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Review

Algae Polysaccharides (Carrageenan and Alginate)—A Treasure-Trove of Antiviral Compounds: An In Silico Approach to Identify Potential Candidates for Inhibition of S1-RBD Spike Protein of SARS-CoV2

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Abstract: For the last three years, the world has faced the unexpected spread of the pandemic of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The high mortality rate and ever-changing shape of the virus are the challenging factors in the effective management of SARS-CoV-2. However, in last three years, research communities have made significant progress in developing vaccines and controlling the spread of the pandemic to a certain extent. These vaccines contain the attenuated pathogens, which after application did not kill the virus but protected the human by enhancing the immune system response during pandemic exposure. However, the negative side effects and the high cost of the synthetic vaccines are always of concern for researchers, consumers, and the government. Therefore, as an alternative to synthetic drugs, natural medicines or natural plant products have piqued researchers' interest. Algae are considered as a treasure house of bioactive compounds such as carotenoids, vitamins, polysaccharides, proteins, etc. These bioactive compounds have been well documented for the treatments of various human ailments such as cancer and cardiovascular diseases. Furthermore, sulfated polysaccharides such as alginate and carrageenan have been reported as having antiviral and immunomodulating properties. Therefore, this review addresses algal polysaccharides, especially alginate and carrageenan, and their application in the treatment of COVID-19. In addition, in silico approaches are discussed for the inhibition of the S1-RBD (receptor-binding domain) of SARS-CoV-2, which attaches to the host receptor ACE2 (angiotensin-converting enzyme 2), and the interaction with the network of relative proteins is also explored, which will help in drug discovery and drug design.

Keywords: algal polysaccharides; alginic acid; carrageenen; COVID-19; molecular docking; in silico studies

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1. Introduction

For the last three years, the world has faced an unexpected pandemic of COVID-19, caused by the novel coronavirus (SARS-CoV-2). The outbreak of this virus affects the lives and survivability of human beings. Although, in the last three years, significant progress has been made by the scientific community in developing vaccines that control the virus spread to a certain extent [1,2]. Although the administration of vaccines enhances the immune response of the body to cope against the infection caused by the ever-changing shape of the mutant RNA virus, the identification of different mutant strains always poses a threat, which necessitates the search for an alternative that can enhance the immune response of the body [2]. In this regard, new experiments have been executed regularly to meet the requirement of a novel, efficient, economic, and nontoxic antiviral candidate.

In last two decades, significant progress has been made with algal metabolites in developing different types of drugs to cure human viral or chronic diseases [3–5]. Algae are a diverse group of photosynthetic organisms found in both fresh and marine aquatic systems. The ubiquitous nature and survivability of algae under different harsh conditions, such as hot, cold, and intense light conditions, confirms the presence of some specific metabolites in their cells. These metabolites are a rich source of high-value foods and important pharmaceutical compounds [6]. The beneficial secondary metabolites, such as phycocyanin, polysaccharides, lutein, vitamin B12, vitamin E, vitamin K, polyphenols, polyunsaturated fatty acids, and polysaccharides, are well documented in a previous study [7]. In addition, antimicrobial, anti-inflammatory, anticancer, immunosuppressive, and other pharmacologically significant properties of these secondary metabolites have been investigated [8–10].

Algal groups are a rich source of secondary metabolites, which have been synthesized during the different phases of growth stages via various metabolic processes [11,12]. However, the cultivation practices and growth conditions are limiting factors during metabolite production [13–15]. Although like other metabolites, algal metabolites also constitute different functional groups, including polyphenols, carotenoids, vitamins, lipids, and polysaccharides, which possess a diverse range of medicinal properties, as documented in the previous study [16,17]. For example, calcium spirulan (Ca-SP), a derivative of *Spirulina platensis*, is reported to inhibit the replication and penetration into the host cells of different viruses such as herpes simplex virus (HSV) type 1, measles, mumps, influenza A virus, and human immunodeficiency virus HIV-1 [18]. Sharaf et al. [19] evaluated the anti-herpetic activity of *Arthrospira fusiformi* and found the application of *A. fusiformis* extract inhibits the multiplication of the herpes virus before and after host infection. Similarly, Silva et al. [20] reported cyanobacterial extract significantly inhibits replication of the influenza virus. In another study, Shih et al. [21] evaluated the potential of allophycocyanin isolated from *Spirulina platensis* against enterovirus and found it had the potential to delay RNA synthesis in the infected cell. Cyanovirin-N, proteins derived from *Nostoc ellipsosporum*, showed broad-spectrum activity against HIV [22], hepatitis C [23], and influenza [24]. Lectins, a protein derived from algae, are also considered the largest antiviral chemical class, which generally target glycoproteins of the virus envelope and help to control viruses' entry into the host cells [25,26]. The most effective antiviral drugs include sulfated polysaccharides, phenolic chemicals, and organic acids [27]. The structural composition of COVID-19 possesses similar structural proteins, and therefore preventive measures can be followed by previous research conducted on algal-derived metabolites [28,29].

In last two decades, several virus outbreaks such as swine influenza, avian influenza, and Ebola have emerged [30,31] and the bioactive chemicals generated from algae have been used as a promising antiviral candidate. *Nostoc* is the genus within the Nostocales order that produces the most metabolites with antibacterial and antiviral activity. Furthermore, *Nostoc* sp. can withstand a wide range of environmental circumstances, allowing them to thrive in various environments [32,33]. Different marine microalgal species extracts advocated to have thousands of novel bioactive compounds with therapeutic potential could be exploited to produce therapeutic agents against some common human viral

diseases [34,35]. Notwithstanding the Brazilian sea, algal crude extracts have been more effective against HSV-1 than HSV-2 [36]. Furthermore, it is warranted to mention that an aqueous extract of *Laurencia obtuse* showed significant inhibitory potential against influenza virus replication during an in vitro experiment [37]. Furthermore, Zaid et al. [38] demonstrated inhibition in the multiplication of the Coxsackie B4 virus, hepatitis A virus, HSV-1, and HSV-2 by employing seaweed extracts of *Ulva Lactuca* and *Cystoseira myrica* in an in vitro study. Thus, the use of different algal metabolites and products offers a way to combat newly emerged viral diseases [39,40].

In the recent past, in silico approaches have been widely used to screen drugs against various diseases in limited time and with less cost [9]. Computational approaches offer several important tools in each step of drug exploration. Various bioinformatics tools are capable of aiding researchers in the recognition and investigation of new drug compounds. The important parameters of in silico methods include virtual screening, molecular docking studies, molecular dynamics simulations, and the determination of ADMET (absorption, distribution, metabolism, excretion, and toxicity) properties [10]. Hence, the current study based on bioinformatic approaches emphasizes the exploration of the potential antiviral activity of algal polysaccharides alginic acid and carrageenan against SARS-CoV-2 targeting the S-RBD protein.

2. Epidemiology and Life Cycle of SARS-CoV-2

Coronaviruses, single-stranded (SS) RNA viruses that cause SARS-CoV-2, generally infect the respiratory tract of humans and some specific birds and bats [41]. The recent outbreak of COVID, as it spread widely in 2019, was termed the novel corona virus 2019, or COVID-19. Initially, the novel corona virus was detected in the city of Wuhan in China and spread widely throughout the world in a very short time interval and infected millions of people worldwide. Thus, it was declared a pandemic by World Health Organization [42,43].

The symptoms of COVID-19, caused by the novel coronavirus SARS-CoV-2, can vary from mild to severe and may appear 2 to 14 days after exposure to the virus. Some individuals infected with the virus may experience no symptoms at all (asymptomatic), while others may develop mild to moderate symptoms. Common symptoms of COVID-19 include fever, sneezing, common cold, body ache, gastrointestinal symptoms, etc. [44]. However, increased levels of cytokines and lymphopeia are some of the critical symptoms of COVID-19 during severe infections [45,46].

The SARS-CoV-2 is an SS RNA having a genome size of 26.4–31.7 kb, with crown-like glycoprotein present on its surface. The genome size of the SARS-CoV-2 is considered the largest in comparison to the other RNA viruses [41,42]. The open reading frame (ORF) of the virus proteins is characterized by the presence of different structural-like nucleocapsid (N) spike (S), envelope (E) or membrane (M) proteins; however, ORF1ab represents non-structural proteins. These structural proteins play a significant role during the infection. For example, S proteins of the virus help in the attachment with the host cell, while E proteins mediate functioning of the interaction between the virus and host cells, the assembly of the virus, and permeability of membrane. The M proteins play a crucial role in the assembly of the corona virus, and the N proteins mediate in the formation of the ribonucleo-capsid complex with the help of some other proteins [47,48]. However, during the recent outbreak of the pandemic, two mutations in the S gene have been reported in previous studies [49,50].

During infection, to complete the life cycle, SARS-CoV-2 enters the human body and attaches to the receptor-binding domain (RBD) with the help of the S-protein and viral receptor ACE2 [51,52]. Furthermore, just after the attachment, the virus removes its capsid or envelope. Then the virus releases its RNA into the cytoplasm of the host cell and acts like mRNA for the translation of different open reading frame (ORF) proteins, which further leads to replication and transcription inside the host cell via the help of regulators and other specific proteins [53]. Then, infected cells produce proteins when they become hijacked by SARS-CoV-2. In this situation, the immune system supports the assembly of SARS-CoV-2 into new copies of virion particles [54,55]. However, the virus enters into the cells via two

mechanisms: endocytosis or direct fusion. In endocytosis-mediated entry, the activation of the spike S protein occurs in endosomes with the help of furin. Further breakdown and fusion happen in endo-lysosomes due to the action of cathepsin L.

However, in direct fusion entry, TMPRSS2 and/or furin, along with other trypsin-like proteases, facilitate the process. In both cases, the viral RNA is released, initiating the late stage of the virus's life cycle, which includes RNA replication, synthesis of viral proteins, maturation, assembly, and the release of new viruses exiting from the cells via exocytosis, releasing the virion to infect the other persons [56–58]. A schematic representation of the SARS-CoV-2 life cycle is presented in Figure 1.

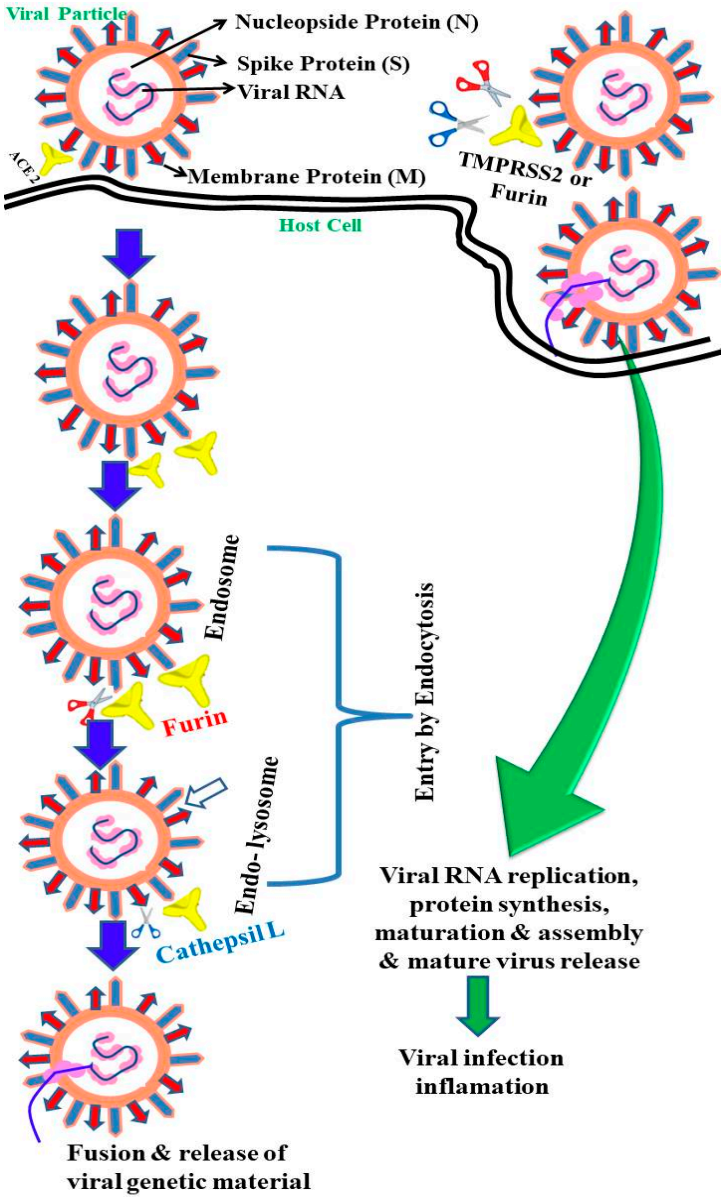

Figure 1. A schematic representation of SARS-CoV-2 life cycle. Figure is taken and modified from Al-Horani et al. [58].

To prevent COVID-19 infection, several vaccines have been discovered by scientific communities or private research firms, which are showing some good responses and tackle the spread of the pandemic to a certain extent. However, scientific communities are also working to search for an alternative to the allopathic vaccines or medicines to conquer the infection economically and without toxifying the human body. In this regard, several plant-based metabolites or secondary metabolites are continuously screened to

evaluate their efficacy against COVID-19 or to boost the immune system. In the previous studies, various authors reported the efficacy of plant metabolites in the management of human ailments, including viral infections [58,59]. Plant metabolites can halt the activity of enzymes involved in the replication cycle of SARS-CoV-2, including papain-like protease and 3CL protease, which check the fusion of the S protein of coronaviruses and the ACE2 of the host, and also inhibit the cellular signaling pathways [60–62].

3. Algal Polysaccharides and Their Potential as Antiviral Agents

Polysaccharides are a group of either similar or different saccharides that are connected with glycosidic bonds [63,64]. These polysaccharide molecules inhibit viral replication by interfering in any stage of the viral life cycle, which generally takes place in phases such as the adsorption of the virus by the host cells, penetration into the host cell, uncoating of capsids, assembly and release of viral particles, or via inactivating virions before infection [65,66]. The life cycle of viruses varies from species to species; thus, the action mechanisms of the algal polysaccharides also varies with the nature of the virus species [63–66].

In the recent past, various polysaccharides, such as carrageenan, alginate, ulvans, and laminarins, have been isolated from both fresh and marine water alga and these polysaccharides have been reported for their potential antiviral properties [63]. These polysaccharides, particularly the sulfated polysaccharides, are conferred with strong polyanionic characteristics and have the ability to block the cationic charge upon the surface of cells in order to prevent virus infection or even adsorption [58]. These sulfated polysaccharides have significant therapeutic potential (Table 1); because they can mimic glycosaminoglycans, sugar-rich molecules that are prevalent in cell membranes [66]. Thus, in this paper, we have considered algal polysaccharides, carrageenans, and alginates to study their impact on SARS-CoV-2. A schematic action mechanisms of algal polysaccharides (AP) during SARS-CoV-2 infection has been presented in Figure 2.

Table 1. Some common algal polysaccharides used as antiviral agents and their mechanism of action.

Algal Polysaccharides	Source	Viral Diseases	Mechanism of Actions
Carrageenan	Red algae	Influenza virus Human immunodeficiency virus Herpes simplex virus	The compound inhibits the binding or entry of the virus to the host cell
Alginate	Brown algae	Human immunodeficiency virus Hepatitis B Virus	Compounds inhibit adhesion of virus to the host cell and also inhibit replication inside the cell
Fucan	Brown algae	Human immunodeficiency virus Herpes simplex virus	By blockage of reverse transcriptase
Agar	Red algae	Influenza virus	By the partial blockage of the adhesion to the endothelial cells
Laminaran	Brown algae	Human immunodeficiency virus	By the blockage of reverse transcriptase
Galactan	Red algae	Human immunodeficiency virus Herpes simplex virus	By inhibiting adhesion of the virus to the host cells and inhibition of replication
Ulvans	Green algae	Human and avian influenza viruses	Inhibit viral reproduction

Carrageenans (CGs) are sulfated linear polysaccharides that alternately contain (1→3)-β-D-galactopyranoses and (1→4)-α-D-galactopyranoses substituted with sulfate esters at the several positions [67]. The position of sulfation determines the active properties of the carrageenans. ICGs have been previously well reported in various algal groups, such as *Agardhiella*, *Eucheuma*, *Chondrus crispus*, *Furcellaria*, *Hypnea*, *Iridaea*, *Gigartina*, *Solieria*, and *Sarconema*, accounting for 30–75% of their dry weight [68–70]. The multifunctional qualities of the CGs, such as biocompatibility, the absence of toxic effects, biodegradable nature, and emulsifying, gelling, and stabilizing abilities, make them popular in the food,

pharmaceutical and cosmetic industries [71]. The presence of antioxidant, antiviral, anticancerous, and excellent drug-transport properties make CGs a suitable or multipurpose agent for the pharmaceutical industry [69].

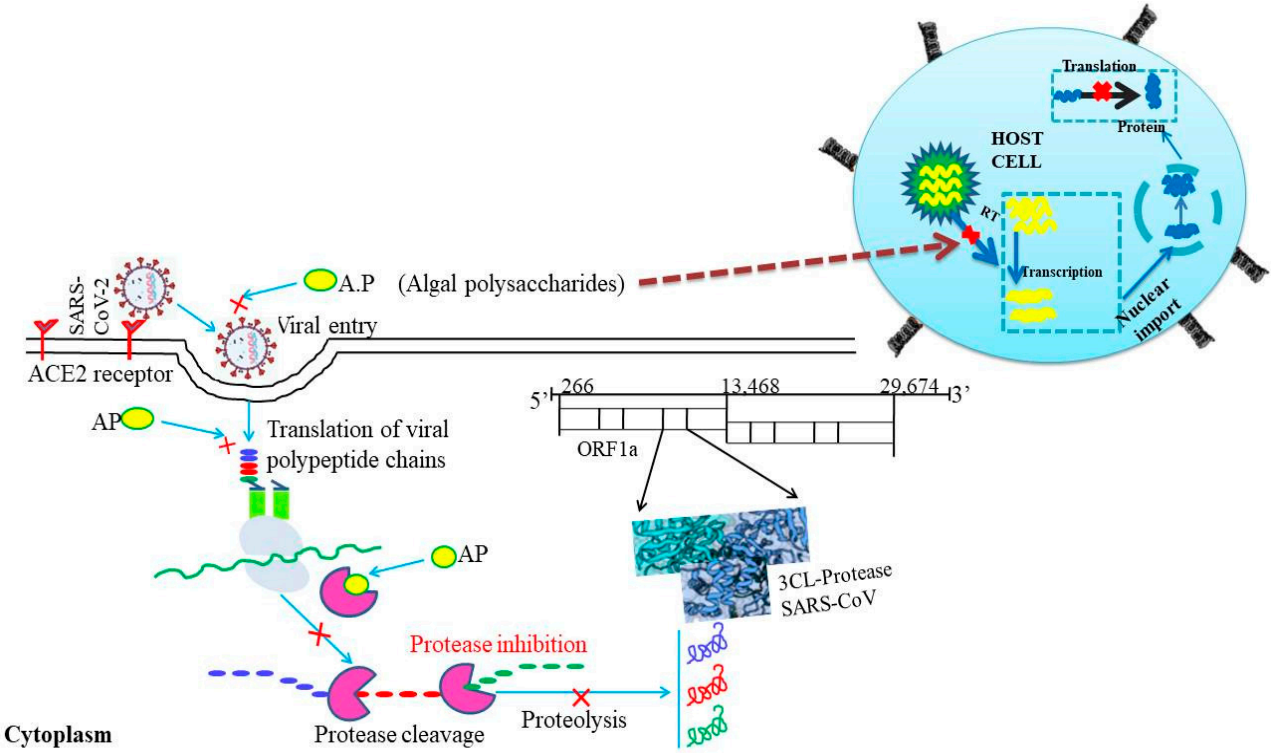

Figure 2. A schematic action mechanisms of algal polysaccharides (AP) during SARS-CoV-2 infection. Figure is modified from Kumar et al. [1].

In previous studies, various authors have reported the pharmaceutical properties of CGs against different viral diseases such as the herpes virus types 1 and 2 [72,73], varicella zoster virus [74], cytomegalovirus [75], HIV [76], human metapneumovirus [77], and influenza virus (IAV) [78]. CG has reportedly been found to be most efficient against enveloped viruses. The antiviral effect of the CG structures help in attaching the virus to its receptor [79,80]. In the latest studies, carrageenans such as ι and λ showed strong inhibitory effects against the SARS-CoV-2 virus [81–83]. Similarly, Song et al. [84] reported the ability of sulfated polysaccharides, ι -CG, to prevent the binding and penetration of SARS-CoV-2 into host cells.

Alginates, the salts of alginic acid, are polysaccharides comprising 13-(1→4)-D-mannosyluronic acid (M), o~-(1→4)-L-glucosyluronic acid (G), and alternating (MG) blocks [85]. In previously published reports, extraction of alginic acid from various algal groups such as *Laminaria*, *Mcrocystis*, and *Ascophyllum* was well documented [86,87]. Like the CGs, alginates have some specific characteristics such as absence of toxic effect and biocompatible nature, which also make them popular in medical science [70]. Alginates have been used generally in the pharmaceutical industry for microencapsulation, wound dressing, and drug delivery [88]. Numerous authors have reported the use of alginic acid in the treatment of various human viral diseases. For example, Mastromarino et al. [89] reported the antiviral activity of alginic acid against the Vero cells of the enveloped group IV rubella virus. Similarly, Bandyopadhyay et al. [90] reported the antiviral activity of alginate hydrogels against the HSV type-1. Sinha et al. [91] reported an anti-HSV-1 effect of sulfonated alginate, and found that antiviral activity enhanced with increasing sulfate ester content. In addition, different authors have reported the anti-HIV-1 and anti-HSV-1 properties of alginic acid [92,93]. These studies provide a primary clue to the use of these algal polysaccharides in the treatment and prevention SARS-CoV-2.

4. ACE2 Host Receptor for S1-RBD of SARS-CoV-2: Its Protein Network

The S (spike) protein consists of S1 and S2 subunits which play essential roles in interactions and membrane fusion, respectively. However, the spike integrates the human ACE2 (angiotensin-converting enzyme 2) with the cell membrane via the S1 subunit of the receptor-binding domain (RBD). In a previous study, it was reported that the RBD of SARS-CoV-2 to ACE2 has ~10- to 20-fold greater efficiency in comparison to the binding potential of the SARS-CoV-2 RBD. Moreover, the SARS-CoV-2 RBD attaches with soluble ACE2 with greater efficacy than SARS-CoV-2. This increased efficiency regarding ACE2 might lead to greater infectivity of SARS-CoV-2 [94].

Cytoscape was employed to assess the PPI network (protein–protein interaction network) to predict protein–protein interactions with ACE2 (Figure 3) and identified the top five interactants and their functions based on their score (Table 2) [95]. The interacted proteins of ACE2 were AGT (angiotensinogen), KNG1 (kininogen-1), SLC6A19 (sodium-dependent neutral amino acid transporter), AAMP (angio-associated migratory cell protein), and DEFA5 (defensin-5). The obtained score of interactants was higher than 0.5, except for AAMP with a lower score (0.491), indicating that disturbances in ACE2 may alter the activity of those interactants. However, the highest score of SLC6A19 (0.999 ~=1) is greatly influenced by ACE2.

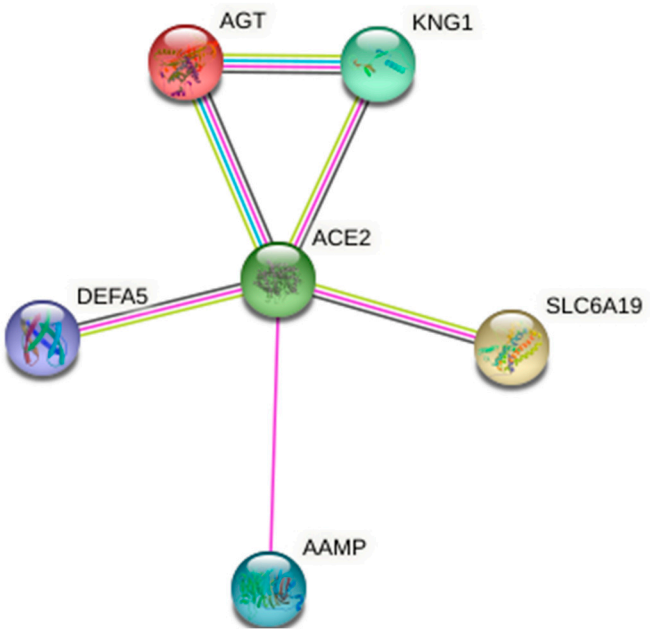

Figure 3. STRING interaction network for ACE2 protein.

Table 2. Score of top 5 interactors in ACE2 network and their functions.

Interactors	Functions	Score
AGT	Major component of the renin–angiotensin system (RAS), an efficient regulator of blood pressure, body fluid, and electrolyte homeostasis.	0.998
KNG1	Plays an essential function in blood coagulation.	0.885
SLC6A19	Transporter, helps in amino acids resorption.	0.999
AAMP	Involved in angiogenesis and cell migration.	0.491
DEFA5	Defensins kill microbes by permeabilizing their plasma membrane.	0.692

The above studies show that the attachment of S1-RBD of SARS-CoV-2 with host receptor ACE2, which have diverse range of metabolic activity.

5. In Silico Approaches for Prediction of the Potentiality of Algal Metabolites (Alginic Acid and Carrageenan) against SARS-CoV-2

In several in vivo and in vitro studies, algal metabolites were favorable in controlling disease virulence factors. Furthermore, the latest omics computer engineering revolution opens a new door to the exploration of the possible role of natural products in drug design. The availability of huge datasets, data curation, in silico studies, and rapid molecular docking methods has enhanced molecular simulations, which are critical for drug discovery [96]. Previously, the antiviral potential of several algal metabolites has been explored, which could also be investigated against COVID-19 by targeting virulent factors of SARS-CoV-2. At present, a novel in silico approach is investigating the therapeutic potential of metabolites against various diseases [97–99]. For instance, it has been explained that algal metabolites such as alginate and carrageenan inhibit the binding of viral particles in host cells [100,101].

5.1. Analysis of Pharmacokinetic Properties of the Ligands

The ADMET properties of the selected compound were analyzed using the admetSAR database. ADMET assessments have specific parameters to determine the drug-like properties of molecules (alginate and carrageenan), e.g., Caco-2 cell permeability, AMES toxicity (the test performed to evaluate the carcinogenic potential of chemicals), and rat acute toxicity LD_{50} (Table 3). The selected metabolites (alginate and carrageenan) reveal permeability for Caco-2 cells and are nontoxic in the assay of AMES toxicity. Rat acute toxicity LD_{50} of alginate and carrageenan was determined at 2.1445 and 2.6262 mol/kg. These results provide strong evidence of the potentiality of alginate and carrageenan to act as a lead drug [98]. Hence, finding the ADMET properties of other algal metabolites could be achieved using the admetSAR database.

Table 3. ADMET analysis of algal metabolites.

Compounds	Caco-2 Permeability	AMES Toxicity	Carcinogens	Rat Acute Toxicity LD50 (mol/kg)
Alginate	Caco2-	Non-AMES toxic	Non-carcinogens	2.1445
Carrageenan	Caco2-	Non-AMES toxic	Non-carcinogens	2.6262

Figure 4 reveals the BOILED-Egg construction to show the passive gastrointestinal absorption (HIA) and brain penetration (BBB) of the selected (a) alginate and (b) carrageenan in the WLOGP-versus-TPSA (a plot drawn for the assessment of gastrointestinal absorption and brain penetration) referential. The white part represents a larger probability of passive absorption by the gastrointestinal tract, and the yellow site (yolk) denotes the brain penetration probability. It is based on a straightforward concept underlying two physicochemical descriptors: (i) WLOGP for lipophilicity and (ii) TPSA for apparent polarity [102]. It is predicted that the (a) alginate and (b) carrageenan molecules follow the rule of the BOILED-Egg model for the prediction of absorption possibility, which explains the high probability for both gastrointestinal absorption and brain penetration.

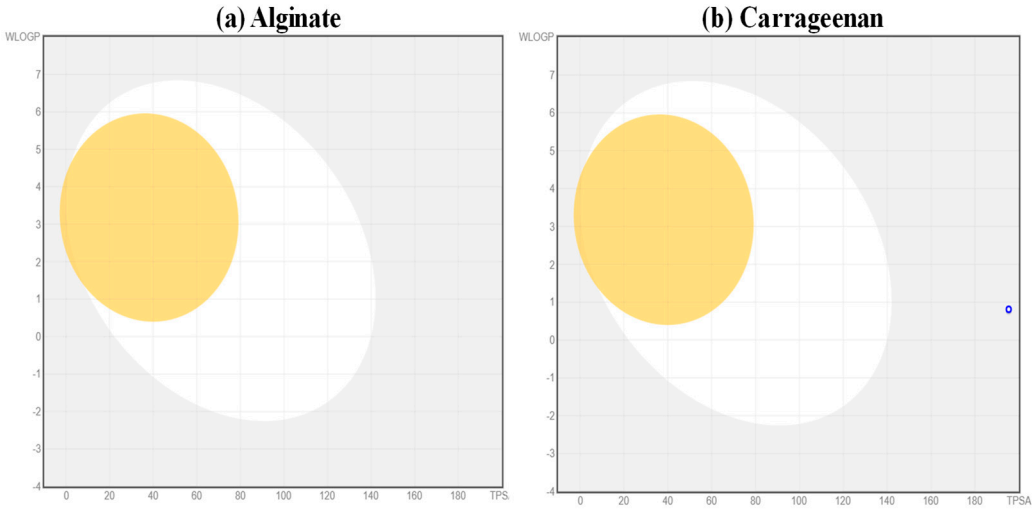

Figure 4. Assessment of passive gastrointestinal absorption (HIA) and brain penetration (BBB) in the functional positions: (**a**) alginate and (**b**) carrageenan in the WLOGP-versus-TPSA referential by using BOILED-Egg construction.

5.2. Prediction of S1-RBD Spike Protein Stability

The graph was obtained from the online server (https://iupred2a.elte.hu; accessed on 17 March 2023) (Figure 5) after the submission of the protein receptor FASTA file to achieve a score of less than 0.5 for the S-receptor binding domain (S-RBD) (PDB ID: 2GHV), which suggested the coherence ability of residues in the spike-protein of SARS-CoV-2 is very high [103]. Thus, potential algal metabolites need to be explored to disrupt the stability of the S-receptor binding domain.

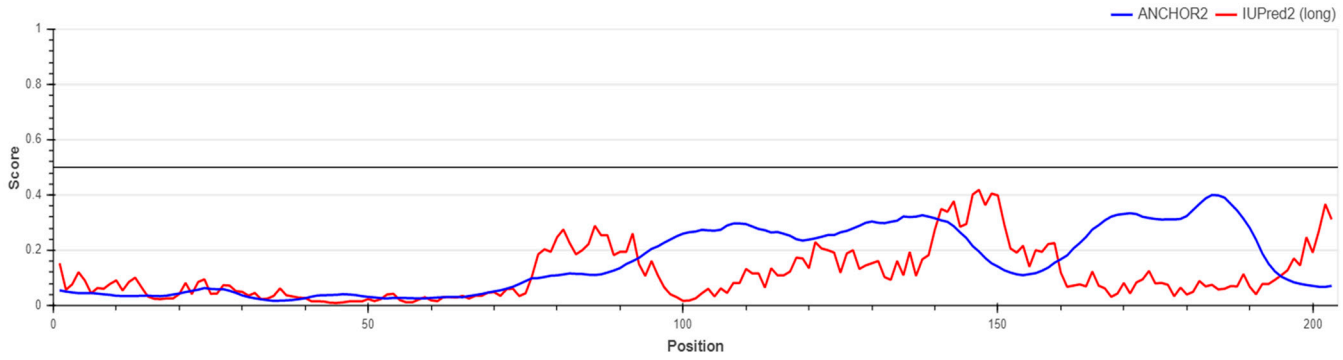

Figure 5. Determination of protein disorder by IUPred online server for receptor RBD (spike protein).

5.3. Interaction of Ligands with S1-RBD of SARS-CoV-2

Molecular docking interactions have played a crucial role in revealing the interactive mode of the active site of small molecules with the targeted receptor protein [104]. The Patchdock Server was employed to perform the molecular docking studies for this research. The crystal structure of the receptor protein (S1-RBD) was retrieved from the RCSB-PDB database with PDB ID 2GHV, while the atomic coordinates of ligand molecules were downloaded in SDF format from the PubChem database (accessed on 17 March 2023). The docking simulation was then carried out using the PatchDock server's enzyme-inhibitor module with default settings. It calculates the Atomic-Contact-Energy (ACE-value) and the corresponding area for the probable ligand interaction on the receptor protein. With the most negative ACE value, the best receptor–ligand complex was chosen. Discovery Studio 4.0 Client was also used to visualize and determine the interactive phenomena between the receptor and the ligand molecules. Figure 6 represents the interactive potential of alginate and carrageenan and S1-RBD of SARS-CoV-2.

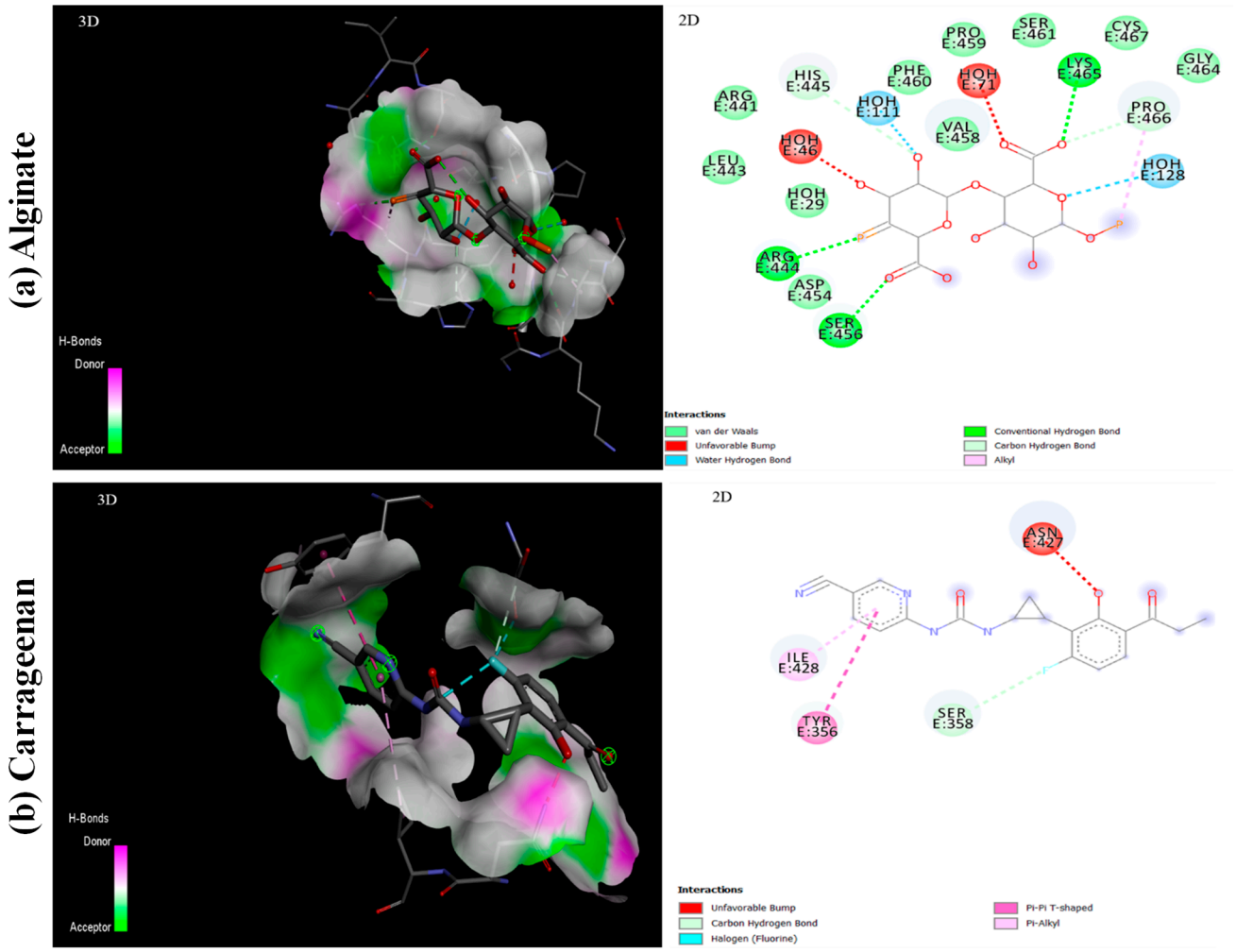

Figure 6. Visualization of structural insight of the interacted algal metabolites (**a**) alginate (**b**) carrageenan with receptor binding protein (RBD) of SARS-CoV-2.

The residues (SER456, ARG444, LYS465, and PRO466) of the S-receptor binding domain (RBD) of SARS-CoV-2 interacted with alginate (Figure 6a) with an ACE value of −112,131.2 J/mol (Table 4). The carrageenan was bound with residues (TYR356, ILE428, and ASN427) of S-RBD (Figure 6b) in which an ACE value of −162,339.2 J/mol was involved (Table 4). The interactive potential of (a) alginate and (b) carrageenan with S-RBD showed that these algal metabolites could prevent the attachment of SARS-CoV-2 with the host surface ACE2 as well as perturbation of other proteins (AGT, KNG1, SLC6A19, AAMP, and DEFA5). Thus, by using bioinformatics tools, the therapeutic potential of several other algal metabolites and interactors could be explored by targeting the virulent factors of SARS-CoV-2.

Table 4. The obtained binding energy of molecules after interacting with the active sites of SARS-CoV-2 receptor proteins.

Compounds	ACE
Alginate	−12,131.2
Carrageenan	−162,339.2

Drug discovery is a time-consuming and expensive procedure with no assurance of accomplishment. However, the introduction of advanced technologies in current times is helping to decrease attrition frequencies, mainly in the later stages of drug development.

In recent decades, molecular docking has played a continuous and vital role in drug discovery research, and consequently saves time and money in promising lead discovery. Natural products are a crucial source of novel chemotypes, and the application of computer-aided drug discovery (CADD) methods in natural-product-based drug discovery must be magnified [105]. The emerging trend of using molecular docking as a device to understand major interactions of algal compounds such as alginate and carrageenan with the virulent target S1-RBD of SARS-CoV-2 is anticipated to influence several decisions. Henceforth, by knowing the interactions of alginate and carrageenan with S1-RBD, natural product chemists would be able to recruit potential algal compounds for screening against COVID-19 and other related viral diseases so that these compounds could be used at advanced stages of drug discovery such as in vitro, in vivo, and clinical studies.

6. Conclusions

To reduce and control of spread, severity, and viral load of SARS-CoV-2, there is a need to explore novel, natural, and alternative medicines. In last two years, significant progress has been made by the scientific community in search of vaccines and medicines against COVID-19, but still we should seek an alternative, which must be economical, with no side effects, and natural. In recent times, scientists have identified and studied various antiviral metabolites derived from algae, examining their pharmaceutical properties. The distinct characteristics of these biologically active constituents obtained from algae make them potential candidates for the development of antibodies and vaccines against SARS-CoV-2. Algae and seaweeds, which are the ancestors of all plants, have undergone extensive investigation in biotechnology, presenting cost-effective opportunities to drive innovation in bio-based industries. These organisms produce a wide range of biometabolites that aid in their adaptation and survival in challenging environments. These specialized natural metabolites hold significant potential as sources of valuable antiviral agents. They have been extensively researched and utilized as microbiota-based therapeutic agents, immunomodulators, glycan therapeutic agents, and antioxidants for the prevention and treatment of SARS-CoV-2. The existing scientific literature provides support for the effectiveness of algae-derived polysaccharides, particularly carrageenan and alginate, against SARS-CoV-2. The present studies based on bioinformatic approaches have elucidated that alginate and carrageenan might open alternative paths for developing new therapeutic approaches for COVID-19 and other viral ailments.

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