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The antiviral potential of algal-derived macromolecules

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ABSTRACT

A diverse range of molecules with anticancer, antiviral, and antibiotic activities has been identified and isolated from algal species. Such metabolites could address unmet clinical needs and be used to fight human diseases. Further, the natural compounds derived from algae present several advantages in terms of sustainable supply, low cytotoxicity and low cost. Seaweeds represent one of the richest known sources of natural antivirals, as well as a significant source of other bioactive compounds. Increasing evidence has demonstrated that algae comprise a vast untapped reservoir of pharmaceutical potential with many underexplored species and underexploited drug candidates, which may be derived from these 'plants of the sea'.

In recent decades, new therapeutic lead compounds including polysaccharides, lectins, terpenes, alkaloids, carotenoids, and sterols, with a broad spectrum of antiviral activities, have been isolated from marine macro- and micro-algae. The current high volume of research studies exploring the antiviral potency of seaweeds epitomises the increased interest in this field. This review focuses on bioactive marine macromolecules with antiviral activities which may serve as a starting point for enhanced knowledge and a stimulus for wider research in this field. The review also seeks to improve the understanding of the antiviral mechanisms and complex structures of algal-derived macromolecules. Since the purification of such structurally complex and frequently heterogeneous extracts and molecular classes remain fraught with difficulty, efforts to decipher the structure and composition of these macromolecules would offer enhanced possibilities for future scientific and pharmaceutical advances.

Contents

1. Introduction

The Holy Grail of viral therapies is to provide an effective vaccine that can halt the spread of the illness effectively and safely. The absence of effective vaccines against a variety of prevalent viral infections, such as dengue virus (DENV), herpes simplex viruses (HSV), and most respiratory-tract viruses, underscore the major challenges that antiviral pharmaceuticals present to academia, the pharmaceutical industry, and policy agenda. Treatment protocols for the most life-threatening viral infections, including coronavirus disease 2019 (COVID-19), involves targeting three main objectives: inhibiting viral replication and spread, minimising life-threatening inflammatory reactions including cytokine storms, and boosting patients' immune responses. Yet, currently, no single drug can hit all those targets; therefore, a combinatorial regime of different treatments should be given, which collectively is not only expensive, but also associated with drug resistance, as well as immediate and delayed adverse effects. Therefore, the unmet need for an effective, safe, and affordable antiviral therapy necessitates searching for alternative solutions. Natural antivirals, which combine potent antiviral activity with low cytotoxicity, could respond to this challenge; thereby representing an effective therapeutic window. Since various algal-derived antiviral compounds can interfere with the replication cycle of viruses, slow down the subsequent infection, or block cell entry, a fuller exploration of novel viral entry inhibitors from natural sources could help expedite the development of preventive therapies or measures against prevalent viral infections (Lin et al., 2014; Pattnaik and Chakraborty, 2020; Zhou and Simmons, 2012).

This work reviews the most recent research on natural algae-derived macromolecules with antiviral activity towards prevalent viral infections. Under the heading of each respective major compound, this article reviews the literature on the algal extracts and compounds with antiviral activities, their mechanisms, and potential medical applications of the most promising seaweed compounds. The review also demonstrates how far the search for new bioactive compounds has progressed to bring such agents to market.

2. General antiviral mechanisms of algal-derived macromolecules

Algae are macro and micro aquatic organisms found in the oceans of the world. They contain a plethora of bioactive molecules that have diverse therapeutic benefits. The classification of algae is complex, and classes are better defined and more accepted than divisions (Dawes et al., 2016). The main classes of algae discussed in this review are brown algae (class *Phaeophyceae*), such as Laminaria and Fucus; red algae (Rhodophyta), such as Chondrous and Palmaria; green algae (*Chlorophyata*), such as Chlorella and Ulva. We also include the blue-green algae which are cyanobacteria (*Cyanophyceae*), such as Nostoc and Spirulina (Fig. 1).

There is exciting evidence emphasising the importance of algal-derived compounds as a source of antiviral, anti-inflammatory and immune modulators that can make them potential candidates for the world's most serious viral infections, including those caused by coronaviruses and human immunodeficiency virus (HIV) (Besednova et al., 2019; Jiao et al., 2011; Pereira and Critchley, 2020; Talukdar et al., 2020). Furthermore, a growing body of evidence refers to the role of algal-derived compounds as immune adjuvants (Sanina, 2019) that can be utilised for vaccine production. Therefore, algal-derived compounds can be employed as an outstanding double-edged sword for the treatment of coronavirus disease 2019 (COVID-19) and other serious viral infections. While the large body of experimental evidence accrued in the literature is encouraging, further preclinical studies and clear clinical trials to assess the efficiency of the many algal compounds are needed (Bule et al., 2018). A review by Ahmadi *et al.* (2015) has interestingly summarised the active antiviral properties of different metabolites produced from various algae against different viral infections (Ahmadi et al., 2015). The brown seaweeds, *Sargassum fusiforme* and *Saccharina japonica,* are examples of seaweed which have been used for thousands of years to treat fever, infections, and laryngitis (Peng et al., 2013). Carrageenan, Galactan and seaweed extract from red algae have demonstrated potential antiviral properties against many human pathogenic viruses including, DENV, human papillomavirus (HPV), HIV, hepatitis A virus (HAV), human rhinovirus (HRV), Alfalfa mosaic virus (AMV), HSV-1, HSV-2, Rauscher murine leukemia virus (RMLV) and influenza viruses. Alginate has demonstrated substantial activity against HIV and hepatitis B virus (HBV), while fucan specifically inhibited HSV1, HSV2, hydrangea chloritic mottle virus (HCMV), vesicular stomatitis virus (VSV), Sindbis virus and HIV-1 (Ahmadi et al., 2015). Naviculan from the diatom, *Navicula directa,* exhibited a potential activity against-HSV-1 and HSV-2 (Dewi et al., 2018). Moreover, polysaccharides from dinoflagellates (*Gyrodiniumim pudicum* and *Cochlodinium polykrikoides*) were found to
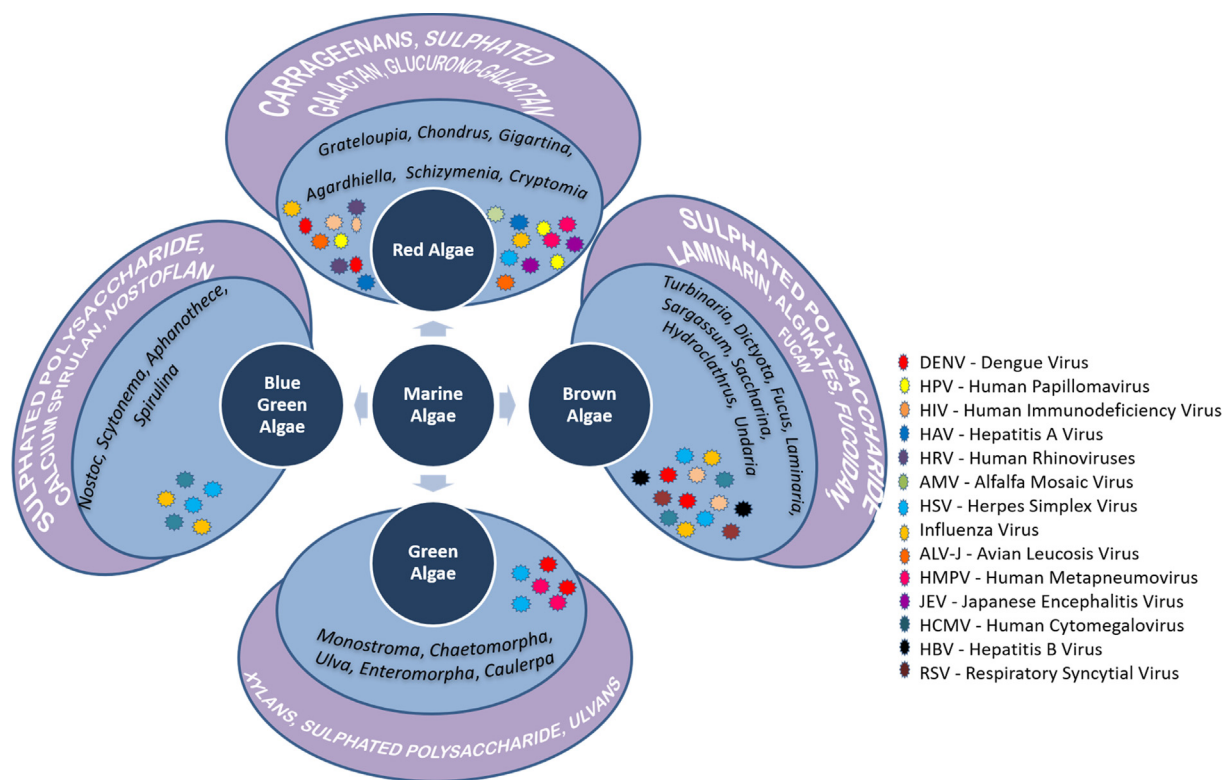
Fig. 1. Distribution of broad-spectrum antiviral polysaccharides in different algal genera. The schematic illustrates different types of marine algae including red, brown, green and blue green that encompass various genera- Grateloupia, Laminaria, Fucus, Ulva, Nostoc, etc. The specific polysaccharides (carrageenans ulvans, fucoidans, alginates, xylans, nostoflans, etc.) exuded by certain genera exhibit broad spectrum antiviral activities against viruses viz. DENV, HPV, HIV, HAV, HRV, AMV, HSV, etc. (abbreviations are given in the schematic). Amongst all, red algae have been found to possess the most extensive antiviral activity. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

inhibit infections of the encephalomyocarditis virus (EMCV), respiratory syncytial virus-A (RSV-A), respiratory syncytial virus-A (RSV-B), parainfluenza-2, influenza A and B viruses (Rodrigues et al., 2017). Nostaflan isolated from *Nostoc flagelliforme* inhibits influenza A virus, HSV-1, HSV-2 and human cytomegalovirus (CMV) (Ulagalanthaperumal and Algae, 2020).

2.1. Viral infection and oxidative stress; the protective role of algal-derived compounds

Reactive oxygen species (ROS) can cause cell death *via* the activation of mitochondrial and receptor-mediated pathways of apoptosis, as well as engaging with signalling pathways, such as mitogen-activated protein kinase (MAPK), the CCAAT-enhancer-binding protein homologous protein (CHOP) and death receptors (DRs) (Obaidi et al., 2020). Immune cells, namely T-lymphocytes, have been shown to exhibit a substantial sensitivity towards the accumulation of ROS (Kesarwani et al., 2013). Furthermore, oxidative stress plays a key role in increasing the susceptibility to various diseases, including HIV infection (Rahal et al., 2014). In addition, CD4-T cells were shown to undergo caspase1-mediated pyroptosis, in which, HIV forced the immune cells to die *via* the inflammatory form of apoptosis or pyroptosis causing a severe depletion of CD4-T cells linked to the induction of chronic inflammation. The interplay between the death of infected cells and inflammation creates a "pathogenic vicious cycle" causing more immune cells to die (Doitsh et al., 2014).

The harmony between oxidative stress and inflammation has previously been reported (Rada et al., 2011; Kim et al., 2008). Oxidative stress induces protein oxidation and lipid peroxidation and nitrite release leads to accumulation of reactive metabolites which consume antioxidant pools of cells particularly glutathione (GSH) (Ghezzi,

2011). The ratio of GSH/ oxidised GSH (GSSG) plays a significant role not only in regulating the oxidative status, but also in controlling cellular immune responses (Ghezzi, 1830) and modulating gene expression (Fratelli et al., 2002). Oxidative stress can induce deoxyribonucleic acid (DNA) mutation and dysregulation of several inflammation-regulatory genes, such as connective tissue growth factor (CTGF), tumour necrosis factor alpha (TNF-α), epidermal growth factor (EGF) (Obaidi et al., 2018), vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and nuclear factor-kappa B (NF-κB) (Prabhakar, 2013). ROS act as a second messenger to amplify pro-inflammatory signal transduction causing dysregulation of MAPK/AP-1, NF-κβ, and Janus kinase-signal transducer and activator of transcription (JAK-STAT) signalling pathways during the early stage of inflammation (Choo et al., 2020). The inflammation induces the release of peroxiredoxin-2 (PRDX2) and thioredoxin (TRX), ubiquitous redox sensing and regulating enzymes. On the other hand, inflammation leads to the activation of macrophages with the release of pro-oxidant cytokines, such as TNF-α, causing a positive feedback loop (Hussain et al., 2016; Salzano et al., 2014). Likewise, upon entry, viruses trigger inflammatory cascades associated with engaging several inflammatory cells. For instance, activated monocytes release TNF-α and interleukin (IL)-1/6 which are orchestrated with the upregulation of iron uptake by reticuloendothelial system (Parameswaran and Patial, 2010). The unleash of TNF-α provides a positional cue that amplifies cellular pro-oxidant status *via* interfering with mitochondrial oxygen transport and dysregulating of NF-KB signalling pathway leading to the activation of several cellular and viral genes (Sansone et al., 2020). Research has documented that the antiviral activities of algal-derived compounds are due to their direct effects on viral replication machinery, curtailing ROS production, improving immune responses, and alleviating adverse inflammatory reactions
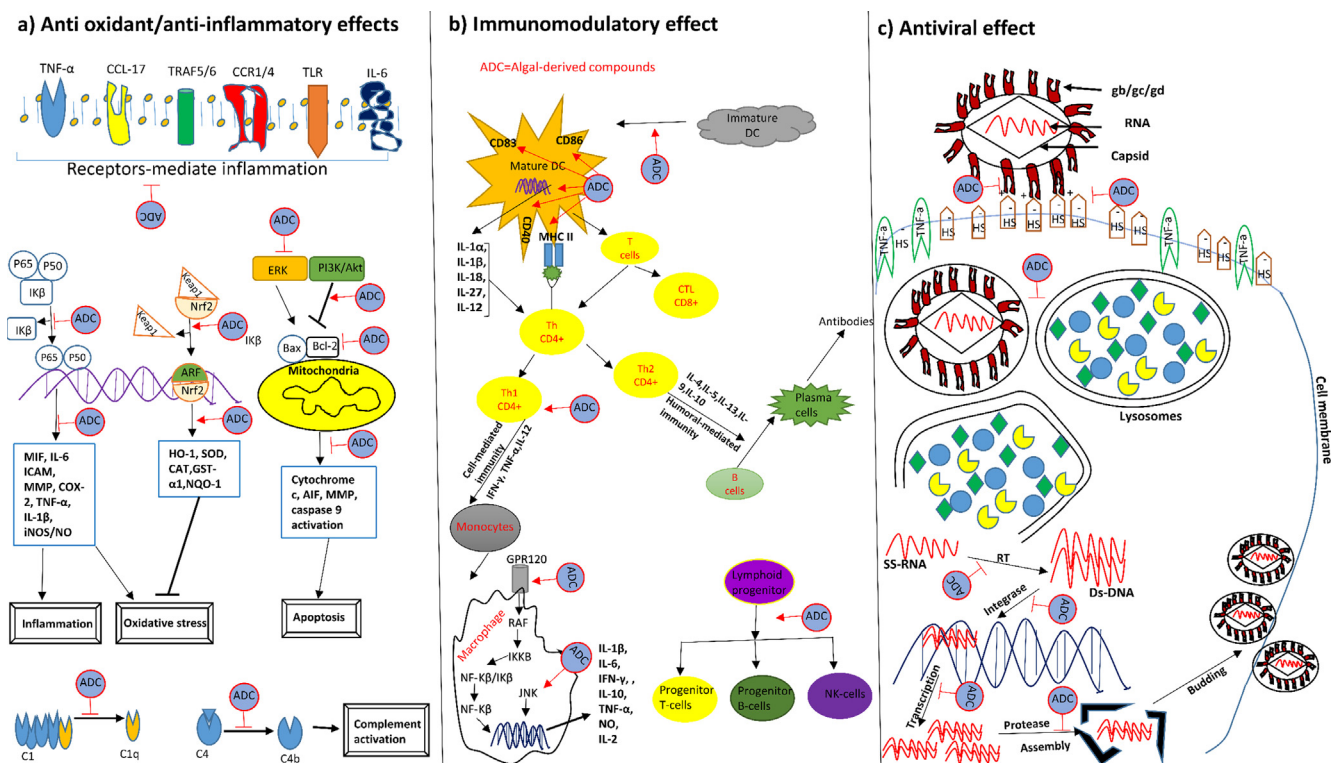
Fig. 2. Potential antiviral mechanisms of algal-derived compounds. a) Antioxidant/anti-inflammatory mechanisms: algal-derived compounds (ADC) can block various inflammation-mediated receptors, including TNF-α, CCL-17, TRAF5/6, CCR1/4 and TLR. ADC also inhibit NF-KB p65/50- mediated the activation of several inflammatory mediators, including ICAM, IL-6, COX and iNOS system. In contrast, ADC augment the activation of Nrf2/ARF antioxidant system. ADC can suppress the phosphorylation of ERK while promote the activation of PI3K/Akt/Bcl-2 signalling cascades. b) Immunomodulatory mechanisms: ADC stimulate the maturation process of DC. ADC can also activate GRP-120, whichleads to the activation of several immunoregulatory-signalling pathways. c) Antiviral mechanisms: ADC block the entry of viruses *via* inhibiting the binding of glycoprotein b (gb) and prevent viral uncoating. ADC can target reverse transcriptase (RT), integrases and viral proteases, therefore, viral assembly and generations of new virions are suppressed.

(Talukdar et al., 2020; Choo et al., 2020; Arulselvan et al., 2016; Lauritano et al., 2016).

Significant evidence has unequivocally unravelled the antioxidant and anti-inflammatory mechanisms of natural compounds derived from algae, including (Fig. 2 a):

a. Blockage of nuclear translocation of the transcription factor NF κB/p65 and, subsequently, activation of pro-inflammatory cytokines TNF-α and IL-6 (Miyachi et al., 2015; Cai et al., 2019). Furthermore, they inhibit the phosphorylation of the inhibitory factor kappa B (IKB). NF-κB/p65 mediates the activation of macrophage migration inhibitory factor (MIF), ICAM1, matrix metallopeptidase (MMP), cyclooxygenase-2 (COX-2) and IL-1β (Fakhri et al., 2019).

b. Inhibition of inflammatory signalling pathways mediated by toll-like receptors 1, 2, 4 and 8 (TLR1, TLR2, TLR4, and TLR8), TNF receptor-associated factor 5 and 6 (TRAF5 and TRAF6), Chemokine (C-C motif) receptor 1 and 4 (CCR1 and CCR4) and Chemokine (C-C motif) ligand 17 (CCL17). Furthermore, suppression of other pro-inflammatory genes, such as TNF (ligand) superfamily member 18 (TNFSF18), IL-6 receptor (IL6R), IL-23 (IL23), signal transducer and activator of transcription 3 (STAT3), and mitogen-activated protein 3 kinase 1 (MAP3K1) were also reported (Robertson et al., 2015).

c. Abrogation of inflammatory pathways mediated by inducible nitric oxide synthase (iNOS), and COX-2 (Jin et al., 2006; Bi et al., 2018).

d. Induction of antioxidant systems *via* facilitating the dissociation of Kelch-like ECH-associated protein 1- nuclear factor erythroid-2-related factor 2 (Keap1/Nrf2), thus promoting nuclear translocation and binding of Nrf2 to the antioxidant response element (ARE) which leads to upregulate the expression of antioxidant defence systems mediated by heme oxygenase-1 (HO-1), glutathione-S-transferase-α1 (GST-α1), NAD(P)H quinone oxidoreductase-1 (NQO-1) (Chen et al., 2019; Shimizu et al., 2015; Wang et al., 2013).

e. Interference with the phosphorylation of extracellular signal-regulated kinase (ERK), while activation of phosphatidylinositol 3-kinase/ protein kinase B/B-cell lymphoma 2 (PI3K/Akt/Bcl-2) signalling cascades. Thus, apoptotic cell death can be halted *via* the inhibition of Bcl-2-associated X protein (Bax)/Bcl-2 complex, as well as *via* neutralisation of the detrimental effects caused by the release of caspases and cytochrome *C* (Fakhri et al., 2019; Pangestuti and Kim, 2011; Silva et al., 2018).

Inhibition of complement activation can occur by both classical and alternative pathways (Jiao et al., 2011; Jin et al., 2015). The complement component C1q was shown to be bound and sequestered by algal-derived compounds and ultimately C1 activation can be inhibited (Tissot and Daniel, 2003). In addition, algal compounds can bind and stabilise C4, thus preventing its cleavage into C4b, the active subunit that is required to form C3 convertase and sequential propagation of the complements (Tissot et al., 2003). The binding of C1q to IgG can be blocked *via* the binding of algal extracts to C1q globular head (Dimasi, 2011).

2.2. The immunomodulatory mechanisms of algal-derived compounds

Algal-derived compounds exhibit a substantial immunomodulatory effect *via* enhancing lymphoproliferation with a marked increase of

both T and B lymphocytes subpopulations, potentiation of natural killer cytotoxicity and boosting IFN-γ/IL-6 (Park et al., 2010) and IFN-γ /IL-2 production (Lin et al., 2015). Furthermore, the enhancement of phagocytic activity and activation of the nitric oxide synthase system have also been documented (El-Boshy et al., 2014). An elegant review by Riccio and Lauritano (Riccio and Lauritano, 2019) shed some light on the immunomodulatory potential of algal-derived products . Mechanistically, these compounds directly induce macrophages to release cytokines, such as IL-6, IL-10 and TNF-α, and activate c-jun N-terminal kinase (JNK) and NF-KB-induced iNOS system, thus increasing NO release (Bae et al., 2006). In addition, sulpholipid-derived algal compounds exhibit an immune adjuvant potential by promoting the maturation of antigen-presenting dendritic cells (DCs), the key player of the adaptive immunity and long-term antigen specific-response (Manzo et al., 2017). DCs have attracted the attention of the scientific community due to their ability to activate and pro-liferate CD4 + helper T (Th) and CD8 + cytotoxic T (CTL) lymphocytes (Steinman and Hemmi, 2006), and they play a key role in vaccine development for prevention and treatment of various diseases (Palucka and Banchereau, 2012). Sulphoglycolipids stimulate the maturation process of DC to CD83 positive cells. Importantly, CD83 marker, an immunoglobulin surface-linked protein, indicates the full maturation of DCs (Zhou and Tedder, 1996) and promotes the expression of other costimulatory CD86 and the antigen-presenting, major histocompatibility class II (MHC-II) proteins. Furthermore, CD83 can effectively block IL-10-mediated membrane-associated RING-CH 1 (MARCH1)- induced proteasomal degradation of CD86 and MHC II (Tze et al., 2011). Moreover, the matured DCs promote T helper 1 (TH1) cells' responses to boost the production of INF-γ and IL-12. Simultaneously, the sulpholipids were found to induce the expression of CD40 and enhance the production of interleukins, such as IL-1α, IL-1β, IL-18 and IL-27, causing a positive feed-back cycle to further stimulate TH-1 (Manzo et al., 2017).

The intricacies of how algal-derived compounds, such as eicosapentaenoic acid (EPA), can activate macrophages was further investigated by Han et al. (Han et al., 2017). The study has established that EPA stimulates GPR120, a G-protein coupled receptors expressed on macrophage surfaces. GPR120 is involved in signal transductions, which regulate glucose and lipid metabolism, angiogenesis and inflammation (Wu et al., 2013). Furthermore, the stimulation of GRP-120 is associated with the phosphorylation of rapidly accelerated fibrosarcoma (RAF), which in turn activates the downstream target ERK1/2. Likewise, RAF phosphorylates and inhibits the inhibitory factor kappa B kinase (IKKβ) that degrades IKB and unleashes NF-KB. The nuclear translocation of the transcription factor NF-KB is associated with activation of iNOS/ system, thus increasing NO production, as well as enhancing IL-1β, IL-6, IFN-γ and TNF-α protein levels (Han et al., 2017) (Fig. 2 b).

2.3. Direct antiviral activity of marine algal-derived compounds

The potential use of algal metabolites as a source of effective, available and safe anti-viral agents has generated a big wave of interest among the scientific community and attracted the attention of drug discovery researchers. A study by Copeland et al. (Copeland et al., 2008) has shown that a potent anti-HSV activity was linked with the presence of sulfphate groups at 2 and 6 positions of the sugar moiety (galactose), while another study found that the 3-O-sulfated octasaccharide exerted a stronger antiherpetic activity than 3-OH octasaccharide (Copeland et al., 2008). The molecular weight and chain length of the bioactive derivatives play a key role in determining the potency of antiviral activity (Witvrouw and De Clercq, 1997). However, compounds with a longer-chain or high sulphate contents demonstrate more powerful antiviral effects even with low molecular weight (Bergefall et al., 2005). In contrast, due to their small sizes, some low molecular weight compounds can easily penetrate into intercellu-

lar spaces and prevent intercellular transmission of viruses (Nyberg et al., 2004; Wang et al., 2001). In addition, the counter ion (cation) that binds sulphate can substantially affect the antiviral activity of algal compounds. For instance, the replacement of calcium (Ca)-spirulan by cadmium (Cd) remarkably reduced the antiviral activity of the compound (Copeland et al., 2008). The long alkyl side chains of some polysaccharides are associated with higher adverse effects, while very short or hydrophilic chains have low antiviral activities. For example, sulphated polysaccharides with tetrasaccharide residues demonstrate 80% lower antiviral activity than those with pentasaccharide residues (Katsuraya et al., 1999; Terada et al., 2005).

Typically, the viral life cycle comprises of six stages: attachment and adsorption, penetration, capsid uncoating, biosynthesis, assembly and release (Wang et al., 2012). Studies have shown that algal-derived products can target one and/or more of those stages (Besednova et al., 2019; Wang et al., 2012; Damonte et al., 2004; Gogineni et al., 2015). Some antiviral mechanisms of algal-derived compounds are outlined below:

I. Viruses employ five different glycoprotein (g) subunits (gB, gC, gD, gH, and gL) to facilitate their entry into host cells. In most instances, gC (sometimes gB) binds to the glycosaminoglycans, preferentially *via* the heparan sulphate (HS) subunit of the host cell membrane (Damonte et al., 2004). The entry of viruses can also be facilitated by gD that binds to a set of TNF superfamily and immunoglobulins or to 3-O-sulphated HS co-receptors termed as herpesvirus entry mediators (HVEMs) (Shukla et al., 1999; Tiwari et al., 2011). Algal-derived polysaccharides can effectively target the N-terminal region of gC and thus interfere with the initial binding of virions to the HS (Mårdberg et al., 2001). For HIV, the V3 loop of the surface viral glycoprotein gp 120 identifies CD4 molecules as their primary targets (Miao et al., 2004). The complex interaction of gp 120-CD4 activates the chemokine receptors CCR5 and CXCR4 that leads to induce conformational changes to another transmembrane pg 41 protein to initialise the fusion step. The polyanionic properties of algal-derived compounds enhance the targeting of cationic moieties of V3 loop of gp 120 causing structural alterations that effectively impair viral binding and adsorption. Such an antiviral effect can be due to either direct binding to the viral cationic glycoproteins, thus displacing them from host cells HS (Mahomoodally et al., 2019), or imposing a static interaction that weakens the linkage of gp to host glycoprotein receptors (Ghosh et al., 2009). Next, viral fusion can also be blocked by the selective binding of algal compounds to the N-terminal residue of gp 41. Therefore, these compounds not only suppress viral cytopathic effects, but also inhibit "syncytium formation" between infected and non-infected cells, which substantially halts the spread and infectivity of viruses (Damonte et al., 2004). Other mechanisms of gp 120 inhibition by a red algal-derived lectin, Griffithsin (GRFT), have extensively been reviewed by Lee (Lee, 2019) . Interestingly, the host cell membrane has been reported to become more hydrophobic following the exposure to algal compounds which can minimise the number of infected cells by viruses (Biesert et al., 1990; Huheihel et al., 2002). Moreover, the binding of GRFT with the viral envelope glycoprotein was irreversibly inactivated, with no evidence of breakthrough infection at 9 days (Kouokam et al., 2011). The aspartic acid residue in each of the glycan binding site plays a crucial role in enhancing glycan's capacity to bind oligomannose glycosylated proteins and improve its viral neutralisation activity. The density of envelope spikes appears to determine the GRFT antiviral activity (Kim et al., 2018). GRFT was also shown to prevent the binding of spike to dipeptidyl peptidase-4 (DPP4), thus inhibiting the Middle East respiratory syndrome coronavirus (MERS-CoV) infec-

tion *via* the interference with the viral infection at early attachment stages rather than at the post-binding step. GRFT can impair the involvement of N-linked glycans on N210 and N487 in receptor binding, which is a core domain conformational with an accessary subdomain on the edge of the core structure of receptor-binding domain (RBD) (Millet et al., 2016).

II. The next step, following viral adsorption, is internalisation and vesicular-driven transportation of viruses to the intracellular organelles, primarily lysosomes. Viral internalisation is initialised by the endocytic uptake of viruses *via* different mechanisms (Mercer et al., 2010). The viral uncoating process has been reported to be interrupted by algal-derived products due to their potential to bind viral capsids and block their interactions with HS. Furthermore, they minimise the infectivity of viruses *via* targeting the conformational changes that occur during the development of virions and their binding to cellular proteins (Buck et al., 2006). The low pH of endosomes mediates conformational changes in the capsid E-glycoprotein (gE) causing uncoating of viruses and release of viral genome to cell cytoplasm. Algal compounds can suppress the fusion of the viral genome-containing vesicle to the endosomes *via* binding to gE and stabilising of nucleocapsid causing abrogation of viral uncoating (Talarico and Damonte, 2007).

III. Essentially, following viral fusion and uncoating of nucleocapsids, viruses employ the reverse transcriptase (RT) enzyme to convert their single stranded ribonucleic acid (RNA) into a double stranded DNA. The viral integrase enzyme is also utilised to integrate viral DNA into the host cell genome. At this stage, zero or only a few copies of viral DNA can be produced or it might remain dormant for years. The host RNA polymerase is then utilised to produce viral genome, as well as mRNA to synthesise long-chain viral proteins, which are then chopped into smaller individual segments by viral proteases. Then viral assembly process is initiated. The assembled viruses contain a single stranded RNA molecule that is enveloped by some of the host outer membrane formed by a combination of protein and sugar called glycoproteins. The last step is viral budding, in which newly synthesised viruses depart host cells to infect others (Gogineni et al., 2015). Binding and inhibition of RT was shown by many algal metabolites (Cai and Jiang, 2010; Ahn et al., 2006), causing suppression of viral lytic potential, inhibition of viral p24 antigen production and blocking of viral syncytia formation (Artan et al., 2008). Inhibition of RT affects the utilisation of small nucleosides by the enzyme to convert viral RNA to DNA. The presence of a sulphate moiety increases RT inhibitor potential of brown algae-derived polysaccharides (Queiroz et al., 2008). A plethora of algal-derived molecules can also interfere with the activity of viral integrases (Ahn et al., 2006). Targeting the catalytic domain of integrase was reported following the exposure to the lamellarin α 20-sulphate-derived algal compounds (Reddy et al., 1999). Furthermore, viral proteases can also be suppressed by algal-derived compounds (Elshabrawy, 2020). Interestingly, a chymotrypsin-like cysteine proteinase (3CLpro) of the notorious Severe Acute Respiratory Syndrome coronavirus (SARS-CoV) can be targeted by Dieckol, a phlorotannin, isolated from the brown algae Ecklonia kurome.. The 3CLpro contains two catalytic dyads: the nucleophilic cysteine residue (Cys145) and the acid-base regulator histidine residue (His41). The study found that Dieckol bound the two catalytic dyads (Cys145 and His41) of the SARS-CoV 3CLpro at a high association rate and formed a strong hydrogen bond with them, thus viral infectivity was effectively abolished (Park et al., 2013) (Fig. 2 c).

3. Antiviral tests for algal macromolecules

The antiviral activity of a natural compound can be evaluated in many ways, either *in vitro* or *in vivo*. Many cell-based assays have been developed for evaluating compounds for activity against viruses using such parameters as maximal effective concentration (EC50), used to evaluate the drug's antiviral potency, and IC50, the half-maximal concentration required to inhibit 50% of viral replication (Azzam et al., 2020). CC50 is also used in antiviral testing, where it refers to a cytotoxic concentration of a compound which reduces the optical density (OD) of treated cells to half of that of untreated cells (Preeprame et al., 2001; Postnikova et al., 2018). A wide range of mammalian cell lines can be used to test these antiviral parameters, including green monkey kidney cells (Vero cells), immortal cell lines, such as Hela, and carcinoma cells, including Hep-2. In addition, viral fish models were also investigated using different cell lines, including trout RTG-2 and carp EPC cell lines (Dewi et al., 2018). Antiviral measurement, mechanism and functional implication on these cell lines can be facilitated by particular analysis of infection process, addition time of compounds and kinetic studies (Dewi et al., 2018). In addition to the antiviral effect test, it is therefore worthwhile to explore affordable and effective pharmaceuticals and new administration means or new delivery devices to guarantee their efficacy and safety (Gherasim et al., 2019). For example, since nasal mucosa serves as the primary site of infection and replication by common cold viruses, the early and targeted nasal administration of iota-carrageenan, a red macroalgal-derived polysaccharide, could inhibit the entry of cold-causing viruses (Eccles, 2020). This hypothesis was demonstrated by three trials of a nasal spray with 0.5% saline and 0.12% iota-carrageen, which could significantly reduce cold symptoms compared to saline solution used as placebo (Eccles et al., 2015).

4. Extraction methods for algal macromolecule

The structurally diverse and heterogeneous composition of algal extracts make their separation and characterisation highly challenging, which in turn, hinders their pharmaceutical development. Since the chemical synthesis and purification of certain structurally complex molecules remains challenging, efforts to decipher the structure and composition of natural compounds would offer enhanced possibilities for future scientific and pharmaceutical advances (Bleakley and Hayes, 2017; Marrone et al., 2018).

There are three main approaches for extracting macromolecules from algae: biological methods, chemical hydrolysis and physical methods (Bhatnagar et al., 2015). Biological approaches refer to the enzymatic degradation methods, such as the use of cellulase to break cell walls. The chemical hydrolysis method is divided into the utilisation of organic or inorganic solvents, whereas the physical extraction method involves using environmentally friendly techniques, like high pressure and cold extraction process and supercritical carbon dioxide (CO_2) fluid extraction (Mendes et al., 2003). In this regard, the selection of appropriate extraction procedures must comply with the legal stipulations on the use of food or medical grade solvents or processes, as well as the predicted nature of the expected/target bioactive compounds. In a study by Santoyo et al. (Santoyo et al., 2010) , the anti-HSV-1 effects of the extracts from microalgae *Chlorella vulgaris* was compared in different extraction solvents (acetone, ethanol and water) with pressurised liquid extraction methods (Santoyo et al., 2010). Both water and ethanol extracts showed a significant inhibitory effect on HSV-1 with IC50 of 61.05 and 80.23 μg/ml, respectively. Gas chromatography–mass spectrometry (GC–MS) analysis suggested that the presence of phytol may contribute to the higher antiviral activity of ethanol extracts than those of water extracts (Santoyo et al., 2010).

Thin layer chromatography (TLC) profiles of extracts of the alga *Ulva fasciata*, harvested from different sites, showed differences in metabolic profiles between sites, while samples from the same site had identical profiles, emphasising the impact and important influence of biotic and abiotic factors on the production of secondary metabolites in the marine environment. In this study the chemical structures were characterised by Fourier-transform infrared (FTIR) spectroscopy and Carbon-13 nuclear magnetic resonance (^{13}C NMR) analyses (Bedoux et al., 2017). A review by Singh and Walia (Singh and Walia, 2018) explored the purification of lectins from red algae using multistep chromatographic techniques or single-step affinity chromatography; the latter being the most frequently used technique due to the carbohydrate specificity of lectins (Singh and Walia, 2018).

5. Marine macromolecules from macroalgae

5.1. Polysaccharides

Polysaccharides, normally located in the cell wall, form the main constituents of algae (70% of dry weight). As such, all algae produce at least one kind of polysaccharide (Hentati et al., 2020). Algae are known to produce different polysaccharides with antiviral activities (Fig. 1), including ulvans, laminarins, agarans, carrageenans, alginates and fucoidans (Ruiz et al., 2017) (Fig. 3). Algal polysaccharides mainly interfere with the viral cycle of replication or improve the host antiviral immune response to inhibit the viral infection (Shi et al., 2017). The heterogeneous nature of algal polysaccharide, causes them to have different physicochemical properties (Rodrigues et al., 2017), which in turn give rise to different biological properties (Shen et al., 2018).

In general, algal-derived polysaccharides with significant antiviral activity generally have a higher level of sulphonation, e.g. carrageenans and alginates (Fig. 3) (Damonte et al., 2004; Mani et al., 2020).

The use of polysaccharides as antiviral agents has rapidly expanded an appreciation of their diverse applications due to their pleiotropic mode of action rather than a single target on the viral replication cycle (Arad et al., 2013). A growing body of research suggests that strategies seeking to inhibit viral infection should aim to interact with virions directly or to mimic the viral invasion process, such as in a binding relevant receptor at the viral attachment stage (Shi et al., 2017; Priyan
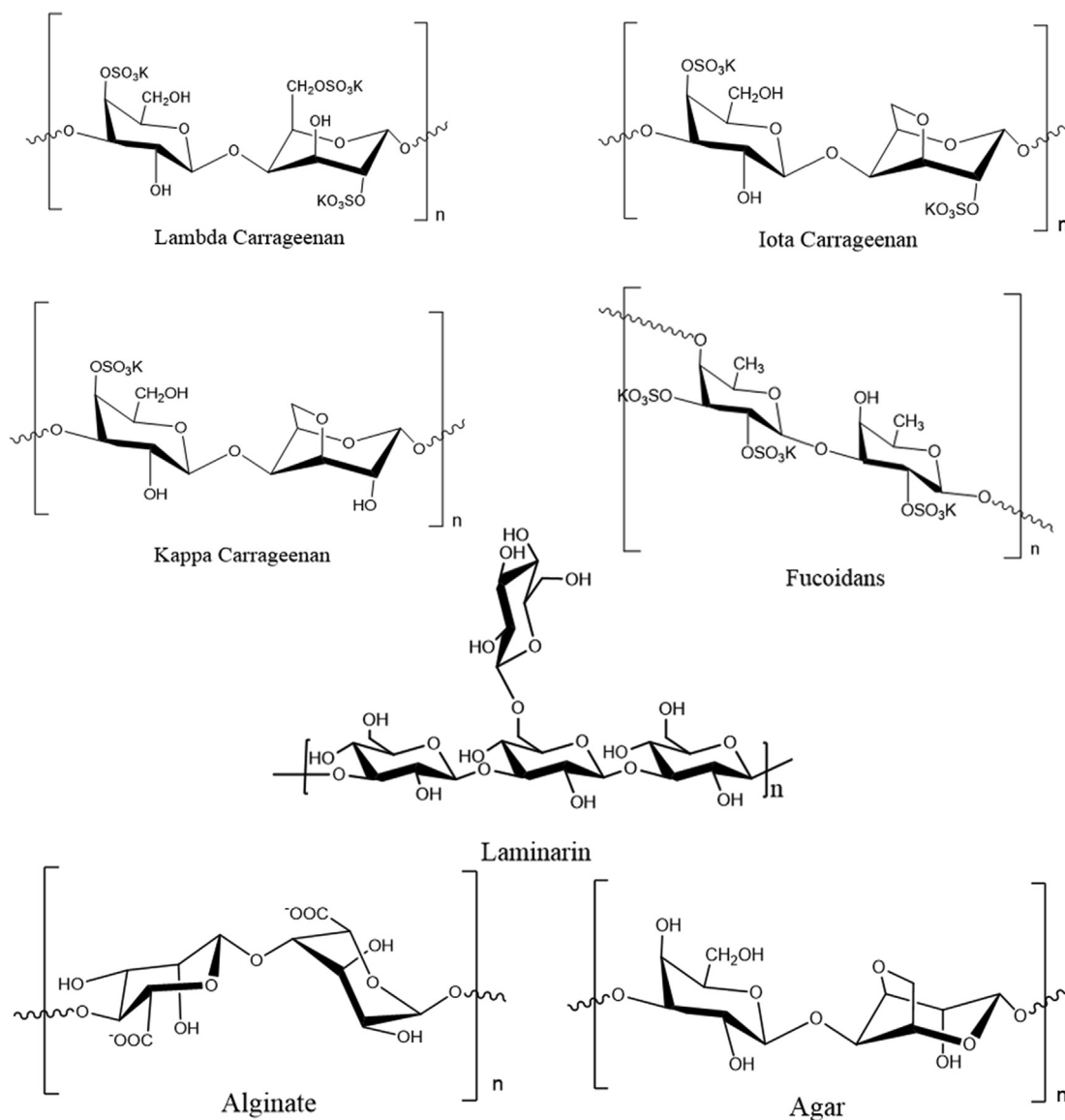

Fig. 3. Antiviral algal polysaccharides. Lambda, kappa and iota carrageenans and agar are produced by red algae while fucoidans, laminarins and alginates are produced by brown algae.

Shanura Fernando et al., 2019). This approach can inhibit a variety of viruses, such as HIV, Moloney murine leukaemia virus (MuLV), and Moloney murine sarcoma virus (MuSV) (Talyshinsky et al., 2002).

5.2. Carageenan

Carrageenan is a hydrophilic linear sulphated polysaccharide and the major component of the red seaweed's cell wall (30–75% of dry weight) (Peng et al., 2013). It is derived from the gelatinous protective layer of the cell wall which protects the alga from the turbulent intertidal ocean habitats. There are different types of Carageenan, including lambda, iota and kappa (Fig. 3). Kappa and iota carrageenan are linear polysaccharides. Kappa has one sulphate group per two galactose molecules and assumes a helical network, while iota also assumes a helical conformation, but with two sulphate groups per two galactose molecules. Lambda-carrageenan has three sulphate groups per two galactose molecules, which does not form a helical structure. Kappa and iota carageenan have widely been used as gelling agents in pharmaceutical formulations (Li et al., 2014; Prasad et al., 2009). The relatively simple extraction process from algae is of importance to the pharmaceutical industry. Since the first description of the *in vitro* antiviral activity of carrageenan in 1958, it has been applied to inhibit a wide range of viruses including HSV, HAV, HPV, DENV, HRV and various enveloped viruses (Silva et al., 2018). This polysaccharide can inhibit the HPV at different stages of viral infection, including the viral adsorption and subsequent uncoating process by directly binding to the virus. Carrageenan (*Schizymenia pacifica*), isolated from red algae, is known to exert an inhibitory effect on HIV reverse transcriptase and replication without adverse effects on cell proliferation *in vitro*, and to disturb the fusion process (e.g., syncytium formation) between infected cells (Neushul, 1990). The similar mechanisms underlying inhibitory activities on avian retrovirus and mammalian retrovirus support a hypothesis that the sulphated residue of carrageenan may play a crucial role in the suppression effect on reverse transcriptase (Ahmadi et al., 2015; Ruiz et al., 2017). However, the iota-carrageenan found in some red seaweed exhibits potent antiviral activity against respiratory virus *via* binding to the viral particles rather than entering the host cell to trigger the immune activities (Dutot et al., 2019). In fact, iota-carrageenan with a strongly negatively charged surface can trap any newly released positively charged viral surfaces within airway mucus; thereby preventing the transmission of newly released viruses from infecting other nasal cells (Eccles, 2020). Iota-carrageenan has also a potent antiviral effect on human metapneumovirus (HMPV) by blocking the binding of virus to lung cells mediated by the fusion protein (Klimyte et al., 2016). Carrageenan derived from *Chondrus cripus* can block the transmission of a wide range of sexually-transmitted viruses, including HIV, HSV, genital warts and HPV, which can cause cervical cancer (Ahmadi et al., 2015).

The most effective fraction of sulphated polysaccharide from *Sargassum latifolium* is composed of higher sulphate ester content and higher molecular weight than other fractions. Thus, the complex reciprocation of structure characteristics, such as distribution of sulphated groups along the backbone, sugar residue and stereochemistry, plays an important role in antiviral activity (Bhatnagar et al., 2015). Low molecular weight carrageenan, as well as its acetylated derivatives, exert promising antiviral responses to influenza and HIV *via* depolymerisation and the sulphation process (Sansone et al., 2020). Indeed, carrageenan displays a 4-fold inhibitory effect compared to heparin on HPV. The mechanism behind the blocking HPV infection is to interfere with the binding process and the resembling heparin sulphate required for cell entry and subsequent infections.

As a promising therapeutic agent for HPV, carrageenan offers many potential advantages including low cytotoxicity, safety profiles, broad-spectrum antiviral activity and relatively production cost (Buck et al., 2006). Carrageenan has a direct viricidal effect on Japanese encephali-

tis virus (JEV) and can also interfere with the virus-host cell attachment and cell entry by interacting with the virus envelop glycoprotein. Flavivirus E, a viral envelop glycoprotein, plays a significant role in the early stage of viral adsorption through host membrane (Nor Rashid et al., 2020). As such, carrageenan has an antiviral potential to combat JEV infections possess multiple advantages of significant inhibitory effects on JEV with minimal cytotoxicity (EC50: 15 μg/ml). The extract of red algae containing polysaccharides confirms a significant inhibitory impact on the release of virus progeny; even when added 48 h post-infection. This confirms that polysaccharides can inhibit both the sequent secondary infection cycle and the cell transformation of virus (Talyshinsky et al., 2002). Carrageenan isolated from *Gigartina skottsbergii* has also demonstrated inhibitory effects on the primary stages of virus replication of HRV (Sansone et al., 2020).

5.3. Galactan

Galactan is another type of polysaccharide that contains a core of galactose units, with structures containing other monosaccharides as sidechains. They can be either sulphated or non-sulphated. They are isolated from the external membrane of red algae and exert antiviral activity towards several enveloped viruses including HSV, DENV, HIV and HAV (Delattre et al., 2011). For example, the galactan from red algae *Agardhiella tenera* has shown promising results against HIV by preventing the adhesion of HIV to the host cell and attachment of HIV gp120 on CD_4^+ T cell (Sansone et al., 2020). Galactan from *Schizymenia binderi* exhibits a highly selective antiviral activity towards HSV *via* blocking viral attachment to host cells, while the DL-galactan extracted from *Cryptomia crenulata* inhibits the multiplication of DENV-2 (Ahmadi et al., 2015). Glucuronogalactan from red algae *Schizymenia dubyi* can decrease the syncytia formation of MT4 cells to almost 1% of untreated infected cells at the concentration of 55 μg/ml (Bhatnagar et al., 2015). The mechanism lies in the fact that polysaccharides can disturb early stages of HIV infection and break the virus-host cell linkage. Moreover, the galactans isolated from red algal genus *Grateloupia, including G. indica, G. filicina*, and *G. longilia,* inhibit the infections of HSV1, HSV2, HIV1 and DENV. Their mechanism of action mainly relies on the inhibitory effect of polysaccharide on the initial phase of HIV infection by blocking the virus-host cell attachment and antiretroviral activity. The antiviral activity of low molecular weight polysaccharide on avian leukosis virus (ALV-J) has also been explored, along with the possibility of using seaweed polysaccharides as veterinary medicine (Sun et al., 2019). A sulphated polysaccharide derived from brown algae *Hydroclathrus clathratus* displays a high inhibitory effect on HIV-1, HCMV and HSV-1 with very low EC50 value due to their unique composition of different monosaccharide, low fucose content, and high content ratio of rhamnose (Wang et al., 2007). Both purified and crude sulphated polysaccharides from brown macroalgae *Turbinaria decurrens* and *Dictyota bartayesiana* display antiviral activity on HIV, indicating these novel and potent natural sources might be a solution to the drug resistance and toxicity of highly active antiretroviral therapy (HAART) when treating HIV in patients (Sanniyasi et al., 2019).

5.4. Laminarin

Laminarin is a water-soluble polysaccharide that consists of β-(1–3)-glucan with β-(1–6)-linkages of 20–25 units (Rioux et al., 2007). Laminarin isolated from brown algae is an uncharged polysaccharide at neutral pH and forms a triple helical conformation under aqueous conditions. This water-soluble linear polymer consists of small amounts of beta (1–6) as branch points to link beta (1–3) glucose residues and ends with 2–3% D-mannitol (Bhatnagar et al., 2015). Brown algae, such as *Laminaria* sp. *Saccharina longicruris, Ascophyllum nodosum and Fucus vesiculosus,* usually store this glucan as chemical energy (Bhatnagar et al., 2015). It can serve as an immunomodulator

or stimulator of humoral immunity and has antiviral properties. Viral infection generally stimulates the immune system of the host cell to launch a series of viral clearance processes. Firstly, IFN-α/β systems trigger the antiviral production and immune-stimulatory proteins by interacting with the cell surface receptors and thereby increasing the efficiency of the natural killer (NK) cells as well as T lymphocytes. The algal polysaccharides can also activate the NK cells or induce antiviral immune responses and help accelerate the clearance of virus to play a critical role in immunoregulatory process. Laminarin isolated from kelp represents a source of new drugs against HIV, since it can block the adsorption of virus on lymphocytes and suppress the reverse transcriptase with high efficiencies and low cytotoxicity at a concentration of 50 mg/ml (Shi et al., 2017). Respiratory syncytial virus (RSV) is a negative-sense single strand RNA virus which can be transmitted by direct or indirect contact with nasal or oral secretions and causes repetitive infection and significant mortality. Polysaccharides isolated from *Laminaria japonica* were found to inhibit virus replication *via* the upregulation of IFN-α level mediated by Interferon regulatory factor 3 IRF3 signalling (Cao et al., 2016). Additional research has established that the extract from brown algae *Laminaria japonica* has antiviral activity against the replication of H5N1 virus (Cao et al., 2016).

5.5. Fucoidans

Fucoidans are water-soluble sulphated polysaccharides that are widely distributed in brown algae. Since they mainly consist of sulphated L-fucose and other monosaccharides, they are also known as fucan, fucosan or sulphated fucan (Stiger-Pouvreau et al., 2016). Fucoidans are referred to as a class of fucose containing sulphated exopolysaccharides with diverse structural functionalities. The components of fucoidans comprise fucose as main building block in α-(1 → 3), α-(1 → 4) and occasionally α-(1 → 2) linkage with other substituents, such as hexoses (galactose, mannose, glucose), pentoses (arabinose, xylose), deoxy sugar (rhamnose), uronic acid (glucuronic acid) and functional groups (sulphate, acetyl), imparting the macromolecule heterogeneous character (Citkowska et al., 2019). The molar composition and structural attributes (molecular weight, degree of branching, acetylation and sulfation, uronic acid content and carbohydrate to protein ratio) of fucoidans may vary amongst and within the species, depending upon the habitats and maturity of seaweeds and techniques employed for isolation and structural characterisation (Catarino et al., 2018; Menshova et al., 2016). The fucoidans structure is predominantly made of either only α-(1 → 3) L-fucopyranosyl units or alternating α-(1 → 3) and α-(1 → 4) L-fucopyranosyl units as backbone, with arbitrary sulphation at C2 and C3 of α-(1 → 4) linked and/or C2 of α-(1 → 3) linked fucose (Ale and Meyer, 2013). In some cases, the sulphate group may be replaced by acetyl groups, other monosaccharides (including fucose) or uronic acid moiety making the structure branched and offering more interaction sites from biotechnological viewpoint (Fig. 4) (Catarino et al., 2018; Ale and Meyer, 2013).

Fucoidan produced from *Fucaceae, Sargassaceae, Chordariaceae* have 12.6–36.0% of L-fucose and 8–25% of sulphate, respectively (Usov et al., 2013). It is noteworthy that fucoidans extracted from different orders of brown algae may have different main chain structures based on different fucopyranose residues (Usov et al., 2013). Fucoidans from *Enteromorpha prolifera* have immunomodulatory activity which can significantly activate the response of Th-1 and subsequently the T cells, increasing the secretion of interleukin-2 (IL-2) (Shi et al., 2017). The fucoidan from sporophyll of *Undaria pinnatifida* has been reported to inhibit the influenza A virus (Cao et al., 2016). Hot water extracts of fucoidan from two different seaweeds, *Dictyota bartayesiana* and *Turbinaria decurrens,* display a high inhibitory activity (around 90%) on HIV and the IC50 values were 1.56 μg/ml and

57.6 μg/ml in both crude and purified fucoidan of *D. bartayesiana*, respectively. In contrast, they were 3 μg/ml and 131.7 μg/ml for both the crude and purified form of *T. decurrens* (Sanniyasi et al., 2019). Fucoidan isolated from *Fucus vesiculosus* exerted an inhibitory effect on HBV by activating MAPK-EKR1/2 signal pathway and the subsequent host immune system, while suppressing HBV replication (Li et al., 2017). Results demonstrate that fucoidan can significantly inhibit the HBV replication in a mouse model and in HepG2.2 cells at 0, 1, 3, 5, and 7 days post-infection, supporting the potential use of fucoidan as a new therapeutic agent against HBV (Luthuli et al., 2019).

Fucoidans isolated from *Saccharina cichorioids* (1 → 3-α-L-fucan), *S. japonica* (galactofucan) and *S. swartzii* (FF2: Fucoidan Fraction 2) also demonstrate a significant inhibitory effect on HIV-1 at low concentrations (Luthuli et al., 2019). The viral infection of DENV can be inhibited by fucoidan, which forms a complex with the virus and then blocks the viral infection (Saleh and Kamisah, 2021). On the other hand, a study by Luthuli et al. (Li et al., 2017) suggests that the sulphate content of fucoidan is not the crucial component in inhibition of HIV, since the fucoidan with the highest sulphate content, isolated from *Sargassum. mcclurei,* exerted a similar inhibitory effect on HIV, when compared to other two fucoidans from *S. polycystum* and *Turbinaria ornata*. The fucoidan with naturally high molecular weight was thus proposed as potential antiviral agent and further *in vitro* and *in vivo* studies are needed before proceeding to clinical trials (Luthuli et al., 2019).

Fucoidans extracted from *Fucus evanescens* have been reported to inhibit HIV-1 *in vitro* and the native fucoidans containing acetyl group (Mw 620 kDa; IC50 value 0.01 μg/ml) demonstrate higher efficacy than their deacetylated counterparts (Mw 20 kDa; IC50 value 0.52 μg/ml) (Menshova et al., 2016; Prokofjeva et al., 2013). Further, fucoidans from *F. vesiculosus* demonstrate high anti-HIV and anti-HSV-1 *in vitro* activities as a function of high sulphation (Catarino et al., 2018). A recent study on anti-SARS-CoV-2 activity has revealed fucoidans as superior candidates over heparin, heparan sulphates and glycosaminoglycans, exhibiting higher binding affinity to the SARSCoV-2S-protein. The greater binding was accredited to multivalent interaction sites at fucoidans for viral particles owing to their three-dimensional branched structure. Further, amongst two tested fucoidans (RPI-27 and RPI-28) with similar branching patterns, the one (RPI-27) with higher molecular weight was found to possess more potent activity than the others, thereby acting as a bigger binding matrix for viral particles (Kwon et al., 2020).

5.6. Ulvans

Green macroalgae have also emerged as an important source of novel antiviral agents and Ulvan is the term assigned to their water-soluble sulphated heteropolysaccharides obtained from their cell walls. The antiviral activities of natural polysaccharides isolated from 10 green macroalgae have been studied on HSV-1 infections. These macroalgae consisted of *Enteromorpha compressa*, three species of *Codium sp.*, *Caulerpa brachypus*, two species of *Caulerpa sp.*, *Monostroma nitidum*, and *Chaetomorpha spiralis* (Capell et al., 2020). They exerted a strong antiviral effect on HSV-1 with IC50 range of 0.38–8.50 mg/ml and low cytotoxicity (Capell et al., 2020). Sulphated polysaccharide from green algae *Ulva fasciata* was found to have virucidal potential and to inhibit cell entry of HMPV (Shi et al., 2017). The sulphated polysaccharide fraction in ulvan isolated from *Caulerpa cupressoides* (Chlorophyta) is different in molecular peculiarities compared with other algal sulphated polysaccharides and the mechanism underlying the antiviral potency on enveloped DENV remains unclear (Rodrigues et al., 2017). Nonetheless, ulvans exerted antagonist activity toward fucoidan for viral inhibition when they were used together, while ulvans alone demonstrated an outstanding effect on blocking viral attachment or entry than fucoidan (Peng et al., 2013).
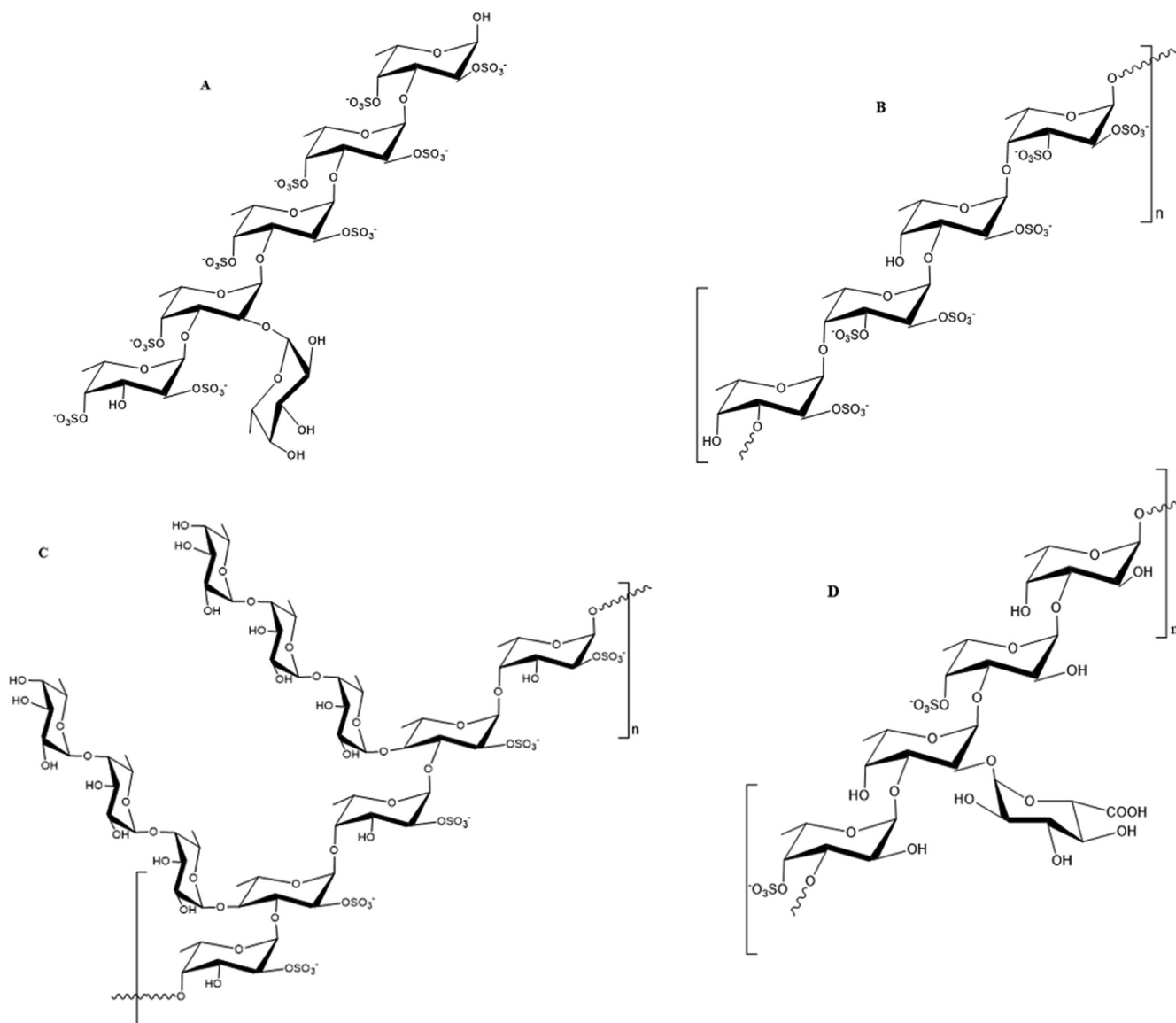
Fig. 4. Fucoidans from different brown algal species. A. *Chorda filum*; B. *F. vesiculosus*; C. *F. serratus*; D. *Cladosiphon okamuranus*. A is a regular chain of α-(1 → 3) L-Fucopyranosyl units with substitution at C2; B is an alternating chain of α-(1 → 3) and α-(1 → 4) L-Fucopyranosyl units; C has a similar backbone as B with branching of α-(1 → 4) L-Fucopyranosyl units; D has a regular chain of α-(1 → 3) L-Fucopyranosyl units with substitution of glucuronic acid at C2.

5.7. Lectin

Lectin is the name given to a group of small proteins that can bind carbohydrates with high affinity and specificity. Several lectins display potent antiviral activities. Marine lectins seem to be especially valuable based on their biological applications. They are classified and identified based on the organisms they are derived from, such as algae, sponge, annelid, mollusc, arthropod, echinoderm, ascidian, amphioxus and fish. Each group can be then sub-categorised into several lectin-producing organisms (Cheung et al., 2015). One of the most potent of these is the previously mentioned red algae-derived, Griffithsin (GRFT); an obligate domain-swapped dimer in which each domain has jacalin-like fold (Lusvarghi and Bewley, 2016). Current research shows that GRFT exerts an inhibitory effect on coronaviruses, such as SARS, hepatitis C virus, JEV, murine herpes simplex virus type 2, HIV and MERS-CoV low systematic toxicity (Mani et al., 2020). GRFT can specifically interact with the SARS-CoV spike glycoprotein and inhibit viral entry, resulting in reduced lung titers, pulmonary edema and necrotising bronchiolitis, when compared with placebo-treated

mice. While the uninfected mice administered GRFT showed perivascular infiltrate in the lung, the condition was largely resolved within six days following the last dose of GRFT (Barnard and Kumaki, 2011). In addition, GRFT shows a viral inhibitory efficacy on porcine epidemic diarrhoea virus (PEDV) by reducing viral RNA loads significantly at all times of addition, but had a relatively weaker inhibitory effect on PEDV by the delayed addition of GRFT than the earlier treatment (Mani et al., 2020). This is linked to GRFT's ability to prevent the attachment of PEDV to host cells and disrupt viral transmission. While its dual functionality distinguishes this lectin form many other antiviral agents (Li et al., 2019), GRFT also affords a range of further advantages including thermostability, little or no toxicity and immunogenicity. In short, GRFT possesses a superior safety profile with no cytotoxicity against a variety of cell types and no cell activation, cytokine or chemokine production (Li et al., 2018). Normally, HIV-1 virions possess 14 spikes per virion particle, while influenza type A virus has 450 spikes (Li et al., 2019). Since four spikes of HIV-1 are necessary for viral infection, GRFT needs to neutralise only four spikes to block the infection of HIV virion. This may be the reason

that GRFT exerts a stronger antiviral effect on HIV compared with other enveloped viruses (Li et al., 2019). Nipah virus can cause fatal encephalitis and respiratory disease in humans and no therapeutic agent is currently available to combat this viral infection (Lo et al., 2020). The synthetic trimeric tandemer of GRFT exhibited a relatively greater potency against Nipah virus than its natural form due to its enhanced capacity of suppressing viral glycoprotein-induced syncytia formation. Similar enhanced antiviral activity was observed for an oxidation-resistant GRFT in Syrian golden hamsters *in vivo* (Lo et al., 2020). Moreover, GRFT can block the adsorption of porcine reproductive and respiratory syndrome virus (PRRSV) since it binds to the PRRSV glycoproteins, thereby preventing the viral attachment to target cells (Li et al., 2018). *Kappaphycus alvarezii*, another red alga, produces a potent antiviral lectin called KAA-2, which exhibits a substantial activity against several influenza strains, including swine influenza virus H1N1. The lectin has demonstrated a remarkable antiviral potential against a wide range of influenza viruses, with EC50 values between 1.71 and 68.56 nM. It specifically targets the viral envelop protein *via* the interaction with mannose rich type N-glycans on the viral surface (Sato et al., 2011).

Other algal-derived lectins with a potent antiviral potential are the brown algae-derived OAAH (*Oscillatoria agardhii* agglutinin homolog) lectin family, the yellow algae-derived legume lectin-like family and the green algae-derived *Galanthus nivalis* agglutinin (GNA)-and MFP2-like families (Barre et al., 2019). The OAAH family possess 10 β-barrel sheets subdivided into two molecules of 5 β strands each (Koharudin and Gronenborn, 2011). High-mannose binding lectin from the brown algae *Kappaphycus alvarezii,* exerts an inhibitory effect on influenza strains by interfering with viral entry into host cells. Another lectin that combats influenza is the *Eucheuma Serra* agglutinin ESA-2 that is derived from *Eucheuma serra*, which has an EC50 of 12.4 nM with no cytotoxicity up to 1000 nM (Singh and Walia, 2018). The legume lectin-like family have "a β-sandwich jelly roll scaffold" (Barre et al., 2019). For instance, *Vicia faba* agglutinin and *Lens culinaris* agglutinin block the fusion of the HIV virus with CD4 immune cells. The mechanism is *via* binding of lectins to the viral glycoprotein gp 120, and inhibition of the carbohydrate-specific linkage between viruses and infected cells (Hansen et al., 1989). HIV-1 reverse transcriptase enzyme can also be inhibited by legume lectin glycine max (Fang et al., 2010). Furthermore, legume lectins restrain human parainfluenza virus type 2 (hPIV-2) *via* targeting virus nucleoprotein, fusion and hemagglutinin-neuraminidase gene synthases. Not only legume lectins inhibit the adsorption and entry of viruses, but they also disrupt actin microfilaments and microtubules, thus interfering with the mechanisms of viral release from infected cells (Uematsu et al., 2012). A high mannose binding lectin with strong specificity for α-1 → 2-linked mannose at the nonreducing terminal has been isolated from green algae *Boodlea coacta* (BCA) and shown to inhibit HIV-1 and influenza viruses. The carbohydrate-binding propensity and high affinity for HIV contribute to the potency of its anti-HIV activity with EC50 8.2 nM (Karadeniz et al., 2015).

Other marine non-algal-derived antiviral lectins have also been investigated extensively and, although outside the remit of this review, they are worth mentioning briefly. For instance, the two marine annelids *Chaetopterus variopedatus* and *Serpula vermicularis,* demonstrate potent anti-HIV action. The 30 kDa lectin derived from *C. variopedatus* is known as CVL. This lectin exerts anti-HIV activity *via* the suppression of cytopathic effect and production of HIV p24 antigens at EC50 values of 0.0043 and 0.057 μM, respectively. The lectin significantly inhibits the early stage of viral replication, during the viral entry into host cells. In addition, it interferes with cell to cell fusion process of infected and uninfected host cells (Wang et al., 2006). Likewise, the *Serpula vermicularis*- derived 50 kDa lectin exhibits anti-HIV activity *via* the inhibition of viral cytopathic effects and p24 antigen production at EC50 values of 0.23 and 0.15 μg/ml respectively (Molchanova et al., 2007). Molluscs represent another marine source

of antiviral lectins. For example, the mussel *Crenomytilus grayanus* was harnessed to isolate 18 kDa lectin that can bind to N-acetylgalactosamine, galactose and mucin-type glycoproteins. It inhibits HIV replication at EC50 = 27.88 μg/ml (Luk'yanov et al., 2007). Arthropods, such as the shrimp *Penaeus monodon*, has been reported by Luo et al. (Luk'yanov et al., 2007; Luo et al., 2003) to be a well-defined source for 19.3 kDa C-type lectin. It can specifically bind lipopolysaccharides and inhibit the cytopathic effect of white spot syndrome virus at EC50 value of 6.25 μg/ml (Luo et al., 2003). Fish, such as flounder *Paralichthys olivaceus,* are used to extract galectin, a lectin with molecular mass of 15.4 kDa that can target β-galactosides. The recombinant galectin-1 can suppress the infectivity of lymphocystis disease virus and neutralises its cytopathic effects. It reduces inflammatory reactions including the upregulation of mx gene expression associated with the viral infection (Liu et al., 2013).

6. Extracts from various cyanobacteria and microalgae

Cyanobacteria and microalgae represent another important reservoir and emerging source of macromolecules for antiviral drug discovery (Singh et al., 2011). A study by Singab et al. (Singh et al., 2011), has shown that *Scenedesmus obliquus* contains the highest polysaccharide content when compared to the other microalgae screened, while the *Spirulina platensis* polysaccharides demonstrate antiviral activities, which could reduce the replication of HCV, coxsackievirus B4, rotavirus and HSV1 at non-toxic doses 1.8 and 1.5 mg/ml (Singab et al., 2018; Nagarajan and Mathaiyan, 2015).

6.1. Polysaccharides

The water-soluble extracts from blue-green algae *Spirulan platensis* contain a sulphated polysaccharide named calcium spirulan (Ca-SP). This polysaccharide causes inhibition of many envelope viruses, including HSV-1, influenza, HIV-1, and HCMV (Dewi et al., 2018; Becker et al., 2013). The hot water extract of *Spirulina maxima* displayed a significant inhibitory effect on the infection of adenovirus type III at a low percentage (20%) with an IC50 5.2 mg/ml, which might be attributed to the presence of sulphated polysaccharides (Dewi et al., 2018). An acidic polysaccharide, named Nostoflan and extracted from *Nostoc flagelliforme*, shows an inhibitory effect on the HSV-1 and HSV-2 while ichthyopeptins A and B from *Microcystis ichthyoblabe* inhibit the infection of influenza A virus (Singh et al., 2011). Nostoflan can also inhibit the fusion of virus in the host cells by blocking the viral binding, but shows no effect on glycoprotein synthesis (Becker et al., 2013) and triggers the immune response to the influenza virus infection in mice (Shi et al., 2017). The extracts from green microalgae *Ellipsoidon* sp., *Chlorella autotrophica,* and red microalgae *Porphyridium cruentum* show encouraging results against enveloped rhabdoviruses, which can infect valuable livestock. These rhabdoviruses include Viral *Hemorrhagic Septicemia* virus (VHSV), which impacts the pig sector and aquaculture African swine fever virus (ASFV) which impacts the aquaculture sector including marine and salmonid fish (Fabregas, 1999).

Microalgae also have a prophylactic effect in hatcheries against fish-contaminating enveloped viruses and mammalian viral diseases. The mortality of *Epinephelus marginatus* due to viral encephalopathy and retinopathy decreased significantly after a prolonged bath in dense culture of *Chlorella minutissima* (Dewi et al., 2018). Tiger shrimp grown in a green culture with extracts of *Dunaliella salina* proved resistant to infection with white spot syndrome virus (WSSV) (Dewi et al., 2018). The inhibitory effect of *Porphyridium* sp. polysaccharide rests on the prevention of early steps in the viral life cycle rather than direct interaction between the polysaccharide and the virus particles. However, the results were less promising than those involving treating the virus with polysaccharides before or at the time of infection. The

strong inhibitory activity of the polysaccharide from *Porphyridium* sp. on the HSV-1 and 2 results from interaction with the viral envelope, with positively charged composition (Talyshinsky et al., 2002). Further, another possible explanation for the antiviral effect of these polysaccharides has been postulated. The specific interaction of the positively charged composition of the viral envelope with polysaccharides, probably through negatively charged amino acid residues, causes conformational or structural changes, leading to better exposure of the antiviral sites (Sun et al., 2019). However, further studies are required to elucidate how *Porphyridium* polysaccharide affects the viral replication cycle.

Polysaccharide AEX from the green algae *Coccomyxa gloeobotrydiformis* can repress the replication of the infectious bursal disease virus (IBDV) *via* regulating the immune system in chickens, implying this bioactive compound could be used in anti-IBDV therapy for poultry (Sun et al., 2019). A sulphated exopolysaccharide derived from the halophilous cyanobacterium, *Aphanothece halophytica,* demonstrated potent antiviral activity against induced pneumonia in mice and reduced immunocompetence by the influenza virus A FM (H1N1) (Dewi et al., 2018). Therefore, this exopolysaccharide could be developed into a therapeutic agent against pneumonia and toward reduction in immunocompetence induced by viruses in mice (Dewi et al., 2018). The extracellular sulphated polysaccharides isolated from dinoflagellate *Cochlodinium polykrikoides* show an inhibitory effect on HIV-1, influenza virus types A and B and respiratory viruses, while the polysaccharide extracted from dinoflagellate *Gyrodinium impudicum* confirmed significant antiviral activity against virus infections caused by EMCV in the pig-farms across many countries (Dewi et al., 2018).

6.2. Lectin

Scytovirin isolated from cyanobacterium *Scytonema varium* is a monomeric lectin with molecular weight of 9.7 kDa and 95 residues organised as two internal repeats (Abdo et al., 2012). Scytovirin inhibits different viruses at a range of IC50 (from 0.3 to 395.5 nM), such as Ebola, HIV, HCV and Marburg virus (Mori et al., 2005). The mechanism of antiviral activity of scytovirin lies in the fact that scytovirin blocks the viral entry *via* interacting with the glucans of the envelop proteins. Despite the high potency of scytovirin against a variety of viruses with little cytotoxicity, its short half-life challenges its efficacy as a therapeutic agent. This could be overcome by modifying the protein to extend the serum half-life, such as PEGylation-modification with polyethylene glycol (Mitchell et al., 2017). Actinohivin is a broadly neutralising prokaryotic lectin which can interact with the envelope protein of SIV. This interaction does not show inhibitory effects on several viral replication assays, indicating that the binding of carbohydrate-binding agents (CBAs) to gp120 glycans is not always necessary for the neutralisation of viral replication (Férir et al., 2012). Microvirin isolated from *Microcystis aeruginosa* is a novel prokaryotic lectin, which displays an inhibitory effect on the infection of a wide variety of HIV-1 strains by binding to multiple glycans on the envelope of virus and subsequently blocking entry of the virus (Mitchell et al., 2017). The monomeric lectin has a reported molecular weight of 14.2 kDa for the 108 residues with 31.5 sequence identity of cyanovirin, a highly potent virucidal protein isolated from cyanobacterium *Nostoc ellipsosporum*. However, microvirin has a much higher safety profile when compared to the cyanovirin (Gondim et al., 2019).

7. Conclusion and perspectives

Marine-derived algal macromolecules present several advantages as potential new therapeutics. These molecules demonstrate a broad-spectrum of antiviral activity against Ebola, HSV, H5N1, SARS, HIV, hepatitis C and fish virus, by inhibiting viral entry and replication.

These compounds can be administered alone or as an adjunct for the pharmacological management of viral infections. Therefore, algal-derived antivirals could potentially become a valuable clinical resource for novel and effective treatment of associated diseases. Although these macromolecules have shown promising antiviral activity *in vitro* and in animal models, an interdisciplinary effort between academia, clinicians and the pharmaceutical industry would be essential to fully characterise chemical structures and determine bioactivity profiles and mechanisms of antiviral activity to progress the development of this class of molecules to address global unmet clinical needs. The identification of target binding sites and inhibitory mechanisms will ultimately advance the understanding of antiviral activities in humans and lead to viable disease solutions.

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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