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(Review Article)

Novel sulphated polysaccharides from marine macroalgae as potential and natural antiviral agents against SARS-CoV-2

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Abstract

Global pandemic diseases are not new to the existing world; however, the modern age is to be ready to defend the present and future pandemic existence. Bacterial pandemic diseases are the most exacerbating cause of people's death, comparatively than viral pandemic diseases up to the 19th century. An intriguing discovery of '*antibiotics*' in the 20th century have almost eradicated the bacterial pandemic diseases and which is still under control by finding new age antibiotics. Henceforth, such an alternative solution for viral pandemic disease is still lacking and as a result, viral pandemics are invading the modern era. The COVID-19 is also one among the viral pandemic disease caused by SARS-CoV-2 virus. It is most successful than SARS-CoV, caused SARS outbreak in 2002-2003; due to spike glycoprotein, which plays a most important role in tropism and transmission of this disease to global pandemic. The mechanism of spike glycoprotein is similar with that of the class I type of viral fusion protein, necessary for viral-host internalization and infection. Intriguingly, the sulphated polysaccharides derived from marine macroalgae are the most successful neutralizing agents of class I type of viral fusion glycoprotein and prevent viral infection. This was proven from several *in vitro* and *in vivo* studies, which are tabulated as a compendium in this study. Therefore, these sulphated polysaccharides would be an alternative solution for the control of viral pandemic diseases in the modern era, as how the discovery of antibiotics eradicated bacterial pandemic diseases.

Keywords: Pandemic diseases; COVID-19; SARS-CoV-2; Macroalgae: Sulphated polysaccharides; Natural antiviral compounds

1. Introduction

1.1. Global pandemic diseases

Pandemic refers to "*all people*" in Greek, and pandemic disease is an epidemic disease originated from a region and has the capability to spread, infect and kill larger proportion of people across international borders and continents globally [1]. In the history, three pandemic diseases notably The Plague (*Black Death*) in 14th Century, Small Pox Outbreak in 15th Century, and 1918 Influenza (*Spanish Flu*) in 19th century are the deadliest, causing approximately 306 million casualties [2,3].

An approximate estimate of 400 million people had lost their lives to global pandemic diseases (64 % by bacteria and 36 % virus) (Table 1) [3]. Until 19th Century, the global pandemic diseases caused in people were shared by both bacteria and viruses at percentage values of 80 and 20 respectively. However, in the 20th and present century, viral pathogenesis alone contributes to 100 % of global pandemic diseases (Fig. 1).

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Table 1 Invasion of global pandemic diseases in humans and its casualties in the past and present [2]

Period (years)	Disease Name	Causative agent	Host Reservoir	Intermediate Host	Casualties
165-180	Antonine Plague	Smallpox or Measles virus	-	-	5000000
541-542	Plague of Justinian	Yersinia pestis bacteria	Rats	Fleas	50000000
735-737	Japanese Smallpox	Variola major virus	-	-	1000000
1347-1351	Black death	Yersinia pestis bacteria	Rats	Fleas	200000000
1520	New World Smallpox Outbreak	Variola major virus	-	-	56000000
1629-1631	Italian Plague	Yersinia pestis bacteria	Rats	Fleas	1000000
1665	Great Plague of London	Yersinia pestis bacteria	Rats	Fleas	100000
1817-1923	Cholera Pandemic 1-6	Vibrio Cholera (bacteria)	-	-	1000000
1885	Third Plague	Yersinia pestis bacteria	Rats	Fleas	12000000
1800	Yellow Fever	Virus	Mosquito	-	150000
1889-1890	Russian Flu	H2N2 Virus	Birds	-	1000000
1918-1919	Spanish Flu	H1N1 Virus	Pigs	-	50000000
1957-1958	Asian Flu	H2N2 Virus	Birds	-	1100000
1968-1970	Hong Kong Flu	H3N2 virus	Birds	Pigs	1000000
1981- present	HIV/AIDS	HIV	Chimpanzee	-	35000000
2009-2010	Swine Flu	H1N1 Virus	Pigs	-	200000
2002-2003	SARS	Coronavirus (SARS-CoV)	Bats	Civets	770
2014-2016	Ebola	Ebola Virus	Wild Animals / Bats	-	11000
2015-present	MERS	Coronavirus (MERS-CoV)	Bats	Camels	850
2019-present	COVID-19	Coronavirus (SARS-CoV-2)	Unknown	Unknown	585727
				Total casualties	414773620
				By Bacteria	264100000
				By Virus	150673620

Note: H1N1 – Hemagglutinin Type 1 and Neuraminidase Type 1 (same abbreviation for all the influenza virus but types hemagglutinin and neuraminidase vary); AIDS – Acquired Immunodeficiency Syndrome; HIV – Human Immunodeficiency Virus; SARS – Severe Acute Respiratory Syndrome; MERS - Middle East Respiratory Syndrome; CoV – Coronavirus; COVID-19 – Coronavirus disease 2019.

Intriguingly, the discovery of antibiotics in 20th century has almost eradicated bacterial origin pandemic diseases. Hence, in the latest centuries (20th and 21st), the rate of casualties has been elevated to 16 % by virus pathogenesis when compared with the past centuries. Now we are facing a deadly pandemic disease COVID-19 caused by SARS-CoV-2 virus and it almost deteriorated the global economy.

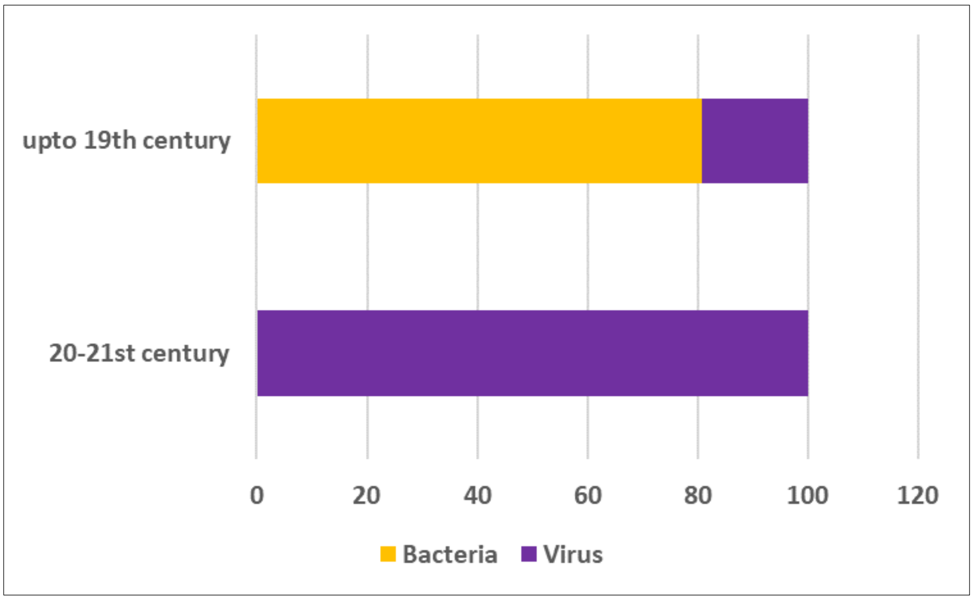

Figure 1 Percentage of casualties caused by the bacteria and viral pandemic diseases on human [2]

2. Coronavirus

Coronaviruses are enveloped viruses, under the order Nidovirales, and are classified into four different genera namely *α, β, γ,* and *δ*, consists of positive-sense RNA as its genome. Including COVID-19, three *β*-coronaviruses had infected human population with deadly pneumonia in the first two decades of 21st century. Severe Acute Respiratory Syndrome (SARS) caused by SARS-CoV, originated from Guangdong Province, China in 2002 with a fatality rate of 10 % by the year 2003, MERS caused by MERS-CoV originated from Arabian Peninsula in the year 2012 with high fatality rate of 35 %. Now, we are facing the global pandemic disease COVID-19 originated from Wuhan Province, China from December 2019 caused by SARS-CoV-2 with case fatality rate of 2.09 % as on 3rd May, 2021 [4].

All the three global pandemic *β*-coronaviruses, namely SARS-CoV, MERS-CoV, and SARS-CoV-2 are zoonotic viruses. Bats are the host reservoir for these pandemic disease-causing viruses with intermediate hosts include Palm civets, dromedary camels, and Pangolins respectively [5,6,7,8]. Other zoonotic originated endemic coronaviruses are HCoV-NL63 and HCoV-229E (α-coronaviruses) and HCoV-OC43 and HCoV-HKU1 (*β*-coronaviruses), which cause about 30 % of mild respiratory tract infections; hence, it is severe in elderly people, immunosuppressed individuals, and young children [9,10]. Presently, there are no specific antiviral treatments or vaccines available to combat any human coronavirus [11].

3. Structure and function

The name coronavirus is based on the projected surface spike glycoproteins on the surface of the enveloped virus gives crown-like structure to the viruses. The genome of the virus is a single-stranded, positive sense, and non-segmented RNA [12]. All the three pandemic *β*-coronaviruses constitutes of genome size 29.751 kbp, 30.119 kbp and 29.903 kbp respectively for SARS-CoV (NCBI Accession number: NC_004718.3), MERS-CoV (NCBI Accession number: NC_019843.3), and SARS-CoV-2 (NCBI Accession number: MN908947.3) (Fig. 2) similar to that of other coronaviruses [13,14,15,16]. All the three genome constitutes of common ORF1ab (nonstructural replicase complex) that are processed into 15 or 16 non-structural proteins (*nsp*) via proteolytic cleavage [17]. Structural proteins include S – Surface spike glycoprotein, E – Envelope protein, M – Membrane protein, and N – Nucleocapsid protein followed by other accessory proteins (Fig. 3). The accessory proteins have no significant homology to the accessory proteins of other coronaviruses. However, SARS-CoV has homology with SARS like coronavirus strain SL-CoV-W1V1 of bat coronavirus [18].

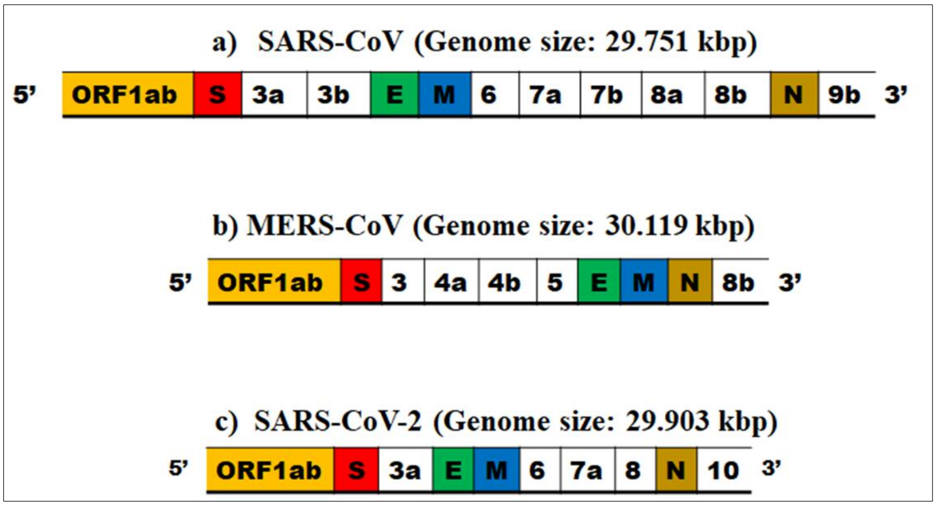

Figure 2 Schematic representation of three pandemic disease-causing β-coronavirus genomes; where, ORF: Open Reading Frame, S: Surface spike glycoprotein, E: Envelope protein, M: Membrane protein, and N: Nucleocapsid protein. In which, ORF1ab refers to nonstructural replicase complex, S, E, M, and N are structural proteins, and other proteins (ORFs 3 to 10) are accessory proteins [13,15,16]

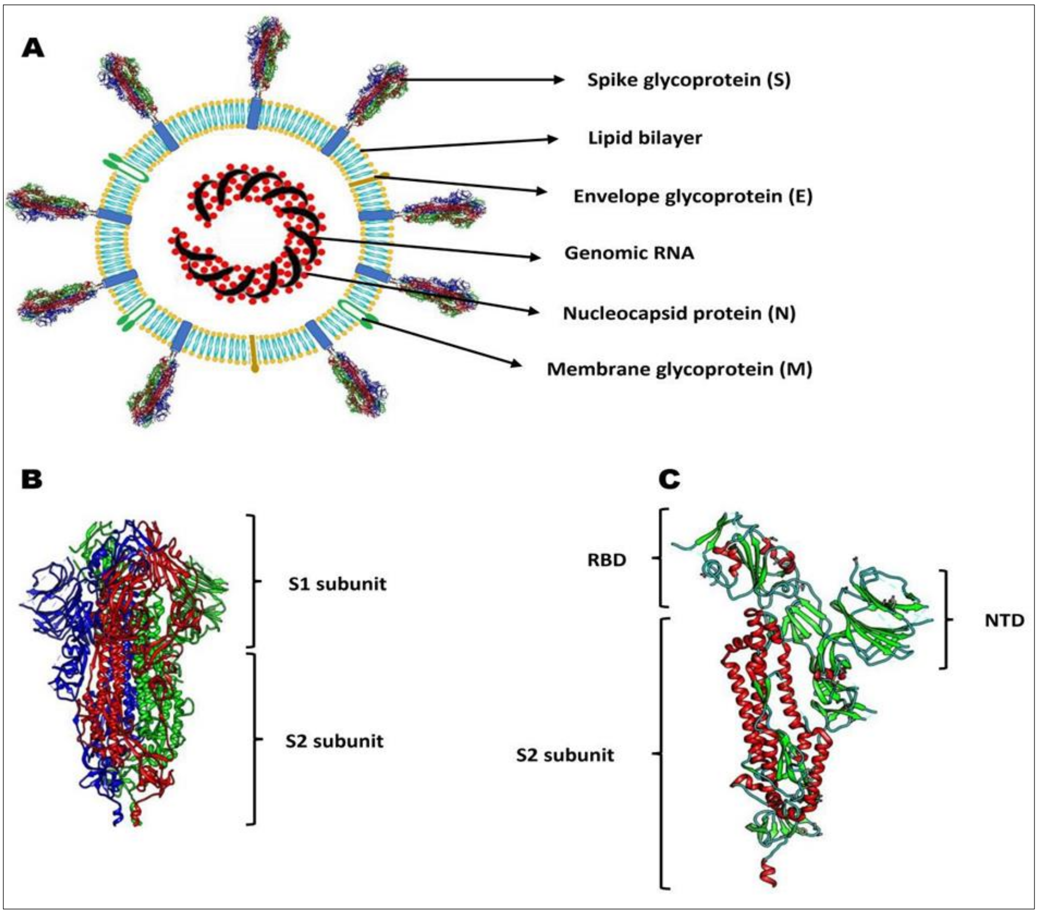

Figure 3 A) Structure of an Enveloped SARS-CoV-2 virus; B) Three dimensional structure of Surface glycoprotein (homotrimer: red, blue & green) depicting S1 and S2 subunits; C) A single monomer of Surface glycoprotein depicts Receptor Binding Domain (RBD), N-terminal Domain (NTD) and S2 subunit

Sequence identity percentage was retrieved for the structural proteins of the three coronaviruses based on pairwise and multiple sequence alignment. As a result, comparatively, SARS-CoV-2 was found closely related to SARS-CoV than MERS-CoV (Table 2). However, the surface spike glycoprotein has sequence identity percentage of only 76.2 between SARS-CoV and SARS-CoV-2. The surface spike glycoprotein consists of about 1255 amino acid residues in SARS-CoV, whereas it is 1273 in SARs-CoV-2 and 1353 in MERS-CoV. This glycoprotein is the most important than any other protein; hence it mediates viral-host entry. The S-protein is a class I viral fusion protein [18,19]. It constitutes of S1 and S2, two different subunits, which functions in binding to the host receptor and mediates viral-host membrane fusion respectively [20]. The functional host receptor is identified as hACE2 for SARS-CoV [21] and SARS-CoV-2 [22,23], whereas, human DPP4 is the functional receptor in the case of MERS-CoV [24].

Table 2 Percentage value of protein sequence identity between the structural proteins of SARS-CoV, MERS-CoV, and SARS-CoV-2

Structural proteins of β-coronaviruses	SARS-CoV and MERS-CoV	SARS-CoV and SARS-CoV-2	MERS-CoV and SARS-CoV-2
S- Surface spike glycoprotein	28.76	77.21	28.59
E- Envelope protein	38.16	96	38.67
M- Membrane protein	42.01	91	40.18
N- Nucleocapsid protein	48	91.17	48.18

In the case of both SARS-CoV and SARS-CoV2, the viral-host entry not only depends on hACE2, it also requires host TMPRSS2 protease and cathepsin B/L activity [22]. Immunohistochemistry and gene expression study, evidently exemplifies the high proliferation of ACE2 and TMPRSS2 in type II alveolar epithelial cells [25,26,2728]. This result is typical for the tropism and pathogenesis of both SARS-CoV and SARS-CoV2 infection [29,30].

After significant receptor binding, the Surface glycoprotein undergoes conformational changes [31,32,33]., in which the interaction between the S1 subunit and the host receptor hACE2, mediates exposure of secondary cleavage site in S2 which is S2' present prior to fusion peptide for the cleavage by host proteases mentioned above [34,35,36,37]. This proteolysis mechanism mediates the binding of fusion peptide into the host membrane followed by conformational changes in S2 results in first heptad (HR1) and second heptad (HR2) extensions [38,39] which mediates viral and host membrane fusion and release of viral genome into the cytoplasm of host cell [40]. This kind of fusion machinery is found similar with that of the class I virus fusion proteins [41,42,43].

The envelope glycoprotein (E-protein) is a pentameric viroporin, serves as an ion transport channel for the viral particle, activates host NLRP3 inflammosome leading to IL-β overproduction and induce apoptosis. Membrane glycoprotein (M-protein) is a homomultimer responsible for viral morphogenesis and assembly and also participates in RNA packaging in virus. Nucleocapsid protein (N-protein) found associated with the genome (RNA) of the virus which are heavily phosphorylated.

The other accessory proteins were considered for the replication of the viral genome *in vitro* [44,45,46,47] However, most of the accessory proteins exhibits viral-host interaction during infection [48,49] by modulating interferon signaling. Hence, thereby collapsing the host antiviral immunity and facilitates viral pathogenesis and infection [50,51,52,53]. Extensive research works have been carried out on the surface spike glycoprotein rather than any other structural protein of coronaviruses, due to its pathogenicity to human host cells.

4. Unique features of SARS-CoV-2 (COVID-19)

Intriguingly, there are only 76.2 % of amino acid sequence identity between the surface spike glycoproteins of SARS-CoV-2 (2019) and SARS-CoV (2002), since all other structural proteins carry about 90 % of sequence identity. Recently, 16.1 % difference was observed in the RBD of surface spike glycoprotein. This significant variation has altered the binding capacity of RBD and viral infection of SARS-CoV-2 [54]. Adding to this, novel glycosylation sites have been discovered in the surface spike glycoproteins of SARS-CoV-2 which might influence the pathogenesis of viral-host infection [54].

However, variation in sequence identity of Surface spike glycoprotein between SARS-CoV and SARS-CoV-2 is ambiguous, since it shared approximately 90 % of sequence identity of all other structural proteins. In contrast, the S glycoproteins of SARS-CoV-2 shares about 97 % of sequence identity with bat SARS like coronavirus SARSrCoV RaTG13 [8]. Similarly, it seems that, the SARS-CoV-2 have had undergone RNA recombination between SARS-CoV strain Rf4092 and bat SARSrCoV strain W1V16 [54]. Therefore, the origin of this 2019 novel coronavirus (COVID-19) by SARS-CoV-2 might have been obtained by the recombination of existing coronaviruses [54]. Henceforth, the "*host-jump*" feature of non-mammal host reservoir to humans and its molecular basis remains unanswerable question [55].

Most recently, Pradhan *et al*. have identified about 4 different amino acid insertions in the S glycoprotein of SARS-CoV-2, which has the similarity with HIV-1 gp120 and Gag protein [56] and are completely absent in any other coronaviruses. One among the insertion is "PRRAR" which was found to be more flexible and feasible for the proteolytic cleavage which renders high infection efficiency [16]. Altogether, these insertions might enhance the pathogenesis of viral particle due to the high flexibility of the S glycoprotein.

In another interesting study, about 100 µg/mL of heparin treatment, 30 min prior to SARS-CoV infection in Vero Cells had inhibited the virus infection by 50 % [57]. Similarly, Heparin inhibited SARS-CoV HSR1 strain partially, which suggested that the enveloped virus particle considered to be equipped with positively charged amino acids which could interact with negatively charged sulfate group of heparins in the host cells. Heparin also inhibited the interaction of V3 region of gp120 of HIV with the host cell and inhibits pathogenesis of HIV [58]. These studies demonstrate that, the polyanionic effect of heparin possess antiviral activity by interactions with host cells and inhibition of virus entry through attachment [59]. Several research studies reported that similar kind of mechanism exists in the sulphated polysaccharide of marine macroalgae.

Potent SARS medications or vaccines are not available in this Corona outbreak and thus, it is the need of the hour to bring up a novel, effective and cheaper drug for the treatment and control of globally pandemic COVID-19 disease.

5. Antiviral Sulphated polysaccharides from Marine macroalgae (Seaweed)

Marine resource is the most promising gift of nature, for providing thousands of varieties of novel bioactive compounds from various marine organisms, and many of them are commercially valuable. Marine ecosystem engulfs almost half of the Earth's biodiversity and it is an infinite source of novel marine derived bioactive compounds [60]. Several antiviral compounds are also reported from marine origin and some of them are in preclinical and clinical stages. In future, these marine derived antiviral bioproducts and reliable new technologies would be a promising strategy for modern medicines including anti-infective drugs [61,62,63]. For example, Penicillin, Aspirin, Digitalis, and Morphine are natural bioactive compounds manufactured as drugs from natural resources [64].

Algae are the premiere source of potential antiviral bioactive compounds [65], in which, the marine macroalgae (seaweed) are marine plants classified into three different classes, namely, *Rhodophyceae* (Red algae), *Phaeophyceae* (Brown algae) and *Chlorophyceae* (Green algae). Table 3 represents the different types of sulphated polysaccharides derived from three different groups of marine macroalgae and are reported to have potential antiviral activity against wide range of human pathogenic viral diseases.

Table 3 Source of sulphated polysaccharides from marine macroalgae and its properties

Source	Sulphated polysaccharide	Monosaccharide units	Molecular weight (kDa)	% of sulfate groups
Rhodophyceae	Agaran	Galactose	60-300	28-30
	Carrageenan	Galactose, 3,6-anhydrogalactose	2-200	18-40
Phaeophyceae	Fucoidan	Fucose, Mannose, Xylose, Rhamnose, Galactose	10-100	31.6
Chlorophyceae	Ulvan	Rhamnose, Xylose, Glucuronic acid, iduronic acid	150-2000	16-23

The sulphated polysaccharides are predominantly distributed in the cell walls of the macroalgae and gives flexibility to the algae. The characteristic feature, structural parameters and molecular weight of sulphated polysaccharides vary largely with diverse bioactive potential including anti-tumor, anticoagulant, anti-inflammatory, and antiviral effects [66,67]. A range between 5-75 % of sulphated polysaccharide content was reported to avail from the dry weight of macroalgal biomass and each macroalgae species tend to synthesize at least a single type of sulphated polysaccharide [59]. In some macroalgae, a single species can synthesize more than two different types of sulphated polysaccharides in their different vegetative structures. These sulphated polysaccharides are the most auspicious choice of antiviral agents due to its potential antiviral activity on resistant, mutant pathogenic viral strains and very least toxicity on host [68]. All the sulphated polysaccharides such as agaran, carrageenan, fucoidan, and ulvan derived from marine macroalgae are proven to have potential antiviral efficacy and could be used as a drug for the treatment of COVID-19 [69]. Similarly, Chen *et al*. also suggested the sulfated polysaccharides coated on gold nanoparticles for a new approach COVID-19 treatment [70].

6. Agaran

The sulphated galactans are the major component of polysaccharides derived from the red algae, which constitutes of linear chains of galactoses with alternating 3-β-D-galactopyranose (G units) and 4-α-D-galactopyranose residues or 4-3,6-anhydrogalactopyranose residues in their structural backbone (Fig. 4) [71], hence, L-series are classified under agarans and D-series as carrageenans [72,73]. However, DL-hybrid galactans are also reported from some red algae [74,75]. Several antiviral studies have been carried out in agarans against DENV-2, HSV-1, and 2 which exhibits efficacy to inhibit the virus with low toxicity to host. Hence, it has a promising value as antiviral agent [76], and the mechanism of inhibition is viral-host interaction [77]. Duarte *et al*., in the year 2004 reported that the agaran sulfate from a red alga *Acanthophora spicifera* exhibits potent antiviral efficacy on HSV-1 and HSV-2 viruses with IC_{50} values of 1.4 and 2 µg/mL respectively [71]. However, a sulfated galactan extracted from another red alga *Schizymenia binderi* also possess antiviral potency on HSV-1 and HSV-2 with IC_{50} values of 0.18 µg/mL and 0.63 µg/mL [78]. Similarly, sulfated galactan isolated from a red alga *Asparagopsis armata* exhibits antiviral efficacy on HIV-1 virus with an IC_{50} value of 8 µg/mL [79].

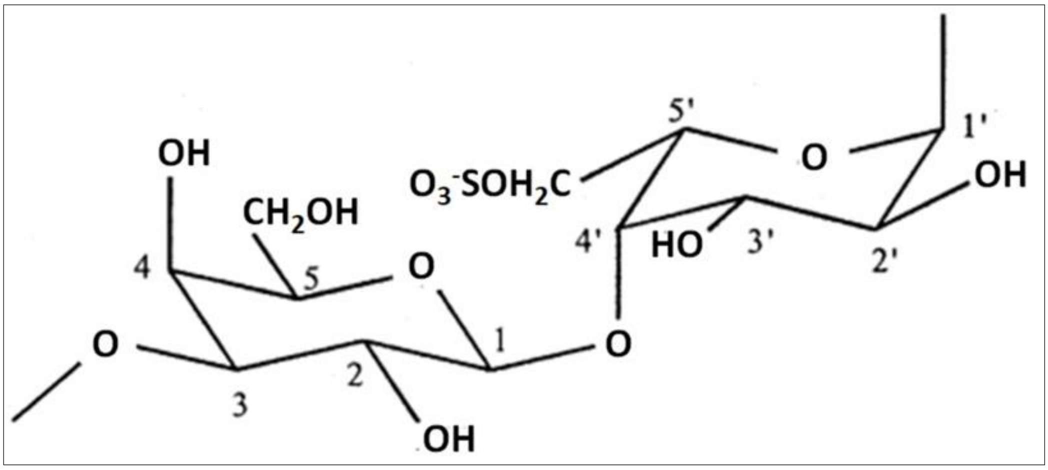

Figure 4 The structure of repeating disaccharide unit of Agaran 6-sulfate derived from *Acanthophora spicifera*, in which the major monosaccharide unit is Agarose with one sulfate group in its moiety [69]

7. Carrageenan

Euchema, Kappaphycus, Hypnea, Gigartina, and *Chondrus* are some of the red algae, reported to yield very large of amount of carrageenans which serves to support marine plants as cellulose in land plants [80]. Naturally, the carrageenans are negatively charged anionic sulphated polysaccharides with 3,6-anhydrogalactopyranose units with sulphate groups on its main chain and its arrangement with the molecule further classify into λ-, κ-, and ι-carrageenan (**Fig. 5**) [81] with distinct antiviral activities on similar kind of viral agents [82]. Carrageenans are the most extensively studied sulphated polysaccharide on antiviral efficacies, which are selective inhibitors of non-enveloped and enveloped human pathogenic viruses by inhibiting the internalization of viral particle into the host cells [83,84].

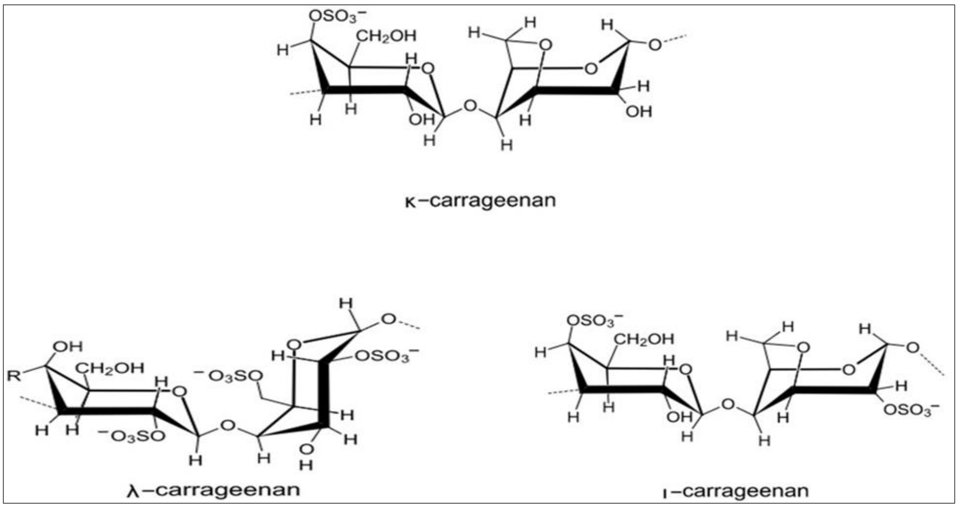

Figure 5 Three major chemical structures of repeating disaccharide units of Carrageenan. Galactan is the common monosaccharide unit in carrageenan. Whereas, kappa carrageenan has one sulfate group, iota carrageenan has two sulfate groups, and lambda carrageenan has three sulfate groups respectively per disaccharide unit [77]

Intriguingly, low molecular weight carageenans ranges from 3 to 10 kDa have promising inhibitory effects on influenza virus *in vivo* due to its acylation and sulfation degree [85]. Carrageenan gels made from *Chondrus crispus* are highlighted for its inhibition of HIV and HSV transmission while applied at genital warts [86]. Carrageenan isolated from a red *alga Callophyllis variegata* exhibits antiviral activities on HSV-1, HSV-2, and DENV2 with IC_{50} values of 0.18, 0.21, and 0.29 μg/mL respectively [76]. Iota- and kappa-carrageenan and its pharmaceutical composition reported to have antiviral efficacy on a group of viruses include adenovirus, paramyxovirus, orthomyxovirus and coronavirus [87]. The pharmaceutical composition with iota or kappa carrageenan was patented to use as a therapeutic agent for upper respiratory tract viral infections and deblocking stuffy nose (International Patent No.: WO2017009351A1) [88,89].

8. Fucoidan

As the name indicates, fucoidan is most commonly composed of L-fucose monosaccharide units in its main chain along with small number of other monosaccharides include glucose, mannose, uronic acid, and galactose (**Fig. 6**) [90]. As other macroalgae, brown algae synthesize fucoidan as its cell wall polysaccharide which gives mucilaginous matrix to the algae. Fucose forms the main backbone chain of fucoidan, linked with 1 → 2 glycosidic linkages, along with 2-3 fucose branching units [91]. However, the structure of fucoidan may vary with respect to different macroalgae genus and even species [92,93]. Therefore, it has a broad range of bioactivities, and each new fucoidan would be a potential antiviral drug. The most prominent antiviral mechanism of fucoidan is, inhibition of virus-host cell interaction and syncytium formation [94] even it has high antiviral activity than the antiviral drug ribavirin [95].

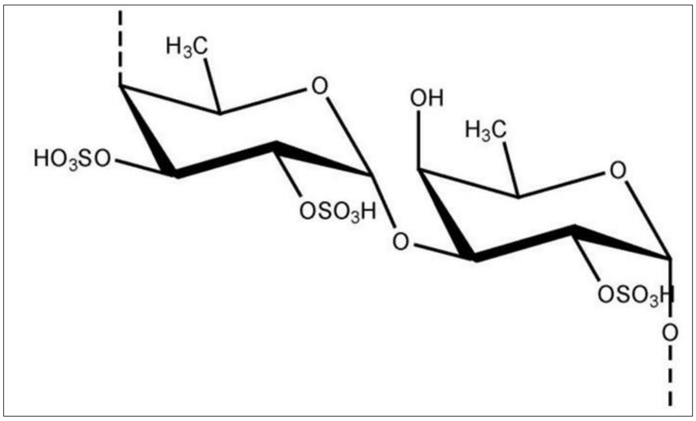

Figure 6 The chemical structure of Fucoidan shows its repeating disaccharide unit with three sulfate groups per unit. Hence, Fucose is its major monosaccharide unit [84]

Interestingly, the fucoidan extracted and purified from *Fucus vesiculosus* shows effective inhibition of reverse transcriptase (RT) enzyme of HIV *in vitro* [96]. In addition to this, incubation of fucoidan (200 mg/mL) with virus prior to infection with host cells inhibits about 100 % of HIV-1 infection [97]. In our recent study on antiviral efficacy of fucoidan, from five different brown algae include *Dictyota bartayesiana, Turbinaria decurrens, Padina pavonica, Stoechospermum marginatum,* and *Spatoglossum macrodontum*, it was resulted that the purified fucoidan content inhibits HIV-1 proliferation by 89 %, 92 % [96], 95.65 %, 85.65 %, and 89.56 % [98] respectively with IC_{50} values of 57.6 ng/mL, 131.7 ng/mL, 295 ng/mL, 346 ng/mL, and 2 ng/mL respectively. In adding to this, fucoidan has also proved to be an effective inducer of immune health [91,99]. An antiviral pharmaceutical composition with particularly with Fucoidan exhibits antiviral efficacy on respiratory viruses include orthomyxovirus and paramyxovirus [88].

9. Ulvan

The sulphated polysaccharide from green algae is referred as Ulvan, and the term came from a green macroalga *Ulva* sp. in which it was extracted and purified. In green macroalgae, ulvan and cellulose are the major constituents of cell wall along with small amounts of glucuronan, and xyloglucan, altogether constitutes about 40 – 55 % of dry algal matter [100]. Several studies have been reported from ulvan with wide range of bioactive features, include antiviral efficacy and immunomodulatory efficacy [101,102,103,104,105]. The sulphated polysaccharide ulvan is composed of iduronic acid (1-9 %), uronic acid (6-20 %), glucose (0.5-6.5 %), xylose (2-12 %), and rhamnose (17-45 %) with sulphate groups (16-23 %) (Fig. 7) [77]. In which, rhamnose is the major monosaccharide unit contributing to the backbone chain in the form of 4-O-*β*-D-glucuronosyl-L-rhamnose and aldobiouronic acid [106,107,108].

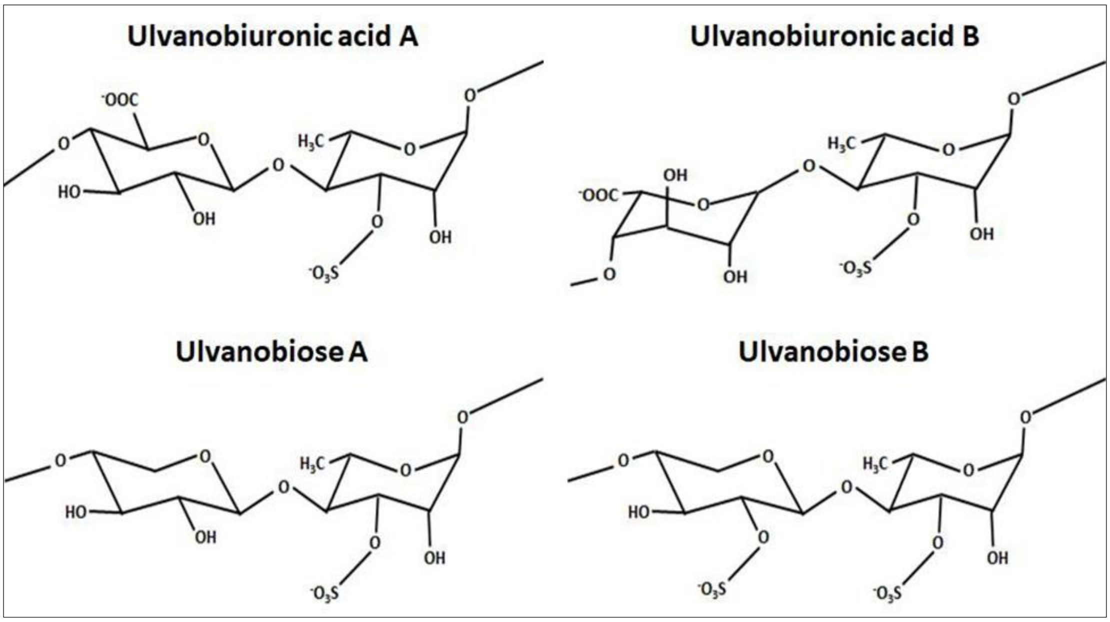

Figure 7 Chemical structure of Ulvan showing four different repeating disaccharide units, in which Rhamnose 3-sulfate is a common monosaccharide unit. Ulvanobiuronoic acid A and B have Glucuronic acid and Iduronic acid respectively. Similarly, Ulvanobiose A and B have Xylose and Xylose 2-sulfate respectively [77]

The ulvan is most commonly found throughout the order, Ulvales of the systemic classification of Chlorophyceae [107,109,110]. The ulvan from *Ulva lactuca* has been reported to inhibit enveloped viral pathogens [111,112,113], due to its high molecular weight and the degree of sulphation. The mechanism of inhibition is also same in as in the case of other sulphated polysaccharides mentioned above (Viral-host interaction) [106]. Ulvan isolated from a green alga *Monostroma latissimum* have been reported to possess antiviral efficacy against HSV-1, HCMV, and HVI-1 viruses with IC_{50} values of 0.78, 1.7, and 1.5 μg/mL respectively [114].

10. Importance of antiviral sulphated polysaccharides

Plethora of antiviral studies have been reported from the sulphated polysaccharides of macroalgae, even it inhibits mutant strains of both HSV and HIV which had become resistant to antiviral drugs such as retroviral and herpetic drugs include acyclovir (ACV), azidothymidine (AZT), and ganciclovir (GCV) [94]. Simultaneously, the inhibitory efficacy of sulphated polysaccharides is mainly based on the inhibition of virus and host cell infection, which hampers viral entry. Many *in vitro* assays are evident that these compounds are effective when supplemented along with the virus or as soon as the infection of virus. It is blatant, that the ionic interaction between the negatively charged receptors of the host cell surface and the positively charged sites of viral outer glycoprotein of the enveloped viruses performs viral-host interaction followed by syncytia formation and infection.

The sulphated polysaccharides are highly dense in negative charge due to the presence of sulphate groups. Therefore, they highly tend to interact with the positively charged viral glycoprotein and inhibit entry into the host cell. Callahan et al. proposed that the negative charge of these compounds not only neutralize the viral glycoproteins, but also gives additional negative charge to the virus and finally disrupts the virus-host interaction [115]. In HIV infection, the interaction of glycoprotein and CD4 complex (gp120-CD4) enhances the protein conformational changes in the gp120 tends to fuse with coreceptors, CCR5 and CXCR4 (Chemokine receptors), then the transmembrane protein gp41 induces membrane fusion of viral particle with host cell membrane. This is the unique feature of the class-I type of fusion mechanism, and in SARS-CoV-2 also similar kind of viral-host interaction takes place. However, the presence of cell surface heparin sulphate might facilitate the HIV-1 entry based on the quantitative contribution [116,117,118]. Therefore, the ionic interaction between V3 loop of gp120 and heparin sulphate ascribes that the polyanionic nature of sulphated polysaccharides also neutralize the V3 loop, but hampering the binding and fusion [119,120]. Additionally, it has been reported that the sulphated polysaccharides interact with the N-terminal domain of gp41 transmembrane protein and inhibits membrane fusion between viral particle and the host cell [121].

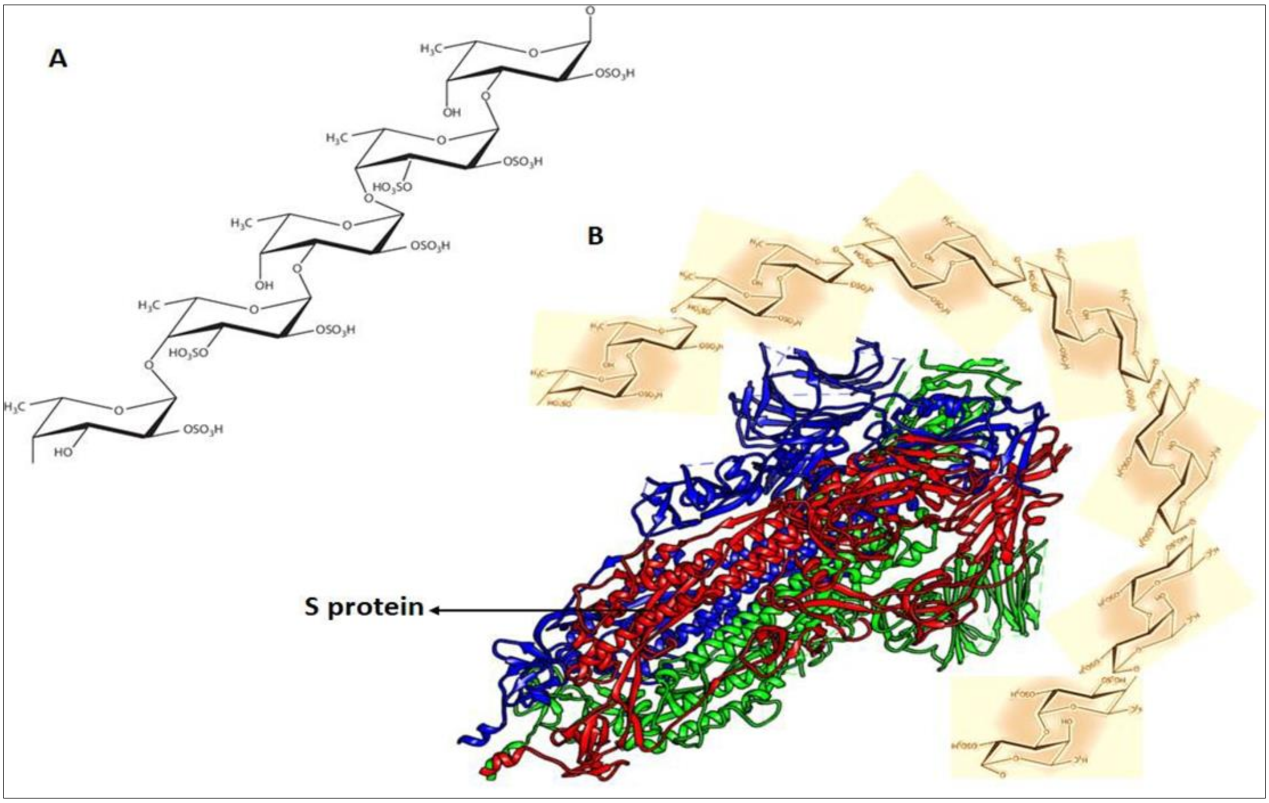

Figure 8 A) Molecular structure of a sulfated polysaccharide (Fucoidan) from brown algae (Phaeophycea); B) A predicted Illustration of neutralization of Surface glycoprotein (Class-I fusion protein) of SARS-CoV-2 by sulfated polysaccharide (Fucoidan), which inhibits viral-host interaction and virus-entry, other sulphated polysaccharide from marine algae may also have similar kind of reaction with S-protein and inhibits viral entry

Prabakaran *et al*. found negatively charged ridges on the receptor which provide an effective site for binding to the positively charged receptor binding domain (RBD) in S-glycoprotein of SARS-CoV. In addition, a greater number of hydrophobic pockets are found on the surface of ACE2 receptor which enhances high binding affinity to the RBD of S-glycoprotein [122]. Iota-carrageenan suppressed the rhinovirus infection in nasal and upper respiratory pathway and inhibits replication in nasal epithelial cells [123]. Similarly, i-carrageenan hampers the influenza virus in the nasal surface epithelia in animal model study and enhances its survival [124].

Consequently, the neutralizing mechanism of inhibition by sulphated polysaccharide is similar with that of the antibody, and also suppresses the virus-induced syncytium formation between the infected and uninfected cells [125] with loss of virus infective ability (Fig. 8). Generally, the sulphated polysaccharide and virion complex is a one-way mode; it is not a reversible process to release viable virion. During pre-infection, the virion-sulphated polysaccharide complex added to the host cell creates a competition between the bioactive compound and the host cell receptor for the positively charged viral glycoprotein (Fig. 8 & 9). Several studies on sulphated polysaccharides reported that the antiviral activity is proportionately enhanced with the molecular weight, ranges between 10-100 kDa [60]. A compendium of research studies carried out on the efficacy of antiviral sulphated polysaccharides from marine macroalgae on several pathogenic viruses has been listed in Table 4.

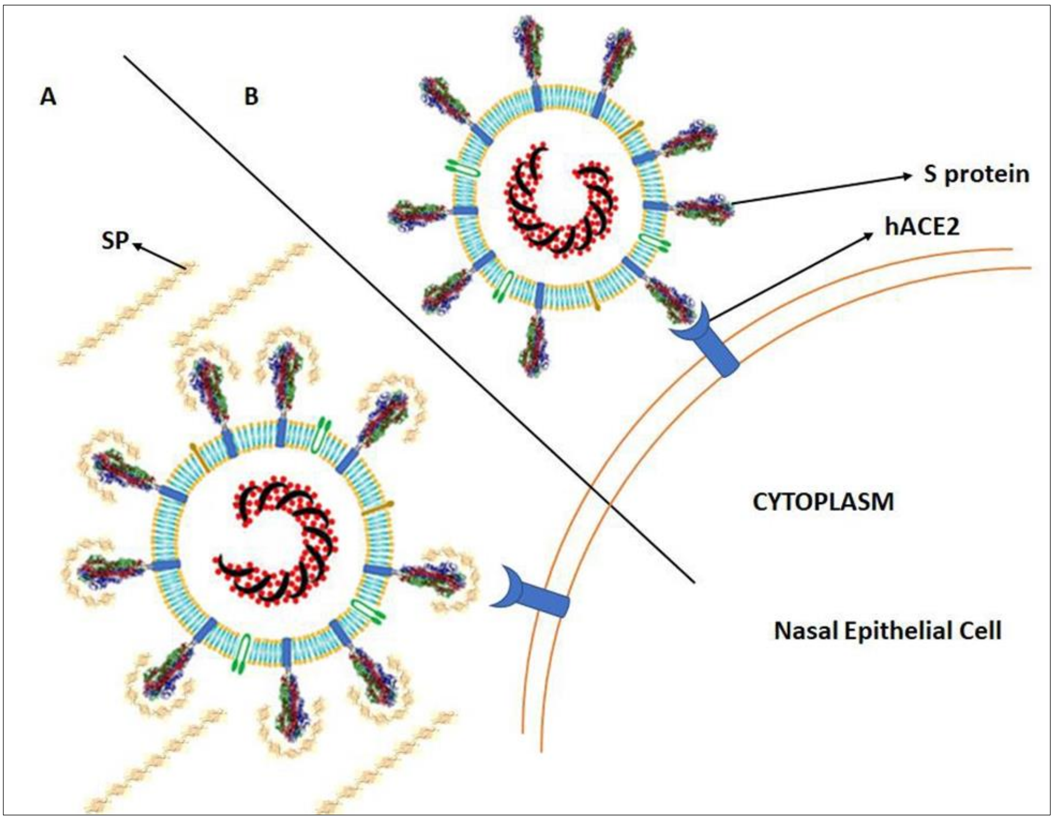

Figure 9 A) Illustration of interaction between Surface glycoprotein (S-protein) and sulfated polysaccharide (SP) of marine algae, which inhibits the interaction of S-protein with hACE-2 (Human Angiotensin Converting Enzyme-2) (receptor) followed by the effective inhibition of viral-host interaction, entry, and syncytia formation; B) SARS-CoV-2 virus infection in human

The three major sulphated polysaccharides such as Carrageenan, Fucoidan and Ulvan reported from three different groups of macroalgae include *Rhodophyceae* (Red algae), *Phaeophyceae* (Brown algae), and *Chlorophyceae* (Green algae). These are proven to have potent antiviral efficacy on several human pathogenic viruses *in vitro* and *in vivo* (Table 4). Hence, these marine sulphated polysaccharides have attracted huge interests and paving way for new age antiviral drugs [126]. However, occurrence of several types of sulphated polysaccharides, differ in its monosaccharide units, molecular structure, molecular weight and even degree of sulfation, are the major drawbacks to find suitable one for the treatment of particular viral diseases. Comparatively, the sulfated polysaccharides from marine algae are the most auspicious choice of antiviral agents than other sources such as plant and microbial origin. Hence, the plant material consists of enormous amounts of metabolites, which is unfavorable for isolation of pure compound and even microbial compounds are least productive and not cost effective. However, cultivation of macroalgae, extraction and isolation of sulfated polysaccharides from marine algae are more feasible and cost effective than any other source of antiviral agents.

Table 4 An extensive illustration of antiviral efficacy of three important sulphated polysaccharides from different marine macroalgae

Macroalgal species or Source	Phylum	Type of SP	Mol. Wt. (kDa)	Cytotoxic value	Viral strain	Viral inhibition value	Mechanism of inhibition	Reference
						TCID/mL		
Cryptosyphonia woodii and *Farlowia mollis*	Rhodophyta	Crude extract	>10	-	HSV-1 and HSV-2	10^2	Viral replication	[127]
				CC_{50} (ug/mL)		CPE_{50} (ug/mL)		
Commercial	Rhodophyta	Iota-carrageenan	-	200	Ad5	>200	Viral protein synthesis	[128]
					ASF	10		
					EMC	10		
					HSV-1	2		
					HSV-2	10		
					Measles	>200		
					Polio, type 1	>200		
					SFV	10		
					Vaccinia	10		
					VSV	>200		
				IU/mL		IU/mg		
Schizymenia pacifica	Rhodophyta	SAE	~ 2000	40,000 to 80,000	HIV-1	30,0000 ± 7000	HIV Reverse Transcriptase	[128]
				CC_{50} (ug/mL)		IC_{50} (ug/mL)		
Agardhiella tenera	Rhodophyta	Galactan sulphate	-	>250	HIV-1	0.5	gp120-CD4 interaction and syncytium formation	[125]
					HIV-2	0.05		

					HSV-1	3		
					HSV-2	2.5		
					CMV	4		
					Vaccinia virus	7		
					Sindbis virus	11		
					Semliki forest virus	85		
					Junin virus	>100		
					Tacaribe virus	>100		
					Parainfluenza virus type 3	55		
					IAV	4		
					IBV	>200		
					RSV	4		
					VSV	14		
					Polio virus type 1	>200		
					Reo virus type 1	>100		
					Coxsackie virus type B4	>200		
				CC_{50} (ug/mL)		IC_{50} (ug/mL)		
Gymnogongrus griffithsiae	Rhodophyta	Carrageenan	-	1000	DENV1	>50	Viral adsorption and internalization	[129]
					DENV2	0.9		
					DENV3	13.9		
					DENV4	>50		
				CC_{50} (ug/mL)		IC_{50} (ug/mL)		

Cryptonemia crenulata	Rhodophyta	Carrageenan	-	1000	DENV1	>50	Viral adsorption and internalization	[129]
					DENV2	1		
					DENV3	14.2		
					DENV4	29.3		
				CC_{50} (ug/mL)		IC_{50} (ug/mL)		
Commercial	Rhodophyta	i-Carrageenan	-	≤ 100	HPV	0.006	Viral protein capsid	[83]
		i-Carrageenan, type II				0.005		
		i-Carrageenan, type V				0.006		
		i-Carrageenan, type Va				0.004		
		j-Carrageenan				0.044		
		j-Carrageenan, type III				0.013		
		j/k-Carrageenan, type I				0.021		
		k-Carrageenan				0.01		
		k-Carrageenan, type IV				0.005		
Commercial	Phaeophyta	Fucoidan				1.1		
Cystoseira indica	Phaeophyta	sulphated fucan	35	>1,000	HSV 1	2.1	Viral adsorption and internalization	[130]
					HSV 2	0.5		
				CC_{50} (ug/mL)		EC_{50} (ug/mL)		

Commercial	Rhodophyta	ʎ carrageenan	-	>1000	DENV-1	>50	Viral adsorption and internalization	[131]
					DENV-2	0.15		
					DENV-3	2		
					DENV-4	4.2		
Commercial	Rhodophyta	i carrageenan	-	>1000	DENV-1	40.7		
					DENV-2	0.4		
					DENV-3	4.1		
					DENV-4	8.2		
Commercial	Rhodophyta	K-Carrageenan	-	>1000	DENV-1	>50		
					DENV-2	1.8		
					DENV-3	6.3		
					DENV-4	>50		
Commercial	Rhodophyta	i- carrageenan	-	>1000	DENV-2 (Vero)	0.4		
					DENV-3 (vero)	1.1		
					DENV-2 (HepG2)	0.14		
					DENV-3 (HepG2)	0.63		
Commercial	Rhodophyta	ʎ carrageenan	-	>1000	DENV-2 (Vero)	0.22		
					DENV-3 (Vero)	0.6		
					DENV-2 (HepG2)	0.17		
					DENV-3 (HepG2)	0.63		
				CC_{50} (ug/mL)		IC_{50} (ug/mL)		

Cladosiphon okamuranus	Phaeophyta	fucoidan	-	> 1500	NDV	0.75	Viral syncytia formation	[95]
				CC_{50} (ug/mL)		IC_{50} (ug/mL)		
Acanthophora specifira (red alga)	Rhodophyta	ʎ carrageenan	-	75.9	HSV-1	80.5	Viral replication	[68]
					RVFV	75.8		
Hydroclathrus clathratus (brown alga)	Rhodophyta	k-Carrageenan	-	100.5	HSV-1	100.5		
					RVFV	95.2		
				CC_{50} (ug/mL)		IC_{50} (ug/mL)		
Kjellmaniella crassifolia	Phaeophyta	fucoidan-	53.6	2752	IAV	34.4	Viral neuraminidase, viral endocytosis	[131]
				CC_{50} (ug/mL)		IC_{50} (ug/mL)		
Fucus evanescens	Phaeophyta	Fucoidan	160	200	HSV-1	53	Viral replication	[132]
					HSV-2	45		
					ECHO	90		
					HIV-1	25		
				CC_{50} (ug/mL)		EC_{50} (ug/mL)		
Commercial	Rhodophyta	Iota Carrageenan	-	200	JEV	15	Viral adsorption and entry	[133]
				CyD_{50} (ug/mL)		ED_{50} (ug/mL)		
Fucus vesiculosus (brown seaweed)	Phaeophyta	fucoidan	10 to 20	50	HIV-1	1	Syncytium formation and RT	[134]
				CyD_{50} (ug/mL)		ED_{50} (ug/mL)		

Schizymenia dubyi	Rhodophyta	Galactan sulfate	-	187.5	HSV-1	5	Syncytium formation and RT	[135]
				187.2	HSV-2	6		
				60	Polio-2	30		
				187.5	VSV	15		
				187.5	HIV-1	10		
				CC_{50} (ug/mL)		IC_{50} (ug/mL)		
Acanthophora spicifera	Rhodophyta	Agaran sulfate	-	>1000	HSV-1	1.4	Viral adsorption and entry	[71]
					HSV-2	2		
				CC_{50} (ug/mL)		IC_{50} (ug/mL)		
Stenogramme interrupta	Rhodophyta	Carrageenan	-	>1000	HSV-1	3.55	Viral glycoprotein and entry	[136]
					HSV-2	1.9		
				CC_{50} (ug/mL)		IC_{50} (ug/mL)		
Cryptopleura ramosa	Rhodophyta	Sulfated galactan	-	476	HSV-1	1.6	Viral adsorption	[137]
					HSV-2	2.4		
				CC_{50} (ug/mL)		IC_{50} (ug/mL)		
Gigartina skottsbergii	Rhodophyta	Carrageenan	-	>1000	HSV-1	0.4	Viral glycoprotein and entry	[138]
				mg/ml (100 uL/day)		PFU/mL		
Gigartina skottsbergii (*in vivo* study)	Rhodophyta	lambda-carrageenan	-	10	HSV-2	<10	Viral inactivation	[139]

				CC_{50} (ug/mL)		% of inhibition		
Commercial	Rhodophyta	k-carrageenan	500 to 800	1000	EV71	92%	Viral inactivation	[140]
				CC_{50} (ug/mL)		IC_{50} (ug/mL)		
Nothogenia fastigiata	Rhodophyta	Sulfated Xylomannan	-	100	HSV-1	0.6	Viral entry and replication	[141]
					HSV-2	2.5		
					HCMV	0.8		
					Poliovirus	>50		
					IAV	0.2		
					IBV	20		
					Parainfluenza 3 virus	>100		
					RSV	0.9		
					Junin virus	10		
					Tacaribe virus	7.8		
					HIV-1	0.25		
					HIV-2	13.4		
					SIV	0.4		
				CC_{50} (ug/mL)		ED_{50} (ug/mL)		
Nothogenia fastigiata	Rhodophyta	Sulphated Xylogalactans	-	>200	HSV-1	15	Viral adsorption and entry	[142]
				CC_{50} (ug/mL)		IC_{50} (ug/mL)		
Bostrychia montagnei	Rhodophyta	Sulphated galactans	43.7	1000	HSV-1	15.4	Viral adsorption and entry	[143]
					HSV-2	12.4		

				CC_{50} (ug/mL)		IC_{50} (ug/mL)		
Leathesia difformis	Phaeophyta	Fucoidan	51	400	HSV-1	0.7	Viral adsorption and glycoprotin gC	[144]
					HSV-2	0.5		
					HCMV	1.9		
				CC_{50} (ug/mL)		ED_{50} (ug/mL)		
Commercial	Rhodophyta	i-carrageenan	-	200	HAV	2.5	Viral adsorption and protein synthesis	[145]
	Rhodophyta	lambda-carrageenan	-			4.5		
	Rhodophyta	k-carrageenan	-			100.3		
				CC_{50} (ug/mL)		$TCID_{50}$ /ml		
Commercial	Rhodophyta	i-carrageenan	-	1000	HRV	102	Virus internalization and replication	[123]
				CC_{50} (ug/mL)		IC_{50} (ug/mL)		
Asparagopsis armata	Rhodophyta	Sulfated galactans	-	500	HIV-1	8	Synctium formation, RT, and Viral replication	[146]
				CC_{50} (ug/mL)		IC_{50} (ug/mL)		
Cladosiphon okamuranus	Phaeophyta	Fucoidan	-	-	DENV1	4.7	Viral glycoprotein	[147]
				CC_{50} (ug/mL)		IC_{50} (ug/mL)		
Sargassum horneri	Phaeophyta	Fucoidan	229	>10000	HSV-1	1	Viral entry and replication	[148]
					HIV-1	1.2		
					HCMV	3.3		

				mg/mL/day		% of inhibition		
Porphyridium sp. (*In vivo* study)	Rhodophyta	sulfated polysaccharide	-	2	HSV-1	95%	Viral adsorption and entry	[149]
					HSV-2	95%		
						$TCID_{50}$ /ml		
Ulva lactuca	Chlorophyta	Ulvan	-	-	IAV	102	-	[150]
				CC_{50} (ug/mL)		IC_{50} (ug/mL)		
Nothogenia fastigiata	Rhodophyta	Sulfated Xylomannans	30	120	HSV-1	0.7	Viral replication	[151]
					HSV-2	0.6		
				CC_{50} (ug/mL)		IC_{50} (ug/mL)		
Monostroma latissimum	Chlorophyta	Ulvan (Rhamnan sulfate)	-	6300	HSV-1	0.78	Viral adsorption and replication	[114]
					HCMC	1.7		
					HIV-1	1.5		
				CC_{50} (ug/mL)		IC_{50} (ug/mL)		
Commercial	Rhodophyta	i-carrageenan	-	>400	H3N2	0.04	Viral entry and Viral replication	[123]
					H1N1	0.2		
				CC_{50} (ug/mL)		IC_{50} (ug/mL)		
Gracilaria corticata	Rhodophyta	Galactan sulfate	1.65	1000	HSV-1	0.19	Viral adsorption and entry	[152]
					HSV-2	0.24		
						IU/mL		

Schizymenia pacifica	Rhodophyta	Carrageenan	100	-	AMV	840000	Viral RT	[153]
				CC_{50} (ug/mL)		IC_{50} (ug/mL)		
Adenocystis utricularis	Phaeophyta	Fucoidan	19	>1000	HSV-1	1.25	-	[66]
					HSV-2	1.63		
				CC_{50} (ug/mL)		IC_{50} (ug/mL)		
Pterocladia cupillacea	Rhodophyta	Sulfated galactan	-	500	HSV-1	3.2	Viral adsorption and entry	[154]
					HSV-2	7.5		
					Pseudo rabies virus	6.2		
					HCMV	12		
				CC_{50} (ug/mL)		IC_{50} (ug/mL)		
Gymnogongrus torulosus	Rhodophyta	Carrageenan	45	1000	HSV-2	0.6	Viral glycoprotein	[155]
					DENV2	0.34		
						% of inhibition		
Fucus vesiculosus	Phaeophyta	Fucoidan	170	-	HIV-1	98.2	Viral RT	[156]
Dictyota mertensii	Phaeophyta	Fucoidan	24	-	HIV-1	99.3	Viral RT	[156]
Lobophora variegata	Phaeophyta	Fucoidan	1400	-	HIV-1	94	Viral RT	[156]
				CC_{50} (ug/mL)		$TCID_{50}$ ug/mL		
Dygenea simplex	Rhodophyta	Galactan sulfate	140	1000	HIV	62.5		[157]
				CC_{50} (ug/mL)		EC_{50} (ug/mL)		
Commercial	Rhodophyta	i-carrageenan	-	>1000	DENV1	40.7	Viral adsorption and replication	[158]
					DENV2	0.4		

					DENV3	4.1		
					DENV4	8.2		
Commercial	Rhodophyta	Lambda-carrageenan	-	>1000	DENV1	>50	Viral adsorption and replication	[158]
					DENV2	0.15		
					DENV3	2		
					DENV4	4.2		
Commercial	Rhodophyta	k-carrageenan	-	>1000	DENV1	>50	Viral adsorption and replication	[158]
					DENV2	1.8		
					DENV3	6.3		
					DENV4	>50		
				CC_{50} (ug/mL)		EC_{50} (ug/mL)		
Commercial	Rhodophyta	i-carrageenan	-	50	DENV2	0.4	Viral glycoprotein and adsorption	[159]
						% of inhibition		
Commercial (*in vivo*)	Rhodophyta	k-carrageenan	3	-	IAV	65.7	-	[81]
				CC_{50} (ug/mL)		% of inhibition		
Ulva fasciata	Chlorophyta	Ulvan	-	100	HMPV	>95 %	Viral adsorption and replication	[112]
				CC_{50} (ug/mL)		IC_{50} (ug/mL)		
Ulva clathrata	Chlorophyta	Ulvan	359800 g/mol	810	NDV	0.1	Viral Synctium formation	[105]
Cladosiphon okamuranus	Phaeophyta	Fucoidan	92.1	1136	NDV	0.01	Viral Synctium formation	[105]
						% of inhibition		

Pelvetia fastigiata	Phaeophyta	Fucoidan	100		HBsAg-anti-HBs (HBV)	91.1		[105]
				CC_{50} (ug/mL)		IC_{50} (ug/mL)		
Commercial	Rhodophyta	k-carrageenan	2	875	IAV	32.1	Viral adsorption and replication	[160]
						IC_{100} (ug/mL)		
Commercial	Rhodophyta	Lambda-carrageenan	310	-	HIV	7.8	Viral glycoprotein and adsorption	[161]
Commercial	Rhodophyta	k-carrageenan	81	-	HIV	3.9	Viral glycoprotein and adsorption	[161]
Commercial	Rhodophyta	i-carrageenan	54	-	HIV	1	Viral glycoprotein and adsorption	[161]
						IC_{100} (ug/mL)		
Commercial	Rhodophyta	Lambda-carrageenan	28	-	HIV	3.9	Viral glycoprotein and adsorption	[162]
Commercial	Rhodophyta	k-carrageenan	19	-	HIV	3.9	Viral glycoprotein and adsorption	[162]
						IC_{50} (ug/mL)		
Dictyota bartayesiana	Phaeophyta	Fucoidan	-	-	HIV	0.05	Viral adsorption and entry	[97]
Turbinaria decurrens	Phaeophyta	Fucoidan	-	-	HIV	0.13	Viral adsorption and entry	[97]
Padina pavonica	Phaeophyta	Fucoidan	-	-	HIV	0.29	Viral adsorption and entry	[98]
Stoechospermum marginatum	Phaeophyta	Fucoidan	-	-	HIV	0.34	Viral adsorption and entry	[98]
Spatoglossum macrodontum	Phaeophyta	Fucoidan	-	-	HIV	0.002	Viral adsorption and entry	[98]
				CC_{50} (ug/mL)		EC_{50} (ug/mL)		

Stoechospermum marginatum	Phaeophyta	Fucoidan	40	1000	HSV-1	3.55	Viral adsorption and entry	[163]
					HSV-2	0.63		
				CC_{50} (ug/mL)		EC_{50} (ug/mL)		
Sphaerococcus coronopifolius	Rhodophyta	Sulfated galactans	308.7	>250	HSV-1	4.1	Viral adsorption and entry	[164]
Boergeseniella thuyoides	Rhodophyta	Sulfated galactans	360.3	>250	HSV-1	17.2	Viral adsorption and entry	[164]
				CC_{50} (ug/mL)		IC_{50} (ug/mL)		
Sargassum swartzii	Phaeophyta	Fucoidan	45	1000	HIV-1	1.56	Viral adsorption and RT	[165]
						EC_{50} (ug/mL)		
Undaria pinnatifida	Phaeophyta	Fucoidan	-	-	HSV-1	5.7	Viral glycoprotein and adsorption	[166]
					HSV-2	1.7		
Splachnidium rugosum	Phaeophyta	Fucoidan	-	-	HSV-1	7.9	Viral glycoprotein and adsorption	[166]
					HSV-2	6.6		
Gigartina atropurpurea	Rhodophyta	Carrageenan	-	-	HSV-1	1.5	Viral glycoprotein and adsorption	[166]
					HSV-2	0.7		
Plocamium cartilagineum	Rhodophyta	Sulfated galactan	-	-	HSV-1	5.4	Viral glycoprotein and adsorption	[166]
					HSV-2	2.4		
				CC_{50} (ug/mL)		IC_{50} (ug/mL)		
Undaria pinnatifida	Phaeophyta	Fucoidan	9	>2000	HSV-1	2.5		[167]
					HSV-2	2.6		
					HCMV	1.5		
					IAV	15		

					Poliovirus	>100		
					Coxsackie virus	>100		
						% of inhibition		
Padina pavonica	Phaeophyta	Fucoidan	160	-	HSV	72.3		[168]
					HAV	73.3		
				CC_{50} (ug/mL)		IC_{50} ug/mL		
Macrocystis pyrifera	Phaeophyta	Fucoidan	-	>1500	Measles virus	1	Viral adsorption and entry	[169]
Eisenia arborea	Phaeophyta	Fucoidan	-	>1500	Measles virus	0.275		
Pelvetia compressa	Phaeophyta	Fucoidan	-	>1500	Measles virus	1		
Ulva intestinalis	Chlorophyta	Ulvan	-	>1500	Measles virus	3.6		
Solieria filiformis	Rhodophyta	Carrageenan	-	>1500	Measles virus	0.985		
				CC_{50} (ug/mL)		IC_{50} ug/mL		
Dictyota dichotoma	Phaeophyta	Fucoidan	23.6	312. 5	HSV-1	7.5		[170]
					CVB3	15.6		
				CC_{50} (ug/mL)		IC_{50} ug/mL		
Sargassum tenerrimum	Phaeophyta	Fucoidan	30	1000	HSV-1	1.4	Viral glycoprotein and adsorption	[171]
						IC_{50} ug/mL		
Sargassum mcclurei	Phaeophyta	Fucoidan	-	-	HIV-1	0.96		[78]
Sargassum polycystum	Phaeophyta	Fucoidan	-	-	HIV-1	0.34		
Turbinaria ornata	Phaeophyta	Fucoidan	-	-	HIV-1	0.39		
				CC_{50} (ug/mL)		IC_{50} ug/mL		
Grateloupia indica	Rhodophyta	Galactan sulfate	60	>850	HSV-1	0.27	Viral adsorption and entry	[172]

					HSV-2	0.31		
				CC_{50} (ug/mL)		IC_{50} ug/mL		
Meristiella gelidium	Rhodophyta	Carrageenan	425.6 to 956.7	>1000	HSV-2	0.05		[173]
					DENV2	0.14		
				CC_{50} (ug/mL)		IC_{50} ug/mL		
Scinaia hatei	Rhodophyta	Sulfated xylomannan	160	>1000	HSV-1	0.5	Viral adsorption and entry	[174]
					HSV-2	0.5		
				CC_{50} (ug/mL)		EC_{50} ug/mL		
Schizymenia binderi	Rhodophyta	Sulfated galactan	380	>1000	HSV-1	0.18	Viral adsorption and entry	[77]
					HSV-2	0.63		
				CC_{50} (ug/mL)		IC_{50} ug/mL		
Callophyllis variegata	Rhodophyta	Carrageenan	95	>1000	HSV-1	0.18	Viral adsorption and replication	[76]
					HSV-2	0.21		
					DENV2	0.29		
				CC_{50} (ug/mL)		EC_{50} ug/mL		
Sargassum patens	Phaeophyta	Fucoidan	-	>2500	HSV-2	1.3	Viral adsorption and entry	[175]
				CC_{50} (ug/mL)		EC_{50} ug/mL		
Sargassum patens	Phaeophyta	Fucoidan	-	>2500	HSV-1	1.5	Viral adsorption and replication	[176]

				CC50 (ug/mL)		IC50 ug/mL		
Fucus vesiculosus	Phaeophyta	Fucoidan	-	-	SARS-CoV-2	>100	Inhibits viral infection	[177]
				CC50 (ug/mL)		IC50 ug/mL		
Undaria pinnatifida	Phaeophyta	Fucoidan	-	-	SARS-CoV-2	>100	Inhibits viral infection	[177]
				CC50 (ug/mL)		IC50 ug/mL		
Red Algae	Ochrophyta	Iota-carrageenan	-	-	SARS-CoV-2	125	Inhibits viral infection	[178]
				CC50 (ug/mL)		IC50 ug/mL		
Brown Algae	Phaeophyta	Fucoidan	-	-	SARS-CoV-2	15.6	Inhibits viral infection	[178]
				CC50 (ug/mL)		EC50 ug/mL		
Saccharina japonica	Phaeophyta	High molecular weight Fucoidan	-	-	SARS-CoV-2	8.3	Inhibits viral infection	[179]

10.1. Pitfalls and solutions

The sulphated polysaccharides have poor adsorption when administered orally which failed to attain clinical trials [180,181]. Intravenous administration might also consider causing toxic effects on the proteins present in the host cells and the anticoagulant activity also a problem in intravenous administration [180]. However, sulphated polysaccharides from different sources have been reported to lack anticoagulant activity. The sulphated polysaccharides are ascribed to use as vaginal antiviral formulation [182,183]. against the spread of sexually transmitted viral diseases. Similarly, administration of sulphated polysaccharides through nasal route may have potential to inhibit the transmission of air borne viral infections including SARS-CoV-2.

A most recent study on enzyme depolymerized and native fucoidan have shown that, both are effective in the inhibition of different stages of HIV-1 replication and similarly, inhibit HSV-2 *in vitro*. However, native fucoidan had high antiviral efficacy than the enzyme depolymerized fucoidan [132]. *In vivo* study also resulted that the intraperitoneal administration of native and depolymerized fucoidan have improved the survival rate, reduced symptoms and weight loss, and suppressed viral load induced by HSV-2 [132]. In another study, synthetic highly sulphated glycomimetic oligomers resemble sulphated polysaccharide inhibits HPV16 inhibition *in vitro* and *in vivo* [182]. Kwon et al. (2020) determined that the high molecular weight Fucoidan isolated from Saccharina japonica had an EC50 value of 8.3 µg/mL against SARS-CoV-2 *in vitro* [179]. These sulfated polysaccharides bound with high affinity to the spike glycoprotein of SARS-CoV-2 virus and inhibits viral entry into the host cell [185]. Similarly, Grassauer et al. (2017), suggested to coat carrageenan on the surface of sanitary items including facial masks, gloves, tissue paper to neutralize the viral particles [89]. Therefore, it needs a greater number of research activities on sulphated polysaccharides from different marine macroalgae for its specific antiviral potential on pathogenic viruses.

11. Future perspectives

More extensive research activities and funding on sulphated polysaccharides against several human pathogenic viruses may benefit during such pandemic invasion. Some of the benefits are,

- It may also be administered as nasal aerosol for the prevention of viral infections.
- Sulphated polysaccharides may benefit as a nanocoating on the surface of PPEs for clinical staffs and in hospitals to efficiently neutralize contagious viral particles.

12. Conclusion

The discovery of antibiotics has deteriorated the bacterial pandemic diseases in the modern age. However, an alternative solution for viral pandemic diseases is still lacking. A greater number of research studies on the sulphated polysaccharides from marine macroalgae have proven its antiviral efficacy on several human pathogenic viral diseases by blocking the class I type of viral fusion glycoprotein. Similar kind of mechanism exits in the SARS-CoV-2 virus causing recent COVID-19 outbreak. Therefore, sulphated polysaccharides could be a potential bioactive compound and antiviral drug against SARS-CoV-2. Marine macroalgae are the cheaper source of sulphated polysaccharide, thus, which can also be useful to neutralize viral pathogens in other mode of applications include PPE, hand sanitizers and hand wash solutions.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare that there is no conflict of interest.

Authors Contribution

The overall concept of the study was conceived by Dr. SE and prepared by RKG and PPR, along with the help, corrections, and suggestions given by Dr. SE.

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