Chapter 25
Antiviral Applications of Macroalgae

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Abbreviations

ASFV	African swine fever virus
Banlec	Banana lectin
BHK-21	Baby hamster kidney (strain-21)
BVDV	Bovine viral diarrhea virus
Ca-SP	Calcium spirulan
CV-N	Cyanovirin
DENV	Dengue Virus
DENV-2	Dengue virus-2
EV 71	Enterovirus 71
gp120	Glycoprotein 120
GRFT	Griffithsin
H5N1	Avian influenza virus
HBV	Hepatitis B virus
HCMV	Human cytomegalovirus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HIV-1	Human immunodeficiency virus-1
HIV-2	Human immunodeficiency virus-2
HPV	Human papilloma virus
HRV	Human rhinovirus
HSV	Herpes simplex virus
HSV-1	Herpes simplex virus-1

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HSV-2	Herpes simplex virus-2
JEV	Japanese Encephalitis Virus
MERS	Middle east respiratory syndrome
NSF	Nostoflan
RTase	Reverse transcriptase
SARS	Severe acute respiratory syndrome
SPMG	Sulfated polymannuroguluronate

1 Introduction

Viral infections are responsible for causing severe acute respiratory syndrome (SARS), Ebola fever, influenza, hepatitis, and several other serious diseases in humans. They are one of the leading causes of death worldwide, among others like cardiovascular diseases and cancer. Enzootic and epizootic viral transmissions are the main sources of emerging human viral diseases. Parrish et al. (2008) emphasized an increase in epizootic transmissions, and which is also the cause of SARS CoV-2 pandemic that has taken its toll on the worldwide population. There is an immediate need for the development of new antiviral drugs as viral epidemics are estimated to increase in the future due to the increase in the interactions between humans and wildlife populations. Figure 25.1 represents a graph that indicates the number of global incidences of common viral infections in the last ten years. Various antiviral drugs have been developed and are being used but they are prone to drug resistance due to their extensive clinical use and side effects (Kim et al. 2011). Hence, exploring non-traditional resources for new compounds with a wide range of applications is being explored.

About 71% of the earth's surface is covered in water; oceans consist of about 97% of the water volume available on earth (Charette and Walter 2010). Macroalgae are multicellular plants found in marine ecosystem and can belong to either eukaryotic or prokaryotic group of organisms. There is no particular definition of macroalgae as it is of polyphyletic origin. They are part of Asian culture in the form of food or traditional remedies and are consumed in dry or wet forms since earlier times. In the last few decades, there is a surge in the studies focused on obtaining biologically active metabolites from them (Kandale et al. 2011). They are a source of various primary and secondary metabolites, which have diverse chemical structures and a wide range of uses (Anil et al. 2017). The secondary metabolites profile is subjected to various physical and biological factors (Gallimore 2017); which can be used either in their natural form as an antiviral drug or their chemical structure can be evaluated to develop their semi-synthetic derivatives.

Various bioactive metabolites such as polysaccharides, tannins, phenolic acids, flavonoids, carotenoids, and bromophenols are derived from macroalgae. The amount of these metabolites in the macroalgae varies with the species. Some of the chemical compounds from these classes of metabolites have shown antiviral properties (Anil et al. 2017).

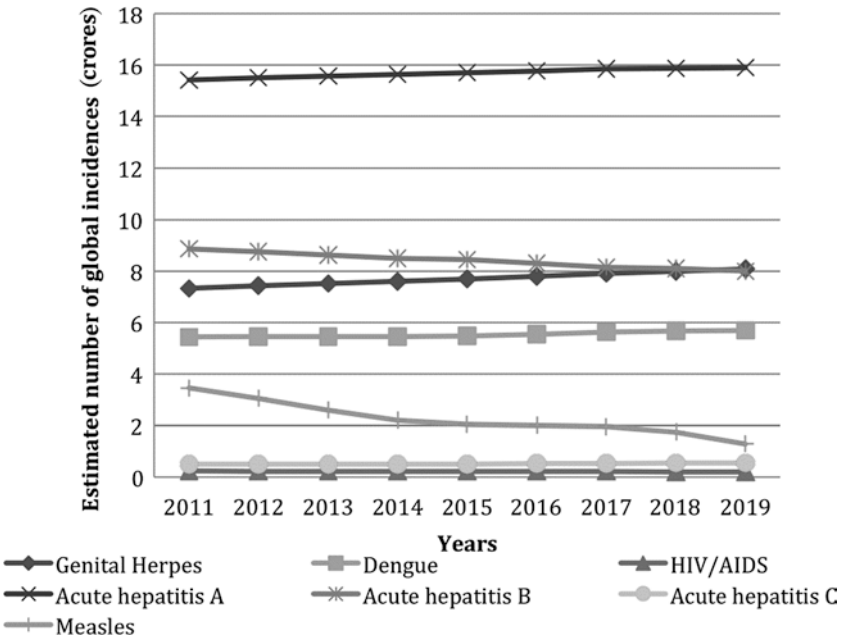

Fig. 25.1 A graph depicting the number of global incidences of genital herpes, dengue, HIV/AIDS, acute hepatitis A, acute hepatitis B, acute hepatitis C, and measles. (Institute for Health Metrics and Evaluation 2021)

2 Antiviral Compounds from Macroalgae

2.1 Polysaccharides

Algal polysaccharides are economical, biodegradable and biocompatible natural non-toxic polymers found in abundance in nature. Figure 25.2 represents the life cycle of the virus and the general mechanism of action of antiviral polysaccharides derived from macroalgae.

2.1.1 Carrageenan

Carrageenan are natural anionic sulfated polysaccharides that are mostly found in the matrix of red algae such as *Gigartina*, *Chondrus*, *Hypnea*, and *Eucheuma.* They share structural and functional similarities with cellulose of higher order plants (Ahmadi et al. 2015).

They are classified based on the presence of 3,6-anhydrogalactopyranose and sulfated groups on the main structure into three types- namely- λ (*lambda*), κ (*kappa*), and ι (*iota*) carrageenan (Fig. 25.3). They selectively inhibit the binding of various enveloped and non-enveloped viruses on the host cells. They are an effective

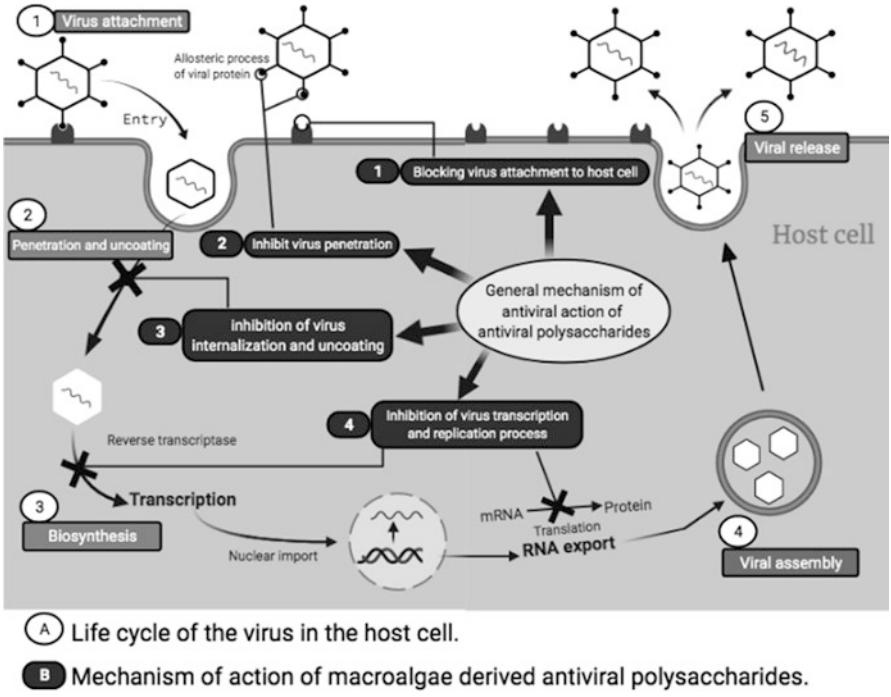

Fig. 25.2 (**a**) Life cycle of the virus in the host cell including (1) virus attachment, (2) penetration and uncoating, (3) biosynthesis (4) viral assembly and (5) viral release. (**b**) Mechanism of action of macroalgae derived antiviral polysaccharides which includes (1) blocking virus attachment to host cell, (2) inhibition of virus penetration (Hans et al. 2020)

inhibitor of human papilloma virus (HPV). λ carrageenan can lead to the inactivation of herpes simplex virus (HSV). 1T1 is a λ carrageenan isolated from *Gigartina skottsbegii* which showed antiviral activity against HSV-2. The activity was displayed in mice due to the interference with the virus attachment stage to the host cells (Carlucci et al. 2004). Carrageenan extracted from *Meristiella delirium* was found to be effective against HSV-2 and Dengue virus-2 (DENV-2) with no cytotoxicity on Vero cells (Paula et al. 2006). ι carrageenan inhibited human rhinovirus (HRV) replication during its primary phase. It also inhibited the replication of the dengue virus in mosquitoes by affecting cell proliferation and protein synthesis, whereas the Vero cell line studies have shown early inhibitory activity due to the presence of some primary receptors (Talarico et al. 2011). κ-carrageenan on sulfation and acetylation inhibits the influenza virus. Molecular weight along with sulfonation groups are linked to the antiviral properties of the acetylated carrageenan against HIV (Yamada et al. 1997). It also binds to Enterovirus 71 (EV 71) and forms carrageenan-viruses complexes, disrupting the virus-receptor interaction which makes it an ideal candidate for the development of anti-EV 71 agents (Chiu et al. 2012).

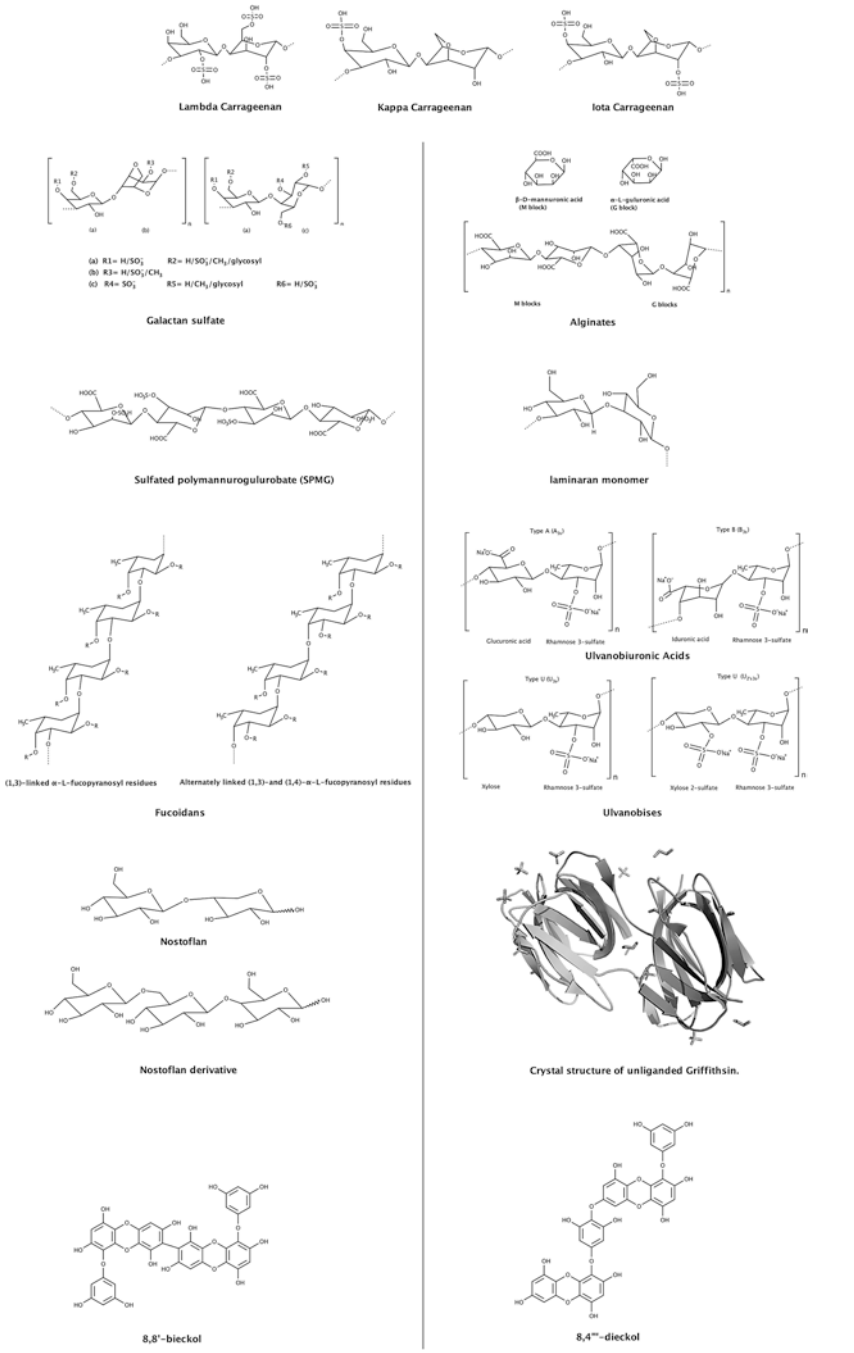

Fig. 25.3 Antiviral compounds from macroalgae. The structure of protein griffithsin was generated by using PyMOL software and protein data bank accession number 2GTY (Ziółkowska et al. 2006)

2.1.2 Galactan

Galactans, also known as sulfated galactans, are found in red algae as the main extracellular polysaccharide. The main structure comprises of linear chains of galactose but there are few exceptions to this. There is an alternate chain of 3-β-D-galactopyranose (G units) and 4-α-D-galactopyranose residues or 4-3,6-anhydrogalactopyranose residues form the structural backbone with the presence of D-unit in carrageenans and L-units in agarans. In some exceptional galactans the DL-hybrids that enclose the G unit is attached to both D and L units (Estevez et al. 2001). Figure 25.3 shows the structure of galactan sulfate derived from red macroalgae. These varied structural forms of galactans are found to be effective against many enveloped viruses, namely HSV-1, HSV-2, DENV, hepatitis A, HIV-1, and HIV-2 (Witvrouw et al. 1994). Antiviral action of these galactans extracted from *Callophyllis variegata* has shown inhibitory effect with less cytotoxicity when tested for HSV-1, HSV-2, and DENV-2 (Rodríguez et al. 2005). Galactan sulfate isolated from *Agardhiella tenera* inhibited adhesion of virus to the cells in HIV-1 and HIV-2. Galactan isolated from *Schizymenia binderi* is highly selective against HSV-1 and HSV-2. (Matsuhiro et al. 2005). Structural hybrids of D, L-galactan, CS2-3 extracted from *Cryptonemia crenulata* has shown inhibition in the multiplication of three clinical strains of DENV-2 virus in a Vero cell line. It gave activity by inhibiting the adsorption of the virus into the host cells (Talarico et al. 2007).

2.1.3 Alginates

Alginates are acid polysaccharides primarily found in brown algae such as *Ascophyllum nodusm*, *Macrocystis pyrifera*, *Laminaria hyperborea*, *Laminaria digitata*, and *Laminaria japonica*. They are anionic linear polysaccharides with a backbone of poly-D-glucuronic acid(G blocks) and poly-D-mannuronic acid (M blocks), with D-guluronic acid and D-mannuronic acid (GM blocks) (Wang et al. 2012). Figure 25.3 shows the structures of M and G blocks. Another drug 911 is an alginate polysaccharide and showed promising anti-HIV-1 and anti-hepatitis B (HBV) results. In the case of HIV-1, it inhibits replication of the virus by decreasing the activity of reverse transcriptase (RTase) which in turn decreases viral adhesion to the host cells. It is effective in both chronic infection of H9 cells and acute infection of MT4 cells *in vitro* as well as *in vivo* (Xianliang et al. 2000). In the case of HBV, 911 inhibits viral replication by decreasing the activity of DNA polymerase (Jiang et al. 2003). A sulfated form of alginate namely sulfated polymannuroguluronate (SPMG) (Fig. 25.3) can be an anti-AIDS drug candidate as it inhibits gp120 from attaching to CD4 molecules on the surface of T cells in case of HIV-1 infection. There is a correlation between the size of SPMG oligosaccharides and their inhibitory action. The SPMG fragment must at least be a hexasaccharide to interact and inhibit gp120 and this property increases with an increase in the size of SPGM fragment (Meiyu et al. 2003; Liu et al. 2005). *In vitro* and *in vivo* studies suggests

the effectiveness of SPMG against HPV infection. It is understood that it blocks HPV binding and entry by interacting with capsid L1 protein (Wang et al. 2020).

2.1.4 Fucan and Fucoidan

These are sulfated polysaccharides with high molecular weight in the range of 100–1600 kDa. They are found in the mucilaginous matrix or intercellular tissues of brown algae and are classified into three major groups i.e. glycuronogalactofucans, fucoidans, and xylofucoglycuronans. The structure of fucan is diverse and depends on the source of brown algae species used for its extraction. Sulfated fucans from *Dictyota mertensii, Lobophora variegata, Fucus vesiculosus, and Spatoglossum schroederi* block the reverse transcriptase activity and prevent HIV infections (Queiroz et al. 2008). They are also obtained from *Cladosiphon okamuranus* having sulfated fucose units and glucuronic acid, which inhibits DENV-2 infection in the BHK-21 cell line (Adhikari et al. 2006). MC26 is a fucose polysaccharide obtained from brown algae *Sargassam piluliferm* found to be effective in influenza with less cytotoxicity (Akamatsu et al. 2003). Fucans obtained from brown algae *Cystoseira indica* is effective against HSV-1 and HSV-2, showing no cytotoxicity for Vero cell culture with a proposed reason that it inhibits virus adsorption to the host cells. (Mandal et al. 2007). Fucoidans consist of L-fucose and less than 10% of other monosaccharides (Fig. 25.3). There is a higher proportion of fucose in the extracellular matrix of brown algae such as mozuku, komby, limu moui, bladderwrack, wakame, sea cucumber, and hijiki. The structure of fucoidans is diverse and repeating alternate sequence of α-1,3-linked sulfated L-fucose with an α-1,4-glycosidic bond which forms the backbone of fucoidans (Tanna and Mishra 2019). They are generally sulfated and acetylated and may contain uronic acid (Berteau and Mulloy 2003; Cumashi et al. 2007; Pomin and Mourão 2008). They are found to be effective against a few human RNA and DNA viruses both *in vivo* and *in vitro* (Witvrouw and De Clercq 1997). They are effective anti-HSV-1 and HSV-2 agents with no cytotoxicity for Vero cell lines. Fucoidans mainly block the adhesion of the virus to the host cells and inhibit viral-induced syncytium formation (Hidari et al. 2008). They exhibit better antiviral potency as compared with ribavirin in the Newcastle disease virus in the Vero cell studies (Elizondo-Gonzalez et al. 2012). They are capable of alternating the proteins of the extracellular matrix and can induce cell apoptosis by affecting cell proliferation (Haroun-Bouhedja et al. 2000; Koyanagi et al. 2003; Aisa et al. 2005; Moon et al. 2008).

2.1.5 Laminaran

Laminaran is a glucan found widely in brown algae such as *Saccharina longicruris*, *F. vesiculosus,* and *Ascophyllum nodosum.* Laminaran is a linear polysaccharide and has β(1 → 3)-linked glucose as the central chain along with β(1 → 6)-linked side-chain branching (Peat et al. 1958). There are two types of laminaran; one with

glucose residues (G-series) and other with terminal D-mannitol residues (M-series) (Nelson and Lewis 1974). Their composition may vary depending on the species and the other physical and biological factors. Laminaran exhibits antiviral properties with low cellular toxicity *in vivo*; they were found to be useful in HIV by inhibiting replication and proliferation of the virus (O'Doherty et al. 2010).

2.1.6 Ulvan

Ulvan is a gelling polysaccharide obtained from *Ulva* species, an edible green seaweed. Ulvans are polyanionic heteropolysaccharide and their sugar composition mainly consist of rhamnose, glucuronic acid, and xylose (Fig. 25.3). However, it contains a wide range of other monosaccharides. α- and β-(1,4)-linked monosaccharides with repeating disaccharide units form the backbone of the ulvan structure. Type A ulvanobiuronic acid and type B ulvanobiuronic acid are the major disaccharide repeating units found in ulvan whereas, ulvanobioses (type U) is the minor disaccharide present (Lahaye and Robic 2007).

2.1.7 Naviculan

It is a high molecular weight polysaccharide made of various sugar moieties like fructose, xylose, rhamnose, mannose, fucose, and sulfate groups. Naviculan is obtained from a diatom *Navicula directa.* It is found to be effective against HSV-1, HSV-2, and influenza virus and works by inhibiting the initial stages of virus replication. Studies suggest its effectiveness against enveloped viruses (Lee et al. 2006).

2.1.8 Calcium Spirulan (Ca-SP)

It is obtained from the marine blue-green algae *Arthrospira plantensis*, and is a novel sulfated polysaccharide. It comprises of ribose, fructose, mannose, glucose, xylose, galactose, rhamnose, galacturonic acid, glucuronic acid, calcium and sulfate. It was found to inhibit virus entry into the host cell during *in vitro* and Vero studies. It is a selective inhibitor of viruses like HSV-1, HCMV, influenza A, measles, HIV-1, polio, mumps, and Coxsackie virus. It also exhibits mild anticoagulant properties (Hayashi et al. 1996). Ca-SP can be a promising new anti-HIV drug candidate.

2.1.9 Nostoflan (NSF)

It is found in edible blue-green algae; *Nostoc flagelliforme.* On hydrolysis NSF yields two types of oligosaccharides namely PA-1 [β-D-GlcAp-(1 → 4)-Xyl-PA] and PA-2 [β-D-GlcAp-(1 → 6)-β-D-Glcp-(1 → 4)-Gal-PA] (Fig. 25.3). It is

proposed to be effective against various enveloped viruses by inhibiting their binding with the host cells. It can be a great candidate for the newer antiherpes drug (Kanekiyo et al. 2005; Thuan et al. 2019).

2.1.10 Xylomannan Sulfate

Xylomannan is a novel anti-freeze agent, that was first isolated from an Alaskan beetle *Upis ceramboides*. Its structure consists of β-D-mannopyranosyl-(1 → 4)-β-D-xylopyranose-disaccharide-repeating units. Some seaweed-derived xylomannan has antiviral properties (Table 25.1). Sulphated polysaccharides can be an option for the development of an anti-COVID drug, since the early symptoms of COVID-19 manifests common cold and flu, with similarities in the mechanism of action of the virus. Carrageenans in the form of nasal spray is an effective treatment for the common cold in adults and children (Ron Eccles et al. 2010). *Iota* carrageenan co-administered with Zanamivir in the form of nasal spray relieves upper respiratory symptoms in the patients suffering from influenza A (R Eccles et al. 2015). Such polysaccharides can be evaluated for their effectiveness against SARS COVID-2 virus. The ability of various microalgal polysaccharides especially ulvans, fucoidans, and carrageenan to inhibit virus adhesion and replication can be tested for the current pandemic (Pereira and Critchley 2020).

2.2 Lectin

Lectins are proteins or glycoproteins that are found naturally in cells that bind reversibly to glycans of glycoproteins, glycolipids, and polysaccharides. They are responsible for cell-cell interaction and protein folding and poses bioactivity; they are used as probes to determine cell surface structure and function. Currently, they are used to develop chemotherapeutic and antiviral agents. They are currently found to be effective against HIV. Griffithsin (GRFT), cyanovirin (CV-N), and banana lectin (Banlec) are some of the promising lectins for the development of antiviral drugs (Lusvarghi and Bewley 2016).

2.2.1 Griffithsin (GRFT)

Griffithsin was first isolated from *Griffithsia* sp., a type of red algae. GRFT is a protein and shows no similarity with any other known protein. GRFT exists as a stable homodimer and every subunit consist of 121 amino acids. GRFT interacts with the terminal sugar moiety of oligosaccharides (Sanchez 2013) (Fig. 25.3). A study on mice infected with the SARS-CoV virus has shown a 100% recovery when administered with GRFT by intranasal route (Ishag et al. 2013). It also showed potential to be a good candidate for the development of topical antiviral agents.

Table 25.1 Antiviral compounds from macroalgae, their significant sources and effectiveness against various viral diseases

Antiviral compound	Significant source	Effective against	References
Carrageenan			
a) λ(*lambda*) carrageenan	*Gigartina skottsbegii* *Chondrus crispus* *Meristiella gelidium*	Herpes simplex Virus (HSV-1 and HSV-2) African swine fever virus (ASFV) Dengue virus (DENV	Carlucci et al. (2004), Paula et al. (2006) García-Villalón and Gil-Fernández (1991) Zhu et al. (2018) Piccini et al. (2020), Paula et al. (2006)
b) κ(*kappa*) carrageenan	*Kappaphycus alvarezii*	Human enterovirus 71 infections.	Chiu et al. (2012) Rudke et al. (2020)
c) ι(*iota*) carrageenan	*Eucheuma denticulatum* *Solieria filiformis*	Human rhinovirus (HRV)infection Herpes simplex virus (HSV-1)	Grassauer et al. (2008) Jönsson et al. (2020) Ana et al. (2021)
Galactan			
a) Sulfated galactan	*Callophyllis variegata*	HSV-1, HSV-2 and DENV-2	Rodríguez et al. (2005)
	Agardhiella tenera	HIV-1 and HIV-2	Witvrouw et al. (1994)
	Schizymenia binderi	HSV-1 and HSV-2	Matsuhiro et al. (2005)
	Cryptonemia crenulata	DENV-2	Talarico et al. (2007)
	Gymnogongrus griffithsiae, *Cryptonemia crenulata*	HSV-1 and HSV-2	Talarico et al. (2004)
	Gracilaria corticata	HSV-1 and HSV-2	Mazumder et al. (2002)
b) DL-galactan hybrid	*Gymnogongrus torulosus*	HSV-2 and DENV-2	Pujol et al. (2002)
Fucan and fucoidan			
a) Galactofucan	*Adenocystis utricularis*	HSV-1, HSV-2	Ponce et al. (2003)
	Dictyota dichotoma	HSV-1	Rabanal et al. (2014)
	Undaria pinnatifida	HSV-1, HSV-2, human cytomegalovirus (HCMV)	Hemmingson et al. (2006)
b) Glucuronic acid, sulfated fucose	*Cladosiphon okamuranus*	DENV-2	Hidari et al. (2008)h
c) Sulfated fucans	*Cystoseria indica*	HSV-1, HSV-2	Mandal et al. (2007)
d) Fucoidan	*Sargassum mcclurei*	HIV-1	Thuy et al. (2015)
	Fucus vesiculosus	Bovine viral diarrhea virus(BVDV)	Güven et al. (2020)
	Laminaria japonica	Avian influenza virus (H5N1)	Makarenkova et al. (2010)
	Sargassum trichophyllum	HSV-2	Lee et al. (2011)

(continued)

Table 25.1 (continued)

Antiviral compound	Significant source	Effective against	References
e) Xylan fucoidan	*Caulerpa brachypus*	HSV-1	Lee et al. (2004)
Ulvan			
	Enteromorpha compressa	HSV	Lopes et al. (2017)
	Ulva intestinalis	Measles virus	Morán-Santibañez et al. (2016)
	Ulva armoricana	HSV-1	Hardouin et al. (2016)
Xylomannan sulfate			
	Sebdenia polydactyla	HSV-1	Ghosh et al. (2009)
	Scinaia hatei	HSV-1 and HSV-2	Mandal et al. (2008)

(O'Keefe et al. 2009; Girard et al. 2018). GRFT binds with the glycoprotein enveloped by the virus and prevents CD4 and other antibodies from binding to the virus (Alexandre et al. 2010). Its immediate antiviral action is a great advantage compared to other antiviral agents which are being evaluated for the same purpose in HIV-1 (Emau et al. 2007). GRFT inhibits HCV, besides it can be effective against enveloped viruses such as the Japanese Encephalitis Virus (JEV), HSV-2, and HPV (Lusvarghi and Bewley 2016). It is also effective for the inhibition of different strains of coronavirus from replicating without cell proliferation. It can be a good candidate to test against respiratory infection for SARS COV-2 pandemic. The antiviral property of GRFT can be in synergism with other lectins (Ziółkowska et al. 2006; O'Keefe et al. 2010).

2.3 Phlorotannins

Phlorotannins are derivatives of a water-soluble polyphenolic compounds called tannins. Phlorotannins consist of polymer-forming phloroglucinol units which are biosynthesized by the acetate-malonate pathway. Phlorotannins are mainly obtained from brown and red algae (Nagayama et al. 2002; Kim et al. 2006). They are effective against the HIV-1 virus and exhibit inhibition of reverse transcriptase, protease, and integrase enzymes which play a vital role in virus replication inside the host cells. When obtained from various sources, they may elicit different inhibitory properties to these target enzymes (Kim and Karadeniz 2011). Phlorotannins derivatives obtained from brown alga *Ecklonia cava* demonstrated inhibition of protease and reverse transcriptase (RT) enzyme. Out of the four phlorotannins derivatives tested, 8,8 ′-bieckol and 8,4 ‴-dieckol (Fig. 25.3) inhibited HIV-1 RT efficiently while showing moderate inhibition towards HIV-1 protease enzyme (Ahn et al. 2004).

3 Conclusion and Future Perspective

Viral infection and re-infections are responsible for deadly diseases in human history and can be highly contagious causing an outbreak of epidemic. It is a lasting challenge for the healthcare sector, as with the rising human population and frequent travel throughout the globe has increased the contact between humans and animals. Countries with higher human-wildlife interactions are more prone to an enzootic and epizootic viral transmission that can be fatal for both humans and wildlife species. Moreover, viruses are a marvel of nature with a complex life cycle and ability to undergo mutations which makes it difficult for the development of antiviral drugs. Developing a vaccine for some old known viruses such as HIV or dengue has been challenging enough. The timely outbreaks of SARS, MERS, Ebola in recent years have called for immediate action for revolutionary discovery and development of antiviral drugs. Viral outbreaks are sudden as we can see in the case of the current SARS COV-2 pandemic; prior knowledge of viruses and the antiviral agents has helped for screening the candidates and for the development of vaccine against SARS-2. Viruses are diverse in their structure and function, thus there is a need for development of antivirals that can target a large group of viruses. Macroalgae are a great source of sulphated and halogenated polysaccharides, lectins, and phlorotannins which are promising candidates for the research and development of new antiviral agents. Most of these moieties are at early phases of development and more extensive investigations are required to develop an effective antiviral drug. The compounds belonging to these groups of metabolites can lead to groundbreaking discovery of new antivirals. They can be evaluated to be used as direct-acting antivirals or in a combination to enhance the effectiveness of already available antivirals. Moreover, they can be useful to cope up with the increasing cases of antiviral resistant strains and new viruses.

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