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Algal Sulfated Polysaccharides: Potent Immunomodulators against COVID-19 in Pandemic 2020

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The sulfated polysaccharides obtained from algae may serve as potential antiviral components, which can fight against corona virus disease (COVID-19) in the present pandemic situation. Here, bioactivity of some important sulfated polysaccharides including carrageenan, galactans, laminaran, alginates, fucoidans, naviculan, calcium spirulan, p-KG03, nostoflan etc. found widely in red, brown and green seaweeds, diatoms, cyanobacteria and microalgae are discussed. Though the vaccines are yet to be released in the market, these sulfated polysaccharides can help to build a stronger immune system and help in minimizing the problem of pandemic 2020 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and can also lower the risk of viral infections in the post-COVID era.

Keywords: Algae; Antiviral property; COVID-19; Pandemic 2020; SARS-CoV-2; Sulfated polysaccharides.

The global scenario has changed, as the novel coronavirus has become a pandemic for human civilization. The World Health Organization (WHO) has reported 216 countries, areas or territories around the world, which are infected by SARS-CoV-2. By the time this report was made (June 2020), the virus had already infected 88,60,331 people, caused more than 4,50,000 deaths and the figures are continually increasing.[1] As of now, no vaccines are available that can lead the fight against this virus by boosting the immune system. Research is going on in various countries for development of vaccine against the virus. Sulfated polysaccharides (SPs), extracted from algae may serve as a potential agent against such novel viruses to solve the global problem at present and in future.

Emerging and re-emerging viral infections continue to pose a key threat to global public health. From the very beginning, the "Spanish flu"or "1918 flu pandemic" was recognized deadly influenza pandemic caused by human influenza A (HIN1) virus. At that time more than 500 million people were affected and 50 million people were estimated to be dead, largest in human history caused by a virus. In 1957 to 1958, the flu pandemic returned as HIN1 subtype (H2N2) and also known as "Asian flu", which originated in Guizhou, China and sacrificed more than 1 million people worldwide. Following this, in 1968 the H2N2 virus genetically modified into H3N2 subtype of HIN1 through antigenic shift and was designated as "Hong Kong flu" which killed about 3 million people around the world. The H3N2 virus returned

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in 1969-1970 resulting in another deadly wave of deaths and circulated as seasonal flu. In 1997, a deadly pathogenic avian influenza A (H5N1) virus launched and spread its wings over humans through the poultry birds and later it modified into various subtypes including H7N9, H9N2 and H7N3. Similarly in 1999 and 2018, a novel paramyxovirus, termed as "Nipah virus (NiV)" was identified as the cause of severe encephalitis outbreak in Malaysia, Singapore and India that took 400-500 lives. In the pandemic flow during 2002-2003, major outbreak happened among the Chinese people, which causing severe acute respiratory syndrome (SARS) by a novel coronavirus "(CoV). Designated as SARS-CoV, it spread over 37 countries. The SARS-CoV virus infected more than 8000 people and took 774 lives with 9.6% mortality rate.[2] The Middle East respiratory syndrome (MERS) in 2012, again caused by a deadly coronavirus, MERS-CoV had a mortality rate of more than 30%. The outbreak continues and several emerging and re-emerging viral pathogens including "Severe fever with thrombocytopenia syndrome (SFTS)", "Bunyavirus" (2010), "Ebola virus" (2014-2016), "Zika virus" (2015) constantly pose a threat to human health.[2]

The most recent outbreak of novel COVID-19 originated in the city of Wuhan, China in December 2019. The virus causes severe pneumonia with acute respiratory infections (ARIs), which gets transmitted by air and person-to-person contact, making it very contagious. Reports state that the ARIs causes high mortality rate due to childhood morbidity.[3] Several viruses associated to respiratory infections including respiratory syncytial virus (RSV), influenza virus, parainfluenza virus (PIV), adenovirus (AdV), rhinovirus (RV), human metapneumovirus (HMPV), human bocavirus (HBoV), human papilloma viruses (KIPyV, WUPyV) and emerging human coronaviruses (HCoV) are reported.[3] More than 6 million people have been infected with novel COVID-19, which is newly identified as 2019-nCoV, classified under Coronaviridae family and recognized as modified clone of SARS-CoV (SARS-CoV-2).[4]

In ancient times, traditional medicines were used to cure respiratory diseases including cold, cough, chronic coughs and bronchitis. It has been found that an unknown mixture of carrageenan obtained from two red algal species, *Chondrus crispus* and *Mastocarpus stellatus* to cure cough of Irish people in 1830s and fought against viral infections.[5] By tradition Japanese people regularly consume seaweeds and iodine in their diet to enhance the immune system. A report has suggested that Hokkaido populations of Japan reduced the infection of COVID-19 at the initial stage by consuming seaweed regularly but to make it 100% curable, people should follow the additional measures like social distancing and isolation.[3] It has been observed that carrageenan nasal spray is an effective treatment that reduces the duration of the viral infection and increased viral clearance during common cold in children and adults.[6] Another study showed that nasal spray containing iota-carrageenan or the combination of "zanamivir" and iota-carrageenan is effective against HIN1 virus by the treatment of upper respiratory tract infections.[7] Interestingly, carrageenan not only fights against respiratory diseases, it reduces the risk of other infections and boost up immunity in children and adults as well.

Some microalgae, cyanobacteria, diatoms and a major group of seaweed contain large amount of uniquely structured long chain sugars polymerized as polysaccharides with many health benefits. Polysaccharides obtained from algae have beneficial acitivities or healing capacities. In the last few decades, algal polysaccharides especially SPs have been studied effectively due to its antiviral[8,9,10] anti-inflammatory[11], antitumor[12], anticoagulant[11], antithrombotic[11], antinociceptive[13] and antioxidant[14] properties.

In the last few decades, with emergence of technology and fast placed lifestyle human immune system is considerably affected. Though development of antiviral drug is a complex process, currently the pharmacological companies and research laboratories have approved the clinical use of around 50 drugs for human use against various viruses including herpes simplex virus (HSV), human immunodeficiency virus (HIV), human cytomegalovirus (HCMV), influenza virus, hepatitis B virus (HBV) and hepatitis C viruses (HCV).[15] First report on antiviral activity of algal SPs was found in 1958 against influenza B or mumps virus[16] and over the years many researchers have worked on it. Most useful SPs obtained from algae are grouped into carrageenan, fucoidans,

galactans, laminarans, alginate derivatives, naviculan, calcium spirulans, p-KG03, nostoflans and sea algae extracts (SAE).

Fucans are group of complex SPs, which occur in mucilaginous matrix of brown algae and grouped into fucoidans, glycuronogalactofucans and xylofucoglycuronans. From the very beginning, fucoidans had potential applications in antiviral activity of many enveloped viruses such as influenza A virus[17], HSV-1[18], HIV[19], Newcastle disease virus (NDV)[20], and canine distemper virus (CDV)[21]. It has been reported that *in vitro* and *in vivo* activity of fucoidans showed various biological activities against DNA and RNA viruses including dengue virus (DENV), HIV, HCMV, measles virus, HSV-1 and HSV-2.[10] Fucoidans showed their antiviral activities by inhibiting viral-induced syncytium formation.

Galactans are major extracellular polysaccharides, widely distributed in red algal groups including *Gracilaria*, *Gelidium*, *Callophyllis*, *Agardhiella*, *Cryptonemia*, *Schizymenia* etc. and have shown their antiviral activity against numerous viruses like DENV, HSV-1, HSV-2, HIV-1, HIV-2 and hepatitis A virus (HAV).[10]

Carrageenans are group of anionic SPs obtained from the matrix of red algae such as *Gracilaria*, *Chondrus*, *Hypnea*, *Eucheuma* and *Gigartina* and classified into lambda, kappa and iota carrageenans. Several reports have suggested that carrageenan are potential inhibitor of human papilloma viruses (HPVs) and prevents initial infection by inhibiting the binding of virus into the host cells.[22] Despite this, lambda-type carrageenan is found to be active against HSV-virion.[23] Replication of human rhinovirus (HRV) can be prevented by iota-carrageenan with suppression of the allosteric activity of virus particles during infection.[24]

Laminaran, is another group of SPs predominantly found in brown seaweed such as *Fucus*, *Ascophyllum*, *Saccharina* and classified into two groups, viz., G-series with glucose units and M-series with D-mannitol units in chain. Laminaran inhibits the reverse transcriptase activity of HIV, which prevents viral replication and proliferation.[10]

Alginates, another group of acidic SPs widely occurred in brown algae like *Laminaria*, *Sargassum*, *Ascophyllum* and *Macrocystis* showed their potential against HBV by suppressing the activity of DNA polymerase. Alginates are also found to be active against HIV infection mainly through the vigorous attachment of gp120 protein with CD4 molecules on the surface of T cells.[10]

Naviculan, is another group of heteropolysaccharides obtained from a diatom called *Navicula directa*, mainly composed of various group of sugars including fucose, mannose, galactose, rhamnose, xylose in addition to sulfate with high molecular weight. Naviculan mainly inhibits the initial stages of viral replication in HSV-1, HSV-2 and influenza virus by blocking viral internalization in the host cells.[25]

The A1 and A2 SPs, found in a marine microalga, *Cochlodinium polykrikoides* are well known for inhibition of the cytotopathogenic effects of influenza virus type A and B in MDCK cells, HIV-1 in MT-4 cells and respiratory syncytial virus (RSV) A and B in Hep-2 cells.[10]

Another group of SPs, p-KG03 obtained from *Gyrodinium impudicum*, was investigated as potent inhibitor for *in vitro* tumor cell growth and encephalomyocarditis (EMCV) virus infection.[10]

Calcium spirulan (Ca-SP), isolated from *Arthrospira platensis* is a novel heteropolysaccharide composed of nine sugars including glucuronic acid, galacturonic acid, glucose, galactose, ribose, mannose, xylose, fructose and rhamnose in association with calcium and sulfate. The antiviral activity of Ca-SP are subjected to inhibition of various viruses including HSV-1, HCMV, influenza A, Coxsackie virus, HIV-1, measles, mumps and polio virus through anticoagulant activity and preventing the entry of virus into the host cell.[10]

Nostoflan (NSF), another novel SPs obtained from *Nostoc flagelliforme* is identified as effective against various enveloped viruses like HCMV, influenza A virus, HSV-1 and HSV-2. Sea algae extract or SAE isolated from a red alga, *Schizymenia pacifica* is a potent inhibitor of reverse transcriptase activity of HIV.[10]

In relation to the above studies, some SPs extracted from algae including ulvans and fucoidans could be potential antiviral agents against SARS-CoV-2. Hence, more research is needed on algal SPs including carrageenans, galactans, laminaran, naviculan, alginates, Ca-SPs, p-KG03,

nostoflan, SAE, A1 and A2 SPs for antiviral therapeutic activities against SARS-CoV-2 and COVID-19. All the scientific and pharmaceutical communities should be concerned about these algal SPs as substitute to antiviral drugs to overcome the pandemic situation of COVID-19 in these desperate times.

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