Review Article

Promising Seaweeds against Human Viruses: A Review

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Seaweeds due to their immense applications in food, agriculture, cosmetics, textile, biomedical and pharmaceutical sector have become inordinate candidates for research. Over the past few decades, research has been focused on algae-driven metabolites such as carrageenan, galactan, laminarin, fucoidan, lectins, phenols and alginate for their diverse applications. Marine algae are constantly being researched for their activity against various human pathogens to establish a permanent alternate therapy with antiviral implications as the main area of focus. In this review, attempts have been made to systematize the anti-viral research of various seaweed-derived compounds and the mechanism of their action against human viruses which would help develop natural antiviral drugs against life-threatening human viruses.

Key words: Seaweeds, algal-driven metabolites, human viruses, antiviral drugs

In the past few years, the perpetual outbreak of deadly viral diseases has taken a heavy toll on human health globally. Vaccines and drugs have successfully worked against some viral diseases such as smallpox and poliovirus and have been able to eradicate them globally but still, the human population is facing serious menaces from many deadly viruses such as hepatitis C virus, Human Immunodeficiency Virus (HIV), Herpes Simplex Virus (HSV) type-I and HSV type-2, dengue virus, chikungunya, influenza virus, rotavirus and Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2)[1]. Despite the continuous endeavors of pharmaceutical companies, we are a long way from winning the battle against viruses. Several issues such as efficacy, safety and cost linked with antiviral drugs need to be dealt with. Moreover, viruses due to their complicated structure and life cycle and development of resistance to antiviral drugs over the period pose a serious encumbrance for the development of an everlasting treatment[2]. Another major threat predictable in the future is the continuous emergence of novel human viruses from other mammals or birds that are capable of being transmitted by humans causing major outbreaks[3]. Considering such concerns there is a need of developing alternate therapies that can overcome the issues linked with currently available antiviral agents and strengthen our immune system to endure viral invasion. Nature has gifted us with a unique ocean of seaweeds inhabiting the marine environment. Seaweeds have become bio resources of considerable economic interest due to their potential to synthesize diverse metabolites including polysaccharides, chlorophyll, xanthophylls, vitamins and essential fatty acids[4-6]. In the past few decades, the bioactive compounds derived from marine seaweeds are being explored as pharmaceutical agents exhibiting promising antiviral, antimicrobial, anti-allergic, anti-inflammatory, antioxidant, anti-cancerous activity, immunomodulatory, neuroprotective and anti-angiogeneic activities[7-10]. Marine polysaccharides are being actively researched for their varied applications in the pharmaceutical sector as Nutraceuticals and therapeutics[11-13]. In particular, the research on the antiviral potential of seaweeds is advancing and opening the way to develop novel antiviral therapy[14-16].

This review has been focused on some detrimental human viruses and contemporary progress made

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on the respective potential antiviral seaweeds with special interpolation of active metabolite acting as an antiviral agent and mechanism of its action.

HUMAN VIRUSES AND OPPORTUNISTIC SEAWEEDS

Hepatitis C Virus (HCV):

HCV infection taints roughly 170 million individuals worldwide[17]. The Hepatitis virus is a single-stranded Ribonucleic Acid (RNA) virus belonging to the family of flaviviruses. Genomic RNA is packed by a core protein which is protected by a bilipid bilayer. Two glycoproteins present in the bilipid layer E1 and E2 constitute virion. The main target organ of the virus is the liver where it attacks hepatocytes causing acute to chronic hepatitis. The virus transmits through blood-to-blood contact[18,19]. Currently available interferon-ribavirin combination therapy is often linked with side effects and a low success rate[20,21].

The exploration led on different seaweeds in this association has demonstrated promising outcomes. Studies suggested that polysaccharide fucoidan isolated from the brown alga *Cladosiphon okamuranus* has exhibited a considerable antiviral effect on HCV replicon in patients with chronic hepatitis[22]. Aqueous extract of red seaweed *Gracilaria tenuistipitata* assayed on hepatocyte-derived carcinoma (Huh-7) cell line significantly inhibited HCV replication and virus-induced cyclooxygenase-2 (transcription factor) expression at promoter transactivation and protein levels[23]. Polysaccharides isolated from seaweeds *Padina pavonica, Sargassum vulgare* of Phaeophyta and *Pterocladia capillacea* and *Laurencia obtusa* of Rhodophyta have shown promising ramifications against the HCV. The effect of polysaccharides was evaluated on *in vitro* model system, liver hepatocellular carcinoma (HepG-2) cells and it was reported that fucoidan, the predominant polysaccharide in Phaeophyta and agar and galactans of Rhodophyta interferes with the attachment of virion to the host cells[24].

HIV:

Two HIV-1 and HIV-2 are members of the genus Lentivirus within the family of Retroviruses[25]. The HIV genome comprises two identical single-stranded RNA molecules that are encased within the core of the virus particle. HIV-1 is more spread worldwide while HIV-2 is restricted to certain regions of Central and Western Africa[26]. The virus enters white blood cells where it integrates its genomic Deoxyribonucleic Acid (DNA) synthesized by reverse transcription into white blood cells of the host followed by chronic progressive destruction of the immune and neurologic system[27]. The currently required life-long antiretroviral treatment is associated with toxicity and significant expense[28].

The studies have confirmed that the brown seaweeds *Ecklonia cava*, *Ishige okamurae*, *Sargassum confusum*, *Sargassum hemiphyllum* and *Sargassum ringgoldianum* collected from the coast of Korea have been shown to inhibit HIV type -1 reverse transcriptase and HIV-integrate and the methanol concentrates of red microalgae *Bossiella* species and *Chondria crassicaulis* restrained cytopathogenicity of HIV-1 at concentration beneath that cytotoxic for Human T-cell (MT4) line[29]. The antiviral effect of fucoidan isolated from brown seaweed *Adenocystis utricularis* was assayed *in vitro* in the human Peripheral Blood Mononuclear Cells (PBMC) primary cell culture. It was demonstrated that fucoidan has potent anti-HIV-1 activity obstructing the initial events of virus replication displaying no cell toxicity[30]. The research work has indicated that water-soluble polysaccharides composed of galactose, 3, 6-anhydrogalactose, uronic acid and sulfate isolated from the red seaweeds *Sphaerococcus coronopifolius* and *Boergeseneiella thuyoides* have a direct inhibitory impact on HIV-1 replication and potential veridical effects evaluated in Vero cells line[31].

The fucoidan extracted from the brown algae *Sargassum polycystum*, *Sargassum mcclurei*, and *Turbinaria ornata* hindered HIV-1 infection on pre-incubation with virus yet not with the cells, impeding the early strides of HIV invasion into target cells[32]. The phenolics containing extract of the red macro alga *Acanthophora spicifera* evaluated on PBMCs was reported to be an efficient anti-HIV-1 agent and possessed anti-HIV-1-reverse transcriptase inhibitory activity[33]. The Research studies undertaken by Sanniyasi *et al.*[34] have manifested that sulfated polysaccharide fucoidan extracted from the brown seaweeds *Dictyota bartayesiana* and *Turbinaria decurrens* collected from the Gulf of Manner regions could successfully restrain the viral adsorption to host cell while assayed on PBMCs hence inhibiting the functioning of HIV-1 strain to a degree comparable to the drug tenofovir that is currently in vogue for antiretroviral activity. The current discoveries demonstrate the polysaccharide fucoidan could be a piece of the potential enemy of HIV drugs, given the examination is broadened.

HSV:

HSV is a double-stranded DNA virus that belongs to the family of Herpesviridae and consists of more than 80 distinct types that are found in nearly all kinds of animals[35]. The most common types of herpes simplex infection are HSV-1 pervasive among Americans causing facial and genital diseases and HSV-2 causing principally genital infections is dominating in African and developing nations, particularly among women[36].

At present, Acyclovir (ACV) and other ACV-related acyclic guanosine analogs, the most common compounds used to target viral DNA synthesis of HSV-I and HSV-2, have been approved for human use[37]. Although these compounds are potent and add to the overall drop of morbidity associated with the viral infection still there is the emergence of viral resistant variants after constant treatment in immunocompromised patients which advocates the persistent quest for novel antiherpetic agents[38,39].

Many studies have reported the existence of anti-HSV bioactive compounds in seaweeds. The sulfated galactan identified structurally in the red alga *Schizymenia binderi* exhibited remarkable specific antiviral activity against HSV-1 and HSV-2 interfering with the early adhesion to the host cells[40]. *Symphyocladia latiuscula*, a red macroalga, has been reported to produce compounds that showed anti-HSV-1 activity assessed in the Vero cells line[41]. Extracts derived from the brown algae *Leathesia difformis*, *Cystoceira myrica*, *Undaria pinnatifida* reported having a bioactive compound consisting of sulfated polysaccharides (fucoidan) have shown strong anti-herpetic activity by inhibiting viral replication[42-44]. In another report, the antiviral activity of *Scinaia hatei*, a red seaweed, against HSV-1 and HSV-2 that inhibits the entry of the virus into the cell is likely to be mediated by algal extract containing sulfated xylomannan and xylans[45,46]. The aqueous extract of the red seaweeds, *Asparagopsis armata*, *Ceramium rubrum*, *Gelidium pulchellum*, *Gelidium spinulosum*, *Hypnea musciformis*, *Plocamium cartilagineum*, *Boergeseneiella thuyoides*, *Pterosiphonia complanata* and *Sphaerococcus coronopifolius* screened for their anti-herpetic activity were capable to inhibit HSV-1 *in vitro* without any cytotoxic effect on Vero cells[47].

Osmundaria obtusiloba (*O. obtusiloba*), a red alga collected from the Brazilian coast was revealed to have antiviral activity against both, HSV-1 and HSV-2, which was likely to be mediated by algal glycolipids interacting with viral glycoproteins[48]. In another exploration, *Hypnea musiformis*, the red seaweed, has shown strong virucidal activity and hindrance of virus binding of HSV-1 and HSV-2 to the host cell. The algal extract exhibited high virucidal activity when treated with plant growth regulators, gibberellin acid and indole acetic acid[49]. A study conducted in Brazil explored more than 36 species of algae for their anti-HSV-1 and HSV-2 activity. The most active anti-HSV extracts were obtained from the four species of the green and the red alga which were mediated by atomaric acid in the green algae *Stylopodium zonale*, some unidentified fatty acids in *Ulva fasciata* and *Codium decorticatum* and halogenated Sesquiterpenes in the red alga *Laurencia dendroidea*[50]. Sulfoquinovosyldiacyl glycerols compounds identified in Brazilian brown seaweed *Sargassum vulgare* have shown strong anti-herpes activity[51]. The early stages of HSV-1 infection and inhibition of viral RNA and DNA synthesis were also strongly hampered by the red alga *Eucheuma gelatina*[52]. Novel bioactive compounds, Chloromethyl 2- (dodecahydro-4,6,7,9-tetrahydroxy-9a-methyl1H-cyclopenta [α]naphtalen-3-yl) acetate isolated from the brown seaweed *Cystoseira myrica* aqueous extracts and 2-((1E,3E)-4-Chloro-2-meracaptobuta-1,3-dienyl)-1,2,3,4,4b,5,6,8a,9,10-decahydrophenanthrene3, 5, 10-triol isolated from the green alga *Ulva lactuca* have shown potential anti-herpetic activity *in vivo* studies[53]. Remarkable research conducted on green alga *Enteromorpha compressa* has demonstrated that extract evaluated on human epithelial type 2 cells has shown total viral inhibition which might be due to the inhibition of viral replication and/or viral protein synthesis[54].

Even though it is difficult to work out whether only one or a blend of a few molecules attributing to the observed anti-HSV-1 and anti-HSV-2 activity of the seaweed extracts, there is the invariable presence of terpenes, fatty acids and phenolic compounds with the observed anti-herpetic activity since these sorts of metabolites, isolated from marine and terrestrial sources, have already been reported to have anti-herpetic activity[55]. The present findings provide bedrock for further experiments on the identification and characterization of specific compounds with high anti-herpetic activities.

Chikungunya Virus (CHIKV):

CHIKV has widespread distribution throughout Asia, Africa, Europe and America[56]. CHIKV is a type of alpha virus that belongs to the family Togaviridae and consists of positive-sense single-stranded RNA. Chikungunya

infection is the most challenging re-emergent disease, with momentous human morbidity and until now one million suspected cases have occurred worldwide[57,58]. Chikungunya is mainly transmitted by *Aedes albopictus* and *Aedes aegypti*. The infection is characterized by chikungunya fever with symptoms that include myalgia, fever, rash and enervative arthralgia, which sustain for months or even years[59]. Till now there is no licensed vaccine available commercially except for some symptomatic treatments against the CHIKV[60]. Several marine algae have displayed promising results against CHIKV.

An alkaloid, caulerpin isolated from the green alga *Caulerpa racemosa* by Esteves *et al.*[61] has exhibited inhibitory and virucidal activity (90 %) against CHIKV-infected Vero cells. Cirne-Santos *et al.* evaluated the extracts of the green alga *Caulerpa racemosa* and the red alga *O. obtusiloba* on CHIKV isolated from the CHIKV-infected patients in Rio de Janeiro, Brazil. The extract manifested an inhibitory effect on CHIKV replication with the Half Maximal Effective Concentration (EC_{50}) of *O. obtusiloba* extract (1.25 µg/ml), considerably lower than that of Chikungunya is mainly transmitted by *Aedes* extract (4.2 µg/ml) justifies these seaweeds as a viable source in the discovery of anti-CHIKV drugs[62]. The compounds identified in Brazilian *O. obtusiloba* were three sulfated bromophenols, two bromophenols, one sterol, and one glyceride[63]. Which could be responsible for the inhibitory effects on chikungunya replication? Extract of *O. obtusiloba* inhibited viral replication for a longer time than the ribavirin used as control at the same concentration and also maintains its inhibitory effect for long periods post-infection. The crude extract and diterpene dolastane obtained from the brown seaweed *Canistocarpus cervicornis* evaluated on Vero cells against CHIKV has shown promising outcomes with EC50 values 3.1 and 1.3 µg/ml respectively. The isolated dolastane has shown 90 % virucidal activity at 10 µM concentration, hence can be used as an effective anti-CHIKV therapeutic over time[64]. The same author with his associates assayed the effect of crude extract, acetylated crude extracts and their fractions prepared from the brown alga *Dictyota menstrualis* on the replication of the CHIKV. The fractions rich in cyclic diterpenes with aldehyde groupings showed significant antiviral activity with EC_{50} values ranging from 0.73-0.90 µg/ml. Combining these fractions with ribavirin produced a synergistic effect displayed by complete viral replication inhibition[65]. In the anti-CHIKV activity, remarkable results have been expressed by terpenoids-rich extract of *Gracillaria dura* with EC_{50} values of 1.25 µg/ml. Further, the terpenoid extract at 5 µg/ml dosage displayed around 90 % virucidal activity against CHIKV[66].

The anti-CHIKV derivatives thus identified can be used for drug designing after successful clinical testing.

Dengue Virus (DENV):

DENV is a member of the Flaviviruses genus of single-stranded positive-sense RNA viruses having four distinct serotypes. DENV is transmitted primarily by the female mosquito *Aedes aegypti*[67] . The virus affects the visceral and central nervous system in humans characterized by the rapid onset of capillary leakage leading to thrombocytopenia, mild-to-moderate liver injury and lethal hemorrhage in the skin and gastrointestinal tract[68]. A necessity to evoke protection against four serotypes might be a notable challenge, as inadequate vaccine-induced immunity against any single serotype hypothetically could incline an individual to serious illness during ensuing natural infection[69]. Various strategies are into account that targets the virus proteins required for replication[69]. Nonetheless, proteins specific drugs could elicit the development of resistant drug variates hence there is a requirement of developing a complementary therapy to control the infection and grim expansion of DENV worldwide.

The evaluation of the anti-DENV activity of DL-galactans extracted from red microalga *Gymnogongrus torulosus* has confirmed that DL-galactans impede the binding of virus glycoprotein to the host cell receptor thus arresting the virus adsorption to the host cell[70]. Two homogenous sulfated polysaccharides kappa/iota/nu carrageenan and the dl-galactan hybrid, isolated from the red seaweeds *Gymnogongrus griffithsiae* and *Cryptonemia crenulata* respectively were strong DENV-2 inhibitors when added together at an early stage of virus infection. The compounds inhibited virus multiplication in Vero and Human hepatoma G2 cells with Half-Maximal Inhibitory Concentration (IC_{50}) values near 1 µg/ml[71]. The polysaccharide, carrageenan isolated from the red alga *Merstiella gelidium* was reported to show anti-DENV-2 activity in mosquitoes and humans as well but the mechanism of action in both the hosts was distinct. In humans, the anti-DENV-2 effect was to prevent the adhesion of the virus to the host cell and in mosquitoes, it hampers the viral protein synthesis[72]. There are reports presenting the anti-DENV-2 activity, attributed to both the sulfated group

and glucuronic acid of polysaccharide fucoidan isolated from the brown seaweed *Cladosiphon okamuranus*. The fucoidan interacts with the envelope glycoprotein of DENV-2 thus preventing the adhesion of the virus to the host cells Baby Hamster Kidney cells (BHK-21)[73]. Investigations on algal extracts (*Canistocarpus cervicornis* and *Padina gymnospora* of Phaeophyta: *Palisada perforata* of Rhodophyta and *Caulerpa racemosa* of Chlorophyta) for their anti-DENV activity assayed on Human derived hepatoma cell line (Huh 7.5) by *in situ* enzyme-linked immunosorbent assay pointed that the seaweed extract might act at an early stage of the viral infection cycle, such as binding or internalization. Studies have confirmed that the antiviral activity of these algal extracts was independent of viral strain and serotype thus enabling them to develop a natural anti-viral drug therapy[74].

The sulfated polysaccharides isolated from the red seaweeds *Grateloupia indica*, *Scinaia hatei*, and *Gracilaria corticata*, the brown seaweeds *Stoechospermum marginatum*, and *Cystoseira indica*, and the green seaweed *Caulerpa racemosa* were assessed for antiviral action against the four serotypes of DENV. The highest antiviral potency was observed against DENV-2 with IC_{50} values in the range of 0.12-20 µg/ml inhibiting DENV-2 adhesion and internalization[75]. A halogenated sesquiterpene, elatol, isolated from the red microalga, *Laurencia dendroidea* exhibited strong *Aedes aegypti* larvicidal activity with IC_{50} value 10.7 ppm which could address an intriguing possibility for a novel compound against the dengue mosquito[76].

Influenza virus:

Influenza is a serious social and economic burden for society. Influenza is a highly infectious airborne disease caused by RNA containing a virus belonging to the family Orthomyxoviridae. The clinical manifestations include febrile illness of the respiratory tract that may lead to respiratory failure under severe infection. The disease is characterized by high morbidity and mortality among all age groups of the population[77]. Currently, available drugs oseltamivir, zanamivir, and riamilovir are fairly effective against influenza virus strains but the continuous use of such specific drugs may lead to the emergence of viral resistance that drives the researchers to explore therapeutic approaches with comprehensive activity[78,79].

A unique and powerful anti-influenza virus compound named MC26, a fucose polysaccharide obtained from the brown seaweed *Sargassum piluliferum* displayed a stronger anti-influenza virus activity with low cytotoxicity *in vivo* and *in vitro* measures when collated with anti-viral drug amantadine and MC24 compound derived from a marine brown alga, *Turbinaria oronata*[80]. The polyphenol phlorotannin, isolated from the brown alga *Ecklonia cava* has been reported to be a potent selective inhibitor of neuraminidase, a surface glycoprotein of the influenza virus[81]. The hybrid carrageenan (i/k/v-carrageenan) isolated from the red alga *Eucheuma denticulatum* as a potential anti-influenza agent with IC_{50} value 276.5 µg/ml when evaluated using the Madin-Darby Canine Kidney cells model[82]. The anti-viral activity against influenza A virus subtype H1N1 by sulfated fucans obtained from the brown seaweeds *Ascophyllum nodosum* and *Fucus vesiculosis* has been well demonstrated[83]. An edible brown alga *Undaria pinnatifida*, contains fucoidan, a sulfated polysaccharide, that inhibited the *in vitro* replication of the influenza A virus, and stimulated both innate and adaptive immune defense functions in virus-infected mice[84]. The findings proved the *in vitro* anti-influenza activity of the red seaweed *Tricleocarpa fragilis* in Madin-Darby Canine Kidney cells[85].

The fucoidan isolated from brown algae *Kjellmaniella crassifolia* effectively blocked Influenza A virus infection *in vitro* with low toxicity and a low tendency of induction of viral resistance. Fucoidan could inhibit the activity of viral neuraminidase to block the release of Influenza A virus[86] recommending that fucoidan can be formed into a novel nasal drop or spray for counteraction and treatment of influenza in the future. Lectins isolated from green alga *Halimeda renschii* and red alga *Kappahycus alvarezii* have successfully hampered the process of cell internalization by coupling with viral envelope protein hemagglutinin[87,88]. The anti-viral action of *Halimeda renschii* was evaluated using NCI-H292 cells (Human lung mucoepidermoid carcinoma cells).

SARS-CoV-2 virus:

The current outburst of an acute respiratory disease associated with a coronavirus, called Coronavirus Disease 19 (COVID-19), with catastrophic social and economic impacts, has resulted in a major epidemic (the 19 epithet refers only to the year it was reported, 2019)[89]. Based on phylogeny, taxonomy, and established practice, the Coronaviridae Study Group (CSG) of the international virus taxonomy committee recognizes this virus as a clone associated with the

coronavirus prototype of the severe acute human respiratory syndrome referred to as SARS-CoV-2[90,91]. Coronaviruses are containing positive-sense single-stranded RNA as genetic material[92]. COVID-19 is a highly infectious disease[93]. Characterized by influenza-like mild to moderate symptoms ranging from dry cough, fever and headache to severe lung injury, and multi-organ failure[94,95].

The world scientific community is working hard towards the development of therapeutics and vaccines which are under various stages of clinical trials[96] and some are on rollout globally. Looking at the current scenario, the global society facing a herculean challenge in battling the pandemic COVID-19, but here are some of the characteristics that various seaweeds have that could be prospective solutions to this global health problem shortly and possibly strengthen us to combat such pandemics in the future.

Research has indicated that carrageenan nasal spray is an effective treatment in children as well as in adults suffering from virus-confirmed common cold symptoms reducing the duration of the disease and recurrence of symptoms[97].

A varied range of metabolites such as sulfated polysaccharides, carrageenan, galactans, laminarin alginates fucoidan, naviculan calcium spirulan found abundantly in the red, brown and green seaweeds, diatoms and cyanobacteria help build a strong immune system and mitigating the SARS-CoV-2 virus-related manifestations[98]. The same fact was reinforced by Pereira and Critchley stating that complex structural sulfated polysaccharides obtained from various groups of algae could be potential antiviral therapeutic compounds[99]. The fucoidan extracted from the brown seaweed *Saccharina japonica* was able to compete with heparin for spike-protein binding while evaluating the *in vitro* antiviral properties of heparin and other closely related sulfated polysaccharides[100]. This study suggested that fucoidans and related sulfated polysaccharides could act as plugs to interfere with spike protein binding to co-receptors in host cells thus enabling the fucoidans for promising clinical use as anti-viral therapeutics (Table 1).

TABLE 1: SEAWEEDS AND CONCOMITANT METABOLITE AGAINST HUMAN VIRUSES

Seaweeds	Active metabolite	Virus	Assessed in cell cultures	References
Red seaweeds				
Gracilaria tenuistipitata	Not reported	HCV	Huh-7 cells	[23]
Gracilaria dura	Terpenoids	CHIKV	Vero cells	[66]
Gracilaria corticata	Carragenan	DENV-2	Vero cells	[75]
Pterocladia capillacea and *Laurencia obtusa*	Agar and galactans	HCV	HepG-2	[24]
Laurencia dendroidea	Halogenated sesquiterpenes	HSV-1	Vero cells	[50]
Bossiella species and *Chondria crassicaulis*	Not reported	HIV-1	MT4 cells	[29]
Sphaerococcus coronopifolius, Boergeseneiella thuyoides	Galactose, 3,6-anhydogalactose, uronic acid, and sulfate	HIV-1 , HSV-1	Vero cells	[31,47]
Acanthophora spicifera	Phenolics	HIV-1	PBMCs	[33]
Schizymenia binderi	Sulfated galactans	HSV-1, HSV-2	Vero cells	[40]
Symphyocladia latiuscula	2,3,6-tribromo-4,5-dihydroxybenzyl methyl ether	HSV-1	Vero cells	[41]
Scinaia hatei	-Sulfated xylomannan and sulfated xylans	HSV-1, HSV-2	Vero cells	[45,46]
	-Carrageenan	DENV-2	Vero cells	[75]
Asparagopsis armata, Ceramium rubrum, Gelidium pulchellum, Gelidium spinulosum, Plocamium cartilagineum, and *Pterosiphonia complanata*	Not reported	HSV-1	Vero cells	[47]

Osmundaria obtusiloba	Sulfoquinovosyl-diacylglycerols	HSV-1, HSV-2,	Vero cells	[48]
	-Bromophenol, sterol, glyceride	CHIKV	Vero cells and retinal neurons of chicken embryos	[62]
Hypnea musiformis	Not reported	HSV-1 HSV-2	Vero cells	[49]
Eucheuma gelatinae	Sulfated polysaccharides	HSV-1	Vero cells	[52]
Eucheuma denticulatum	i/k/v-carrageenan	Influenza virus	MDCK cells	[82]
Gymnogongrus torulosus	dl-galactan	DENV-2	Vero cells	[70]
Gymnogongrus griffithsiae	Sulfated kappa/iota/nu carrageenan	DENV-2	Vero and HepG-2 cells	[71]
Cryptonemia crenulata	dl-galactan hybrid	DENV-2	Vero and HepG-2 cells	[71]
Merstiella gelidium	Carrageenan	DENV-2	Vero cells	[72]
Palisada perforata	Not reported	DENV-2	Huh 7.5 cells	[74]
Grateloupia indica	Carrageenan	DENV-2	Vero cells	[75]
Tricleocarpa fragilis	Not reported	Influenza virus	MDCK cells	[85]
Kappahycus alvarezii	Mannose specific lectins	Influenza virus	MDCK cells	[88]
Brown seaweeds				
Cladosiphon okamuranus	Fucoidan	-HCV	Huh-7 cells	[22]
		-DENV	BHK-21 cells	[73]
Padina pavonica	Fuciodan	HCV	HepG-2	[24]
Padina gymnospora	Not reported	DENV	Huh 7.5 cells	[74]
Sargassum vulgare	-Fuciodan	HCV	HepG-2 cells	[24]
	Sulfoquinovosyl-diacylglycerols	HSV-1	Vero cells	[51]
	Fucoidan	HIV-1	----------	[29]
Sargassum confusum, Sargassum hemiphyllum, and *Sargassum ringgoldianum*	Fucoidan	HIV-1	PBMCs	[32]
Sargassum polycystum, Sargassum piluliferum and *Sargassum mcclurei*	Fucose polysaccharide M26	Influenza virus	MDCK cells	[80]
Ecklonia cava	-Fucoidan	HIV-1	----------	[29]
	-Phlorotanins	Influenza virus	----------	[81]
Ishige okamurae	Fucoidan	HIV-1	----------	[29]
Adenocystis utricularis	Fucoidan	HIV-1	PBMCs	[30]
Turbinaria ornata	Fucoidan	HIV-1	PBMCs	[32]
Turbinaria decurrens	Fucoidan	HIV-1	PBMCs	[34]
Dictyota bartayesiana	Fucoidan	HIV-1	PBMCs	[34]
Dictyota menstrualis	Cyclic diterpenes	CHIKV	Vero cells	[65]
Leathesia difformis	Fucoidan	HSV-1	Vero cells	[42]
Cystoseira myrica	Naphthalene skeleton containing compound	HSV-1	Vero cells	[43,53]
Cystoseira indica	Fucoidan	DENV	Vero cells	[75]
Undaria pinnatifida	Fucoidan	-HSV-1	-Evaluated in mice	[44]
		-Influenza virus	-Evaluated in mice	[84]
Canistocarpus cervicornis	-Diterpene dolastane Not reported	CHIKV	Vero cells	[64]
		DENV	Huh 7.5 cells	[74]

Stoechospermum marginatum	Fucoidan	DENV	Vero cells	[75]
Ascophyllum nodosum and *Fucus vesiculosis*	fucans	Influenza virus	MDCK cells	[83]
Kjellmaniella crassifolia	Fucoidan	Influenza virus	MDCK cells	[86]
Saccharina japonica	Fucoidan	SARS CoV-2 Virus	*In vitro* studies	[100]
Green seaweeds				
Stylopodium zonale	Atomaric acid	HSV-1	Vero cells	[50]
Ulva fasciata	Not identified	HSV-1	Vero cells	[50]
Ulva lactuca	Phenanthrene skeleton containing compound	HSV-1, HSV-2	Vero cells	[53]
Codium decorticatum	Not identified	HSV-1	Vero cells	[50]
Enteromorpha compressa	Sulphated polysaccharides	HSV-1	Human epithelial type 2 cells	[54]
Caulerpa racemosa	Caulerpin	-CHIKV	Vero cells	[61]
		-CHIKV	Vero cells and retinal neurons of chicken embryos	[62]
		-DENV-2	Vero cells	[74]
Halimeda renschii	Lectins	Influenza virus	NCI-H292	[87]

CONCLUSION

This review suggests the significant inhibitory activity of seaweeds against a variety of human viruses. In most cases, the antiviral effect is mediated through algal-driven polysaccharides that inhibit the replication of the virus by hampering the early stages of the virus life cycle or ameliorating the immune system of the host to expedite the process of virus elimination. The fucoidan derived from brown algae is assuming a significant part in several viral infections. Despite the many advantages of using seaweeds as antiviral agents such as cost-effective production, low cytotoxicity, and broad-spectrum antiviral effect, the most of investigation is limited to *in vitro* examination. *In vivo* studies using human models are crucial for the development of antiviral therapeutics. As marine polysaccharides have complex structural diversity, therefore underlying mechanism and relationship of antiviral action and structure of these polysaccharides need to be researched. The present reviews provides a ground for further investigations on identification and isolation of characteristic anti-viral compounds. Given the high potency and minimal side effects, these natural antivirals together with current therapies can be used as promising antivirals after evaluation in human cell cultures and clinical trials.

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