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ANTIVIRAL PROPERTIES OF MICROALGAE AND CYANOBACTERIA

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ABSTRACT

The recent outbreak of Corona Virus Disease (COVID-19) and the surge in accelerating the development of a vaccine to fight against the SARS-CoV-2 virus has imposed greater challenges to humanity worldwide. There is lack of research into the production of effective vaccines and methods of treatment against viral infections. As of now, strategies encompassing antiviral drugs and corticosteroids alongside mechanical respiratory treatment are in practice as frontline treatments. Though studies have reported that microalgae possess antiviral properties, only a few cases have presented the existence of antiviral compounds such as algal polysaccharides, lectins, aggluttinins, scytovirin, algal lipids such as sulfoquinovosyldiacylglycerol (SQDG), monogalactosyldiacylglycerides (MGDG) and digalactosyldiacylglycerides (DGDG), and algal biopigments especially chlorophyll analogues, marennine, phycobiliproteins, phycocyanin, phycoerythrin and allophycocyanin that are derived from marine and freshwater microalgae. Given the chemodiversity of bioactive compounds from microalgae and the present scenario, algal biotechnology is seen as a prospective source of antiviral and anti-inflammatory compounds that can be used to develop antiviral agents. Microalgae with potential as antivirals and microalgae derived functional compounds to treat viral diseases are summarized and can be used as a reference in developing algae-derived antivirals to treat SARS-CoV-2 and other similar viruses.

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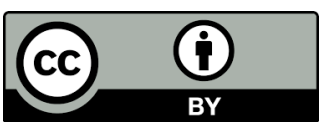

1 Introduction

Research activities to classify compounds used to prevent and treat severe and acute viral infections are now a priority and society has been hesitant and unable to seek scientific solutions (Liu et al., 2020). The complex life cycle and the distinctive nature of the viruses have made it highly difficult to discover definite remedies against viral infections (Murrell et al., 2011).

A variety of diseases, such as hepatitis C (HCV), human immunodeficiency virus (HIV) and dengue virus (DENV) still affects the majority of people of the world's population over decades, despite comprehensive studies of effective vaccines and viral infection treatment over the last century (Graci & Cameron, 2005).

To date, the development of vaccines against certain viruses such as HIV and HCV has proven to be an intractable strategy and specific vaccine are not found against many common viral infections, including herpesviruses (Ahmadi et al., 2015) and respiratory tract viruses such as Severe Acute Respiratory Syndrome and Middle East Respiratory Syndrome.

Besides, drug resistance of various viruses (HIV-1 and HSV), to available antiviral agents has often been a significant obstacle for antiviral medications (De Clercq, 2002).

The complex aquatic ecosystem has given the world of the marine environment a range of algae from micro-organisms to giant algae. Microalgae and cyanobacteria have been used for millennia as food in ancient Asian, African, and South American cultures. However, only by the middle of the past century biotechnology for microalgae begin to evolve (Mendes et al., 2003).

Microalgae and cyanobacteria provide immense prospects in industries such as pharmaceuticals, foodstuffs, or cosmetics for isolating natural substances of considerable commercial interest. Further, numerous research studies have evidenced the antiviral property of microalgal compounds (Mayer & Hamann, 2005) that proposes microalgae as a potent source for a natural antiviral agent. This review article summarizes the antiviral activities of the purified biomolecules from the microalgae.

2 Algae derived biomolecules as antiviral agents

2.1 Polysaccharides

Research by Gerber et al. (1958) found that an important source of antiviral agents with polysaccharides was the inhibition of influenza B viruses by marine algae polysaccharides. Anti-viral activity of other red algae-insulated polysaccharide fractions against HSV and HIV-1 have been recorded over the past two decades. Since then, several studies have shown that some algae-driven polysaccharides have antiviral potential and underlying action mechanisms as shown in Table 1.

The sulphated exopolysaccharides of marine microalgae such as *Porphyridium* sp. and *Cochlodidium polykrikoides* are found to interact with certain enveloped viruses like HSV and HIV, preventing them from reaching the host cells (Amaro et al., 2011) and also exhibited antiviral action against type 1 and 2 HSV in both *in vitro* and *in vivo* rabbits and rats (Huleihel et al., 2001). The antiviral property of the polysaccharides from *Porphyridium* sp. was due to the neighboring attachment of HSV-1 particles to polysaccharides (Batinic & Robey, 1992). Also, naviculan is an extracellular sulphated polysaccharide produced by *Navicula directta* diatom. The naviculan contains galactose, rhamnose, xylose, fucose, sulfate, and manna that reported to have an antiviral effect on HSV-1and HSV-2 (IC_{50} range 7–14µg / mL). Besides, naviculan hinders influenza viruses at the early stages of virus-related response, possibly preventing the virus from entering the host cells (Lee et al., 2010).

Cyanobacteria contain vital antiviral compounds. *Arthrospira platensis* is a blue-green alga that consists of exopolysaccharides. This exopolysaccharide has an antiviral activity for Koi Herpes Virus (KHV), which is accountable for significant economic losses in common carp and koi (Reichert et al., 2017). Polysaccharides enriched fraction at 18 to 36 µg/mL inhibits the replication of the virus (Haslin et al., 2001). *S. platensis* extract is known as calcium spirulan (Ca-SP) which is a form of sulphated polysaccharide. Ca-SP consists of ribose, mannose, galactose, fructose, and rhamnose which will intrude the replication of both enveloped (HIV, influenza A) and non-enveloped (HSV, polio, cytomegalovirus) viruses (Takebe et al., 2013).

2.2 Proteins

Proteins with antiviral activities are also produced by various species of cyanobacteria and microalgae. Glycoproteins or carbohydrate-binding proteins are known as lectins.

Lectins can bind with carbohydrates and carbohydrate moieties of glycoconjugates. Different lectins that exert anti-HIV activity by attaching strongly with carbohydrate moieties on the glycosylated HIV envelope have been identified over the last decade (Huskens & Schols, 2012).

HIV shows a mannose-rich glycoprotein gp120 on its surface envelope which is essential for the virus to bind to the target cells' cellular receptor CD4 (Tiwari et al., 2009). Besides this, there is a strong antiviral activity produced by *Scenedesmus obliquus* hydrolysates Sd, Sd1 and Sd2 against Coxsackie virus B (Afify et al., 2018).

Table 1 Polysaccharides from microalgae and cyanobacteria having antiviral activities

Compounds	Microalgae	Viruses	Authors
Sulfated polysaccharide	*Navicula directa*	Influenza-A	Ahmadi et al., 2015
Highly sulfated polysaccharide	*Porphyridium cruentum*	HSV-2, HSV-1, Vaccina	Huang et al., 2007
Sulfated exopolysaccharide	*P. purpureum*	Vaccina	Radonic et al., 2010
Sulfated polysaccharide	*Porphyridium cruentum*	Varicella zoster virus	Huleihel et al., 2001
Exopolysaccharides	*Rhodella reticulata*	Murine sarcoma and leukemia viruses	Talyshinsky et al., 2002
Extracellular sulfated polysaccharide	*Cochlodinium polykrikoides*	Influenza , parainfluenza-2	Hasui et al., 1995
Calcium spirulan	*Arthrospira platensis*	measles,influenza	Radonic et al., 2010
Nostaflan	*Nostoc flagelliforme*	Influenza A virus	Goss & Jakob, 2010
Carrageenan	*Gigartina skottsbergii*	Influenza virus, HSV-1,DENV, HSV-2, , HIV	Dye, 2014
Galactan	*Cryptonemia crenulata*	HSV-1, HSV-2, HIV-1, HIV-2, DENV	Delattre et al., 2011
Alginate	*Macrocystis pyrifera*	HIV	Zheng et al., 2020
Fucan	*Adenocytis utricularis*	HSV-1, HCMV, HSV-2, HIV-1	Salehi et al., 2020
Laminaran	*Ascophyllum nodosum*	HIV	Edwards et al., 2019

2.3 Lipids

Many algal lipids have exhibited antiviral activity to a lesser degree relative to polysaccharides and proteins. Compounds such as sulfoquinovosyldiacylglycerol (SQDG) and monogalactosyldiacylglycerides (MGDG) are primarily sulfolipids and glycolipids (Buck et al., 2006). The high anti-HIV activity was detected in *Lyngby alagerheimii* and *Phormidium tenue's* SQDG (Gustafson et al., 1989). *Spirulina*'s methanol extract with an IC_{50} value of 25.1µg/mL has antiviral activity against HIV-1 (Zalah et al., 2002; Yim et al., 2004; Li et al., 2008).

2.4 Pigments

Different pigments in microalgae and cyanobacteria have shown various biological activities. For example, chlorophyll analogs in *Dunaliella primolecta* (Ohta et al., 1998) have demonstrated anti-HSV activity. *Haslea ostrearia* is a marine diatom that produces blue pigment, a water-soluble fraction containing marennine (EC_{50} value of 14 µg/mL), was able to inhibit HSV-1 replication in vitro cells. Additionally, this element prolonged the development of syncytia caused by HIV-1 on cells of MT2 (Kamat et al., 1992; Shih et al., 2003). Phycobiliproteins, the natural coloring in food and pharmaceutical products, are the key photosynthetic additive in cyanobacteria and red algae. The two most commonly known phycobiliproteins are *Arthrospira* phycocyanin and *Porphyridium* phycoerythrin. They have reported showing antiviral properties that turned them into a promising material for health applications. Table 2 states the commercial application of the algae and cyanobacteria derived antivirus compounds.

Conclusion

Various biological activities, including the transcendent antiviral effect, have been documented for algal purified molecules. Numerous pharmacological studies have been only conducted in host cells as *in vitro* studies. Nevertheless, *in vivo* studies are essential to promote the usage of microalgal products in the pharmaceutical industry as effective anti-viral agents. Additionally, new experiments to explore the antiviral activities against infectious viruses, including clinical trials, are another area for further research.

Table 2 Commercial application of the algae and cyanobacteria derived antivirus compounds

Microalgae	Commercial Supplement	Brand	Benefits	Authors
Spirulina	Apogen Children Granules	Febico	Flu, influenza, enterovirus, virus respiratory syncytial and dengue virus	Febico, 2021
Gigartina papillata	Red Marine Algae Plus	Pure Planet	Oral herpes, shingles,genital herpes, mononucleosis, HIV, and influenza	Kelly Harrington, 2020
Aphanizomenon flosaquae	Blue-Green Algae	Source Naturals	HIV/AIDS	Zizzo et al., 2020
Spirulina	Apogen capsules	Febico	Flu, influenza, enterovirus, dengue virus, and respiratory syncytial virus	Febico, 2021

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