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COVID 19: A 'GLOBAL THREAT' CAUSING AN ALARMING SIGNAL AND THE ROLE OF ALGAE IN THE MANAGEMENT OF PANDEMIC

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ABSTRACT

The outbreak of SARS-CoV-2 has shattered the globe, infected more than 80 million people and at least 1.7 million people have died. Covid-19, acronym of corona virus disease 2019 has shut down the whole world and derailed the global economy. Historical pandemics have plagued humanity since antiquity. Civilization and its modernization have increased the risk of transmission of diseases along with the growth and development of varied mutant strains. Invading viruses and their transcription factors are recognized and lysed by Cytotoxic-T lymphocytes and NK (Natural Killer) cells. Innate immunity and immune response mechanism of an individual serves as a pivot in combating these infections. Algae an extremophile contains several immunomodulatory, immunostimulatory and antiviral secondary metabolites which not only strengthens the host's immune response mechanism but also inhibits activity of many viruses. These biomolecules are proven to be of paramount importance in biomedical and pharmaceutical industries and hence these natural molecules can be explored to develop drugs targeting SARS-CoV-2. The aim of this review is to promote algae as food and drug highlighting its nutraceuticals, antioxidants, antibiotic, antiviral properties and mechanism providing resistance to the host against the emerging and invading pathogens.

Keywords- Covid-19, Algae, Immunomodulatory, Antiviral Compounds

INTRODUCTION

VIRUS AS HUMAN PATHOGEN

The viruses that replicate in human host through contact transmission constitute a small part of the spectrum of different types of intracellular parasites of whose host ranges extends from vertebrates to protozoa and from plants and fungi to bacteria **[1]**. Picornaviruses, Ortervirales, and Nidovirales viruses cause a large number of human diseases **[2, 3]**. The incidences of emerging and/or re-emerging viral infections have significantly affected human health since antiquity **[4]**. Emerging pathogens are described as new etiologic agents that have recently been introduced into a population causing infectivity.

PANDEMICS OF VIRAL ORIGIN

The "Spanish flu," responsible for tens of millions of casualties in the early twentieth century, was a natural calamity, one of the most devastating in human history. The flu pandemic returned in 1957 as an "Asian flu" and then again in 1968 as a "Hong Kong flu" which killed about three million people. The flu re-emergence in 2009 as "swine flu" took 18,500 lives **[5]**.

In its epidemic course during 2002–2004, a new coronavirus, or severe acute respiratory syndrome (SARS-CoV-1), infected more than8000 people globally across 29 countries. In December 2019 SARS-CoV-2 a new strain of coronavirus emerged in Wuhan, Hubei Province; CHINA, associated with an acute respiratory disease, called coronavirus disease 19 (COVID-19), is the third documented leak of an animal coronavirus for humans in just two decades, which resulted in a pandemic (the 19 epithet refers only to the year it was reported, 2019). The Coronaviridae Study Group (CSG) of the International Virus Taxonomy Committee, classified the virus and named it as the taxa of the Coronaviridae family and evaluated the role of this human pathogen, provisionally naming 2019-nCoV, within the Coronaviridae **[6]**.

EPIDEMIOLOGY AND IMMUNOLOGY OF CORONA

Virus associated acute respiratory infections are the major cause of morbidity and mortality worldwide. Syncytial virus, Parainfluenza virus, Influenza virus, Rhinovirus and Adenovirus **[7-10]** accounts for most of the respiratory infections. Over the past few years, newly characterized viruses were also associated with respiratory infections, such as human Metapneumovirus, the emerging human Coronaviruses human Bocavirus and the new human Papilloma viruses KIPyV and WUPyV **[11, 12]**.

Based on the phylogeny, taxonomy, and setup practices, the CSG recognizes Corona virus(SARS-CoV-1)as a clone associated with the coronavirus prototype of the

severe acute human respiratory syndrome, referred to as SARS-CoV-2 **[13, 14]**.

SARS-CoV-2 uses angiotensin converting enzyme 2 (ACE2) cellular receptor for entry into the host cell through binding of its spike (S) protein followed by S protein priming using the serine protease TMPRSS2. SARS-CoV 2 contains four structural proteins viz. spike (S), nucleocapsid (N), membrane (M), and envelop (E) that may act as antigens. These antigens may induce neutralizing antibodies in the human body and increase CD4+ / CD8+ T-cell responses. ACE2 is a critical negative regulator of the renin-angiotensin system (RAS), modulating proper fluid-salt-balance and blood pressure in the human body. Its expression promotes dilation of blood vessels resulting in low blood pressure.

ACE2 is expressed in lungs, initiating primary stages of infection of COVID-19 through inhaled respiratory droplets. Multiple organs of the human host like heart, kidney and intestine, liver, testes, brain and adipose tissue contains ACE2 as a regulator for healthy cardiac function, preventing acute lung failure from infection and promoting optimal beta-cell functions of the pancreas. Therefore, if the ACE2 function is blocked by SARS-CoV-2, its regulatory activities are inhibited. The expression and importance of ACE2 in human host systems variations are the cause of vulnerability to COVID-19. Its expression is higher in men than women, which may be a potential reason why men are more likely to suffer severe complications of COVID-19 comparatively than women. Regulation of beta-cell function to maintain production level of insulin and blood pressure may be the possible cause of the higher susceptibility of diabetic and hypertensive patients to undergo severe complications from COVID-19.

Although the fatality is likely to be associated with respiratory distress, reports of meningitis, pancreatic damage, gastrointestinal disorders and cardiac dysfunction associated with COVID-19 are available. Once the virus has entered and translated inside the human host, it has to fight with the individual's immune response mechanisms. Increased levels of pro-inflammatory molecules, like interleukin-6 (IL-6), and high neutrophil to lymphocyte ratios (NLR) in infected host are also found. Lymphocyte are responsible for the production of antibodies, in respond to a specific antigen. A study related to the virus induced immune response mechanism in host cells investigated that the role of T cells, a subset of lymphocytes, were an important factor in eliminating virus infection.

SARS-CoV-2 enters nasalepithelial cells via ACE2, it blocks the triggering of certain

antiviral interferon pathways, which could be the first and front line defense mechanism of the host system. The assaulted airpassage epithelial cells produce IL-6 and other pro-inflammatory mediators instead, which activates neutrophils at the site of the infection. Type III interferon is anti-inflammatory and respond to the infective viruses. Cytotoxic T cell recognize and destroy the infected cell, further taken up by phagocytic cells to get lysed. Elevated levels of IL-6 andIL-8, in severe cases of COVID-19, suppresses the functions of cytotoxic T cells. IL-6 also inhibits the production of regulatory, T cells response. 'Cytokine storm syndrome' is a term which include cell-specific immunodeficiency, dramatic neutrophil influx, acute respiratory distress and organ failure.

Our understanding of the virus is still not exactly filtered. Mutants of COVID-19 are emerging frequently. As with all science, we need to continue the refinement and revision of our hypotheses. In the meantime, we should continue to be mindful of vulnerable populations, supporting ongoing basic and translational research working on the trail of vaccine and treatment development **(Figure 1)**.

ROLE OF ALGAE IN IMMUNOLOGY

The algae are considered as an evolutionary link on this planet. They are the Extremophiles and it is attributed to the production of various classes of Secondary metabolites. These metabolites can be used effectively against many diseases including viral infections. Carrageenan, Agar, Fucoidan, Laminaran, and Naviculan are some of such metabolites which have the high potentiality to act against the viral infections. The carbohydrates of algae are found to be effective against the replication mechanisms of viruses such as AIDS, Influenza, Coronavirus, Dengue, Adenovirus, Cytomegalic virus, human Leukemia viruses. Similarly, some proteins found in algae are known to be effective against many viruses causing Measles, Herpes, AIDS, Hepatitis, Influenza and Ebola diseases.

Algae metabolites interferes with the adsorption process of virus thus inhibit the attachment on to the cell wall of the host, preventing replication of the virus, and preventing the virus from spreading from one cell to another. In such a situation, they could be effective on Covid-19 **(Figure 2)**.

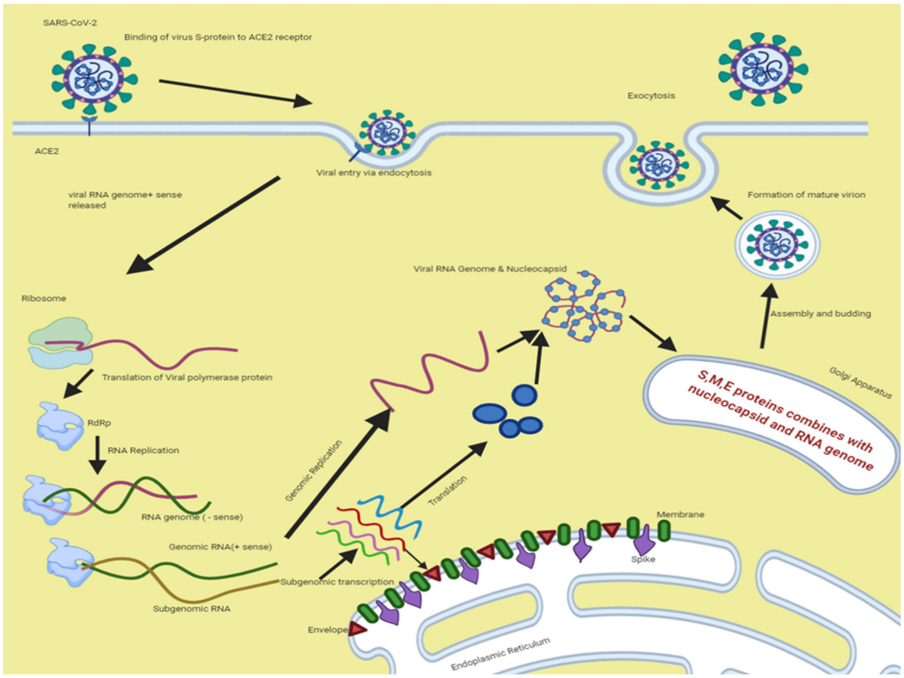

Figure 1: Mechanism of pathogenesis of Sars-CoV-2

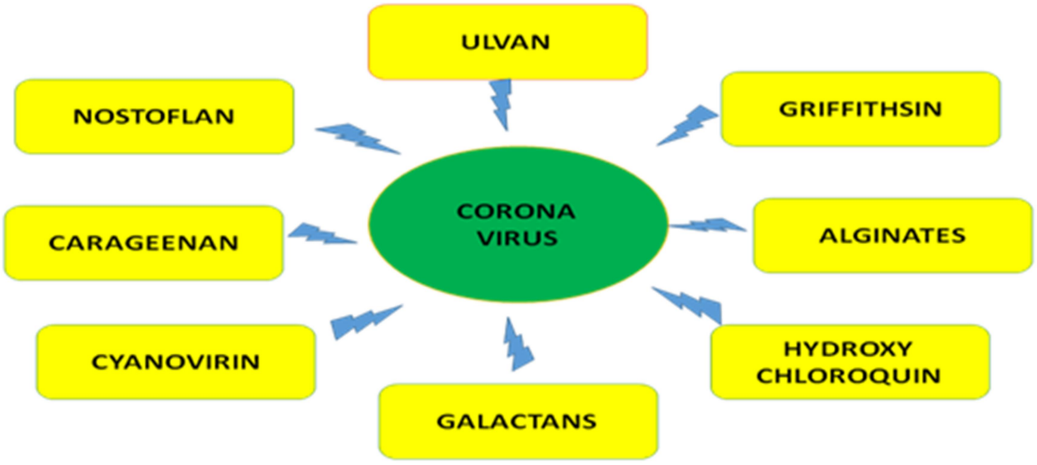

Figure 2: Algae based Antiviral compounds

Algae found in any part of the world can be grown easily controlled laboratory condition. Therefore, it is possible to yield easily the effective medicines of Covid-19 from algae. Research is now being pursued in the direction of identification of the most effective elements. The algae metabolites are proved to be effective in enhancing the Innate and Adaptive Immune responses. Algal derived bioactive compounds are well reported for their Immunostimulatory, Antimicrobial, Anti-inflammatory and Immune enhancing properties that can be potentially used as therapeutic agent for breaking the host- pathogen interaction. Cyanobacterium *Spirulina* is commercially produced for human consumption and is typically used as a health food supplement due to its high Protein content, Lipids, Vitamins, Essential amino acids, Minerals,

Photosynthetic pigments, and biologically active substances including Phycocyanin, Chlorophyll, and β-carotene.

Historically, Irish moss or carrageen; an unspecified mixture of naturally coexisting red seaweeds, *Chondrus crispus* and *Mastocarpus stellatus* has a large number of medical applications, some of which date back to 1830s.It is still widely used in Ireland to make traditional medicinal teas and anti-cough preparations to combat colds, bronchitis, and chronic coughs. It is said to be particularly useful for dislodging mucus and has antiviral properties **[15]**.

The microalgae *Arthrospira platensis*is high in amino acids and vitamins proved to be as immunity booster agents for human beings. So this alga can be recommended to use against pandemic viral infection as a preventive remedy.

Some of the algae show the antiviral properties. The first report of marine algal polysaccharides as a potential source against viral infections was elucidated **[16]**. After this, the exploration of algal components against viruses emerged exponentially. Researches and Scientists found the potential benefits of Sulfated Polysaccharides as an antiviral compound. International Journal on Emerging Technologies highlighted the potentiality of the seaweeds against the viruses **[17]**. The potential antiviral properties of the aqueous extract of marine seaweeds *Neodilsea americana* and *N. integra* were proved and patented (U.S. patent numbers 4,162,308 and 4,162,309) **[18]**. Nonomura, patented (U.S. patent number 4,522,814) the technology to use the alga *Cryptosiphonia woodii* as an antiviral agent and also well exhibited the clinical efficiency too against the Herpes simplex virus **[19]**. The use of Sulfated Polysaccharides and Carrageenan against the Retrovirus and Human Immunodeficiency virus was patented **[20]**. The Carrageenans were found to inhibit Rhinovirus from entering and replicating in the host cells. Galactan Sulphate (GS) is an external polysaccharide extracted from the marinered algae. *Agardhiella tenera* was used for extracting GS and tested against the viral infections HIV-1 and HIV-2, and it was proved to be an active antiviral agent. Ahmadi described the antiviral properties of various metabolites produced from algae against viral infections **[21]**. Carrageenan, Galactan and Seaweed extract from Red algae show potential antiviral properties against many human pathogenic viruses. Alginate, Fucan and Laminaran extracted from Brown seaweeds also confers antiviral properties. Naviculan extracted from the Diatom species *Navicula directa* has the potential antiviral activity against Herpes simplex viruses. Polysaccharides extracted from marine dinoflagellates (*Gyrodiniumim*

pudicum and *Cochlodinium polykrikoides*) showed potential antiviral activities against viral infections (Influenza A, and B viruses and parainfluenza-2). Calcium spirulan extracted from Blue-green algae, *Arthrospira platensis* is effective against HSV-1,mumps, measles, polio, influenza, Coxsackie, HIV-1. Nostaflan isolated from Nostoc *flagelliforme* is active against HSV-1, HSV-2, influenza A virus, human Cytomegalovirus. **Table 1 and Table 2** represent important algal biomolecules, species and mechanism.

Table 1: Algal derived Polysaccharide with Anti Viral Activity

S. No.	Polysaccharides	Species	Activity	References
1	Carrageenan	*Chondrus, Gigartina, Hypnea, Porphyridium* and *Eucheuma*	Inhibits binding of virus to host cell, interferes with S binding as sulfated polysaccharides bind tightly to the S-protein of SARS-CoV-2. Iota-carrageenan is reported to inhibit SARS-CoV-2 infection in Vero cell cultures.	Kwon *et al* 2020,[22] S. Bansal *et al* 2020.[23]
2	Alginates	*Laminaria hyperborea*, *Laminaria digitata*, *Laminaria japonica*, *Ascophyllum nodosum*, and *Macrocystis pyrifera*	Polysaccharide drug 911 inhibits the viral replication by decreasing and suppressing activity of reverse transcriptase and DNA polymerase defense. Drug 911 is found to inhibit the acute infection of MT4 cells and the chronic infection of H9 cells with HIV-1.	X.L Xin *et al* 2000 [24], X Xin *et al* 1999 [25], B Jiang *et al* 2003 [26]
3	Galactans	*Agardhiella tenera, Callophyllis variegate,Schizymeniabinderi, Cryptonemia crenulata*	Extracellular polysaccharides with linear chains of galactoses produced by *A. tenera*exhibit antiviral potency against enveloped viruses including herpes simplex virus-1 and -2 (HSV-1 and HSV-2), DENV, HIV-1 and HIV-2, and hepatitis A virus (Hep A) by blocking the replication of virus and the syncytium formation between uninfected and infected cells. A D, L-galactan hybrid C2S-3 from C. crenulata inhibits the multiplication of DENV-2 in Vero cell lines.	M. Witvrouw *et al* 1994 [27] , L. B Talarico *et al* 2007 [28]
4	Fucans	*Dictyota mertensii*, *Lobophora variegata*, *Fucus vesiculosus*, *Spatoglossum schroederi* , *Cladosiphono kamuranus, Sargassum piluliferum, Adenocytis utricularis, Undaria pinnatifida, Stoechospermum marginatum and Cystoseira indica*	Sulphatedfucans have been found to block the activity of reverse transcriptase; MC26 from S. piluliferum has strong anti-influenza activity with low cytotoxity. Some fucoidans have antiviral potential against RNA and DNA viruses.HSV-1 and HSV-2, dengue virus, and cytomegalovirus.	K.C. Queiroz*et al* 2008 [29], E. Akamatsu *et al* 2003[30]
5	Nostoflan	*Nostoc flagelliforme*	This acidic polysaccharide has antiviral activity against viruses with carbohydrate cellular receptor. It inhibits human cytomegalo virus and Influenza A virus by inhibiting virus binding processes.	B.A. Whitton *et al* 2007 [31]
6	Calcium spirulan	*Spirulina platensis*	It shows promising anti viral activity HSP, HSV-1 and HIV-1	Thayashi *et al* 1996 [32]
7	Sea algae extract	*Schizymenia pacifica*	Inhibits the replication of reverse transcriptase in Rauscher murine leukemia virus and avian myeloblastosis virus.	H.Y. Nakashima *et al* 1987[33]
8	Laminarin	*Laminaria japonica, Ecklonia kurome, Eisenia bicyclis*	A bio compatible compound prevents the adsorption of HIV reverse transcriptase.	S. Muto *et al* 1992 [34]
9	Naviculan	*Navicula directa*	A sulphated polysaccharide showed inhibitory affecton cell–cell fusion between CD4-expressing and human immunodeficiency virus (HIV) gp160-expressing cells. Antiviral activity against Herpes simplex virus 1 and 2 has been reported.	J.B. Lee *et al* 2006 [35]
10	A1 and A2 polysaccharide	*Cochlodinium polykrikoides*	A1 and A2, extracellular sulphated polysaccharide inhibits the cytopathic effect of influenza virus types A, human immunodeficiency virus type 1 in MT-4 cells B in MDCK cells and respiratory syncytial virus types A and B in H Ep-2 cells.	M. Hasui *et al* 1995 [36]

Table 2: Algal derived Lectin with Anti-Viral Activity

S. No.	Lectin	Species	Activity	References
1	Griffithsin	*Griffithsia* sp	It inhibits HIV-1 by preventing mannose-binding to gp120 and improves humoral immune response to gp120. Inter-virion crosslinking and aggregation of gp120 is another mechanism of anti HIV-1 mechanism of Griffithsin. Through specific binding to S proteins griffithsin prevents infection of SARC-CoV infection.	Banerjee K *et al* 2011 [37], Lusvarghi *et al* 2016 [38], B.R. O'Keefe *et al* 2010 [39], Lee C [40]
2	*Oscillatoriaagardhii* agglutinin (OAA)	*Oscillatoria agardhii*	Inhibits HIV replication in MT-4 and syncytium formation between HIV-1-infected and uninfected T cells	Férir G *et al* 2014 [41]
3	Cyanovirin-N	*Nostoc ellipsosporum*	Shows antiviral activity against HIV, Ebola, Influenza A and B and other enveloped viruses.	Philipp E. Schilling *et al* 2020 [42]
4	KAA-2 and BCA	*Kappaphycus alvarezii*	Anti cancerous agent and inhibits influenza virus strains H1N1-2009 by binding hemagglutinin (HA) on the viral envelope.	Hung, L.D *et al* 2020 [43], E. Pickett *et al* 2018 [44]
5	Scytovirin	*Scytonema varium*	It inhibits SARS-CoV, Zaire ebolavirus,HIV and Marburg virus by binding to mannose-rich oligosaccharides on the envelope glycoprotein, blocking entry into target cells.	Besednova *et al*, N.N. ,2019 [45], Neha Sami *et al* 2020 [46]

Two faculty members of Indian Institute of Technology Indore (IIT) and one of Devi Ahilya Vishwavidyalaya (DAVV) jointly carried out the research which has been published in research journal Phytotherapy on November 18. The research team includes Dr. Kiran Bala and Prof. Hemachandra Jha from IIT Indore and Dr. Hemendra Singh Parmar from DAVV. According to these research scientists, due to frequent occurrence of mutations in coronavirus, the impact of the vaccine may be limited **[47]**. Through algae broad spectrum anti-viral drugs can be prepared which have a similar effect on the different strains of viruses. The new Coronavirus mutations are imposing threats in the prophylactic measures. In a part of that, this article deals with the use of the algae as a potential source against virus infections that could be established against not only on the current pandemic COVID -19 but can effectively be used in next future if any such viral break down occurs. Brown algae (fucoidans) could be implicated against virus s SARS-CoV-2. **[48, 49 and 50]**.

The use of immune-boosting nutraceuticals has the international potential to help to combat and control Coronavirus infections through the activation of Immune Response and alleviating the oxidative stress.

CONCLUSION

Future scope of algae as an immunomodulatory agent

In the changing environment, the threat of emergence of new zoonotic viruses is looming over mankind. As the world is fighting against Covid-19, the threat of other deadly viruses leading to disease X may come into reality. Hence, in the midst

of the vaccine trials that would lead to immunization against Corona virus, some of the alternative steps should be taken into consideration for utilizing the characteristics of various seaweeds which may provide a glimpse into potential solutions of this global health problem in the near future and possibly forearm us for any future pandemics.

Many types of nutraceuticals, which are derived from natural resources such as animals, plants and microorganisms, have been reported and are in use. Algae comprising prokaryotic cyanobacteria and other eukaryotic forms are rich bio resource of active compounds of nutraceutical and therapeutic importance. The use of cyanobacterium *Spirulina* based nutraceuticals is well explored under controlled *in-vitro* conditions and clinical studies and is commercialized.

Researches on algae based vaccines that are edible are going on **[51]**.Work is been done to make vaccines by genetically modifying algae for oral vaccines for Covid-19 **[52]**. To prevent the recurrence of such pandemics and prepare us for future threats, further research to use algae in combating viruses and improving immunity is of paramount importance.

Conflict of Interest- Author declares no conflict of interest.

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