Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review

A state-of-the-art review on fucoidan as an antiviral agent to combat viral infections

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ABSTRACT

As a significant public health hazard with several drug side effects during medical treatment, searching for novel therapeutic natural medicines is promising. Sulfated polysaccharides from algae, such as fucoidan, have been discovered to have a variety of medical applications, including antibacterial and immunomodulatory properties. The review emphasized on the utilization of fucoidan as an antiviral agent against viral infections by inhibiting their attachment and replication. Moreover, it can also trigger immune response against viral infection in humans. This review suggested to be use the fucoidan for the potential protective remedy against COVID-19 and addressing the antiviral activities of sulfated polysaccharide, fucoidan derived from marine algae that could be used as an anti-COVID19 drug in near future.

1. Introduction

World Health Organization (WHO) has confirmed the occurrence of novel coronavirus (nCoV-2019) on January 12, 2020 in Wuhan, China. WHO has termed COVID-19, the first unknown acute respirational tract infection (Guo et al., 2020). COVID-19 cases spread rapidly worldwide and were labeled a pandemic on March 11, 2020 (Elengoe, 2020). The most communal indicators of COVID-19 comprise cough, fever, headache, sore throat, breathlessness, and fatigue, which gradually lead to the death of the patients. The death is due to severe infection in the respiratory tract, pneumonia and multiple organ failure. People with diabetes, cardiovascular problems, hypertension, cancer, HIV, and several auto-immune disorders have a great life threat due to COVID-19 (Singhal, 2020).

The fresh and marine ecosystems are rich in biodiversity and hold a potential source of sulfated polysaccharides (Behera et al., 2020; Behera et al., 2021; Dash et al., 2020; Dash et al., 2021; Maharana et al., 2019; Pradhan, Maharana, Bhakta, & Jena, 2021; Pradhan, Patra, Behera, et al., 2020; Pradhan, Patra, Dash, et al., 2021). Algae-derived sulfated polysaccharides such as fucoidan have potentially been used as an antiviral agent (Pagarete et al., 2021; Pradhan, Bhuyan, et al., 2022; Pradhan, Nayak, et al., 2022; Pradhan, Patra, Nayak, et al., 2020). Many marine algae species contain large amounts of complicated structural sulphated polysaccharides that have been demonstrated to impede enveloped virus replication (Pereira & Critchley, 2020). To date, several bioactive compounds from marine algal sources have been screened (Mohanty et al., 2020; Pradhan, Nayak, Patra, et al., 2021; Pradhan, Patra, et al., 2022), isolated and tested for their therapeutic value from which fucoidan is promising. Previously, the antiviral activities of sulfated polysaccharides such as fucoidan has been tested against human cytomegalovirus, human enterovirus, influenza virus, HIV-1 (Human immunodeficiency virus type-1), HSV (Herpes simplex virus), hepatitis B virus, murine norovirus, and RSV (respiratory syncytial virus) (Shi et al., 2017; Wang et al., 2012). With this notation, the fucoidan can exert

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promising therapeutic value against coronavirus to halt the disease progression.

Immunity is considered the primary concern during the treatment of viral infections, such as COVID-19 (Dhar & Mohanty, 2020). Studies on antiviral immunity have been demonstrated against several viral diseases and fucoidan has displayed promising effect (Wang et al., 2012). To date, many sulfated polysaccharides from plant and animal sources, including marine organisms and microorganisms, have been tested against HIV and HSV (Alam et al., 2021). Nutraceuticals from *Spirulina* have been well explored and commercially available as an innate and adaptive immunity booster against HIV and HSV (Hayashi et al., 1996; Ratha et al., 2021). Hence, the use of immune-boosting algal-derived fucoidans may contribute a leading role to combat against coronavirus infections via alleviating innate immune responses. Although vaccination against COVID-19 has developed and is in force, no clinically approved drugs have been approved for therapeutic purposes. Hence, the outbreak needs an imperative retort from the scientific community for the development of novel synthetic as well as natural drugs as immune boosters against COVID-19. As limited research has been carried taking algal-derived sulfated polysaccharides concerning fucoidan, in this review, we have focussed on this aspect that might be castoff as an antiviral drug against SARS-CoV-2.

2. Coronaviruses and their pathogenesis

Coronaviruses (CoVs) are single-stranded RNA viruses commonly seen in humans and animals (V'Kovski et al., 2021). It causes several respiratory disorders and intestinal infections with life-threatening bronchiolitis and pneumonia. Persons with a compromised immune system are particularly vulnerable to CoV infection (Subbarao & Mahanty, 2020). This virus was called new coronavirus (nCoV) by the International Committee on Virus Taxonomy (ICTV), and it was previously known as SARS-CoV-2, which causes COVID-19 sickness (Liu et al., 2020). Novel coronavirus-2019 is a rounded virus similar to other reported coronaviruses. The virus has a capsid made up of nucleocapsid protein (N-protein) and the viral genome is present inside it.

Furthermore, the capsid is covered by a cover from which various structural proteins are derived. There are three types of essential structural proteins were found on the envelope surface such as spike proteins (S), membrane proteins (M), and envelope proteins (E) (Huang et al., 2020). Amongst these three proteins, S-proteins show outcrop and mediated the viral entry into the host cell and stretch the crown-like appearance to the virus (Fig. 1).

2.1. Host and coronavirus interaction: The basis of disease

The ORF1 of Coronaviruses contains unique genes on the downstream region that encrypt structural proteins essential for viral multiplication (Huang et al., 2020). Coronavirus glycoprotein spikes are critical for virus attachment and penetration into host cells (Huang et al., 2020). The coronavirus entry depends upon the cellular proteins such as HAT (Human Airway trypsin-like proteases), cathepsins, TMPRS2 (transmembrane protease serine 2), which support spike protein splitting, which leads to further penetration (Subbarao & Mahanty, 2020). Coronavirus needs ACE2 (Angiotensin-Converting Enzyme 2) as a key receptor in human cells (Parasher, 2021). The spike proteins can bind to the ACE2 receptor. It causes a conformational change that promotes membrane fusion via the endosomal route and the release of viral RNA into the host (Wan et al., 2020). The translation of ORF1a and 1b into polyproteins pp1a and pp1ab start the replication of CoVs. The proteolytic cleavage of these proteins gives rise to non-structural proteins (NSPs). The NSPs come together to create the RTC (Replicase-Polymerase Replication-Transcription Complex), which is involved in the viral genomic RNA replication and subgenomic RNA transcription (Wan et al., 2020) to produce structural proteins by translation and other accessory proteins. The buildup of gRNA and viral proteins leads to fast-track virions (Chatterjee et al., 2020). After the assembly process is complete, the nucleocapsid is budded, then transported through secretory vesicles, and the host cell is released. The endoplasmic reticulum to golgi intermediate complex assembly pathway leads to budding (ERGIC) (Chatterjee et al., 2020). The pathogenesis of novel coronavirus pathogenesis and replication of novel coronavirus pathogenesis is shown in Fig. 2.

2.2. Pathogenesis

The pathogenesis of novel coronavirus infection displays a close similarity to infection of SARS CoV with aggressive inflammation. SARS-CoV-2 is spread mainly through respiratory dews, comparable to other coronaviruses that cause respiratory illness (Jin, Yang, et al., 2020). Chills, a dry cough, temperature, a painful throat, exhaustion, and breathing difficulties are common symptoms of COVID-19 infection. COVID-19 cases that are severe Shortness of breath and low blood oxygen levels characterize ARDS (acute respiratory distress syndrome), which leads to lung failure. The biopsy specimens from the liver, lung, and heart tissue of Covid-19 patients showed alveolar impairment, hyaline membrane formation, and modest microvesicular steatosis, indicating ARDS, and showed modest microvesicular steatosis, indicating ARDS (Huppert et al., 2019).

SARS CoV-2 infects cells by infiltrating them and connecting with the ACE2 protein (Perrotta et al., 2020). The virus's multiplication and release cause the host cell to enter pyroptosis. The onset of pyroptosis releases PAMPs (pathogen-associated molecular patterns) and DAMPs (damage-associated molecular patterns) with subsequent generation of pro-inflammatory markers (Tay et al., 2020). Immune cells are recruited to the infection site by these protein molecules, which increase

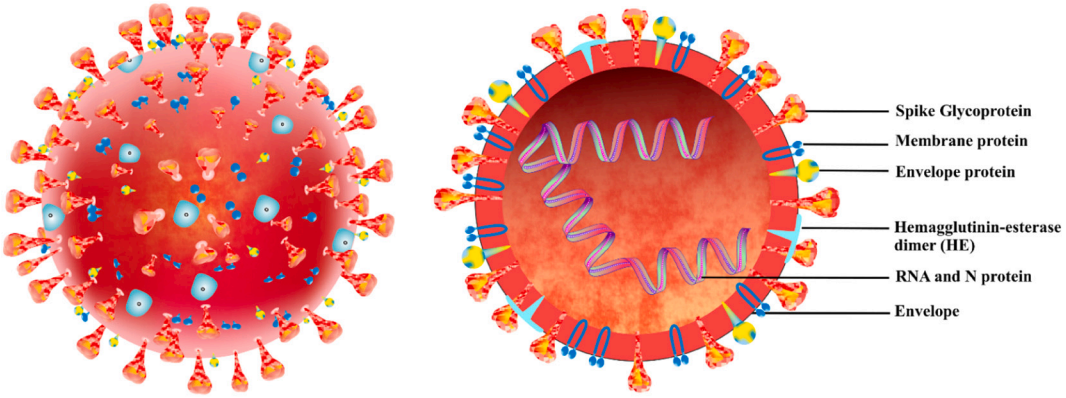

Fig. 1. Structure of the novel corona virus.

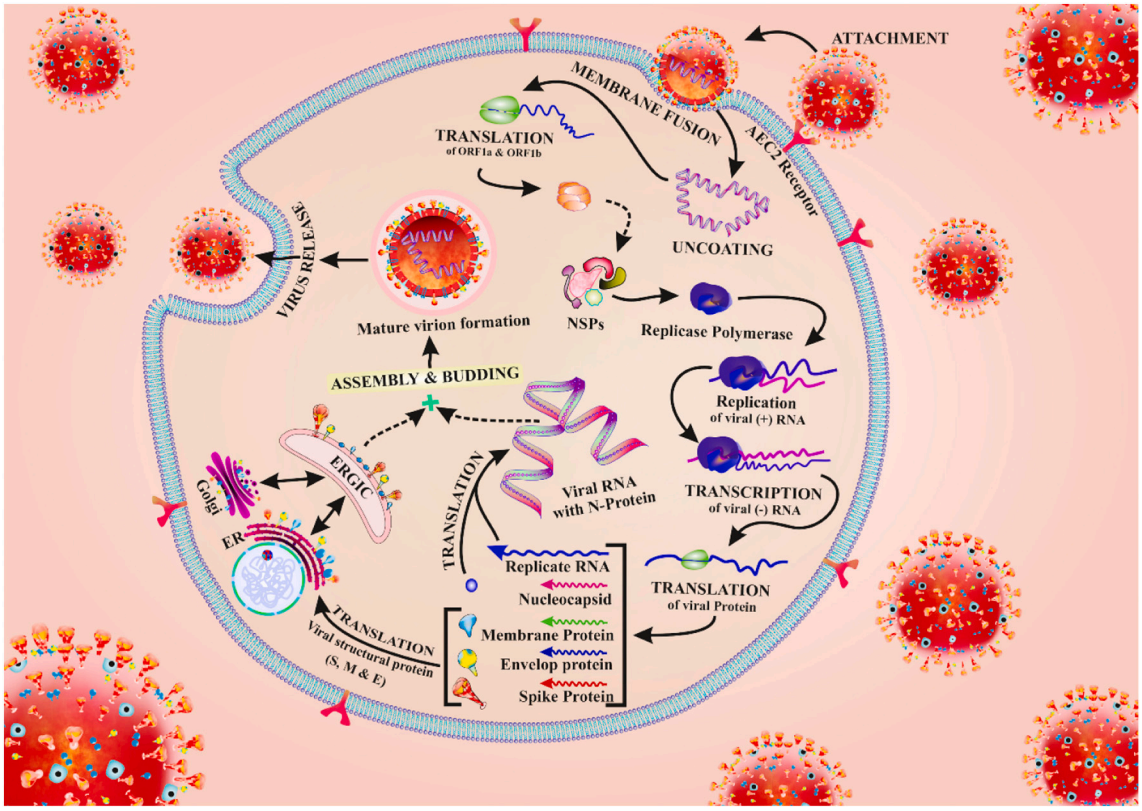

Fig. 2. The viral entry and replication of novel coronavirus pathogenesis.

inflammation. Monocytes, T-cells, and macrophages are examples of immune cells (Schijns & Lavelle, 2020). The cells may compromise the air-blood barrier by eliminating vascular endothelial cells and airway epithelial cells, resulting in collateral tissue harm. The high expression of ACE2 receptor in endothelial cells and airway epithelial cells is used by coronavirus to penetrate inside the cell (Flerlage et al., 2021). As a result, acute illness is caused by virus infection and by overexcited immune responses.

3. Algae-derived sulfated polysaccharides and their potential role as antiviral agents

Sulfated polysaccharides are potent antiviral agents due to their diverse structure. They have a pivotal role in boosting the host antiviral retort by preventing virus attachment, adsorption, and viral reproduction. Systematic studies on the antiviral activity of marine algae-derived polysaccharides have been achieved both in vitro and in precise animal models. Marine algae are rich in sulfated polysaccharides that prevent the replication of viruses clinically tested against HSV-1. Polysaccharides from *Spirulina platensis* has displayed antiviral activity against HSV-1, measles virus, influenza A virus, mumps virus, human cytomegalovirus, and HIV-1 (Hayashi et al., 1996). Sulfated polysaccharides inhibit antiviral pathways and act as potential replication inhibitors of retroviruses such as HIV-V (Buck et al., 2006). Carrageenan, a common polysaccharide isolated from red algae such as *Gigartina*, *Chondrus*, *Eucheuma* and *Hypnea* exhibits antiviral activity against virus infection. Carrageenan blocks the viral entry by inhibiting host cell binding capacity (Li et al., 2017). It limits the dengue virus's reproduction in mosquitoes and mammalian cells (Buck et al., 2006).

Moreover, it plays an operative role against HPV (human papillomavirus), leading to genital warts and cervical cancer (Zeitlin et al., 1997). Carrageenans with low molecular weight (3–10 10 kDa) display a repressing effect against the influenza virus (Grassauer et al., 2008; Hilliou et al., 2006). The nasal spray carrageenan administration (Iota-carrageenan), also recognized as "super-shedders," is operative against the communal cold by improving viral clearance and reducing the disease duration. Carrageenan extracted from red algae (*Schizymenia pacifica*) restricts infection of avian as well as mammalian retroviruses by activating reverse transcriptase function and subsequent inhibition of viral replicate. In addition, carrageenan also prevents the binding between the host and viruses at the early stages of infection (Koenighofer et al., 2014).

Extracellular polysaccharides such as galactoses isolated from red algae *Agardhiella tenera* display antiviral properties against DENV, HIV-1, HIV-2, HSV-1, HSV-2, and Hep A virus (Hepatitis A virus) (Myriam Witvrouw et al., 1994). With low cytotoxicity, galactans isolated from *Callophyllis variegata* show antiviral action against HSV-1, HSV-2, and DENV-2 (Rodríguez et al., 2005). The antiviral efficacy of sulfated galactan isolated from *Schizymenia binderi* effectively counter HSV-1 and HSV-2 (Matsuhiro et al., 2005). Extracellular sulfated polysaccharides such as A1 and A2 from *Cochlodinium polykrikoides*, reduce blood coagulation by inhibiting influenza A and B virus in MDCK cells. It is also effective against respirational virus types A and B in Hep-2 cells and immunodeficient virus type-1 in MT-4 cells (Hasui et al., 1995). Sulfated *exo*-polysaccharide derived from *Gyrodinium impudicum* display antiviral properties against EMCV (Encephalomyocarditis virus) without toxicity in HeLa cells (Yim et al., 2004). It also inhibits influenza A virus duplication via targeting adsorption and integration into the host cell (Yim et al., 2004).

3.1. Algae-derived sulfated polysaccharide modulates antiviral mechanism via inhibiting virus attachment, penetration, interiorization, uncoating transcription, and translation process

The main stages of the virus life cycle are classified as attachment of virus, viral penetration, uncoating, biogenesis, viral assembly, and release of a virus that play a key role during viral infection and disease progression (Fig. 3). Algae-derived sulfated polysaccharides display

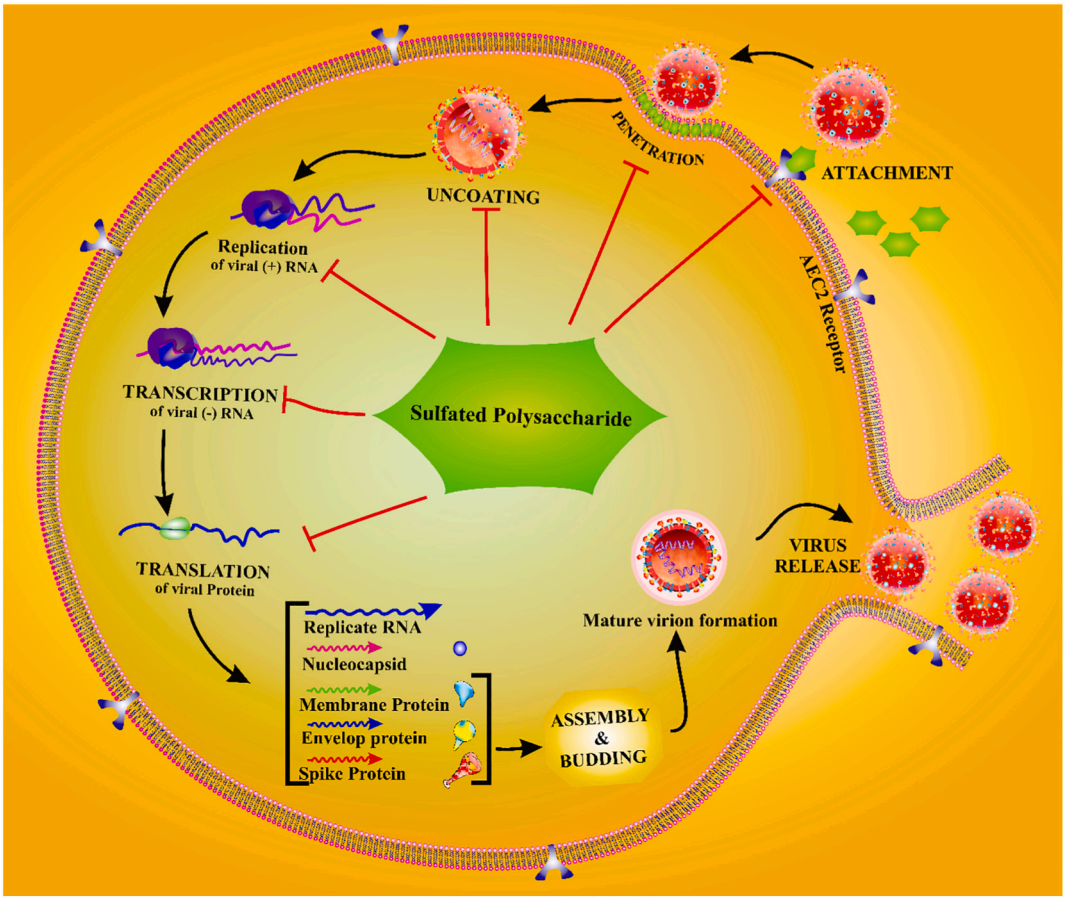

Fig. 3. Sulfated polysaccharides (SPs) modulates antiviral mechanism of via inhibiting virus attachment, penetration, interiorization, uncoating and transcription and translation process.

exceptional molecular structures and exert potential antiviral properties by inhibiting several phases of the viral life cycle by directly deactivating virions before contamination starts or hindering its reproduction inside the host cell. Marine seaweeds are a promising source and rich in polysaccharides and give attention to the development and discovery of antiviral drugs.

The ionic interface between positively charged exterior glycoproteins on the encapsulated viral surface and negatively charged components of the host cell's surface causes early contact during the viral attachment. The presence of sulfate residues interacts with the positively charged area of viral glycoprotein, causing a higher density of negative charge on the cell surface and disrupting the first virus-cell interaction (Sepúlveda-Crespo et al., 2017). The sulfated polysaccharide may impede virus entry into the host cell by directly limiting virus binding to the cell surface. When the virus connects to the host cell, it causes irreversible adsorption via electrostatic interaction between the host cell and viral receptors. Some sulfated algal polysaccharides interact with virus receptors, preventing virus infection by blocking contact with the host cell surface or directly interacting with virions. Several investigations have revealed that negative charges on fucoidan's sulfate group interact with the virus by masking the positive charge on viral receptors (Wang et al., 2012). The virus infiltrates the host cell by invaginating the outer membrane and producing a vacuole. It is then transported to endosomes and additional intracellular organelles through the intracellular fluid or cytoplasm. The virus interacts with the cell membrane or forms a compartment within the cell that encloses the virus after endocytosis, modifying the shape of the virus's capsid. Specific signals are produced after the interaction of the virus with receptor protein around the endosome, uncoating and releasing the virions (Mercer et al., 2010). The virus replicates inside the host cell after internalization and uncoating. Sulfated polysaccharides interfere with virus internalization by interaction with the viral membrane proteins. Moreover, they bind to carbohydrate groups on the polypeptide chains of the virus to prevent it from penetrating host cells. Sulfated polysaccharides also attach to the allosteric location of the viral capsid, thus preventing the virus from uncoating inside the host cell. Several algal-derived polysaccharides can hinder virus transcription and replication once they reach the host cell by interfering with replicating enzymes like reverse transcriptase or by blocking the synthesis of proteins from m. RNA (messenger RNA) (Queiroz et al., 2008).

4. Intricate role of fucoidan as an antiviral agent

Fucoidan, the chief composition of the extracellular background of brown algae, is rich in fucose and sulfated polysaccharide. Fucoidan is a complicated structure with l-fucose molecule, sulfate groups, and one or more mannose, galactose, xylose, glucose, rhamnose, glucuronic acid, arabinose, and acetyl groups. Typically, there are two forms of homo-fucose in fucoidan (type (I) encompasses repeated (13))-l-fucopyranose and type (II) include alternating and repetitive (13)- and (14)-l-fucopyranose chains, as well as standard backbone chains. Fucoidan is the most frequent brown seaweed backbone chain. Type I (A) and type II (B) are represented in the figure and the molecular structure of isolated fucoidan used against SARS-CoV-2 such as *F. vesiculosus* (C) and *Undaria pinnatifida* (D) (Fig. 4).

Viral infections cause enormous health problems leading to death. Initially, nucleoside drugs were used as antiviral drugs and have several side effects such as acute renal failure, cardiac arrest, hepatological

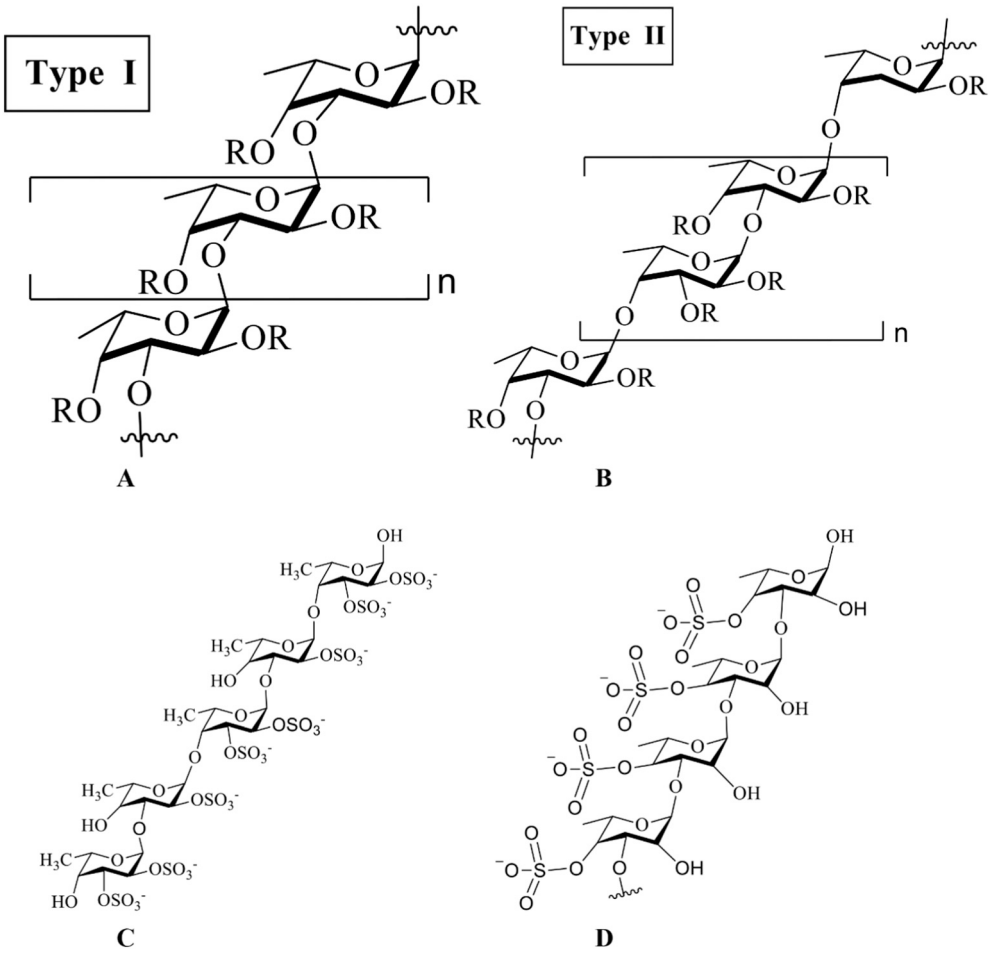

Fig. 4. The most common backbone chains of brown seaweed fucoidan type I (A), type II (B). The molecular structure of isolated fucoidan used against SARS-CoV-2 such as *F. vesiculosus* (C) and *Undaria pinnatifida* (D).

dysfunction and gastrointestinal problems (Marchetti et al., 1995). Therefore, searching for new and effective drugs without toxicity has gained more importance in the present times (Patra, Nayak, Patro, Pradhan, Sahu, et al., 2021; Patra, Pradhan, Nayak, Behera, Das, Patra, and Bhutia, 2021b; Patra, Pradhan, Nayak, Behera, Panda, Das, and Jena, 2021c; Patra, Pradhan, Nayak, Behera, Rout, Jena, and Bhutia, 2021d). Natural polysaccharides have alleviated specific viral infections (Marchetti et al., 1995). In this context, the search for natural antiviral specific to sulfated polysaccharides from marine sources has been attentive in recent times. The degree of sulfation, sulfate group content, molecular weight, monosaccharide composition, molecular structure conformation, and stereochemistry are key factors in sulfated polysaccharides' antiviral action fucoidan. Sulfated polysaccharides with low molecular weight and high sulfate concentration have greater antiviral activity (Duarte et al., 2001).

Fucoidan is a type of sulfated polysaccharide that provides a wide spectrum of antiviral activity with minimal toxicity (Queiroz et al., 2008). Inclusively, fucoidan prevents HIV, human cytomegalovirus, HSV, bovine viral diarrhea virus, and influenza virus by inhibiting viral adsorption onto cells, thus hindering viral entry (Dinesh et al., 2016; Mandal et al., 2007; M. Witvrouw & De Clercq, 1997). Interacting with the positively charged portion of viral envelope glycoproteins important in virus attachment helps the virus attach; fucoidan suppresses virus attachment to host cells (Harden et al., 2009; J. B. Lee, Hayashi, Hashimoto, et al., 2004). The antiviral effect of fucoidan is mediated by Immune cells' phagocytic function and humoral immunity. The LMWF extracted from *L. japonica* can boost up immune action and raise thymus and spleen indexes. Furthermore, LMWF can raise the half hemolysin value (Sun et al., 2018). Fucoidan extracted from *Undaria pinnatifida* is beneficial against HSV-1 through reducing viral reproduction and activating innate and adaptive immune systems (Hayashi et al., 2008). The anti-HSV activity of fucoidan appears to depend on a sulfate at C-4 of the unit of the (1–3)-linked fucopyranosyl (Mandal et al., 2007). Wang et al. (2017a, 2017b) recently published a study that targeted *Kjellmaniella crassifolia* fucoidan infection is limited by viral neuraminidase and the cellular EGFR pathway (536 kDa, 30.1% sulfate content). The findings open that the *K. crassifolia* fucoidan inhibited IAV infection in in vitro model with little toxicity and had a broad anti-IAV range. Moreover, it had a short tendency to induce viral struggle, surpassing the standard anti-IAV medication amantadine. Before infection and after adsorption, *K. crassifolia* fucoidan can deactivate virus particles via binding to viral neuraminidase (NA) and inhibited the activity of NA to hunk the release of IAV. In addition, intranasal treatment of fucoidan derived from *K. crassifolia* to IAV-infected mice significantly increased the survival and reduced the viral titers. Furthermore, a novel nasal drop or spray of *K. crassifolia* fucoidan prevented the influenza virus in subsequent infection (Wang et al., 2017a, 2017b). LMWF fractions such as LF1 and LF2 derived from *L. japonica*, which include 42.0%and 30.5% fucose; 19.8% and 23.9% galactose; 5.3% and 3.7% uronic acid; and 30.7% and 32.5% sulfate, respectively, showed excellent antiviral activity in in vitro models at doses of 1.2 and 2.4 mg/mL (Sun et al., 2018). After intravenous treatment of LMWFs (2.5, 5, 10, and 15 mg/kg; 14 days), in vivo results showed that LF1 and LF2 were able to lengthen the survival duration of mice infected with the virus, as well as dramatically increase the value of immune organs, immune cells, phagocytosis, and humoral immunity. LMW fucoidans extracted from *L. japonica* displayed antiviral

activity in both in vitro (2.5, 5, 10, 15 mg, adenovirus, I-type influenza virus, and Parainfluenza virus I were used to infect Hep-2, Hela and MDCK cells) as well as in vivo (virus-infected mice; 2.5, 5, 10, 15 mg kg^{-1}) (Sun et al., 2018). Fucoidan extracted from *K. crassifolia* could be used to combat extremely pathogenic strains like H5N1 and H7N9. Fucoidan has the immense potency to be used as a novel nasal drop or sprig for influenza therapy (Moscona, 2009). In mice, fucoidan extracted from *Fucus evanescens* (130–400 kDa) worked as an adjuvant by encouraging the development of definite antibodies against HBV's surface antigens, like HBs-AG (Liang, 2009). Fucoidan from *Fucus vesiculosus* repressed HBV reproduction in in vivo and in vitro models by activating the EKR signalling pathway. It also increased the type I interferon production by activating the host immune system (Kuznetsova et al., 2017). In addition to this, fucoidan can be used as an individual drug or in combination with other drugs to treat HBV. HBV replication was considerably suppressed in a rat model of fucoidan (100 mg) of 0–7 days after infection with HepG2.2.15 cells. Mechanistically, *F. vesiculosus* extracted fucoidan activated the MAPK-ERK1/2 pathway and elicited the expression of IFNs, thereby resulting in a decrease in HBV DNA and associated proteins synthesis.

Current treatments towards HIV are cost-prohibitive with several side effects. Fucoidans could repress the contamination in Jurkat cells with pseudo-HIV-1 elements, which preferentially hold envelope proteins of HIV-1 (Prokofjeva et al., 2013). Fucoidans from *Saccharina cichorioides* (1.3-α-l-fucan) and *S. japonica* (galactofucan) displayed a substantial repressing effect on HIV-1. In addition, even at negligible concentrations (0.001–0.05 μg/mL), fucoidans demonstrated inhibitory efficacy against the transduction of lentiviral cells. Fucoidan isolated from *S. swartzii* can be used as a potential anti-HIV agent (Dinesh et al., 2016). *Adenocystis utricularis* fucoidan inhibited the HIV-1 infection by hindering the entry of the virus (Trinchero et al., 2009). Crude Fucoidan fractions such as FF1 and FF2 (Total content of sugar in the FF1 and FF2 61.8% and 65.9%; the content of sulfate 19.2% and 24.5%, the uronic acid content 17.6% and 13.4%, and the Mw 30 and 45 kDa, respectively) were extracted from *S. swartzii* displayed anti-HIV-1 properties. Moreover, at doses (1.56 and 6.25 g/mL), FF2 fraction showed anti-HIV-1 efficacy, as evidenced by a >50% decrease in HIV-1 p24 antigen levels and the activity of reverse transcriptase. Fucoidan from *Sargassum mcclurei* can hunk the entry of the HIV-1 virus (Thuy et al., 2015). *S. polycystum* (FSP), *S. mcclurei* (FSM), and *Turbinaria ornata* (FTO) fucoidans demonstrated anti-HIV activities with IC50s ranging from 0.33 to 0.7 g/mL (Thuy et al., 2015). These fucoidans suppressed the HIV-1 infection when pre-incubated with the virus but not with the cells after infection, indicating that they can limit HIV entrance into aimed cells at an early stage (Thuy et al., 2015).

With no cytotoxicity, Fucoidan (galactofucan) from *Adenocystis utricularis* inhibited HSV-1 and HSV-2 (Ponce et al., 2003). Moreover, *Dictyota dichotoma* fucoidan (galactofucan) inhibited HSV-1 by decreased plaque formation (Rabanal et al., 2014). Fucoidan (glucuronic acid, sulfated fucose) isolated from *Cladosiphon okamuranus* inhibited DENV-2 directly binding to the spike protein (Hidari et al., 2008). Sulfated fucans isolated from *Cystoseira indica* inhibited adsorption of HSV-1, HSV-2 (Mandal et al., 2007). Xylan-fucoidan extracted from *Caulerpa brachypus* displayed inhibitory activity against HSV-1 via inhibiting attachment, penetration, and later stages of replication (Lee, Hayashi, Maeda, & Hayashi, 2004). Fucoidan isolated from *Fucus vesiculosus* exhibited antiviral activity against BVDV (Bovine viral diarrhea virus) via inhibition of the binding of the virus (Güven et al., 2020). Fucoidan extracted from *Laminaria japonica* hindered the H5N1 (Avian influenza virus) (Makarenkova et al., 2010). Galactofucan isolated from *Undaria pinnatifida* displayed potent antiviral activity, restricting viral entry and host-virus binding in HSV-1, HSV-2, and HCMV virus (Hemmingson et al., 2006). Fucoidan extracted from *Sargassum trichophyllum* showed promising antiviral activity via inhibiting the virus adsorption, penetration and replication in the HSV-2 virus (Lee et al., 2011). Fucoidan from *C. okamuranus* displayed antiviral potency against NDV La Sota (Newcastle Disease Virus) with low-toxicity than Ribavirin. In addition, it also inhibited early stages of viral infection within 0–60 min. Post-infection treatment displayed 48% reduction in viral infection and abridged HN protein expression. Moreover, it inhibited syncytia formation (70%) via exact communication between fucoidan and the F0 protein (Elizondo-Gonzalez et al., 2012). Fucoidan extracted from brown seaweed, *Sargassum wightii* and *Artemia franciscana* on *Penaeus monodon* has been found to be effective against white spot syndrome virus (WSSV) with reported mortality of 61.65% (Sivagnanavelmurugan et al., 2012) (see Table 1).

5. Fucoidan modulates antiviral activity against SARS-CoV-2

A wide range of fucoidans was used to examine the current pandemic produced by the SARS-CoV-2 in vitro and in vivo models. In in vitro models, fucoidan demonstrated direct inhibitory efficacy against SARS-CoV-2, indicating that it could be useful as a therapeutic drug. The fucoidan fractions have an inhibitory effect on viral spike protein binding. In an in vitro infection model, unfractionated of fucoidan from *F. vesiculosus* and *U. pinnatifida* showed minimal efficacy against SARS-CoV-2 (Fitton et al., 2021). Fucoidan (15.6 μg/mL) inhibited SARS-CoV-2 in vitro via binding to the S glycoprotein of the virus. Sulfated polysaccharides (9.10 μg/mL) inhibited SARS-CoV-2 in vitro model via S glycoprotein binding (Song et al., 2020a, b). LMW and HMW extracted from *S. japonica* are expected to display in vitro antiviral properties against SARS-CoV-2 via binding to S-proteins of SARS-CoV-2. HMW fucoidan (8.3 μg/mL) from *Saccharina japonica* are more potent than LMW (16 μg/mL) (Kwon et al., 2020). Sulfated fucan extracted from *Lytechinus variegatus* and sulfated galactan isolated from *Botryocladia occidentalis* demonstrated an SGP binding efficacy and transduction efficacy of a third progeny lentiviral (pLV) vector. It modulated pLV-S particles even with an IC_{50} of lower ng to higher μg/L (Tandon et al., 2021). Sulfated galactofucan (1, 3-linked-L-Fucp residues sulfated at C4 and C2/C4 and 1, 3-linked-L-Fucp residues sulfated at C4 and branched with 1, 6-linked-D-galacto-biose) reduced interaction between SARS-CoV-2 SGPs and heparin, but not ACE2 (Jin, Zhang, et al., 2020a, 2020b). Sulfated fucoidan and crude polysaccharides, isolated from six seaweed species such as *Laminaria japonica*, *Undaria pinnatifida sporophyll*, *Sargassum horneri*, *Hizikia fusiforme*, *Porphyra tenera*, *Codium fragile* inhibited viral infection with an IC_{50} value (12–289 μg/mL) against SARS-CoV-2 pseudo virus in HEK293/ACE2 (Yim et al., 2021b, a).

The crude polysaccharide extracted from *S. horneri* exhibited robust antiviral activity, with an IC_{50} value of 12 μg/mL, to prevent the entry of the COVID-19 virus (Yim et al., 2021b, a). The crude polysaccharide from *H. fusiforme* can also hinder SARS-CoV-2 infection with an IC_{50} value of 47 μg/mL (Yim et al., 2021b, a). The higher molecular weight (>800 kDa), higher total carbohydrate (62.7–99.1%), higher fucose content (37.3–66.2%), and highly branched structures contribute towards their antiviral activity. Fucoidan (3.90–500 μg/mL) can prevent the SARS-CoV-2 entry into the cell via binding to the S glycoprotein (Song et al., 2020a, b). Fucoidan at a 0.01–10% concentration prevented the respirational tract infections triggered by the SARS-CoV-2 virus (Flaviviridae et al., 2020). Fucoidan, at an approximate concentration of 83 nM binds to the spike protein of the SARS-CoV-2 in in vitro model, averting its host cell binding (Kwon et al., 2020). Moreover marine sulfated polysaccharides displayed potent inhibitory activities against SARS-CoV-2 at concentrations of 3.90–500 μg/mL (Song et al., 2020a, b). Fucoidan significantly restores the ΔΨm of HPBMC, suggesting that fucoidan can be useful to improve mitochondrial homeostasis after SARS-CoV-2 infection (Díaz-Resendiz et al., 2022). Crude polysaccharides from seaweeds inhibit SARS-CoV-2 Virus entry (Yim et al., 2021b, a). Rhamnan sulfate from *Monostroma nitidum* displayed strong antiviral activities against wild type SARS-CoV-2 and the delta variant in vitro (Song et al., 2021). Sulfated galactofucan from *Saccharina japonica* showed strong binding ability to SARS-CoV-2 SGPs, suggesting that might be a good candidate for preventing and/or treating SARS-CoV-2

Table 1
Intricate role of fucoidan as an anti-viral agent against human pathogenic viruses and their mode of action.

Sl. no	Sources of fucoidan	Viruses involved	Mode of action	References
1	*L. japonica*	HSV-1	Boost immune function and raise thymus and spleen indexes.	(Sun et al., 2018)
2	*Undaria pinnatifida*	HSV-1	Reducing viral replication and activating innate and adaptive immune systems	(Hayashi et al., 2008)
3	*Kjellmaniella crassifolia*	IAV infection	Inhibition of viral neuraminidase and cellular EGFR pathway in vitro model	(Wang et al., 2017a, 2017b)
4	*Kjellmaniella crassifolia*	IAV infection	Induce viral resistance, surpassing the standard anti-IAV medication amantadine and inactivate virus particles via binding to viral neuraminidase (NA) and inhibited the activity of NA to block the release of IAV	(Wang et al., 2017a, 2017b)
5	*Kjellmaniella crassifolia*	IAV-infected mice	Significantly increased the survival and reduced the viral titers	(Wang et al., 2017a, 2017b)
6	*Kjellmaniella crassifolia*	influenza virus	Prevents the virus in subsequent infection	(Wang et al., 2017a, 2017b)
7	LMWF fractions from *L. japonica*	virus-infected mice	Modulates the lengthen the survival duration of virus-infected mice, as well as dramatically increase the quality of immune organs, immune cells, phagocytosis, and humoral immunity	(Sun et al., 2018)
8	LMWF fractions from *L. japonica*	I-type influenza virus, adenovirus and Parainfluenza virus I were used to infect Hep-2, Hela and MDCK cells	Modulates the lengthen the survival duration of virus-infected mice, as well as dramatically increase the quality of immune organs, immune cells, phagocytosis, and humoral immunity	(Sun et al., 2018)
9	LMWF fractions from *L. japonica*	virus-infected mice	Modulates the lengthen the survival duration of virus-infected mice, as well as dramatically increase the quality of immune organs, immune cells, phagocytosis, and humoral immunity	(Sun et al., 2018)
10	*K. crassifolia*	H5N1 and H7N9	Antiviral activity	(Moscona, 2009)
11	*Fucus evanescens*	HBV	Inhibited HBV replication in in vivo	(Kuznetsova et al., 2017)
12	*Fucus evanescens*	HBV	Inhibited in in vitro models by activating the EKR signal pathway	(Kuznetsova et al., 2017)
13	*Fucus evanescens*	HepG2.2.15 cells	Modulates MAPK-ERK1/2 pathway and stimulated the expression of IFNs and decrease in HBV DNA and associated proteins synthesis	(Kuznetsova et al., 2017)
14	*Fucus evanescens*	Infection in Jurkat cells with pseudo-HIV-1	Suppressing the infection	(Prokofjeva et al., 2013)
15	*Saccharina cichorioides*	HIV-1	Displayed a significant inhibitory effect	(Dinesh et al., 2016)
16	*S. japonica* (galactofucan)	HIV-1	Displayed a significant inhibitory effect	(Dinesh et al., 2016)
17	*S. swartzii*	HIV	Antiviral effects	(Dinesh et al., 2016)
18	*Adenocystis utricularis*	HIV-1	Inhibited via blocking the entry of the virus	(Trinchero et al., 2009)
19	*S. swartzii*	HIV-1	Reduction in HIV-1 p24 antigen levels and reverse transcriptase activity	(Dinesh et al., 2016)
20	*Sargassum mcclurei*	HIV-1	Inhibited via blocking the entry of the HIV-1 virus	(Thuy et al., 2015)
21	*S. mcclurei*	HIV-1	Inhibition of virus with low IC_{50} value ranging from 0.33 to 0.7 g/mL and limit HIV entry into target cells at an early stage	(Thuy et al., 2015)
22	*S. polycystum*	HIV-1	Inhibition of virus with low IC_{50} value ranging from 0.33 to 0.7 g/mL and limit HIV entry into target cells at an early stage	(Thuy et al., 2015)
23	*Turbinaria ornata*	HIV-1	Inhibition of virus with low IC_{50} value ranging from 0.33 to 0.7 g/mL and limit HIV entry into target cells at an early stage	(Thuy et al., 2015)
24	*Adenocystis utricularis*	HSV-1 and HSV-2	Inhibition of virus without toxicity	(Ponce et al., 2003)
25	*Dictyota dichotoma*	HSV-1	Inhibition of virus through reduction in plaque formation	(Rabanal et al., 2014)
26	*Cladosiphon okamuranus*	DENV-2	Inhibition of virus via direct binding to the spike protein	(Hidari et al., 2008)
27	*Cystoseira indica*	HSV-1, HSV-2	Antiviral activity via inhibition of adsorption	(Mandal et al., 2007)
28	*Caulerpa brachypus*	HSV-1	Antiviral activity via inhibiting attachment, penetration, and later stages of replication	(Lee, Hayashi, Maeda, & Hayashi, 2004)
29	*Fucus vesiculosus*	BVDV (Bovine viral diarrhea virus)	Anti-viral activity via inhibition of the binding of the virus	(Güven et al., 2020)
30	*Laminaria japonica*	H5N1	Inhibition of virus	(Makarenkova et al., 2010)
31	*Undaria pinnatifida*	HSV-1, HSV-2, and HCMV virus	Antiviral activity via inhibiting the viral entry and host-virus binding	(Hemmingson et al., 2006)
32	*Sargassum trichophyllum*	HSV-2	Anti-viral activity via inhibiting the virus adsorption, penetration and replication	(Lee et al., 2011)
33	*C. okamuranus*	NDV La Sota (Newcastle Disease Virus)	Anti-viral activity via inhibited early stages viral infection via abridged HN protein expression. Moreover, it inhibited syncytia formation (70%) via specific interaction between fucoidan and the F0 protein	(Elizondo-Gonzalez et al., 2012)
34	*Sargassum wightii* and *Artemia franciscana*	white spot syndrome virus (WSSV)	*Penaeus monodon* has been found to be effective against with reported mortality of 61.65%	(Sivagnanavelmurugan et al., 2012)

(Jin, Zhang, et al., 2020a, 2020b).

6. Preclinical efficacy status of fucoidan

Preclinical progress, also known as preclinical studies or nonclinical studies, is a stage of drug development that occurs before clinical trials (human testing) and collects essential feasibility, iterative testing, and drug safety data, usually in laboratory animals. Preclinical studies' major goals are to select a starting, safe dose for first-in-human studies and to analyse the product's potential toxicity, which usually includes new medical devices, prescription medications, and diagnostics. Companies utilise exaggerated numbers to show the dangers of preclinical research, such as the fact that only one out of every 5000 molecules that go from drug discovery to preclinical development becomes an approved medicine. In this regards, fucoidan gaining the attraction of preclinical test, fucoidan from *Kjellmaniella crassifolia* significantly increased the survival and reduced the viral titers IAV-infected mice (Wang et al., 2017a, 2017b). Low molecular weight of fucoidan from brown algae *Laminaria japonica* tested in an infected mouse model displayed a prolonged survival time of mice infected with HPIV 1 (Sun et al., 2018). Sulfated polysaccharide *Laminaria japonica* was tested in an infected mouse model. IV injection of low molecular weight fucoidan showed a

prolonged survival time of virus-infected mice (Leibbrandt et al., 2010). Furthermore, fucoidan from *Undaria pinnatifida* has been demonstrated to inhibit influenza A virus in vivo replication in mice infected models by lowering viral replication and enhancing humoral immunity (neutralizing antibodies) (Kyoko Hayashi et al., 2013; Synytsya et al., 2014). Orally administration of fucoidan (7.04 mg/day) from *Undaria pinnatifida* significantly reduced gross lung pathology (consolidation) in a BALB/c mouse model of severe H1N1 (PR8) influenza, when administered at the same time as the viral infection (Richards et al., 2020). Sun et al. isolated two LMWF fractions from *L. japonica*. In vivo data showed that LF1 and LF2 were able to extend the survival duration of virus-infected mice (Sun et al., 2018). From the above preclinical status fucoidan as well as LMWF (low molecular weight fucoidan) may be further developed to be used for clinical purposes. Although the aforementioned findings suggest that fucoidan could be a promising anti-viral medication, more in vivo research is still needed before clinical trials can begin (see Table 2).

7. Immunomodulatory activity of fucoidan against SARS-CoV-2 via microbiota-based therapy

Immunity is the primary concern in COVID-19 suffering individuals (Sen et al., 2021). After treating with drugs, the patients gradually become immune-compromised (De Mello et al., 2020)]. SARS-CoV-2 causes gastrointestinal disorders in almost 20% of patients suffering from it (Heo et al., 2017). Effenberger et al. (2020) reported that 61% of the patients suffer from the gastrointestinal disorder, diarrhea and nausea. Therefore, natural immunomodulators from algae seem to be promising as a drug aspect against SARS-CoV-2 with minimal drug-related toxicity (Zuo et al., 2020). A recent pilot study on microbiome composition of stool samples from 15 hospitalized patients who suffered from COVID-19 with healthy individuals revealed poor gut health in SARS-CoV-2 suffering individuals (Zuo et al., 2020).

On the other hand, a healthy gut microbiome is essential for modulating antiviral immunity via improving gut flora (Zuo et al., 2020). In such circumstances, algae-based sulfated polysaccharides can be used as food supplements to enhance gut microbiota and reduce the infection of novel SARS-CoV-2. Gut microbiota symbiosis associated with ACE2 plays a pivotal role in improving antiviral immunity by stimulating interferon production, decreasing immunopathology, increasing natural killer (NK) and cytotoxicity in COVID-19 suffering patients (He et al., 2020). Marine sulfated polysaccharides such as fucoidans trigger human gut microbiota and maintain the host health via controlling proper metabolism, the epithelial barrier integrity and immune system as prebiotics and nutritional food supplements (Tamama, 2021). Seaweeds are rich in vitamins and minerals and rich in sulfated polysaccharides that can be used as dietary supplements to COVID-19 patients. Previously, it was found that algal peptides exhibited a anti-Spike protein of COVID19 through in silico study (MubarakAli et al., 2021).

Moreover, fucoidan isolated from different macroalgal species display promising immunomodulation activity (Pradhan, Patra, Behera, et al., 2021). Fucoidan from *Cladosiphon okamuranus* consumption modulates human gastrointestinal disorders such as diarrhea, gas and bloating. It also triggered microbiota composition (Fields et al., 2020). Fucoidan from *Sargassum mcclurei* modulates immune systems via modulating gut microbiota and upregulating toll-like receptors 2 and 4 (TLR2 and TLR4) (Neyrinck et al., 2017). Fucoidan isolated from *Sargassum polycystum* modulates the gut microbiota and triggers immunity. Sulfated polysaccharides isolated from *Ascophyllum nodosum* activate the abundance of beneficial firmicutes and bacteroidetes (Chen et al., 2018). Moreover, Other Algae-based polysaccharides also exhibit beneficial effects to human gut microbiota (Pereira & Critchley, 2020). *Sargassum muticum* and *Osmundea pinnatifida* extracts have been used as novel functional foods and positively influence human gut microbiota (Rodrigues et al., 2016). The immunomodulatory properties of fucoidan isolated from Brown algae is promising (Wu et al., 2016). LMW

Table 2
Role of fucoidan as an anti-viral agent against in light of SARS-CoV-2 virus and their mode of action.

Sl. no	Sources of fucoidan	Viruses involved	Mode of action	References
1	*F. vesiculosus*	in vitro infection model (SARS-CoV-2)	Inhibitory antiviral effect on viral spike protein binding to S glycoprotein against SARS-CoV-2	(Fitton et al., 2021)
2	*U. pinnatifida*	in vitro infection model (SARS-CoV-2)	Inhibitory Antiviral effect on viral spike protein binding to S glycoprotein against SARS-CoV-2	(Fitton et al., 2021)
3	*Saccharina japonica* (LMW)	SARS-CoV-2	Displayed in vitro anti-viral properties against SARS-CoV-2 via binding to S-proteins of SARS-CoV-2	(Kwon et al., 2020)
4	*Saccharina japonica* (HMW)	SARS-CoV-2	Displayed in vitro anti-viral properties against SARS-CoV-2 via binding to S-proteins of SARS-CoV-2	(Kwon et al., 2020)
5	*Lytechinus variegatus*	SARS-CoV-2	Demonstrated a SGP binding efficiency and transduction efficiency of a third generation lentiviral (pLV) vector and modulated pLV-S particles even with an IC_{50} of low ng to high μg/L	(Tandon et al., 2021)
6	*Botryocladia occidentalis*	SARS-CoV-2	Demonstrated a SGP binding efficiency and transduction efficiency of a third generation lentiviral (pLV) vector and modulated pLV-S particles even with an IC50 of low ng to high μg/L	(Tandon et al., 2021)
7	Saccharina japonica	SARS-CoV-2	Inhibited interaction between SARS-CoV-2 SGPs and heparin, but not ACE2	(Jin, Zhang, et al., 2020a, 2020b)
8	*Undaria pinnatifida*	SARS-CoV-2 pseudo virus in HEK293/ACE2	Inhibited viral infection with an IC_{50} value of 12–289 μg/mL	(Yim et al., 2021b, a)
9	*Laminaria japonica*	SARS-CoV-2 pseudo virus in HEK293/ACE2	Inhibited viral infection with an IC_{50} value of 12–289 μg/mL	(Yim et al., 2021b, a)
10	*Hizikia fusiforme*	SARS-CoV-2 pseudo virus in HEK293/ACE2	Inhibited viral infection with an IC_{50} value of 47 μg/mL	(Yim et al., 2021b, a)
11	*Sargassum horneri*	SARS-CoV-2 pseudo virus in HEK293/ACE2	Inhibited viral infection with an IC_{50} value of 12 μg/mL	(Yim et al., 2021b, a)
12	*Codium fragile*	SARS-CoV-2 pseudo virus in HEK293/ACE2	Inhibited viral infection with an IC_{50} value of 12–289 μg/mL	(Yim et al., 2021b, a)
13	*Porphyra tenera*	SARS-CoV-2 pseudo virus in HEK293/ACE2	Inhibited viral infection with an IC_{50} value of 12–289 μg/mL	(Yim et al., 2021b, a)
14		SARS-CoV-2	Prevent the entry of virus into the cell via	(Song et al., 2020a, b)

(*continued on next page*)

Table 2 (*continued*)

Sl. no	Sources of fucoidan	Viruses involved	Mode of action	References
	Fucoidan from *Porphyra tenera*		binding to the S glycoprotein	
15	Fucoidan from *Porphyra tenera*	SARS-CoV-2	Prevented the respiratory tract infections	(Flaviviridae et al., 2020)

fucoidans such as LF1 and LF2 could enhance the spleen index, thymus index, phagocytic index, half hemolysin and phagocytosis coefficient value even at doses of 2.5, 5, 10, 15 mg/kg. The aforementioned results indicated that LMW fucoidans can recover the eminence of immune organs, enlightening immune cell phagocytosis and humoral immunity of virus-infected cells (Sun et al., 2018). Nanoparticular CpG-adjuvanted SARS-CoV-2 S1 protein triggers broadly neutralizing and Th1-biased immunoreactivity in mice (Lin et al., 2021). The viral immune responses against COVID-19 and dermatologic immunomodulator targets are shown in Fig. 5.

8. Fucoidan in immunocompromised patients as well as patients with comorbidities

Immunocompromised people have a diminished the ability to fight aganist infections and other disorders. The immune system has been weakened in primary immunocompromised people. Many types of primary immunodeficiency illnesses can benefit from treatments that enhance the immune system (Sobh & Bonilla, 2016). The signs and symptoms of primary immunodeficiency disorders fluctuate based on the type, and also vary from person to person. Inflammation and infection of internal organs, blood disorders (low platelet count or anaemia), digestive problems (cramping, loss of appetite, nausea and diarrhea), and symptoms of immunocompromised disorders such as frequent and recurrent pneumonia, bronchitis, sinus infections, ear infections, meningitis, or skin infections, inflammation and infection of internal organs (Sobh & Bonilla, 2016). People with the illness will benefit from new therapies and a higher quality of life as a result of ongoing research (Oguntibeju, 2012). Immunomodulatory properties of fucoidan have interesting applications, such as vaccine adjuvants (Kyoko Hayashi et al., 2013). Fucoidan from *Undaria pinnatifida* (9 kDa) tested in H1N1 (A/NWS/33) virus yield in the mucosa of immunocompetent and compromised mice was reduced and stimulated mucosal immunoresponse with IC_{50} value 15 μg/mL 5 mg/day post infection (Kyoko Hayashi et al., 2013). Furthermore, fucoidan from *Undaria pinnatifida* has been shown to inhibit influenza A virus in vivo replication in infected mice and improve innate immunity (natural killer and macrophage activity) via immunity pathways (Kyoko Hayashi et al., 2013; Synytsya et al., 2014). Hayashi et al. discovered that a fucoidan isolated from *Undaria pinnatifida* had anti-IAV activity enhancing immune system in mice, in mice with normal and reduced immunity (Kyoko Hayashi et al., 2013). Fucoidans could also be employed as vaccine adjuvants in mice, activating spleen cells and increasing antigen-specific antibody production (Kim & Joo, 2015). Intranasal administration of fucoidan from *Kjellmaniella crassifolia* (10 and 20 μg/day) treatment significantly increases the survival of IAV-infected mice and improved the immunity (Fukushi et al., 2011). Fucoidan could be a promising candidate in immunocompromised patients.

8.1. Summary and future prospective

Algal sulfated polysaccharides could be used as antiviral drugs as individual entities or in combination with clinically approved antiviral drugs, which can combat COVID-19. Although the vaccination program has started, sulfated polysaccharides like fucoidan can still exert potential immunomodulatory efficacy against COVID-19 infection. Moreover, it can also modulate severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and lesser the risk of viral contaminations in the post-COVID era. Furthermore, fucoidan can act as food supplements that can limit the injury of the respiratory system post-viral

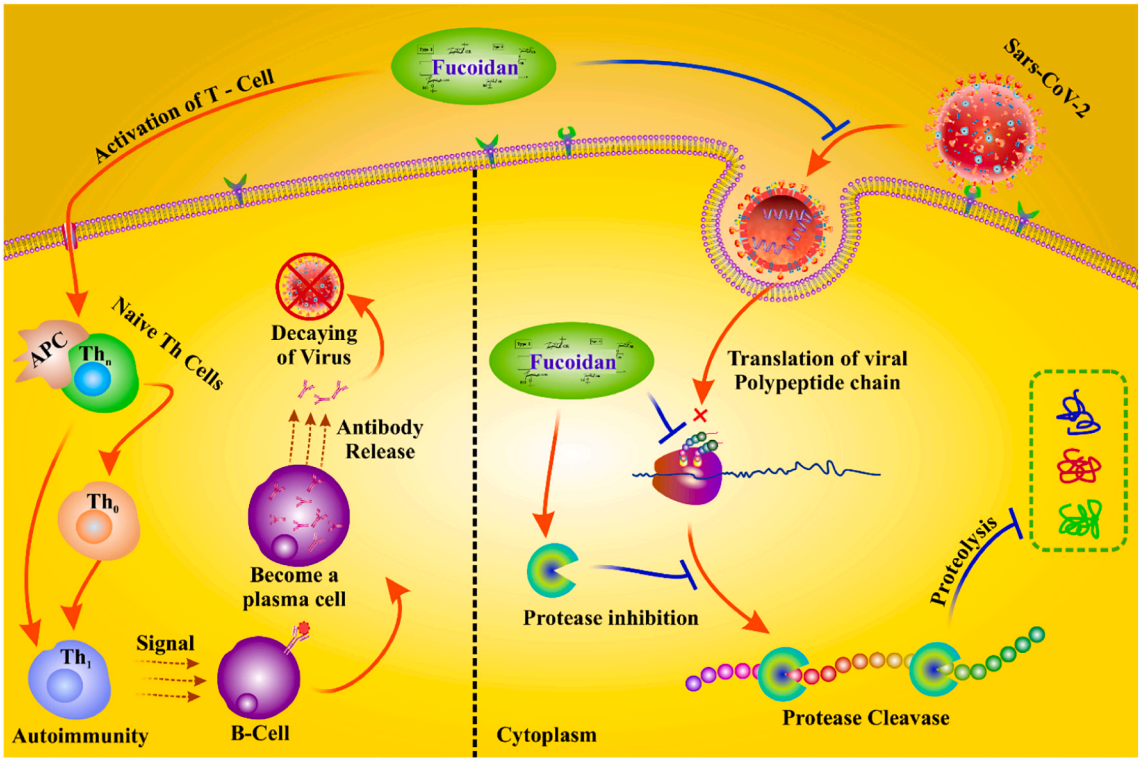

Fig. 5. Fucoidan inhibit the attachment and viral entry. Moreover, fucoidan activate immune responses against COVID-19 patients via activation of T-cell.

infections via restoring innate immune function and preventing inflammation. Study of the chemical composition, antiviral potency, and mechanisms associated with SARS-CoV-2 of sulfated polysaccharides with the special notation to fucoidan is urgently needed to be established as an antiviral agent as well as an immunomodulator in pharmaceutical sectors.

CRediT authorship contribution statement

Biswajita Pradhan: Writing - original draft, Writing - review & editing, figure editing, Visualization, Proof correction. **Rabindra Nayak**: Writing & figure editing, Proof correction. **Srimanta Patra**: Writing & editing, Proof correction. **Pradyota Kumar Behera**: Drawing the molecular structure. **Prajna Paramita Bhuyan**: Writing - review & editing, **Amiya Kumar Mandal**: formal analysis, **Chhandashree Behera**: formal analysis, **Jang-Seu Ki**: suggestion. **Siba Prasad Adhikary**: suggestion, proof correction. **Davoodbasha MubarakAli**: Review & editing, supervision, correction, suggestion, proof correction. **Mrutyunjay Jena**: Review & editing, supervision, correction, suggestion, proof correction.

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Fundings

Not applicable.

Research involving human participants and/or animals

No Human participation and/or Animal have been used in this study.

Informed consent

The corresponding author on behalf of all coauthors agrees to accept the informed consent of compliance with ethical standard.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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