kim, M. S. (2020). Inhibition of SARS-CoV 3CL protease by flavonoids. *Journal of Enzyme Inhibition and Medicinal Chemistry*, *35*, 145–151.

Joung, H. Y., Son, E., Pyo, S., & Hong, K. L. (2005). Novel sulfated polysaccharide derived from red-tide microalga Gyrodinium impudicum strain KG03 with immunostimulating activity in vivo. *Marine Biotechnology*, *7*, 331–338.

Kanekiyo, K., Hayashi, K., Takenaka, H., Lee, J. B., & Hayashi, T. (2007). Anti-herpes simplex virus target of an acidic polysaccharide, nostoflan,

from the edible blue-green alga Nostoc flagelliforme. *Biological and Pharmaceutical Bulletin*, *30*, 1573–1575.

Kanekiyo, K., Lee, J. B., Hayashi, K., Takenaka, H., Hayakawa, Y., Endo, S., & Hayashi, T. (2005). Isolation of an antiviral polysaccharide, nostoflan, from a terrestrial cyanobacterium, Nostoc flagelliforme. *Journal of Natural Products*, *68*, 1037–1041.

Karadeniz, F., Kang, K. H., Park, J. W., Park, S. J., & Kim, S. K. (2014). Anti-HIV-1 activity of phlorotannin derivative 8,4‴-dieckol from Korean brown alga *Ecklonia cava*. *Bioscience, Biotechnology, and Biochemistry*, *78*, 1151–1158.

Keicho, N., Itoyama, S., Kashiwase, K., Phi, N. C., Long, H. T., Ha, L. D., … Quy, T. (2009). Association of human leukocyte antigen class II alleles with severe acute respiratory syndrome in the Vietnamese population. *Human Immunology*, *70*, 527–531.

Kelso, A., & Hurt, A. C. (2012). Drug-resistant influenza viruses: Why fitness matters. *Nature Medicine*, *18*(10), 1470–1471.

Khan, M. T., Ali, A., Wang, Q., Irfan, M., Khan, A., Zeb, M. T., … Weib, D.-Q. (2020). Marine natural compounds as potents inhibitors against the main protease of SARS-CoV-2—A molecular dynamic study. *Journal of Biomolecular Structure and Dynamics*, *1*, 1–11.

Kitazato, K., Wang, Y., & Kobayashi, N. (2007). Viral infectious disease and natural products with antiviral activity. *Drug Discoveries & Therapeutics*, *1*, 1–9.

Knoops, K., Kikkert, M., Van Den Worm, S. H. E., Zevenhoven-Dobbe, J. C., van der Meer, Y., Koster, A. J., … Snijder, E. J. (2008). SARS-coronavirus replication is supported by a reticulovesicular network of modified endoplasmic reticulum. *PLoS Biology*, *6*, 1957–1974.

Koehn, F. E., Sarath, G. P., Neil, D. N., & Cross, S. S. (1991). Halitunal, an unusual diterpene aldehyde from the marine alga *Halimeda tuna*. *Tetrahedron Letters*, *32*, 169–172.

Krylova, N. V., Ermakova, S. P., Lavrov, V. F., Leneva, I. A., Kompanets, G. G., Iunikhina, O. V., … Zaporozhets, T. S. (2020). The comparative analysis of antiviral activity of native and modified fucoidans from brown algae *Fucus evanescens* in vitro and in vivo. *Marine Drugs*, *18*, 224.

Kuba, K., Imai, Y., Ohto-Nakanishi, T., & Penninger, J. M. (2010). Trilogy of ACE2: A peptidase in the renin-angiotensin system, a SARS receptor, and a partner for amino acid transporters. *Pharmacology and Therapeutics*, *128*, 119–128.

Kuri, T., & Weber, F. (2010). Interferon interplay helps tissue cells to cope with SARS-coronavirus infection. *Virulence*, *1*, 273–275.

Kuznetsova, T. A., Smolina, T. P., Makarenkova, I. D., Ivanushko, L. A., Persiyanova, E. V., Ermakova, S. P., … Kryzhanovsky, S. P. (2020). Immunoadjuvant activity of fucoidans from the brown alga *Fucus evanescens*. *Marine Drugs*, *18*, 1–15.

Lahaye, M., & Robic, A. (2007). Structure and function properties of Ulvan, a polysaccharide from green seaweeds. *Biomacromolecules*, *8*, 1765–1774.

Lakshmi, S. A., Shafreen, R. M. B., Priya, A., & Shunmugiah, K. P. (2020). Ethnomedicines of Indian origin for combating COVID-19 infection by hampering the viral replication: Using structure-based drug discovery approach. *Journal of Biomolecular Structure & Dynamics*, *23*, 1–16.

Laroy, W., Contreras, R., & Callewaert, N. (2006). Glycome mapping on DNA sequencing equipment. *Nature Protocols*, *1*, 397–405.

Lau, Y. L., Peiris, J. S. M., & Law, H. K. W. (2012). Role of dendritic cells in SARS coronavirus infection. *Hong Kong Medical Journal*, *18*, S28–S30.

Lee, J., Ohta, Y., Hayashi, K., & Hayashi, T. (2010). Immunostimulating effects of a sulfated galactan from *Codium fragile*. *Carbohydrate Research*, *345*, 1452–1454.

Lee, J. B., Hayashi, K., Hirata, M., Kuroda, E., Suzuki, E., Kubo, Y., & Hayashi, T. (2006). Antiviral sulfated polysaccharide from *Navicula directa*, a diatom collected from deep-sea water in Toyama Bay. *Biological and Pharmaceutical Bulletin*, *29*, 2135–2139.

Lee, S., Stokes, K. L., Currier, M. G., Sakamoto, K., Lukacs, N. W., Celis, E., & Moore, M. L. (2012). Vaccine-elicited $CD8^+$ T cells protect against respiratory syncytial virus strain A2-Line19F-induced pathogenesis in BALB/c mice. *Journal of Virology*, *86*, 13016–13024.

Li, G., Chen, X., & Xu, A. (2003). Profile of specific antibodies to the SARS-associated coronavirus. *New England Journal of Medicine*, *349*, 508–509.

Li, W., Moore, M. J., Vasilieva, N., Sui, J., Wong, S. K., Berne, M. A., … Farzan, M. (2003). Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature*, *426*, 450–454.

Li, X., Geng, M., Peng, Y., Meng, L., & Lu, S. (2020). Molecular immune pathogenesis and diagnosis of COVID-19. *Journal of Pharmaceutical Analysis*, *10*, 102–108.

Lim, M. A., & Pranata, R. (2020). The insidious threat of jamu and unregulated traditional medicines in the COVID-19 era. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*, *14*, 895–896.

Lo, M. K., Feldmann, F., Gary, J. M., Jordan, R., Bannister, R., Cronin, J., … de Wit, E. (2019). Remedesivir (GS-5734) protects African green monkeys from Nipah virus challenge. *Science Translational Medicine*, *11*, 1–12.

Lo, M. K., Jordan, R., Arvey, A., Sudhamsu, J., Shrivastava-Ranjan, P., Hotard, A. L., … Spiro, C. F. (2017). GS-5734 and its parent nucleoside analog inhibit Filo-, Pneumo-, and Paramyxoviruses. *Scientific Reports*, *7*, 1–7.

Lo, M. K., Spengler, J. R., Krumpe, L. R. H., Welch, S. R., Chattopadhyay, A., Harmon, J. R., … Spiropoulou, C. F. (2020). Griffithsin inhibits nipah virus entry and fusion and can protect Syriangolden hamsters from lethal nipah virus challenge. *The Journal of Infectious Diseases*, *221*(Supplement_4), S480–S492.

Loya, S., Bakhanashvili, M., Kashman, Y., & Hizi, A. (1995). Peyssonols A and B, two novel inhibitors of the reverse transcriptases of human immuodeficiency virus types 1 and 2. *Archives of Biochemistry and Biophysics*, *316*, 789–796.

Loya, S., Reshef, V., Mizrachi, E., Silberstein, C., Rachamim, Y., Carmeli, S., & Hizi, A. (1998). The inhibition of the reverse transcriptase of HIV-1 by the natural sulfoglycolipids from cyanobacteria: Contribution of different moieties to their high potency. *Journal of Natural Products*, *61*, 891–895.

Lu, R., Zhao, X., Li, J., Niu, P., Yang, B., Wu, H., … Tan, W. (2020). Genomic characterisation and epidemiology of 2019 novel coronavirus: Implications for virus origins and receptor binding. *The Lancet*, *395*, 565–574.

Mandal, P., Mateu, C. G., Chattopadhyay, K., Pujol, C. A., Damonte, E. B., & Ray, B. (2007). Structural features and antiviral activity of sulphated fucans from the brown seaweed Cystoseira indica. *Antiviral Chemistry and Chemotherapy*, *18*, 153–162.

Masters, P. S. (2006). The molecular biology of coronaviruses. *Advances in Virus Research*, *65*, 193–292.

Matsuhiro, B., Conte, A. F., Damonte, E. B., Kolender, A. A., Matulewicz, C., Mej, E. G., & Zu, E. A. (2005). Structural analysis and antiviral activity of a sulfated galactan from the red seaweed Schizymenia binderi (Gigartinales, Rhodophyta). *Carbohydrate Research*, *340*, 2392–2402.

McCandless, E. L., & Craigie, J. S. (1979). Sulfated polysaccharides in red and brown algae. *Annual Review of Plant Physiology*, *30*, 41–53.

Mehta, P., McAuley, D. F., Brown, M., Sanchez, E., Tattersall, R. S., & Manson, J. J. (2020). COVID-19: Consider cytokine storm syndromes and immunosuppression. *The Lancet*, *395*, 1033–1034.

Menachery, V. D., Schäfer, A., Burnum-Johnson, K. E., Mitchell, H. D., Eisfeld, A. J., Walters, K. B., … Baric, R. S. (2018). MERS-CoV and H5N1 influenza virus antagonize antigen presentation by altering the epigenetic landscape. *Proceedings of the National Academy of Sciences of the United States of America*, *115*, E1012–E1021.

Michalak, I., & Chojnacka, K. (2015). Algae as production systems of bioactive compounds. *Engineering in Life Sciences*, *15*, 160–176.

Millet, J. K., Séron, K., Labitt, R. N., Danneels, A., Palmer, K. E., Whittaker, G. R., … Belouzard, S. (2016). Middle East respiratory

syndrome coronavirus infection is inhibited by griffithsin. *Antiviral Research*, *133*, 1–8.

Mohamed, S. F., & Agili, F. A. (2013). Antiviral sulphated polysaccharide from brown algae *Padina pavonia* characterization and structure elucidation. *International Journal of ChemTech Research*, *5*, 1469–1476.

Morán-Santibañez, K., Peña-Hernández, M. A., Cruz-Suárez, L. E., Ricque-Marie, D., Skouta, R., Vasquez, A. H., … Trejo-Avila, L. M. (2018). Virucidal and synergistic activity of polyphenol-rich extracts of seaweeds against measles virus. *Viruses*, *10*, 1–14.

Moulaei, T., Alexandre, K. B., Shenoy, S. R., Meyerson, J. R., Krumpe, L. R., Constantine, B., … O'Keefe, B. R. (2015). Griffithsin tandemers: Flexible and potent lectin inhibitors of the human immunodeficiency virus. *Retrovirology*, *12*, 1–14.

Moulaei, T., Shenoy, S. R., Giomarelli, B., Thomas, C., McMahon, J. B., Dauter, Z., … Wlodawer, A. (2010). Monomerization of viral entry inhibitor griffithsin elucidates the relationship between multivalent binding to carbohydrates and anti-HIV activity. *Structure*, *18*, 1104–1115.

Murugan, N. A., Pandian, C. J., & Jeyakanthan, J. (2020). Computational investigation on Andrographis paniculata phytochemicals to evaluate their potency against SARS-CoV-2 in comparison to known antiviral compounds in drug trials. *Journal of Biomolecular Structure and Dynamics*, 1–12.

Nagle, V., Gaikwad, M., Pawar, Y., & Dasgupta, S. (2020). Marine red alga *Porphyridium* sp. as a source of sulfated polysaccharides (SPs) for combating against COVID-19. *Preprints 2020*, 2020040168.

Nahas, R., Abatis, D., Anagnostopoulou, M., Kefalas, P., Vagias, C., & Roussis, V. (2007). Radical-scavenging activity of Aegean Sea marine algae. *Food Chemistry*, *102*, 577–581.

Nakashima, H., Kido, Y., Kobayashi, N., Motoki, Y., Neushul, M., & Yamamoto, N. (1987). Purification and characterization of an avian myeloblastosis and human immunodeficiency virus reverse transcriptase inhibitor, sulfated polysaccharides extracted from sea algae. *Antimicrobial Agents and Chemotherapy*, *31*, 1524–1528.

Niemeyer, D., Zillinger, T., Muth, D., Zielecki, F., Horvath, G., Suliman, T., … Muller, M. A. (2013). Middle East respiratory syndrome coronavirus accessory protein 4a is a type I interferon antagonist. *Journal of Virology*, *87*, 12489–12495.

O'Keefe, B. R., Giomarelli, B., Barnard, D. L., Shenoy, S. R., Chan, P. K. S., McMahon, J. B., … McCray, P. B., Jr. (2010). Broad-Spectrum in vitro activity and in vivo efficacy of the antiviral protein Griffithsin against emerging viruses of the family Coronaviridae. *Journal of Virology*, *84*, 2511–2521.

Ohta, Y., Lee, J. B., Hayashi, K., & Hayashi, T. (2009). Isolation of sulfated galactan from Codium fragile and its antiviral effect. *Biological and Pharmaceutical Bulletin*, *32*, 892–898.

O'Keefe, B. R., Smee, D. F., Turpin, J. A., Saucedo, C. J., Gustafson, K. R., Mori, T., … Boyd, M. R. (2003). Potent anti-influenza activity of cyanovirin-N and interactions with viral hemagglutinin. *Antimicrobial Agents and Chemotherapy*, *47*, 2518–2525.

Park, H. J., Kurokawa, M., Shiraki, K., Nakamura, N., Choi, J. S., & Hattori, M. (2005). Antiviral activity of the marine alga Symphyocladia latiuscula against herpes simplex virus (HSV-1) in vitro and its therapeutic efficacy against HSV-1 infection in mice. *Biological and Pharmaceutical Bulletin*, *28*, 2258–2262.

Park, J. Y., Jeong, H. J., Kim, J. H., Kim, Y. M., Park, S. J., Kim, D., … Ryu, Y. B. (2012). Diarylheptanoids from *Alnus japonica* inhibit papain-like protease of severe acute respiratory syndrome coronavirus. *Biological and Pharmaceutical Bulletin*, *35*, 2036–2042.

Park, J. Y., Kim, J. H., Kwon, J. M., Kwon, H. J., Jeong, H. J., Kim, Y. M., … Ryu, Y. B. (2013). Dieckol, a SARS-CoV 3CL^{pro} inhibitor, isolated from the edible brown algae *Ecklonia cava*. *Bioorganic and Medicinal Chemistry*, *21*, 3730–3737.

Paula, P. C., Talarico, L. B., Noseda, M. D., Silvia, S. M., Damonte, E. B., & Duarte, M. E. R. (2006). Chemical structure and antiviral activity of carrageenans from *Meristiella gelidium* against herpes simplex and dengue virus. *Carbohydrate Polymers*, *63*, 459–465.

Peiris, J. S. M., Guan, Y., & Yuen, K. Y. (2004). Severe acute respiratory syndrome. *Nature Medicine*, *10*, S88–S97.

Pereira, H. S., Leão-Ferreira, L. R., Moussatché, N., Teixeira, V. L., Cavalcanti, D. N., Costa, L. J., … Frugulhetti, I. C. P. P. (2004). Antiviral activity of diterpenes isolated from the Brazilian marine alga Dictyota menstrualis against human immunodeficiency virus type 1 (HIV-1). *Antiviral Research*, *64*, 69–76.

Perlman, S., & Netland, J. (2009). Coronaviruses post-SARS: Update on replication and pathogenesis. *Nature Reviews Microbiology*, *7*, 439–450.

Plouguerné, E., De Souza, L. M., Sassaki, G. L., Cavalcanti, J. F., Romanos, M. T. V., da Gama, B. A. P., … Barreto-Bergter, E. (2013). Antiviral sulfoquinovosyldiacylglycerols (SQDGs) from the Brazilian brown seaweed *Sargassum vulgare*. *Marine Drugs*, *11*, 4628–4640.

Ponce, N. M. A., Flores, M. L., Pujol, C. A., Becerra, M. B., Navarro, D. A., Córdoba, O., … Stortz, C. A. (2019). Fucoidans from the phaeophyta *Scytosiphon lomentaria*: Chemical analysis and antiviral activity of the galactofucan component. *Carbohydrate Research*, *478*, 18–24.

Pooja, S. (2014). Algae used as medicine and food-ashort review. *Journal of Applied Pharmaceutical Sciences and Research*, *6*, 33–35.

Preeprame, S., Hayashi, K., Lee, J. B., Sankawa, U., & Hayashi, T. (2001). A novel antivirally active fucan sulfate derived from an edible brown alga, Sargassum horneri. *Chemical and Pharmaceutical Bulletin*, *49*, 484–485.

Priya, R., & Sujatha, V. (2020). AYUSH for COVID-19: Science or superstition? *Indian Journal of Public Health*, *64(Supplement)*, S105–S107.

Pujol, C. A., Errea, M. I., Matulewicz, M. C., & Damonte, E. B. (1996). Antiherpetic activity of S1, an algal derived sulphated galactan. *Phytotherapy Research*, *10*, 410–413.

Qing, G.-c., Zhang, H., Bai, Y., & Luo, Y. (2020). Traditional Chinese and western medicines jointly beat COVID-19 pandemic. *Chinese Journal of Integrative Medicine*, *26*, 403–404.

Radonić, A., Thulke, S., Achenbach, J., Kurth, A., Vreemann, A., König, T., … Nitsche, A. (2010). Anionic polysaccharides from phototrophic microorganisms exhibit antiviral activities to vaccinia virus. *Journal of Antivirals andAntiretrovirals*, *2*, 51–55.

Rajkumar, R. P. (2020). Ayurveda and COVID-19: Where psychoneuroimmunology and the meaning response meet. *Brain, Behavior, and Immunity*, *87*, 8–9.

Rechter, S., König, T., Auerochs, S., Thulke, S., Walter, H., Dörnenburg, H., … Marschall, M. (2006). Antiviral activity of Arthrospira-derived spirulan-like substances. *Antiviral Research*, *72*, 197–206.

Richards, J. T., Kern, E. R., Glasgow, L. A., Overall, J. C., Deign, E. F., & Hatch, M. T. (1978). Antiviral activity of extracts from marine algae. *Antimicrobial Agents and Chemotherapy*, *14*, 24–30.

Sanniyasi, E., Venkatasubramanian, G., Anbalagan, M. M., Raj, P. P., & Gopal, R. K. (2019). In vitro anti-HIV-1 activity of the bioactive compound extracted and purified from two different marine macroalgae (seaweeds) (*Dictyota bartayesiana J.V.Lamouroux and Turbinaria decurrens Bory*). *Scientific Reports*, *9*, 1–12.

Sarkar, B., Ullah, A., Tuz, F., Afrin, M., & Araf, Y. (2020). Immunoinformatics-guided designing of epitope-based subunit vaccines against the SARS Coronavirus-2 (SARS-CoV-2). *Immunobiology*, *225*, 151955.

Serkedjieva, J. (2000). Antiherpes virus effect of the red marine alga *Polysiphonia denudata*. *Zeitschrift für Naturforschung C*, *55*, 830–835.

Sheahan, T. P., Sims, A. C., Leist, S. R., Schäfer, A., Won, J., Brown, A. J., … Baric, R. S. (2020). Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. *Nature Communications*, *11*, 222.

Silva, T. S., Salomon, P., Hamerski, L., Walter, J., Menezes, R. B., Siqueira, J. E., … Miranda, M. (2018). Inhibitory effect of microalgae

and cyanobacteria extracts on influenza virus replication and neuraminidase activity. *PeerJ*, *6*, e5716.

Simmons, G., Reeves, J. D., Rennekamp, A. J., Amberg, S. M., Piefer, A. J., & Bates, P. (2004). Characterization of severe acute respiratory syndrome-associated coronavirus (SARS-CoV) spike glycoprotein-mediated viral entry. *Proceedings of the National Academy of Sciences of the United States of America*, *101*, 4240–4245.

Snijder, E. J., van der Meer, Y., Zevenhoven-Dobbe, J., Onderwater, J. J. M., van der Meulen, J., Koerten, H. K., & Mommaas, A. M. (2006). Ultrastructure and origin of membrane vesicles associated with the severe acute respiratory syndrome coronavirus replication complex. *Journal of Virology*, *80*, 5927–5940.

Soares, A. R., Robaina, M. C. S., Mendes, G. S., Silva, T. S. L., Gestinari, L. M. S., Pamplona, O. S., … Romanos, M. T. V. (2012). Antiviral activity of extracts from Brazilian seaweeds against herpes simplex virus. *Brazilian Journal of Pharmacognosy*, *22*, 714–723.

Subhash, G. V., Kumar, G. R. K., Sapre, A., & Dasgupta, S. (2020). Possible prevention of COVID 19 by using linoleic acid (C18) rich algae oil. *AIJR Preprints*, *36*, 1–9.

Talarico, L. B., & Damonte, E. B. (2007). Interference in dengue virus adsorption and uncoating by carrageenans. *Virology*, *363*, 473–485.

Talarico, L. B., Duarte, M. E. R., Zibetti, R. G. M., Noseda, M. D., & Damonte, E. B. (2007). An algal-derived DL-galactan hybrid is an efficient preventing agent for in vitro dengue virus infection. *Planta Medica*, *73*, 1464–1468.

Tang, F., Chen, F., & Li, F. (2013). Preparation and potential in vivo anti-influenza virus activity of low molecular-weight κ-carrageenans and their derivatives. *Journal of Applied Polymer Science*, *127*, 2110–2115.

Tian, X., Li, C., Huang, A., Xia, S., Lu, S., Shi, Z., … Ying, T. (2020). Potent binding of 2019 novel coronavirus spike protein by a SARS coronavirus-specific human monoclonal antibody. *Emerging Microbes &Infections*, *9*, 382–385.

Tiwari, V., Shukla, S. Y., & Shukla, D. (2009). A sugar binding protein cyanovirin-N blocks herpes simplex virus type-1 entry and cell fusion. *Antiviral Research*, *84*, 67–75.

Tran, N. M., Dufresne, M., Helle, F., Hoffmann, T. W., François, C., Brochot, E., … Castelain, S. (2014). Alginate hydrogel protects encapsulated hepatic HuH-7 cells against hepatitis C virus and other viral infections. *PLoS ONE*, *9*, 16–17.

Ueno, M., Nogawa, M., Siddiqui, R., Watashi, K., Wakita, T., Kato, N., … Ariumi, Y. (2019). Acidic polysaccharides isolated from marine algae inhibit the early step of viral infection. *International Journal of Biological Macromolecules*, *124*, 282–290.

Uryu, T., Ikushima, N., Katsuraya, K., Shoji, T., Takahashi, N., Yoshida, T., … Yamamoto, N. (1992). Sulfated alkyl oligosaccharides with potent inhibitory effects on human immunodeficiency virus infection. *Biochemical Pharmacology*, *43*, 2385–2392.

Vallim, M. A., Barbosa, J. E., Cavalcanti, D. N., De-Paula, J. C., da Silva, V. A. G. G., Teixeira, V. L., & de Palmer Paixão, I. C. N. (2010). In vitro antiviral activity of diterpenes isolated from the Brazilian brown alga Canistrocarpus cervicornis. *Journal of Medicinal Plants Research*, *4*, 2379–2382.

Walls, A. C., Park, Y. J., Tortorici, M. A., Wall, A., McGuire, A. T., & Veesler, D. (2020). Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. *Cell*, *181*, 281–292.

Wang, H., Yang, P., Liu, K., Guo, F., Zhang, Y., Zhang, G., & Jiang, C. (2008). SARS coronavirus entry into host cells through a novel clathrin- and caveolae-independent endocytic pathway. *Cell Research*, *18*, 290–301.

Wang, H., Li, Y. L., Shen, W. Z., Rui, W., Ma, X. J., & Cen, Y. Z. (2007). Antiviral activity of a sulfoquinovosyldiacylglycerol (SQDG) compound isolated from the green alga *Caulerpa racemosa*. *Botanica Marina*, *50*, 185–190.

Wang, M., Cao, R., Zhang, L., Yang, X., Liu, J., Xu, M., … Xiao, G. (2020). Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Research*, *30*, 269–271.

Wang, S. F., Chen, K. H., Chen, M., Li, W. Y., Chen, Y. J., Tsao, C. H., … Chen, Y. M. A. (2011). Human-leukocyte antigen class i Cw 1502 and class II DR 0301 genotypes are associated with resistance to severe acute respiratory syndrome (SARS) infection. *Viral Immunology*, *24*, 421–426.

Wang, W., Wu, J., Zhang, X., Hao, C., Zhao, X., Jiao, G., … Yu, G. (2017). Inhibition of influenza A virus infection by fucoidan targeting viral neuraminidase and cellular EGFR pathway. *Scientific Reports*, *7*, 1–14.

Wieczorek, M., Abualrous, E. T., Sticht, J., Álvaro-Benito, M., Stolzenberg, S., Noé, F., & Freund, C. (2017). Major histocompatibility complex (MHC) class I and MHC class II proteins: Conformational plasticity in antigen presentation. *Frontiers in Immunology*, *8*, 1–16.

Williams, A. E., & Chambers, R. C. (2014). The mercurial nature of neutrophils: Still an enigma in ARDS? *American Journal of Physiology - Lung Cellular and Molecular Physiology*, *306*, L217–L230.

Wittine, K., Saftić, L., Peršurić, Ž., & Pavelić, S. K. (2019). Novel antiretroviral structures from marine organisms. *Molecules*, *24*, 3486.

Witvrouw, M., & De Clercq, E. (1997). Sulfated polysaccharides extracted from sea algae as potential antiviral drugs. *General Pharmacology*, *29*, 497–511.

Witvrouw, M., Este, J. A., Mateu, M. Q., Reymen, D., Andrei, G., Snoeck, R., … de Clercq, E. (1994). Activity of a sulfated polysaccharide extracted from the red seaweed *Aghardhiella tenera* against human immunodeficiency virus and other enveloped viruses. *Antiviral Chemistry and Chemotherapy*, *5*, 297–303.

Woodrum, B. W., Maxwell, J. D., Bolia, A., Banu Ozkan, S., & Ghirlanda, G. (2013). The antiviral lectin cyanovirin-N: Probing multivalency and glycan recognition through experimental and computational approaches. *Biochemical Society Transactions*, *41*, 1170–1176.

Xiong, C., O'Keefe, B. R., Byrd, R. A., & McMahon, J. B. (2006). Potent anti-HIV activity of scytovirin domain 1 peptide. *Peptides*, *27*, 1668–1675.

Xu, Z., Shi, L., Wang, Y., Zhang, J., Huang, L., Zhang, C., … Wang, F.-S. (2020). Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *The Lancet Respiratory Medicine*, *8*, 420–422.

Yakoot, M., & Salem, A. (2012). Spirulina platensis versus silymarin in the treatment of chronic hepatitis C virus infection. A pilot randomized, comparative clinical trial. *BMC Gastroenterology*, *12*, 32.

Yang, Y., Zhang, L., Geng, H., Deng, Y., Huang, B., Guo, Y., … Tan, W. (2013). The structural and accessory proteins M, ORF 4a, ORF 4b, and ORF 5 of Middle East respiratory syndrome coronavirus (MERS-CoV) are potent interferon antagonists. *Protein & Cell*, *4*, 951–961.

Yao, X., Ye, F., Zhang, M., Cui, C., Huang, B., Niu, P., … Liu, D. (2020). In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV2-2). *Clinical Infectious Diseases*, *71*, 732–739.

Yim, J. H., Kim, S. J., Ahn, S. H., Lee, C. K., Rhie, K. T., & Lee, H. K. (2004). Antiviral effects of sulfated exopolysaccharide from the marine microalga Gyrodinium impudicum strain KG03. *Marine Biotechnology*, *6*, 17–25.

Yong, C. Y., Ong, H. K., Yeap, S. K., Ho, K. L., & Tan, W. S. (2019). Recent advances in the vaccine development against Middle East respiratory syndrome-coronavirus. *Frontiers in Microbiology*, *10*, 1–18.

Yu, H., Jiang, L. F., Fang, D. Y., Yan, H. J., Zhou, J. J., Zhou, J. M., … Long, B. G. (2007). Selection of SARS-coronavirus-specific B cell epitopes by phage peptide library screening and evaluation of the immunological effect of epitope-based peptides on mice. *Virology*, *359*, 264–274.

Yue, Y., Li, Z., Li, P., Song, N., Li, B., Lin, W., & Liu, S. (2017). Antiviral activity of a polysaccharide from Laminaria japonica against enterovirus 71. *Biomedicine and Pharmacotherapy*, *96*, 256–262.

Zandi, K., Salimi, M., & Sartavi, K. (2007). *In vitro* antiviral activity of the red marine alga from Persian gulf, *Gracilaria salicornia* against herpes simplex virus type 2. *Journal of Biological Sciences*, *7*, 1274–1277.

Zhang, L., & Liu, Y. (2020). Potential interventions for novel coronavirus in China: A systematic review. *Journal of Medical Virology*, *92*, 479–490.

Zheng, H. Y., Zhang, M., Yang, C. X., Zhang, N., Wang, X. C., Yang, X. P., … Zheng, Y. T. (2020). Elevated exhaustion levels and reduced functional diversity of T cells in peripheral blood may predict severe progression in COVID-19 patients. *Cellular and Molecular Immunology*, *17*, 541–543.

Zheng, W., Chen, C., Cheng, Q., Wang, Y., & Chu, C. (2006). Oral administration of exopolysaccharide from Aphanothece halophytica (Chroococcales) significantly inhibits influenza virus (H1N1)-induced pneumonia in mice. *International Immunopharmacology*, *6*, 1093–1099.

Zhu, W., Ooi, V. E. C., Chan, P. K. S., & Ang, P. O. (2003). Isolation and characterization of a sulfated polysaccharide from the brown alga Sargassum patens and determination of its anti-herpes activity. *Biochemistry and Cell Biology*, *81*, 25–33.

Ziółkowska, N. E., O'Keefe, B. R., Mori, T., Zhu, C., Giomarelli, B., Vojdani, F., … Wlodawer, A. (2006). Domain-swapped structure of the potent antiviral protein griffithsin and its mode of carbohydrate binding. *Structure*, *14*, 1127–1135.

Ziółkowska, N. E., Shenoy, S. R., O'Keefe, B. R., McMahon, J. B., Palmer, K. E., Dwek, R. A., … Wlodawer, A. (2013). Crystallographic, thermodynamic, and molecular modeling studies of the mode of binding of oligosacchairdes to the potent antiviral protein griffithsin. *Proteins: Structure, Function, and Bioinformatics*, *670*, 661–670.

Zumla, A., Chan, J. F. W., Azhar, E. I., Hui, D. S. C., & Yuen, K. Y. (2016). Coronaviruses-drug discovery and therapeutic options. *Nature Reviews Drug Discovery*, *15*, 327–347.

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