Vol 3 | Issue 1 | Pages 19-31

Journal of Industrial Biotechnology

Research Article

DOI: 10.36959/967/630

Algal and Cyanobacterial Polysaccharides as Promising Antiviral Agents against Human Viruses

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Abstract

Recently the morbidity, mortality and economic losses due to rapid transmission of Coronavirus (COVID-19) worldwide has incentivatedan urgent call for the scientists to discover efficient antiviral drugs for human health. Marine polysaccharides have long been recognized for their biological activities with huge application potentials in biomedical field. Their antiviral activities have been well documented against various types of infectious viruses and new studies proving their antiviral potential are frequently coming out. This paper is an attempt to compile the latest developments in research regarding the antiviral potential of algal polysaccharides, including macroalgae (red, brown, green), microalgae and cyanobacteria, against infectious human viruses. Furthermore, their possible mechanisms of antiviral actions will also be discussed briefly. This information will provide an insight for the utilization of algal polysaccharides to prevent the virulent viruses which are yet to be well treated.

Keywords

Algal polysaccharides, Antiviral activity, Mechanisms, Drug development, Sulfated polysaccharide

Introduction

Algae, have great potential as the producers of commercially significant natural compounds with numerous nutraceutical and pharmaceutical applications [1-3]. Algae are a diverse group of oxygen-generating photosynthetic organisms with simple reproductive system which play a key role in ecosystems as primary producers. Macroalgae are multi cellular organisms, on the basis of pigmentation they are generally classified as Phaeophyta (brown algae) Rhodophyta (red algae) and Chlorophyta (green algae) [4]. Both macro and microalgae are significant owing to their capability to accumulate a huge array of compounds with variety of biological activities. At cellular level, algae produce primary and secondary metabolites including complex organic compounds, polyunsaturated fatty acids, phytopigments (xanthophylls and carotenoids), phenolic substances, docosahexaenoic acid, carbohydrates, vitamins, tannins, peptides and Terpenoids [5-10]. The chemical composition of algae varies greatly among species with growth habitats, environmental conditions, seasonality and geographic areas. Algae are remarkable living cells as a source of valuable bioactive molecules since several species are Generally Recognized as Safe (GRAS) attributable to lack of harmful toxins and other pathogenic microbes [11]. The FDA (Food and Drug Administration) has approved several marine-derived natural compounds as therapeutic drugs, and many of them are currently in various stages of clinical trials [12]. Around 40 compounds of sulfated polysaccharides from marine algae are commercially available in the market, and many more are being implemented at the preclinical or clinical stages of human trials [13].

Polysaccharides, as natural bioactive compounds with useful chemical and biological characteristics, are gaining extensive research interests in recent times. Polysaccharides have also been broadly investigated for their biomedical and pharmaceutical application potentials [14]. Marine sulfated polysaccharides are being investigated as a possible source of biologically active compounds for drug development [15]. Algal polysaccharides have been known to have antitumor,

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Accepted: April 01, 2022

Published online: April 04, 2022

Citation: Khazi MI, Liaqat F, Li C, et al. (2022) Algal and Cyanobacterial Polysaccharides as Promising Antiviral Agents against Human Viruses. J Ind Biotechnol 3(1):19-31

antiviral, antioxidant, antimicrobial, anticoagulant, and anti-inflammatory effects [13,16].

In recent years, despite the development of vaccines and drugs to treat various infectious and/or harmful viruses, rapid spread of viral diseases are striking the world to a great extent. For instance, Human Immunodeficiency Virus (HIV) and Hepatitis C Virus (HCV) are serious threat to human health worldwide. Some viruses, such as Herpes Simplex Viruses (HSV-1 and HSV-2), dengue virus, and most respiratory-tract viruses, have no reliable vaccines [17]. Moreover, new viral infectious diseases have emerged in recent times. Ongoing worldwide pandemic of COVID-19 since the end of last year is a fitting example to quote here. It is found that the virus mutations are constantly occurring in infection, therefore, new antivirals are indispensable [18]. Toxicity, drug efficacy, and costs of the vaccines are still the unsolved problems, which are predominantly higher in developing world due to the inaccessibility of drugs [19]. Likewise, the emerging resistance to existing antiviral treatments by many viruses such as HIV type 1 or HSV-1 is becoming a major impediment in the treatment of viral diseases, encouraging the search for more efficient antiviral agents [17]. Nowadays, microalgal and cyanobacterial compounds have already gained considerable attention as potential antiviral agents. These natural compounds from marine sources are deliberated as the most auspicious antiviral agents with minimum toxicity to host cells. For instance, sulfated polysaccharides including fucoidans, p-KG03, heparin and dextran sulfate are known for their broad-spectrum antiviral activity against several types of viruses [20]. This review work is thus carried out to present the updated information about the antiviral activities of marine algae (macro, microalgae and cyanobacteria), by focusing on their polysaccharides. This review focuses on reporting the main advances published over the last 15-20 years.

Potential Antiviral Algal Polysaccharides

Macroalgae polysaccharides

Polysaccharides are abundant in macroalgae, accounting for up to 70% of their dry weight. In recent time, special research consideration has been given to the isolation and characterization of marine macroalgae due to their biological activities and plentiful health benefits in food and medical sectors. Among the algae polysaccharides, macroalgae polysaccharides were extensively studied, compared to their unicellular microalgal and cyanobacterial counterparts. Polysaccharides are complex and heterogeneous macromolecules made up of long chains of monosaccharides that are joined together by glycosidic linkages. They break down into its constituent oligosaccharides or monosaccharides when hydrolyzed. They have a variety of structures, ranging from heavily branching to linear. Algal polysaccharides mostly include mucopolysaccharides, storage, and cell wall polysaccharides. Laminarin, alginic acid, sargassan, and fucodin are found in brown algae. Carrageenans, agars, xylans, galactan, floridean, and porphyrin as a mucopolysaccharide are found in red algae. Whereas, green algae contain galactans, xylans and sulfuric acid polysaccharides [21]. The algal polysaccharides are species-specific and grouped into sulfated and non-sulfated categories [22, 23]. Their composition and proportion varies greatly among species with growth, morphological stage of algal life cycle and environmental conditions, seasonality and geographic areas [24, 25]. Sulfated polysaccharides (S-PS) areglycosaminoglycans, contains hemi-ester sulfate groups in the sugar residues, which play storage and structural roles in algae. The biological activities of S-PS normally depends on their complex interaction of structural features such as, molecular weight, sulfation, branching, glycosidic linkages, sulfate content, sugar composition and stereochemistry [1]. Therefore, understanding of their structures may lead to successful elucidation of their biological activities. Many species of marine algae contain significant amount of S-PS that have been shown *invivo/invitro* activity against a broad range of viruses such as HIV, herpes, tagoviruses, paramyxoviruses, rhadoviruses and dengue virus [26-28]. Polysaccharides from various marine algae have been extensively investigated for their biological activities [1, 21, 29].

Red algae (Rhodophyta)

Red algae are one of the ancient and largest groups of eukaryotic algae that are known as the source of unique sulfated galactans. The red algae usually contain hydrocolloids (carrageenan and agar), xylans, floridian, starch, cellulose and mannans [30, 31]. Among them, carrageenans are extensively studied for their antiviral potential against a variety of viruses.

Carrageenan is an anionic S-PS with high molecular weight (MW), composed of alternate units of α-d-galactose or 3,6-anhydro-α-d-galactose and β-d-galactose, linked together by α-(1,3) and β-(1,4) glycosidic bound [32]. Carrageenan is most widely studied polysaccharide of red algae which is mostly extracted from the genera *Chondrus*, *Gigartina*, *Hypnea*, and *Eucheuma*. Based on sulfate content and position, carrageenans categorized into kappa (κ), iota (ι), and lambda (λ) carrageenans [3, 33]. The bioactivity of carrageenans have been demonstrated against many viruses, for instance, herpes simplex virus (HSV-1 and HSV-2), human immunodeficiency virus (HIV), Human cytomegalovirus and vesicular stomatitis virus (VSV) [33]. In a recent report, Song et al. (2020) [34] found strong antiviral effects of ι-carrageenan extracted from red algae against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Rothan and Yusof (2020) [35] also reported the potential of carrageenan against Japanese Encephalitis Virus. In a study by Girond et al. (1991) [36] the researchers found a significant antiviral activity of ι-, λ- and κ-carrageenans against hepatitis A virus (HAV) because of their inhibitory action on the viral replication Moreover, Gomaa and Elshoubaky (2016) [37] reported the inhibition of Rift valley fever virus (RVFV) and HSV-1 replication by carrageenan obtained from a red alga *Acanthophora specifira*. In another study, ι-carrageenan was reported to inhibit Influenza A Virus by successfully inhibiting virus adsorption to the host cells [38]. Furthermore, a nasal spray containing ι-carrageenan had showed promising results for the successful treatment of initial common cold symptoms [39]. Several other studies also demonstrated the inhibition effect of ι-carrageenan against non-enveloped human viral pathogens such as HAV and papilloma viruses invitro [40].

The antiviral effects of carrageenans primarily linked with their MW and the degree of sulfation [26]. Due to high MW and reduced tissue-penetrating capability of carrageenan, its antiviral applications are limited [19]. However, the lower MW carrageenan oligosaccharides obtained by enzymatic or chemical degradation can easily contact to the virus, resulting in an increased bioactivity. More recently, Tang, et al. (2013) [41] investigated the *invivo* anti-influenza virus activity of low molecular weight carrageenans, their acetylated derivatives, and an acetylated and sulfated derivative in FM1-induced pulmonary oedema model. According to the findings, the antiviral activity of carrageenan was enhanced after the addition of an acetyl group and sulfation indicating that proper acetylation degree and sulfation degree demonstrating that the degree of acetylation and sulfation is critical for antiviral properties of S-PS. Moreover, Wang, et al. (2011) [42] found that low MW oligosaccharides of κ-carrageenan have shown significant antiviral effect against influenza A H1N1 virus by inhibiting the viral replication both invivo and invitro. Yamada, et al. (2000) [43] also reported the promising ability of depolymerized sulfated kappa- and iota-carrageenan to inhibit replication of HIV.

Galactan is another important sulfated polysaccharides commonly found in red alga. It has been demonstrated in the earlier studies that galactans have antiviral efficacy against HIV and HSV, pseudo rabies virus and human cytomegalovirus. Galactan can inhibit the viral entry to the host and also can suppress the viral replication [44]. Galactan can also block the replication of virus and the syncytium formation between uninfected and infected cells (Exploring algae and cyanobacteria as a promising natural source of antiviral drug against SARS-CoV-2). Bouhlal, et al. (2011) [45] have isolated sulfated polysaccharides from red algae (*Boergeseniella thuyoides* and *Sphaerococcus coronopifolius*) and reported their antiviral activities against HIV and HSV. They further reported that S-PS have inhibitory effects on invitro replication of the HIV at 12.5 µg/mL concentration, while they inhibited the HSV-1 replication in Vero cells at 4.1 and 17.2 µg/mL concentration.

Brown algae (Phaeophyceae)

Marine derived S-PS from brown algae, have gained increasing attention as potential antiviral drugs. Fucoidans are anionic polymers produced by brown algae and they contain L-fucose, sulfate groups and other monosaccharides [29, 46]. Their biological properties are associated with their physical characteristics such as structure of the main chain, sulfation pattern, MW, monosaccharide composition and acetate groups [47]. In a recent study, Sun, et al. (2020) [48] Purified fucoidans (SHAP-1 and SHAP-2) which possess high amount of sulfate groups from brown algae *Sargassum henslowianum* and evaluated their inhibitory activity against both HSV-1 and HSV-2 with no cytotoxicity. Sanniyasi, et al. (2019) [49] purified fucoidan from two brown algae, evaluated their anti-HIV activity, and reported that the IC50 value of the purified fucoidan extracts of *Turbinaria decurrens* and *Dictyota bartayesiana* were 131.7ng/ml and 57.6ng/ml, respectively. An earlier study also testified that the fractions of fucoidans extracted from *Leathessia marina* possess good anti-HSV-1, HSV-2 and anti-human cytomegalovirus potential by inhibiting the viral adsorption [50]. Likewise, the antiviral activity of the native and modified fucoidans (modified with enzyme) from *Fucus evanescens* against HSV-1, HSV-2, HIV-1 and enterovirus on Vero and human MT-4 cell lines were studied and the results indicated that native fucoidan more effectively inhibited the HSV (HSV-1 and HSV-2) replication than modified fucoidans. Whereas, both native and modified fucoidans showed similar antiviral activity against enterovirus and HIV-1 [47]. Wang, et al. (2017b) [51] demonstrated the potent antiviral activity of fucoidan derived from brown algae *Kjellmaniella crassifolia* against Influenza A Virus and reported that fucoidan efficiently blocked influenza virus infection *invitro* with low toxicity. In addition, polysaccharides extracted from *Sargassum fluitans* showed antiviral effects against HSV-1 *invitro* without cytotoxicity [52].

Laminaran is a non-sulfated molecule, however it can exist in sulfated form, primarily present in brown algae including *Ascophyllum, Fucus*, *Saccharina.* Laminaran is classified into two groups: M-series with D-mannitol units and G-series with glucose units in chain [33]. Laminarans were previously reported to inhibit viral replication, proliferation and reverse transcriptase activity of HIV [53].

Alginate is a non-sulfated anionic hydrophilic polymer normally obtained from brown algae including *Laminaria*, *Macrocystis*, *Ascophyllum*, *Sargassum, Durvillaea, Lessonia, Ecklonia*species. It has been frequently investigated for its biological activities [54, 55] and used for various applications in food, cosmetics, paper, and pharmaceutical industry [21]. Alginate is known to have antiviral activity against HIV infection mostly via the strong attachment of gp120 protein with CD4 molecules on the surface of T-cells [56]. It is a heteropolysaccharide consisting of 1,4-linked β-D-mannuronic acid (M) and 1,4 α-L-guluronic acid (G block) residues arranged in homogenous (poly-G, poly-M blocks) or heterogenous (GM blocks) block-like patterns [57]. The use of alginate in wound dressing products is becoming more prevalent. Alginate has also been identified as an immunogen that protects against infectious diseases in both animals and humans. In a semi-dilute state, aqueous solutions of these alginate derivatives demonstrated the usual rheological features of physically cross linked, gel-like networks, which may be beneficial for cartilage repair and regeneration. Furthermore, alginate hydrolysates and derivatives demonstrate exceptional bioactivities, including stimulation of human keratinocytes, acceleration of plant root growth, migration of human endothelial cells, and enhancement of penicillin synthesis from *Penicillium chrysogenum* [58]. The alginate polysaccharide 911 was reported to inhibit HIV reverse transcriptase along with DNA polymerase activity of Hepatitis B virus (HBV) [59,60].

Green algae (Chlorophyta)

Ulvan is the most important sulfated polysaccharide of green algal cell wall such as *Ulva* [61]. *Ulvan* is a sulfated hetero-polysaccharide comprised of disaccharide units of glucuronic acid or iduronic acid attached by a sulfated 1,4 L-rhamnose unit with trace amounts of xylose and glucose [62].

Many studies reported the potent antiviral activity of ulvan and other sulfated polysaccharides of green algae against HSV, Japanese encephalitis virus (JEV), dengue virus (DENV), measles virus (MeV) and influenza virus H1N1 [26, 63-66]. Ivanova, et al. (1994) [67] also reported dose dependent and strain-specific significant antiviral effect of the ulvan extracted from green algae on influenza A virus. Aside from above mentioned polysaccharides, many studies reported the antiviral activities of other sulfated polysaccharides, such as, rhamnan sulfate extracted from different marine algae. For example, Lee, et al. (2004) [68] extracted different S-PS from various green algae and assayed for anti-HSV-1 activity and demonstrated the significant antiviral effects with IC50 values of 0.38 - 8.5 micro g/mL. In a recent study, Terasawa, et al. (2020) [69] demonstrated the antiviral activity of rhamnan sulfate derived from the green alga *Monostroma nitidum* against influenza A virus and reported the inhibition of both virus adsorption and entry steps. In addition, Rhamnan sulfate also shown inhibition effects against HIV, human cytomegalovirus, HSV-1, HSV-2, measles virus, mump virus and human corona virus [68-71]. Antiviral studies of algal polysaccharides including red, brown and green algae against infection viruses along with their reported mechanisms of action are summarized in the Table 1.

Antiviral activity of eukaryotic microalgal polysaccharides

Microalgae have ability to produce a variety of valuable polysaccharides. These polysaccharides serve mainly as structural and storage molecules. During *invitro* cultivation of algal cells in broth medium, soluble fraction of polysaccharides dissolve from the cell surface to the medium, while the bound fraction consisting of 50-70% of polysaccharides remain attached to the cells. The microalgal polysaccharides protect the cells against desiccation and ensure its stability against environmental stress (temperature, pH, and salinity, oxidative stress). Algal polysaccharides have unique characteristics including, composition, structure, stability and fluid dynamics. Above all, the bioactivities of polysaccharides is a vital character to make them value-added products with various potential applications [72].

Various studies have verified the antiviral activities of polysaccharides obtained from marine microalgae against various types of infections viruses as presented in Table 2. Huheihel et al. (2002) [73] Reported impressive antiviral activity of sulfated polysaccharides from red microalga against HSV-1 and HSV-2. The findings also provided an indirect evidence for a strong interaction between the polysaccharide and HSV, and a weak interaction with the cell surface. Santoyo, et al. (2012) [74] Studied the antiviral activity of microalgal extracts against HSV-1 at different stages during viral infection. The results revealed that the extracts were effective against HSV-1 intracellular replication [74]. Hasui, et al. (1995) [75] Reported the antiviral efficiency of extracellular sulfated polysaccharides from *Cochlodinium polykrikoides* against different viruses with no cytotoxic effects to the host cells. The inhibition of viruses was attained at concentrations that were not noticeably inhibitory to the blood coagulation process. Furthermore, Kim, et al. (2012) [20] found that a sulfated polysaccharide (p-KG03) extracted from the marine microalga *Gyrodinium impudium* displayed significant antiviral effect on influenza A virus. Further studies disclosed that the involved mechanism of antiviral action was the inhibition of virus replication. The inhibition was maximized when p-KG03 is added within 6 hours after viral infection, indicating that primarily the viral attachment and internalization processes were targeted by algal polysaccharide.

Cyanobacterial polysaccharides

Cyanobacteria are a large and well-known group of microorganisms that are capable of performing oxygenic photosynthesis and also possess some typical prokaryotic features [76]. Cyanobacteria are capable of producing a large chemo-diversity of polysaccharides, playing different roles within the cells. These polysaccharides have gained increasing interests due to a very large variety of chemical structures and as a consequence, a great variety of physicochemical and potential original biological properties [76]. Chitin, cellulose, glycogen, starch, agar and carrageenan are some most abundant natural polysaccharides produced by cyanobacteria. A sulfated polysaccharide known as calcium spirulan composed of rhamnose, 3-O-methyl-rhamnose, 2,3-di-O-methyl-rhamnose, 3-O-methylxylose, uronic acids, sulfate groups and calcium ions was found in *Arthrospira platensis*. Nostoflan, another cyanobacterial polysaccharide, found in terrestrial cyanobacterium, *Nostoc flagelliforme* contains glucose, xylose, galactose, mannose and glucuronic acid on the non-reducing ends. Nostoflan has low cytotoxicity and a broad spectrum of antiviral activity as well as immunostimulatory activity [77]. Ca-spirulan showed potent and broad-spectrum activity against HIV-1, HIV-2, influenza and several other enveloped viruses. They inhibit the reverse transcriptase activity of HIV-1 and also prevent virus-cell attachment. They also inhibit the fusion between HIV-infected and uninfected CD4+ lymphocytes, a mechanism that greatly enhances viral infectivity [78].

Antiviral potential of cyanobacterial polysaccharides against different viruses along with their mechanism of action is summarized in Table 3. Intracellular polysaccharide produced by *Arthrospira platensis*, has been seen to exhibit antiviral activity against several viruses *invitro* by inhibiting the penetration of the virus into the host cells used [79]. Radonić, et al. (2011) [80] also showed that the anionic exopolysaccharide TK V3 produced by cyanobacteria *A. platensis* exhibited antiviral activity both *invitro* and *invivo* against two strains of Vaccinia virus and an Ectromelia virus. Moreover, an acidic polysaccharide nostoflan was reported to have antiviral activity against HSV-1, HSV-2, human cytomegalovirus, and influenza A virus [81]. Polysaccharides from *Spirulina maxima* and *S. platensis* have also shown antiviral potential against different viruses [82]. These findings suggest that cyanobacterial polysaccharides are having good potential to be used as starting material for antiviral drug development. Therefore, the identification of more antiviral cyanobacterial polysaccharides and to determine their potential as effective antiviral therapeutics are prerequisite.

Table 1: Antiviral activity of macroalgal polysaccharides

Macroalgae	Compounds	Mechanism of action	Virus	In vitro/In vivo	Reference
Red Alga					
Nothogenia fastigiata	Sulfated xylomannan	Inhibition of replication	HSV-1 and HSV-2	In vitro (Vero cells, HEp-2 and BHK-21)	(Pujol et al., 1995)
Bostrychia montagnei	Sulfated galactans	Inhibition of replication	HSV 1 and 2	In vitro (Vero, African green monkey kidney cell line)	(Duarte et al., 2001)
Asparagopsis armata	Sulfated galactans	Inhibition of replication	HIV	In vitro (MT4 and CEM cell lines)	(Haslin et al., 2001)
Gracilaria corticata	Sulfated galactans	Inhibition of attachment	HSV-1 and HSV-2	In vitro (Vero, African green monkey kidney cell line)	(Mazumder et al., 2002)
Gymnogongrus torulosus	DL- hybrid galactans	Inhibition of the binding of envelope glycoprotein with the cell receptor	HSV-2, dengue virus 2	In vitro (Vero, African green monkey kidney cell line)	(Pujol et al., 2002)
Gymnogongrus griffithsiae and Cryptonemia crenulata	κ,ι,ν-carrageenan carrageenan G3D and the DL-galactan hybrid C2S-3	Inhibition of adsorption and internalization	Dengue virus	Invitro (Vero cells, human hepatoma cell line HepG2, human diploid foreskin fibroblast cell line PH and The C6/36 HT mosquito cell line from *Aedes Albopictus*)	(Talarico et al., 2007)
Sebdenia polydactyla	Sulfated xylomannans		HSV-1	In vitro (Vero, African green monkey kidney cell line)	(Ghosh et al., 2009b)
Euchema denticulatum, Gigartina acicularis and Kappaphycus cottonii	Carrageenan	Inhibition of attachment	HSV-1 and Poliovirus	In vitro (Vero, African green monkey kidney cell line)	(Montanha et al., 2009)
Grateloupia indica, Scinaia hatei and Gracilaria corticata	Sulfated polysaccharides	Inhibition of adsorption and internalization	Dengue virus	In vitro (Vero, African green monkey kidney cell line)	(Pujol et al., 2012)
Acanthophora specifira	Carrageenan	Inhibition of viral replication	HSV-1 and RVFV	In vitro (Vero, African green monkey kidney cell line)	(Gomaa and Elshoubaky, 2016)
Solieria filiformis	Sulfated Polysaccharides		Measles virus	In vitro (Vero, African green monkey kidney cell line)	(Morán-Santibañez et al., 2016)
Rhodymenia pseudopalmata, Solieria filiformis and Hydropuntia cornea	Polysaccharides	-	HSV-1	In vitro (Vero, African green monkey kidney cell line)	(Bedoux et al., 2017)
Brown Alga					
Gigartina acicularis, Euchema denticulatum, Kappaphycus cottonii	Carrageenan	Inhibition of attachment and interference with the subsequent stage replication	HSV-1 and Poliovirus	In vitro (Vero, African green monkey kidney cell line)	(Montanha et al., 2009)
Sphacelaria indica	Sulfated polysaccharides	Interference with virion particles or masking viral structures	HSV-1	In vitro	(Bandyopadhyay et al., 2011)
Stoechospermum marginatum and Cystoseira indica	Sulfated polysaccharide	Inhibition of adsorption and internalization	Dengue virus	In vitro (Vero, African green monkey kidney cell line)	(Pujol et al., 2012)
Sargassum mcclurei; Sargassum polycystum; Turbinara ornata.	Fucoidans	Inhibition of viral entry	HIV	In vitro (HEK293T cells and U373-CD4-CXCR4 cells)	(Thuy et al., 2015)
Laminaria japonica	Polysaccharide	upregulation of IRF3 signaling-mediated IFN-a production	Respiratory syncytial virus	In vitro (HEK293 cells)	(Cao et al., 2016)
Sargassum swartzii	Fucoidan	Reverse transcriptase inhibition	HIV-1	In vitro (Human peripheral blood mononuclear cells)	(Dinesh et al., 2016)

Hydroclathrus clathratus	Carrageenan	Inhibition of replication	HSV-1 and RVFV	In vitro (Vero cells GMK cells)	(Gomaa and Elshoubaky, 2016)
Macrocystis pyrifera, Eisenia arborea, Pelvetia compressa,	Sulfated Polysaccharides	-	Measles virus	In vitro (Vero, African green monkey kidney cell line)	(Morán-Santibañez et al., 2016)
Sargassum fluitans	Polysaccharides	-	HSV-1	In vitro (Vero cell line)	(Bedoux et al., 2017)
Fucus vesiculosus	Fucoidan	Inhibition of replication	Hepatitis B	In vivo (HepG2.2.15 cells) and In vitro (C57BL/6 mice)	(Li et al., 2017)
Kjellmaniella crassifolia	Fucoidan	Inhibition of neuraminidase	Influenza A virus	In vitro (MDCK cells and A549 cells)	(Wang et al., 2017b)
Laminaria japonica	Acidic polysaccharide (LJ04)	Inhibition of apoptosis and induction of IFN-β expression	enterovirus 71	In vitro (African green monkey kidney (MA104), human rhabdomyosarcoma (RD) and human embryonic kidney (HEK) cell lines)	(Yue et al., 2017)
Dictyota bartayesiana and *Turbinaria decurrens*	Fucoidan	-	HIV-1	In vitro (Blasted Peripheral blood mononuclear cells)	(Sanniyasi et al., 2019)
Laminaria japonica	Fucoidans	-	Noroviruses	In vitro (RAW cells) and in vivo (Mice)	(Kim et al., 2020)
Saccharina japonica	Fucoidans (RPI27 and RPI-28)	-	SARS-CoV-2	In vitro (Vero-E6 cells and Vero-CCL81)	(Kwon et al., 2020)
Green Alga					
Monostroma latissimum	Rhamnan sulfate (RS)	Inhibition of adsorption and viral replication	HSV-1, human cytomegalovirus and HIV-1	In vitro (Vero, African green monkey kidney cell line and human embryonic lung cells)	(Lee et al., 1999)
Chaetomorpha crassa, Chaetomorpha spiralis, Caulerpa brachypus, Caulerpa scalpelliformis,Caulerpa okamurae,Codium fragile, Codium adhaerens, Codium latum Monostroma nitidum,	Sulfated polysaccharides	Inhibition of the early stages and late steps of replication	HSV-1	In vitro (Vero cell line)	(Lee et al., 2004)
Ulva lactuca	Sulfated polysaccharide	Inhibition of viral adsorption	JEV	In vitro (Vero, African green monkey kidney cell line) and In vivo (Female C3H/HeN mice)	(Chiu et al., 2012)
Caulerpa racemosa	Sulfated polysaccharide	Inhibition of adsorption and internalization	Dengue virus	In vitro (Vero, African green monkey kidney cell line)	(Pujol et al., 2012)
Ulva intestinalis	Sulfated polysaccharides	-	Measles virus	In vitro (Vero cell line)	(Morán-Santibañez et al., 2016)
Enteromorpha compressa	Chemically modified polysaccharide (SU1F1)	Inhibition of replication	HSV	In vitro (human larynx epithelial cells carcinoma)	(Lopes et al., 2017)
Monostroma latissimum	Sulfated rhamnan	Inhibition of adsorption and viral replication	Enterovirus 71	In vitro (Vero, African green monkey kidney cell line) and in vivo (ICR mice)	(Wang et al., 2018)
Monostroma nitidum	Rhamnan Sulfate	Inhibition of adsorption and entry steps	Influenza A virus	In vitro (Vero, MDCK, and HeLa cells) and in vivo (Female BALB/c mice)	(Terasawa et al., 2020)
Monostroma nitidum	Sulfated glucuronorhamnan	Inhibition of viral replication before or during viral adsorption	Enterovirus 71	In vitro (Vero and Madin-Darby canine kidney cell line) In vivo (ICR mice)	(Wang et al., 2020)

Table 2: Antiviral activity of eukaryotic microalgal polysaccharides

Microalga	Compounds	Mechanism of action	Virus	*In vitro*/*In vivo*	Reference
Cochlodinium polykrikoides	Sulfated polysaccharide	Inhibition of cytopathic effects	Respiratory syncytial virus (A and B), Influenza virus (A and B), HIV-1	*In vitro* (HEp-2 cells, MDCK cells, MT-4 cells)	(Hasui et al., 1995)
Porphyridium sp.	Sulfated polysaccharide	Inhibition of viral adsorption and the production of new viral particles	HSV-1 HSV-2, Varicella zoster virus	In vitro (Vero, green monkey kidney cells)	(Huleihel et al., 2001)
Porphyridium sp.	Sulfated polysaccharide	Inhibition of cytopathic effects	HSV-1 and HSV-2	*In vivo* (Rats and Rabbits)	(Huheihel et al., 2002)
Porphyridium sp. *Rhodella reticulata*	Polysaccharide	Inhibition of virus absorption and effect late step after provirus integration	Murine leukemia virus and murine sarcoma virus	*In vitro* (NIH/3T3 mouse fibroblast cells)	(Talyshinsky et al., 2002)
Gyrodinium impudicum	Sulfated polysaccharide	Inhibition of cytopathic effect	Encephalomyocarditis virus	*In vitro* (HeLa cells)	(Yim et al., 2004)
Navicula directa	Polysaccharide	Inhibition of hyaluronidase	HSV-1, HSV-2, Influenza A virus	*In vitro* (Vero and MDCK cells)	(Lee et al., 2006)
Chlorella vulgaris	Polysaccharide	-	HSV-1	In vitro (Vero, African green monkey kidney cell line)	(Santoyo et al., 2010)
Porphyridium purpureum	Exopolysaccharide	Inhibition of viral entry	Vaccinia virus and Ectromelia virus	*In vitro* (HEp-2 cells and Vero C1008 cells)	(Radonić et al., 2011)
Dunaliella salina, Haematococcus pluvialis	Polysaccharide	Inhibition of intracellular replication	HSV-1	*In vitro* (Vero, African green monkey kidney cell line)	(Santoyo et al., 2012)

Table 3: Antiviral activity of prokaryotic cyanobacterial polysaccharides

Cyanobacteria	Compounds	Mechanism of action	Virus	*In vitro*/*In vivo*	Reference
Arthrospira platensis	calcium spirulan	Inhibition of cytopathic effects and syncytium formation	HSV-1 and HIV-1	*In vitro* (MT-4,19 Molt-4 clone No. 8,20 cells, Molt-4/HTLV-IIIB21 cells and HeLa cells)	(Hayashi et al., 1996)
Arthrospira maxima	Polysaccharide	Inhibition of virus absorption and penetration	HSV-1, HSV-2, pseudorabies virus, and human cytomegalovirus	*In vitro*	(Hernández-Corona et al., 2002)
Nostoc flagelliforme	Acidic polysaccharide (nostoflan)	Inhibition of virus absorption	Influenza A virus, HSV-1, HSV-2, human cytomegalovirus	*In vitro* (Vero, HEL, MDCK, and HeLa cells)	(Kanekiyo et al., 2005)
Arthrospira platensis	Polysaccharide (spirulan-like molecules)	Inhibition of viral entry and protein synthesis	Human cytomegalovirus, HSV-1, human herpesvirus type 6 and HIV-1	*In vitro* (Primary human foreskin fibroblasts, Vero, 293T cells and MDCK cells)	(Rechter et al., 2006)
Arthrospira platensis	Anionic exopolysaccharide (TK V3)	Inhibition of entry	Vaccinia virus and Ectromelia virus	*In vitro* (HEp-2 cells and Vero cells)	(Radonić et al., 2011)

Mechanism of Antiviral Activity

The mechanisms for antivirus activity of polysaccharides are yet to be completely understood however, few possible antiviral mechanisms have been proposed frequently. In this section, various antiviral mechanisms are briefly discussed on the basis of previous reports in the literature.

Inhibition of viral adsorption

The attachment of virus to host cells by electrostatic interactions is the primary step of viral incursion into the hosts. The following procedure is attained by converting the unstable reversible electrostatic interactions into stable irreversible binding. Algal polysaccharides have ability to inhibit viral infection by targeting the viral adsorption. Generally, the polysaccharides adopt two main strategies to inhibit viral attachment; interacting directly with virions, stimulating the viral protein to bind to the particular host cell receptors [83]. The blockage of viral attachment or internalization is the general antiviral mechanisms of these polysaccharides. Algal polysaccharides can inhibit viral adsorption and attachment process by direct interaction with virus particles or by

attaching with specific viral receptors on the host cell surface. Inhibition of viral attachment by polysaccharides is attributed to their interaction with positive charges on the virus or on the cell surface which inhibits penetration of virus into the hosts [12, 19, 27, 84]. Additionally, polysaccharides can inhibit reverse transcriptase to prevent the production of new viral particles. However, the exact stage of viral replication with which they interfere remains to be expounded [18]. In sulfated polysaccharides, the negatively charged sulfated groups can play a role in antiviral activity. Therefore, the size and degree of sulfation of these compounds can be correlated relatively well with their capacity to inhibit viral infection of cells. Furthermore, diversity of the linkage chemistry and composition of the sugar units are factors that define not only the functional properties, but also the target specificity of sulfated polysaccharides [20].

The potential of algal polysaccharides against viruses was first reported by Ginsberg, et al. (1947) [85] and Gerber, et al. (1958) [86] who observed the inhibitory effect of polysaccharides extracted from *Gelidium cartilagenium* and *Carrageenin* on growth of mumps and influenza B virus in embryonated eggs. Furthermore, Ehresmann, et al. (1977) [87] observed the inhibitory effect of polysaccharides extracted from *Farlowia mollis* and *Constantinea simplex* on herpes simplex and hypothesized that herpes virus inhibition was due to the blockage of viral adsorption. Since then, several studies have reported the inhibition of viral entry as mechanism of action of algal polysaccharides towards various viruses [27,80,81,88,89]. In a recent finding, Terasawa, et al. [69] noted the inhibition of influenza A virus adsorption by rhamnan sulfate produced by *Monostroma nitidum* [69]. Carrageenan extracted from red edible seaweeds was recently reported to inhibit early stages of Japanese Encephalitis Virus infection and attachment [35]. A recent study revealed that sulfated polysaccharides bind tightly to the S-protein of SARS-CoV-2 invitro, demonstrating that they can act as decoys to interfere with S-protein binding to the heparan sulfate co-receptor in host tissues, inhibiting viral infection [90].

Inhibition of viral internalization

The internalization of most viruses frequently comprises of three steps: (a) uptake of virus by endocytoses, (b) vesicular transport through the cytoplasm, (c) transfer to endosomes and intracellular organelles. The uncoating of virus usually occurs after the completion of viral internalization process into host cells. Various algal polysaccharides, particularly sulfated polysaccharides, can interfere with virus internalization and uncoating by blocking the allosteric process of viruses [19]. Up until now, the antiviral approach targeting viral internalization and the uncoating stage is normally the interference with the release of DNA and RNA from the endosome by blocking the structural alterations in the viral glycoprotein [83]. For example, Buck, et al. (2006) [40] reported that carrageenans extracted from *Eucheuma denticulatum* can constrain the viral infection by binding directly to the capsid of human papillomavirus, which in turn, inhibited the interactions between the capsid and host cell receptors. According to Talarico, et al. (2007) [91] and Talarico, et al. (2011) [92] ι-carrageenans could inhibit not only viral adsorption, but also viral internalization of HSV and the Dengue virus. Moreover, in a study divers classes of sulfated algal polysaccharides were found to inhibit dengue virus internalization [27]. Polysaccharides can prevent the membrane fusion activity during virus-host interaction by interfering with membrane proteins responsible for fusion events. Polysaccharides can bind to fusion proteins and inactivate them by declining their hydrophobic properties. They can also bind with sugar groups linked to the polypeptide chains of the virus thus inhibiting their penetration [12].

Inhibition of viral replication

The replication of viruses consists of the synthesis of viral messenger RNA from "early" genes (with exceptions for positive sense RNA viruses), viral protein synthesis, possible assembly of viral proteins, and viral genome replication facilitated by early or regulatory protein expression. Algal polysaccharides have been observed to hinder the viral transcription and replication by direct intrusion with viral replication enzymes or inhibition on other intracellular targets [83]. Nakashima, et al. (1987) [93] were the first to observe that extract from the marine red alga *Schizymenia pacifica* showed antiviral activity against HIV due to either the inhibition of viral attachment/penetration, or the selective inhibition of HIV reverse transcriptase and replication. Various studies have reported the inhibition of viral replication by algal polysaccharides against different viruses [28,37,94,95]. In a study, Girond, et al. (1991) [36] Showed a potent inhibitory effect of ι, λ and κ-carrageenans on the replication of hepatitis A virus (HAV). Polysaccharide extracted from *Sphaerococcus coronopifolius* belong to the family of λ-carrageenans exerts its antiviral effect by effectively inhibiting HSV-1 adsorption to host cells and a direct inhibitory effect on HIV-1 replication [45]. Moreover, Gomaa and Elshoubaky (2016) [37] reported the inhibition of HSV-1 and RVFV replication by carrageenan polysaccharides isolated from red alga *Acanthophora specifira*. Viral replication of rhinovirus (HRV) was also inhibited by ι-carrageenans [96]. Furthermore, ι-carrageenans significantly blocked viral replication process and increased the survival of host cells containing influenza virus H1N1 strain [38].

Immuno-stimulatory Effects

As the first mechanism of defense, infection of viruses may usually induce the antiviral immune responses of host cells in which the interferons play a vital role in protection of host cell and viral inactivation process. It is believed that the interferons are able to enhance the antiviral activity since they can elicit the production of antiviral and immune-modulating proteins by interacting with cell surface receptors. The process can increase the activity of macrophages, natural killer cells and T lymphocytes which are key weapons of the immunoregulatory system [83].

Studies have been demonstrated that algal polysaccharides can stimulate the immune response by binding to recognition receptors (mannose receptors or Toll-like receptors (TLR)) on the surface of macrophages this binding of polysaccharides to cell receptors might be possible due to their structural similarities with bacterial lipopolysaccharides [97]. Recently,

a few studies reported the immune-stimulatory effects of algal polysaccharides that help in inhibition of viral and speed up viral clearance. Kim, et al. (2011) [98] assessed the antiviral activity of water-soluble sulfated polysaccharides extracted from *Ulva prolifera* and reported that the sulfated polysaccharide could modulate the immune responses. Zhang, et al. (2015) [99] studied the immune functions of four algal (*Ascophyllum nodosum*, *Macrocystis pyrifera, Undaria pinnatifida* and *Fucus vesiculosus*) fucoidans and the results indicated that fucoidans have strong immune-modulation effect through the activation of T cells and NK cells. They further suggested that fucoidans could be possible therapeutic agents for infectious diseases and an excellent resource for vaccine production. An acidic polysaccharide from brown algae *Laminaria japonica* was found to inhibit apoptosis and inducing IFN-β expression against enterovirus 71 [100]. In another study, polysaccharide from *Laminaria japonica* has shown its role in up-regulation of IRF3 signaling-mediated IFN-α production against respiratory syncytial virus [101]. These findings established that algal polysaccharides could not only inhibit viral entry and replication, but also stimulate the immune system to cope with infectious pathogens. Possible antiviral mechanisms of algal polysaccharides discussed above are presented in Figure 1.

Antiviral activity of the S-PS differs quantitatively as well as qualitatively in dependence on their structure, Algal S-PS consisting of 35-60 sulfate groups per hundred sugar residues have shown the best antiviral activity [102]. The degree of sulfation has a key influence on the antiviral activity of a polysaccharide, higher the degree of sulfation, the better their antiviral potency. Some other characteristics of polysaccharides, including the degree of polymerization, branching and chemical composition of carbohydrate moieties might also play an important role in their antiviral properties. Additionally, structural diversity, molecular mass, the position of sulfate groups and polymeric backbone, charge density, and molecular composition of uncharged portions can also influence on the antiviral potential of polysaccharides [84]. The degree of sulfation, acetylation, and other chemical changes can be successfully adopted to enhance the antiviral activity and immune-stimulatory effect of polysaccharides. For instance, desired molecular weight of polysaccharides can be achieved by depolymerization, allowing them to penetrate more efficiently into the cell and exert greater antiviral activity. Furthermore, enveloped viruses are more susceptible to polyanionic inhibitors than non-enveloped viruses. Another crucial aspect in maintaining antiviral action for a longer period of time is the slower breakdown of polyanions contained in the PS [12]. *Invivo* antiviral activity of S-PS is typically depends on their capabilities to block the attachment of virus to the host cells, however, irreversible interaction with virions leading to virucidal action plays an additional role [102].

Conclusion

In recent years, much consideration has been given to the discovery of natural antiviral compounds particularly from marine sources. Marine algae are considered as valued sources of a huge array of bioactive compounds from the blue water, and polysaccharides are one of them. The information compiled in this review depicts clearly the astonishing potential of algal polysaccharides against variety of infection caused by virulent viruses. However, the *invivo* mechanism of their antiviral actions is not fully understood

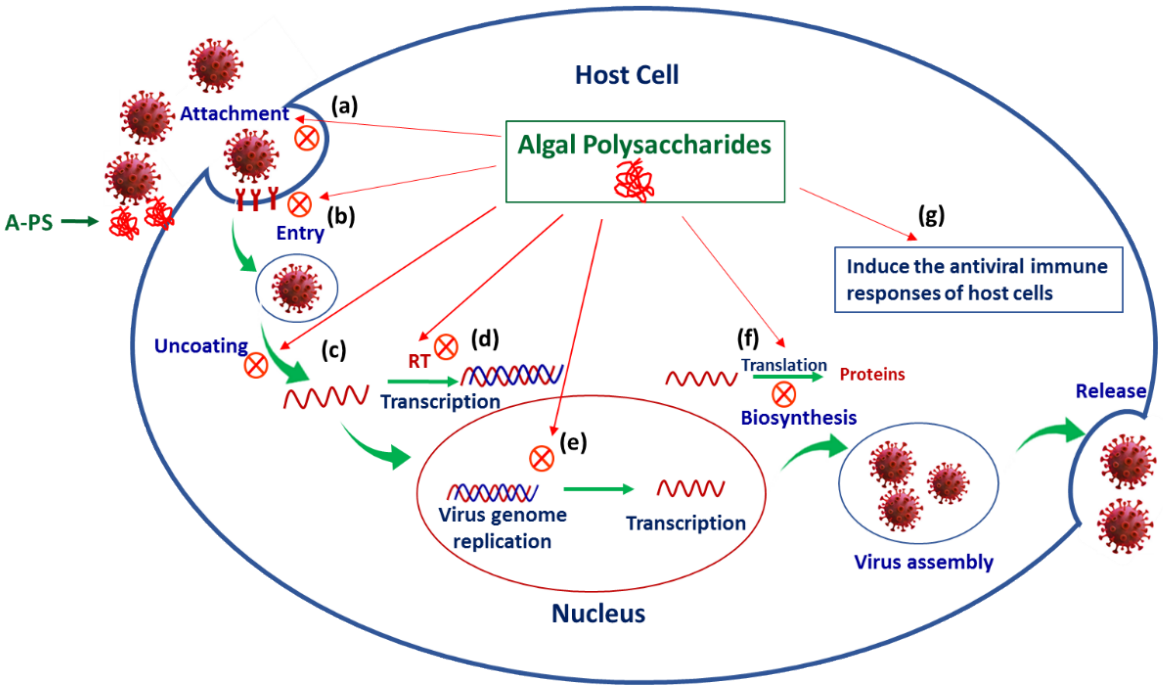

Figure 1: Mechanisms of antiviral action of algal polysaccharides (a) inhibition of viral adsorption (b), (c) inhibition of viral internalization and uncoating (d), (e), (f) inhibition of viral transcription, replication and proteins formation (g) activation of immune system.

and a lot of research is still to be done to discover specific antiviral mechanisms. Antiviral polysaccharides of microalgae and cyanobacteria are less explored in comparison to macroalgae. Therefore, it may be an imperative area to focus in future research. Algal polysaccharide antiviral mechanisms suggest that these natural compounds can be used in both the prevention and treatment of viral infections. For instance, the role of polysaccharides in preventing viral attachment and entry demonstrated that viruses can be inactivated before infection begins. On the other hand, polysaccharides have the potential to stimulate the immune system, which may aid in the treatment of viral infections by removing the virus from affected cells through the immunological defense systems. Algal polysaccharides should be further investigated as antiviral agents through animal studies and clinical trials. These polysaccharides have a number of advantages over other antiviral drugs, such as, safety, low production costs, broad spectrum of antiviral activity, unique mode of actions and low risk of viral drug resistance. Furthermore, these polysaccharides are not only bioactive but also non-toxic, biocompatible and chemically modifiable. They can be exploited as candidate drugs, healthcare products, vaccine adjuvants, nanomaterials, drug delivery systems, dietary supplements and food additives. Choosing the most promising drug candidates from the vast array of available polysaccharides will be a challenge. The literature reporting *invivo* antiviral effects of S-PS is limited, therefore, extensive studies regarding the *invivo* performance of antiviral polysaccharides are indispensable before their utilization in controlling emerging infectious viruses.

Declarations

The authors declare no conflict of Interest.

Author contributions

Conceptualization, Mahammed Ilyas Khazi, Fakhra Liaqat, Pengcheng Fu; formal analysis, Mahammed Ilyas Khazi, Fakhra Liaqat, Chenshuo Li; investigation, Mahammed Ilyas Khazi, Fakhra Liaqat, Chenshuo Li; writing-original draft preparation, Mahammed Ilyas Khazi, Fakhra Liaqat; writing-review and editing, Mahammed Ilyas Khazi, Fakhra Liaqat, Jian Li, and Pengcheng Fu; supervision, Pengcheng Fu; project administration, Pengcheng Fu; funding acquisition, Pengcheng Fu. All authors have read and agreed to the published version of the manuscript.

Acknowledgement

This study was supported by Talented Young Scientists Program, Ministry of Science and Technology, China, and Research start-up funds from Hainan University (KYQD_ZR2017271), China. We would like to thank the Hainan University for the support provided to Mahammed Ilyas Khazi during his research work.

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DOI: 10.36959/967/630