



## Sulfated Polysaccharide from Marine Red Microalga *Porphyridium* against SARS-CoV-2 - A Mini-Review

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### Abstract

The recent pandemic of coronavirus, COVID 19, has made researchers to search for novel antidotes against SARS-CoV-2. Utilizing all the available information on this pandemic scientific communities are currently working hard to find antidote. Activity of sulfated polysaccharides is observed on both enveloped and non-enveloped virus against the binding or entry inside the cell. Exopolysaccharides from *Porphyridium* have antiviral SPs which are active against respiratory coronaviruses. Sanitary items can be coated with these bioactive compounds to prevent COVID-19 infections.

**Keywords:** Porphyridium; COVID-19; Polysaccharides; Carrageenan

### Abbreviations

°C: Degree Celsius; µg/ml: Microgram Per Milliliter; COVID-19: Coronavirus; Immunodeficiency 2019; EPS : Exopolysaccharides; GRAS : Generally Regarded as Safe; H1N1: Influenza A Virus Sub-type H1N1; hACE-2: Human Angiotensin-Converting Enzyme-2; HBV : Hepatitis B Virus; Hcl : Hydrochloric Acid; hCov OC43 : Human Coronavirus OC43 ; HIV: Human Immunodeficiency Virus; HRV : Human Rhinovirus ; HSV-1 and 2 : Herpes Simplex Virus 1 and 2; MERS-CoV: Middle East Respiratory Syndrome Coronavirus ; MuLV: Murine Leukemia Virus; MuSV: Harvey Murine Sarcoma Virus; RBD: Receptor-Binding Domain; RNA: Ribonucleic Acid; SARS-CoV: Severe Acute Respiratory Syndrome Coronavirus; SPs : Sulfated Polysaccharides ; USFDA: United States Food and Drug Administration; VACV: Vaccinia Virus; VHSV: Viral Hemorrhagic Septicemia Virus

### Introduction

In the past few years, more than 30 antiviral drugs are approved for clinical use [1]. Ginsberg, *et al.* in 1947 reported for the first

time that polysaccharides with high molecular weight bear antiviral activity [2]. It took almost 17 years after this report to demonstrate that heparin inhibits herpes simplex virus [3]. Since viruses are getting resistance to the drugs rapidly, there are high demand for developing novel drugs with improved action. Natural sources of such novel drugs can give a promising approach to screen for antiviral compounds. Natural sources like bacteria, algae, fungi plants and animals have potential to produce such anti-viral compounds to fight against these rapidly developing viruses.

Tremendous antiviral potential has been reported from natural compound like polysaccharides especially sulfated polysaccharides (SPs) [4]. Polysaccharides are originally derived from plant sources such as cell walls, seeds, tree exudates and tuber/root [5,6] ; or from animals (chitin, hyaluronan and chondroitin sulfate) [7,8]. Additionally, hydrocolloids like gellan, wellan and xanthan are also produced from bacteria and fungi [9,10]. Huge number of polysaccharides are produced by different types of algae. These polysaccharides can be of various nature including structural type, storage

type and some also mucopolysaccharides. Macroalgae also referred to as seaweeds contain tremendous amount of such polysaccharides [11].

Carrageenan; [12], Agar, Agar [13], Fucoidan [14]; Laminaran and rhamnan sulfate [15] are some of the important antiviral polysaccharides from macroalgae [16]. Glycans, group of polysaccharides, are readily available carbohydrate form in the nature. There is an increasing market demand for naturally extracted polysaccharides to incorporate into food, pharmaceutical products and even cosmetic products. Such a high demand is barely possible to fulfill alone by macroalgae. These macroalgae are cultured in natural resources like marine beaches and their cultivation and harvesting depends purely upon the environmental conditions. To overcome the production uncertainties unicellular microalgae, such as red alga *Porphyridium*, is a striking alternative. *Porphyridium* can be grown annually in open and closed systems such as raceway ponds and photobioreactors to achieve high biomass [17,18]. This alga was reported for the first time from India by Gaikwad, *et al.* in 2009 which can be used for bio-refinery approach [19].

*Porphyridium* is a red microalga whose sulfated polysaccharides encapsulate its' cells. In the growth medium the outer part of this capsule gets solubilized to form exopolysaccharides. These polysaccharides are high molecular weight ( $5-7 \times 10^6$  Da) [20] complex sugar molecules composed of 10% glucuronic acid, 22% galactose, 24% glucose and 38% xylose with minor concentrations of arabinose, rhamnose, and mannose [21]. As these are biocompatible and biodegradable in nature, they are used in variety of applications including medicines, food, and cosmetics [22]. Pujol, *et al.* in 2007 carried out studies which suggested that there are many sulfated carbohydrates produced by marine algae, blue-green algae and also animals inhibit a number of viruses infecting humans and animals. The main purpose of this article is to recognize the potential of sulfated polysaccharides from marine algae as anti-viral agent in context of currently available data [23]. Our empathetic on COVID-19 pandemic is limited but developing with more research. Information detailed in this work is based on research carried out by other researchers in various viruses.

### Coronavirus

Coronavirus is a virus from the family coronaviridae which can lead to respiratory discomforts like MERS-CoV, SARS-CoV and com-

mon cold [24]. Outbreak of COVID-19 occurred in early December 2019 by a novel SARS-CoV-2 virus also known as Betacoronavirus in Wuhan city of China [25,26]. Group of coronaviruses are known as enveloped viruses with genetic material in the form of plus stranded RNA. These viruses are the largest in size among RNA viruses. The envelope of this virus display spike proteins in the shape of crown which play a vital role in the attachment with the host cell receptor leading to entry inside the cell [27,28]. These viruses can mutate their own genetic material and adapt to the new environment [27].

The role of the Wuhan Seafood Wholesale Market in transmission of the COVID -19 disease is unclear. This market was linked to many initial cases of COVID-19 suggesting that the disease may have spread from animals to humans [29]. A genomic study carried out by Yu, *et al.* in 2020 provides evidence that the virus was introduced from yet unknown location into the market from where it has spread rapidly. According to them transmission within humans might have happened earlier to this incidence [30]. Spread of the COVID-19 is similar to flu and can be transmitted from infected person to healthy person, principally by physical contacts, while coughing, handshaking, talking with the infected person and sneezing. It was found during SARS-CoV that fomites could carry virus particles up to 96 hrs on its surface and hence can be the same in COVID-19 transmission [31]. Multiple studies have been conducted to find cure and prevention of the disease COVID-19. Sulfated polysaccharides can be one such preventive compound to combat against COVID-19.

### Sulfated polysaccharides (SPs)

Algae are the natural sources of Polysaccharides available with very low cost. These are non-toxic and safe to handle with biodegradable properties and in many cases are biocompatible [32]. Sulfated polysaccharides are macromolecules comprising complex group of polysaccharides exhibiting impeding medical and bioactive properties [33,34]. SPs are generally found in saline environment especially in algae, plants and animals. These SPs are the compound which are of increased interest by biomedical and pharmaceutical industries to apply in their products and medicines [35]. According to Aquino, *et al.* during the evolutionary process, salt adaptation might have developed sulfated polysaccharides in organisms [36]. This was confirmed when *Rupia maritime* was

cultivated in both fresh and saline water. Sulfated polysaccharides are chiefly observed only during the saline water cultivation process. They also cultivated *Oryza sativa* in the condition of salt stress which produced carboxylated polysaccharides instead of SPs. This proposes that the adaptation against salt stress is primarily developed by oppositely charged plant cell wall.

Marine vertebrate and invertebrate animals are principal source of sulfated polysaccharides like heparin [37]. In 2010 Pomin demonstrated that marine invertebrates have capacity to produce sulfated fucans and galactans [38]. Reports indicate absence of SPs in land organisms [39]. Since sulfated polysaccharides are found mainly in marine organisms, they are concentrated more for production of such compounds. Chondroitin sulfate and heparin are two chief sources of active antiviral SPs from marine animals [40].

The SPs blocks the viral attachment to cell surface molecules. The SPs shows similar binding site on CD4 that of HIV-gp120 binding site. Binding of SPs to this lymphocyte inhibit the binding of monoclonal antibodies leading to disruption of CD4-gp120 interaction. SPs shield off the positive charged site on V3 loop of gp120 protein in HIV preventing the viral attachment to cell surface [41].

The SPs anionic nature is involved in blocking of the viral attachment to the host. SPs provide a network of three-dimensional gel over the viral cell surface thus preventing the exposure of cationic domains leading to blockage of the attachment with host cell [42]. Kwon., *et al.* studied the binding efficiency of SPs to the SARS-CoV-2 S-protein *in vitro* and concluded that these SPs are highly effective in blocking the entry of SARS-CoV-2 to the host cell [43]. Salih., *et al.* studied marine sulfated polysaccharides using molecular docking and dynamic simulating experiments to find out the interaction of MSPs with RBD of s- protein and hACE-2 receptors on SARS-CoV-2. They found out that apart from heparin, sulfated galactofucan, sulfated polymannuroguluronate, sulfated Mannan, sulfated heterohamnan and chondroitin sulfate are potential in binding to the receptor sites of SARS-CoV-2 and thus blocking their entry on host cells [44].

Song., *et al.* 2020 studied four marine sulfated polysaccharides, for their inhibitory activity against SARS-CoV-2. Namely, sea cucumber sulfated polysaccharide (SCSP), fucoidan from brown algae, iota-carrageenan from red algae, and chondroitin sulfate

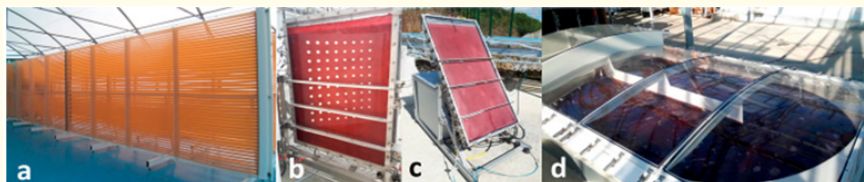
C from sharks (CS). Among these three SCSP, fucoidan, and carrageenan have shown significant antiviral activities at concentrations ranging from 3.90-500  $\mu\text{g mL}^{-1}$ . Hence, they could be used to treat COVID-19 [45].

Marine green, red and yellow algae are wide sources of SPs. Studies have been carried out on the antibacterial activities of SPs from red alga *Gracilaria arcuate* on five pathogenic fish bacteria which indicates versatile action of these polysaccharides [46]. Algae based SPs are favored over animal-based SPs due to its vegan source. These SPs are generally excreted out along with mucilaginous exopolysaccharides (EPS). One such alga is *Porphyridium* belonging to Rhodophyta.

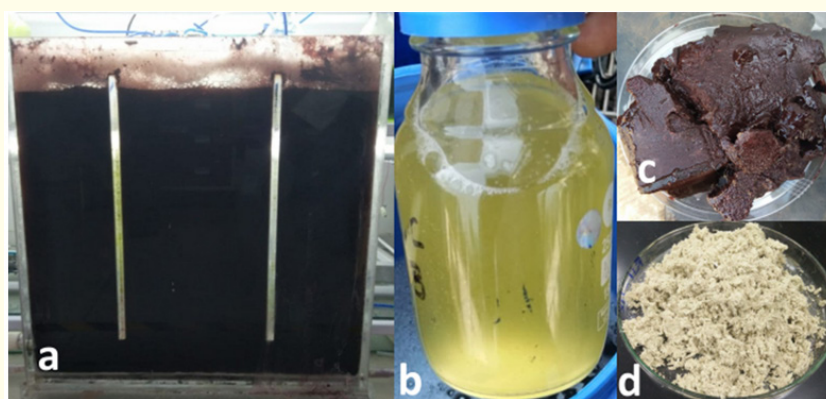
### Sulfated polysaccharides from red alga *Porphyridium*

Commercial large-scale cultivation of *Porphyridium* is carried out for its various products [47] (Figure 1). It has many clinically important compounds in the exopolysaccharides. The secretion of exopolysaccharides occurs at the stationary phase during cultivation. Many research studies have demonstrated the potential use of this alga as antiviral, antibacterial and anti-inflammatory agent. High growth rate ( $0.48 \text{ h}^{-1}$ ) [48] and high EPS production (up to 2.5 g/L) [49] makes this alga favorite choice of cultivators (Figure 2.)

Arad, S. and colleagues in 1985 cultivated *Porphyridium aeruginum* as it is unicellular organism with higher growth rate over other red macroalgae. The phycocolloids also termed as EPS are formed by *Porphyridium* outside the cells in dissolved conditions which makes the liquid viscous. Since these phycocolloids contain mixture of sulfated sugars they are termed as sulfated polysaccharides [50]. The main composition of polysaccharides from *Porphyridium* are glucose, xylose, sulfated esters and galactose with minor presence of hexuronic acids [51,52] and fractions of glucuronic acid and galacturonic acid [53]. The polysaccharide produced from *Porphyridium* is a heteropolymer similar to Carrageenan as sulfated galactans of other red macroalgae. When specific viscosity of polysaccharide was compared with lambda and kappa carrageenans, it was found to be more viscous and hence preferred over others (Figure 3) [51].



**Figure 1:** Commercial cultivation of *Porphyridium cruentum* by various industries: (a) Vertical PBR cultivation in Greensea, Mèze, France; (b) Flat plate vertical photobioreactor with artificial incident light; (c) Inclined flat plate photobioreactor under exposed under sun light (AlgoSolis), (d) Raceway ponds in AlgoSolis with closed transparent cover. Source: Gagnard., et al. 2019.

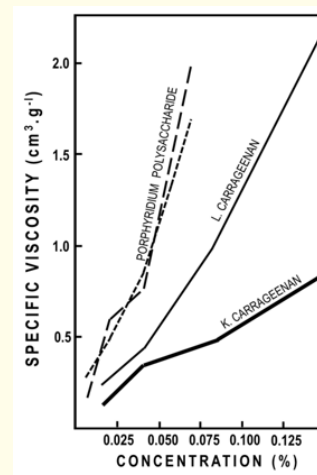


**Figure 2:** Production of biomass of *Porphyridium* and EPS in the in-house facility a: cultivation of alga in vertical flat panel photobioreactor; b: Supernatant containing EPS after centrifugation; c: algal biomass as wet slurry; d. exopolysaccharides after drying.

### Carrageenans and their importance in clinical trial

Studies have been carried out by many researchers to validate the clinical benefits of biologically active molecules from red algae to fight against coronaviruses. Carrageenan is one such compound that has antiviral property in human health care. According to Periera L. (2018) carrageenans have ability to inhibit binding of many enveloped and non-enveloped viruses selectively [54].

Certain marine algae were reviewed for bioactivity of their SPs by Jiao, G., et al. in 2011. Though Agarans and carrageenans show structural similarity, agarans have galactans in the 4-linked  $\alpha$ -galactose residues of the L-series and D-series. High molecular weight carrageenans are classified as per the pattern of sulfation and presence of 3,6-anhydro-galactose on D-units [55].



**Figure 3:** Comparison between viscosities of polysaccharide from *Porphyridium* and lambda and kappa carrageenans [51].

Studies were conducted on patients reporting common cold caused by coronaviruses in 2014. Medical practitioners-initiated treatment with nasal spray containing carrageenan in patients showing early cold symptoms. 50% of patients were treated with iota-carrageenan nasal spray three times in a day for one week and 50% patients were supplemented with placebo nasal spray. Patients receiving carrageenan reduced duration of cold than those who received placebo spray. Furthermore, relapses were also accounted in the study which confirm lesser relapse in case of patients treated with carrageenan nasal spray compared to placebo treatment. Viral titer was also found to be lower in patients treated with carrageenan [56]. Morokutti-Kurz, M., (2017) treated patients reporting sore throat with hexylresorcinol, Amylmetacresol/ 2,4-dichlorobenzyl alcohol or carrageenan lozenges as active ingredients. As per the results only carrageenan lozenges were active against H1N1n, HRV8, HRV1a, CoxsackievirusA10 and hCoV OC43 [57]. Similar studies were conducted on patients reporting rhinitis and sinusitis caused by HRV1a and hCoV OC43. Treatment included two active components as xylometazoline HCl and iota-carrageenan without influencing each other and exhibiting their decongestion and antiviral activities respectively [58].

Carrageenan derived from red algae at the concentration of 400 µg/ml inhibits cell death in case of coronavirus infected patients. Among three types of carrageenans, iota, lambda and kappa, only iota carrageenan demonstrated cell death inhibition at very low concentration of 4 µg/ml. other two types require quite high concentration to show positive effects. They also noted that carrageenan pretreated cells remain well protected against coronavirus infection. These results indicate the positive response of carrageenan against coronavirus infection when applied onto solid surface of sanitary material like glove, tissue, masks, cotton swab, etc. [59]. Leibbrandt, *et al.* carried out a study in 2010 on oseltamivir resistant H1N1 influenza strains which was pandemic in 2009. They used iota carrageenan to find its action against this virus and concluded as a potent inhibitor of Influenza-A virus infection [60].

Recently iota carrageenan from red alga is incorporated into nasal spray Nasitrol® which is launched by Amcyte Pharma in US with the belief that it can resist the transmittance of COVID-19 [61]. According to one clinical trial study, nasal spray containing iota-carrageenan significantly prevented COVID-19 among healthcare workers who were taking care of COVID-19 patients in hospital [62].

### Extraction of carrageenan

A reliable commercial extraction method for kappa, iota and lambda carrageenan was demonstrated by Ramalingam and colleagues in 2003 from marine macroalgae. Extraction of Lambda and iota carrageenans are processed through sun-dried and washed biomass. This is followed by washing dried material in hot environment and filtering the material. The filtrate is evaporated and carrageenans precipitated using alcohol precipitation. The precipitated carrageenans are collected after centrifugation which is dried and powdered [63].

### Safety aspects of carrageenan

In the past 600 years and before, carrageenan has been included in the food applications. Carrageenan is recognized as safe (GRAS) due to its safe use of history since long time by USFDA [64]. Carrageenan is usually found excreted along with exopolysaccharides which contain many other important polysaccharides. The presence of which may also enhance the efficacy of carrageenan.

### Exopolysaccharides extraction from *Porphyridium*

By using cross flow membrane filtration technique, Balti R, *et al.* 2018 extracted EPS from *Porphyridium*. The extraction of crude EPS is also possible from alcohol by concentrating the liquid. Chilled ethanol 90-100% and centrifuged supernatant are mixed in equal volumes and exposed to 4°C overnight. This treatment increases the concentration of EPS. After precipitation, the EPS obtained is dried for further use [65].

### Exopolysaccharides from *Porphyridium* and their antiviral applications

It is evident that animals and algae from marine environment produce sulfated polysaccharides with antiviral activity against many viruses [52]. Exopolysaccharides extracted from various marine red algae are summarized for their antiviral activity by Raposo, *et al.* in 2013. *Porphyridium* EPS is known to control viruses like retrovirus, VARICELA ZOSTER VIRUS [24] HSV-1 and 2 [66], MuSV/MuLV, MuSV-124, VHSV, HBV, AFRICAN SWINE FEVER VIRUS, VACV and VACV-GFP, VESICULAR STOMATITIS VIRUS and ECTROMELIA VIRUS [52]. This makes it a unique application in medicinal field.

*Porphyridium* EPS is demonstrated to boost immunity in mouse. This is achieved by improving proliferation of spleen cells and de-

veloping a greater number of killer cells. The antiviral activity of sulphated polysaccharides is determined by the degree of sulfation. In some semisynthetic polysaccharides it is documented that high sulfation of polysaccharides leads to higher antiviral activity [40].

In 2018, Lemos D., *et al.* extracted and analyzed EPS from *Porphyridium* and found the coexistence of antiviral carrageenan with agar and xanthum gum. Along with exopolysaccharides *Porphyridium* also secretes important sugar molecules like N-acetylglucosamine that are known to bind pathogen with slight modification in the saccharide part [67]. The same is also used as a substrate for production of most common sialic acid (N-Acetylneuraminic acid), that act as a surface receptor for most of the influenza viruses [68]. Chemically synthesized clinical molecules containing this sialic are used to produce inhibitors of neuraminidase which is potential against influenza viruses [69].

## Conclusion

From several analytical reports globally carried out on antiviral activity of SPs from *Porphyridium*, it can be concluded that this molecule can be a great source to combat viral diseases. Its immune boosting property supports the multipurpose use of SPs in COVID-19 pandemic. Marine polysaccharides from seaweeds have great antiviral activities and specifically against SARS-CoV-2. Polysaccharides are believed to interact with the binding of SARS-CoV2 and HSPG or EGFR pathway. Polysaccharides can also changes induce structural changes of SARS-CoV2 RBD protein [70]. As mentioned earlier, coronaviral respiratory disorders are controlled by carrageenans from different biological sources including *Porphyridium* and hence its role in the current pandemic situation is also expected to be admirable. The spreading rate of COVID-19 is huge and created a serious threat to the world which requires very rapid research for preventing and curing the disease. To add a brick to the building of research we can attempt SPs and carrageenan extracted from *Porphyridium* in clinical studies and help to reduce viral spread. Due to presence of multiple compounds in the EPS of *Porphyridium*, this organism and its compounds can change the scenario in treating and preventing COVID-19 pandemic. To find the preventive application, SPs can be coated on respiratory masks and in sanitary products as antiviral agents. This review can help scientists build strong base in developing products for fighting against the virus causing COVID-19 and treating the symptoms.

## Conflict of Interest

There are no conflicts of interest in the current review paper.

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