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CAN ALGAE DEFEAT COVID-19 VIRUS?

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ABSTRACT

Coronavirus disease (COVID-19) is an infectious disease caused by a newly discovered coronavirus and mainly targets the respiratory system. The current therapy includes giving concentrated oxygen through nasal tubes, antivirals (remdesivir) and immunomodulators (tocilizumab) along with other symptomatic treatment. But the issue with these treatment options is that they are limited in stock and expensive, thus not all patients can economically afford them. Algae can prove to be an effective alternative as it is cheap and easy to grown in laboratories. It contains chemo-diverse compounds that have multiple therapeutic properties including anti-viral, anti-inflammatory, anti-oxidant and immune booster properties. Algae can be genetically modified to produce spike proteins that can be utilized in serological antibody testing for SARS-CoV-2 virus and for manufacturing vaccine antigen against COVID-19. Certain specific blue-green algae and red algae contain various compounds that have immunomodulatory property, boost the immune system and provide various vitamins and minerals to the body. Extracts from these algae can be used as supplements that can help prevent COVID-19 infection or at least reduce the severity of the symptoms.

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INTRODUCTION

Coronavirus disease (COVID-19) is an infectious disease caused by a newly discovered coronavirus and mainly targets the respiratory system.^[1] COVID-19 emerged from the city of Wuhan, Hubei Province, China in December of 2019 and has spread rapidly to 72 countries to date.^[2] On 30. January 2020, the WHO Emergency Committee announced a global health emergency pertaining to the multiplying cases reported in China and various other locations throughout the world.^[3] On 11 February 2020, International Committee on Taxonomy of Viruses (ICTV) announced the name “severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)” for the newly discovered virus.^[4] COVID-19 can be transferred from person to person by direct or indirect contact with mucous membranes in the eyes, mouth or nose of an infected patient. It can also be transmitted through aerosols of respiratory droplets and infected sputum of the patient.^[2] The estimated incubation period of SARS-CoV-2 is found to be 3–7 days (range, 2–14 days).^[5] The rampant growth of affected individuals led the World Health Organization (WHO) to declare a global pandemic on 11 March 2020.^[6]

At the onset of the disease, the main symptoms of COVID-19 are fatigue, fever, dry cough, myalgia and dyspnoea, along with less common symptoms like nasal congestion, headache, runny nose, sore throat, vomiting and diarrhoea^[2,7]. Patients with severe condition generally experience dyspnoea and/or hypoxemia after 1 week of onset, followed by septic shock, ARDS, difficult-to-cure metabolic acidosis, and coagulation dysfunction that may develop rapidly^[8]. In some cases, it is observed that severe and critical patients only experience a low fever, or even no obvious fever, and similarly mild patients show only low fever, mild fatigue and no pneumonia. Though it should be noted that such asymptomatic or mild cases can also spread SARS-CoV-2 to other individuals.^[2]

The diagnostic kits and vaccines available in the market for COVID-19 are expensive and the main purpose of the review on Algae based vaccines and diagnostic kits is to draw people’s attention towards research on this topic.

DIAGNOSTIC KITS:

To detect and identify the exponentially developing COVID-19 cases, countries have developed various testing methods that are dependent on testing capacity, public health resources, and the extent of spread of virus in the community^[9]. The Centres for Disease Control and Prevention (CDC) has given priority for testing of these 3 groups:

- a) Hospitalized patients with manifestations similar to COVID-19
- b) Other symptomatic people at risk for poor outcomes
- c) People who had close contact with someone who has suspected or confirmed COVID-19 within 14 days of symptom onset or has a history of travel in an affected area^[9].

The diagnostic test kits which are available in market and are approved by ICMR (Indian Council of Medical Research) are:

- **Molecular test: RT-PCR Kits**

Reverse transcription PCR (RT-PCR) has proved to be a sensitive and powerful procedure for analysing RNA^[10]. Its enhanced specificity is especially helpful for immunological research, which often requires analysis of proteins derived from different spliced variants of the original transcript^[11]. This test is used for the qualitative detection of nucleic acid from SARS-CoV-2 in upper and lower respiratory specimens of individuals suspected of being infected with COVID-19^[12,13].

- **Rapid Antigen test**

This test helps to identify a person currently infected with SARS-CoV-2 virus in a short period of time. The antigen disappears after the infection has been resolved^[14]. If the sample is positive for coronavirus, coloured lines will develop on the paper strip in 15-20 minutes. Though, this test is not as accurate as RT-PCR^[15].

- **Serological test: Rapid Antibody Test; ELISA and CLIA Kits**

Antibody tests help to detect the antibodies produced by the immune system of the COVID-19 infected patients to fight against the SARS-CoV-2 virus. These antibodies take several days or weeks to be produced after the coronavirus infection and may remain in the blood of the patient for several weeks after recovery hence why this test, inspite of being accurate and highly sensitive, cannot be utilised for diagnosis of COVID-19^[16,17].

WHAT ARE ALGAE AND ITS BASIC USE

Algae is defined as a large and extensively diverse group of eukaryotic and photosynthetic organisms. All the organism that are part of this group do not necessarily share a common ancestor and thus are polyphyletic^[18,19].

Algae are known to exist in different types of waterbodies including seas, oceans, rivers, lakes, ponds and even frozen snow^[20]. Algae can also grow on land and at some unexpected places like tree trunks, animal fur, hot springs and desert crusts^[21]. They are usually green but some algae contain certain pigments that impart different colour to their appearance. For example, algae containing carotenoid pigment appear to be red in colour, providing a red hue to the surface that they grow on (commonly seen on snow)^[22].

MORPHOLOGICAL FEATURES OF ALGAE: -

- They can perform photosynthesis because they contain chlorophyll^[20].
- They can be either unicellular or multicellular.
- They are eukaryotic but don’t possess a well-defined structure (root, stem, leaves not present)
- They require moisture and hence present near waterbodies.
- They can reproduce both asexually (spore formation) and sexually.
- They usually grow independently but can occasionally be found in a symbiosis with another organism.

TYPES OF ALGAE

- Euglenophyta (Euglenoids)
- Chrysophyta (Golden-brown algae and Diatoms)
- Pyrrophyta (Fire algae)
- Chlorophyta (Green algae)
- Rhodophyta (Red algae)
- Paeophyta (Brown algae)
- Xanthophyta (Yellow-green algae) ^[23]

USES OF ALGAE: -

- Marine algae play a significant role in the ecological cycle.
- Different species of marine algae can either be used as food or can be processed to extract chemicals utilized in industrial, cosmetic, food, dairy and pharmaceutical products ^[24].
- Biofuels like Biodiesel, Bioethanol, biobutanol and Hydrogen gas can be produced by cultivating and processing algae ^[24, 25].
- In Asia, naturally growing seaweed is an extensively consumed food product ^[24,26].
- Algae contain carbohydrate, protein enzymes, fiber, vitamins (A, B1, B2, B6, niacin and C), and minerals (iodine, potassium, iron, magnesium and calcium) which can be extracted to make supplements ^[24, 27].
- Algae are marketed as “functional foods” or “nutraceuticals” which represents foods containing bioactive compounds, or phytochemicals that act as immune boosters and can be used for other therapeutic purposes including (e.g., anti-inflammatories, disease prevention) ^[28,29].
- Algae has therapeutics properties like antiviral, antioxidant, anticancer and thus can be used for production of certain medicines ^[24, 30, 31].

ALGAE IN DIAGNOSIS

The tests used for the detection of SARS-CoV-2 and diagnosis of COVID-19 can be divided into two major categories: -

- Test for detection of viral RNA antigen through molecular testing of the specimen from the upper respiratory tract.
- Test for detection of anti-SARS-CoV-2 antibodies/immunoglobulins through serological testing ^[32].

Serological test kits can be produced with the assistance of the derivatives of microalgae. They are especially useful for the test kits that follow the immunoassay procedure. Immunoassay testing is based on the principle of binding of an antibody or an antigen to a specific antibody of interest ^[33], for which microalgae derivatives can be incorporated owing to its binding capacity. Different methods are being researched where microalgae can be utilized to extract proteins (i.e., viral protein antigens) which are used for the detection of the anti-SARS-CoV-2 antibodies formed in the patients infected by COVID-19 ^[34, 35].

Algae can be cultivated rapidly and efficiently in a laboratory through photosynthetic or heterotrophic method. It can be genetically modified so that they produce a specific recombinant protein and have proven to be capable of folding complicated eukaryotic proteins ^[34].

Large-scale production of serological tests is restricted due to the limited quantity of the viral protein produced using a cost-effective method. The tests being currently used are produced from chemicals extracted from insects or mammalian cells which is an expensive and complicated procedure. Algae on the other hand can be efficiently modified to produce the required viral protein and are inexpensive to grow. Microalgae is especially used for this purpose as it can be modified easily through genetic engineering such that it produces the proteins that mimic the ones produced by humans ^[36].

Researchers at Canada's Western University and Suncor company have conducted an experiment proving that algae are cheap to grow and can easily produce the required viral protein ^[36].

As the antibodies develop after a few days of SARS-CoV-2 infection, this assay method cannot be used for the diagnosis of acute infection. But as this method is one of the optimum indicators of prior immune response to the COVID-19 antigen and thus can be used to determine if an individual is immune to COVID-19 or not ^[37].

Apart from the antibody determination testing, the recombinant spike protein can also be used in the production of the vaccine antigen. Nearly all the vaccines available currently incorporate the SARS-CoV-2 spike protein in their formulation. The immune response to the vaccines given to the global population also needs to be monitored to gauge the vaccine efficacy and the need for booster dose as the response starts waning over time ^[37].

To increase the availability of economical and efficient antibody tests and vaccines throughout all the countries of the world, it is essential that the viral protein can be produced on an excessively large scale within affordable expense which can be achieved using microalgae ^[37].

Amid the COVID-19 crisis, the global market for Algae estimated at US\$782.9 Million in the year 2020, is projected to reach a revised size of US\$1.2 Billion by 2027, growing at a CAGR of 6.2% over the analysis period 2020-2027. Open Pond Cultivation, one of the segments analysed in the report, is projected to record a 6.2% CAGR and reach US\$980.2 Million by the end of the analysis period. After an early analysis of the business implications of the pandemic and its induced economic crisis, growth in the Raceway Pond Cultivation segment is readjusted to a revised 5.6% CAGR for the next 7-year period ^[38].

ALGAE IN TREATMENT

The formulation of vaccines consists of weakened or inactive parts of a specific antigen that stimulates the immune system to react against it^[39, 40]. Recently, in some vaccines instead of the actual antigen, blueprints that produce the antigen are present that help to stimulate a stronger immune response over a longer period of time and eliminate the need of a booster dose.^[41] In the case of both, antigen and blueprint vaccines, the weakened antigen doesn't manifest the disease but instead triggers the immune system of the injected person to respond against the antigen in the similar way as it would fight against the actual infection. Currently, the three major authorized and approved COVID-19 vaccines that are available or are undergoing Phase 3 clinical trial include: -^[42]

- mRNA vaccines: - this is a blue print type of vaccine that contains certain materials that help our cells to generate a harmless protein that is similar to that present in the SARS-CoV-2 virus. Our bodies perceive this protein as a harmful foreign substance and fights against it^[42, 43]. Our immune system then produces T-lymphocytes and B-lymphocytes that memorize the method to fight this foreign substance if the body is ever infected by COVID-19 in the future.^[44]
- Protein subunit vaccines: - this vaccine consists of certain harmless parts (proteins) of the SARS-CoV-2 virus instead of the whole microorganism. When injected into the body, the immune system is activated to fight against the foreign protein. T-lymphocytes and antibodies are produced by the body that will remember how to protect the body against the virus if the person is infected by COVID-19 in the future^[42, 45].
- Vector Vaccines: - in this type of vaccine, a modified virus (vector) that is different from the virus causing COVID-19 is injected in the human body. This virus instructs our cells to produce a spike protein that is present on the surface of the SARS-CoV-2 virus. The immune system fights against this foreign protein and produces T-lymphocytes and B-lymphocytes that remember how to fight this virus if the body is ever infected by COVID-19 in the future.^[46]

Various companies like Bharat Biotech, Serum Institute of India, AstraZeneca, Pfizer-BioNTech, ModernaTX, Johnson & Johnson's Janssen (J&J/Janssen), etc have been able to successfully produce and test m-RNA vaccines.

ALGAE IN VACCINE

Third-generation plant-based vaccines can be developed for prevention of COVID-19 by either expressing antigenic spike protein of SARS-CoV-2 that would trigger active immunity or expressing antibody to fight the infection through passive immunity.^[47, 48]

Plant-based vaccine involves cloning the vaccine candidate into a plant expression system, which is capable of promoting the expression of the candidate gene in the plant, which then produces the antigenic or protective protein^[49] as shown in Fig (1). This approach enables vaccine production by using plants as bioreactors and growing them for multiple generations, thereby ensuring continuous manufacturing and availability^[50].

Algae is used to produce the recombinant spike protein for serological testing, but this protein can also be utilized as a vaccine antigen used to produce the SARS-CoV-2 vaccines^[35]. One of the research groups in Italy experimented using single-celled algae *C. reinhardtii* and proved that it can be used to produce the spike protein of SARS-CoV-2 which is now used for serological testing and can potentially be used for vaccine antigen too.^[35]

One of the advantages of employing algae for developing vaccine is that the algae can be lyophilized and encapsulated to make an oral vaccine preparation in which the algae cell wall can protect the spike protein antigen from the gastric fluids and ensure that it moves on to the intestinal immune system^[51, 52].

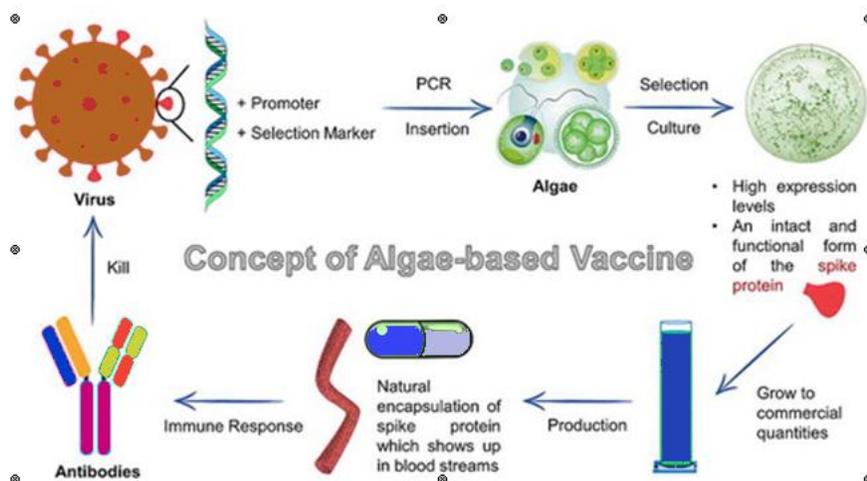


Figure 1: Concept of Algae based Vaccine.

ALGAE AS IMMUNE BOOSTERS

Apart from antibody tests and vaccines, algae and algae-derived compounds can be used for other purposes in the fight against COVID-19. Algae can be an excellent source for developing antiviral drugs as it shows chemo-diversity and contains compounds having virus suppressing properties and immune booster ability.^[31]

Spirulina platensis (blue green algae):

Spirulina extract has shown various in vitro therapeutic properties including antiviral, anti-HIV, anti-inflammatory, anti-microbial, antioxidant and immunomodulatory properties^[53,54,55]. Hence it has multiple medical utility and is considered as an immune-booster and immune system potentiator. It is manufactured commercially for human consumption and usually used to produce health dietary supplements because it contains high levels of proteins, lipids, vitamins, essential amino acids, minerals, photosynthetic pigments, and biologically active substances (phycocyanin, chlorophyll, and β -carotene)^[56]. Spirulina increases the body's immunity by various mechanism like enhancing Natural Killer cell function, macrophage phagocytic activity, activation of CD⁴⁺ T-cells and production of IFN- γ which helps in preventing viral infections^[56-58].

Research has shown that C phycocyanin, present in Spirulina extract, is a pigment-binding protein that can work as immunomodulator and suppress the cytokine storm in COVID-19 patients.^[59] It can be formulated into dietary supplement that can be used to prevent severe complications of COVID-19 like cytokine storms, acute respiratory distress syndrome and acute lung injury.^[60] This can especially be helpful in high-risk population including elderly people and people with other severe medical conditions^[61]. Arthrospira platensis is another blue green algae that can potentially act against encapsulated RNA virus and thus might be useful in fighting against corona virus.^[53]

Porphyridium algae (red algae):

This algae is used to derive sulphated polysaccharides (SP) which can be used in the production of antiviral drugs and can be incorporated in the sanitary products like tissue paper, protective face masks, gloves, cotton swabs, etc.^[62] One of the sulphated polysaccharide compound called Carrageenan has an antiviral property and can be used as a part of COVID-19 therapy. In a research study on coronavirus infected patients, half the patients were given nasal spray containing carrageenan thrice daily for seven days and the other half were given placebos during the early period of infection. It was observed that nasal carrageenan spray significantly reduced the viral propagation as compared to placebos.^[63] Similar to this a molecule named Q-griffithsin made out of red algae Griffithsia, and Nicotiana benthamiana shows anti-viral properties act as potent preventor against HIV and now tests are being carried to check its activity against COVID-19^[64]. Apart from SPs, exopolysaccharides extracted from Porphyridium can inhibit the binding of the SARS-CoV-2 virus to the host cell.^[65]

CONCLUSION

Now is the time when COVID-19 virus is spreading with a tremendous speed and is becoming deadly. Proper treatment regimen has been guided by WHO and is being updated whenever better alternatives are being researched on. In most of the countries, vaccines are being available against COVID-19 virus but these vaccines may cause financial crisis to country's Health Care Department at a long run. Algae has proved to possess anti-viral properties and can be modified according to the virus by promoting the expression of the candidate gene in algae and produce the spike protein of SARS-CoV-2. By doing so vaccines manufacturing and availability would increase as algae are easy to cultivate and cost-effective. Algae can also be useful as immunity boosters as some algae like Arthrospira platensis, Spirulina platensis, Porphyridium and many more already have inherent anti-viral properties. While not just in treatment, Algae can also be used in antibody detection in patients who have either fought against COVID-19 virus or have been vaccinated and possessing antibodies against COVID-19 virus.

More researches should be done on Algae against SARS-CoV-2 and should be used as an effective tool in Diagnosis and treatment of COVID-19.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest

ABBREVIATIONS

<i>SARS-CoV-2</i>	: Severe Acute Respiratory Syndrome Corona Virus 2,
<i>WHO</i>	: World Health Organisation,
<i>ARDS</i>	: Acute Respiratory Distress Syndrome,
<i>ICTV</i>	: International Committee on Taxonomy of Viruses,
<i>CDC</i>	: Centres for Disease Control and Prevention,
<i>ICMR</i>	: Indian Council of Medical Research,
<i>HIV</i>	: Human immunodeficiency virus,
<i>CD⁴⁺ T-cells</i>	: cluster of differentiation 4 T-cells,
<i>IFN-γ</i>	: Interferon gamma,
<i>SP</i>	: Sulphated polysaccharides

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