

Antiviral and Immuno Modulating Role of Super Food Spirulina and Covid-19

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ABSTRACT

Over the centuries, infectious diseases caused by viruses have seriously threatened human health globally. Currently, COVID-19 - the causative pathogen of Coronavirus Disease, has rapidly spread across China and around the world, causing an outbreak of acute infectious pneumonia. So far no specific anti-virus drugs or vaccines are available for the treatment of this sudden and lethal disease, there is an urgent need to find an alternative solution to prevent and control the replication and spread of the virus. Spirulina is a microscopic edible blue-green vegetable algae and it is considered as one of the richest sources of protein, all amino acids, organic vitamins and Bio-chelated minerals required for human body. Besides nutrition, it is loaded with unique phytonutrients like antioxidant phycocyanin, polysaccharides and sulfolipids that prevent inflammation, enhance the immune system, possibly reducing risks of infection and cancer. It is indicated as a safe food supplement, and the World Health Organization has supported it as a health nutrient.

Here we have summarized the available information concerning the immune boosting and antiviral activity of spirulina based on clinical trial using PubMed and Web of Science. The results of the searching greatly support that Spirulina presents both immune boosting and antiviral effects. Calcium Spirulan (Ca-SP) - a natural sulfated polysaccharide and Cyanovirin-N (CV-N) - Carbohydrate-binding agent (CBAs) isolated from spirulina are potent antiviral agents. Many clinical and Pre-clinical research reported that both exhibited antiviral activity against many viruses such as hepatitis, HIV, influenza, herpes virus Herpes simplex virus type 1, human cytomegalovirus, measles virus and mumps virus. Based on this review, spirulina could be considered as therapeutics antiviral agent for coronavirus.

KEYWORDS: *Spirulina plantensis, Immune Booster, Anti-inflammatory, Antioxidant, Antiviral*

INTRODUCTION

Viral infections remain a major worldwide cause of morbidity and mortality. Among the most aggressive viral infections are Ebola, AIDS (acquired immunodeficiency syndrome), influenza, and SARS-CoV 19 (severe acute respiratory syndrome). Viral respiratory diseases such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) always pose a severe threat to people. First identified in late December 2019, a novel coronavirus (2019-nCoV; SARS-CoV-2) has affected many provinces in China and multiple countries worldwide. The viral outbreak has aroused panic and a public-health emergency around the world, and the number of infections continues to rise. Coronaviruses (CoVs) are relatively large viruses containing a single-stranded positive-sense RNA genome encapsulated within a membrane envelope. The viral membrane is studded with glycoprotein spikes that give coronaviruses their crown-like appearance. On February 11, 2020, the World Health Organization (WHO) announced the disease caused by this novel virus as coronavirus disease-2019 (COVID-19). The most common symptoms of patients include fever (98.6%), fatigue (69.6%), dry cough, and diarrhea [1]. Patients with mild illness may present with

symptoms of an upper respiratory tract viral infection. These include dry cough, mild fever, nasal congestion, sore throat, headache, muscle pain, and malaise. Patients with severe disease present with severe pneumonia, acute respiratory distress syndrome (ARDS), sepsis, or septic shock [2].

Micronutrient deficiencies develop for a variety of reasons, whether geographic, socioeconomic, nutritional, or as a result of disease pathologies such as chronic viral infection. As micro and macro nutrients are essential for a strong immune response, deficiencies can significantly dampen both the innate and the adaptive arms of antiviral immunity. Besides nutritional deficiency, oxidative stress and inflammation are strongly associated with viral infection. A recent research 2020 by Livan Delgado-Roche, a and Fernando Mestab from Mexico reported the possible link among oxidative stress, inflammation and the pathogenesis, severity and mortality risk in patients affected by SARS-CoV infection [3]. Hence there is a need for antiviral agents along with micronutrients which is rich in immunity booster, antioxidant and anti-inflammatory activity. Spirulina is rich in micro and macro nutrients we require and packed with

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potent antioxidant, anti-inflammatory, antiviral agents which act as a supportive therapeutic approach in treatment of viral infection.

Spirulina has become popularly known as a “super food” or “food for the future” due to the great diversity and concentration of nutrients it contains. It is the most nutritious, concentrated whole food source found in nature. Spirulina is marketed throughout the world as a food supplement or as an active ingredient in functional foods and beverages. It has attained considerable acceptance for the health benefits it bestows on consumers in Europe, North America, parts of Asia and Oceania. Spirulina’s concentrated nutrition makes it an ideal food supplement for people of all ages and lifestyles.

Spirulina is scientifically named *Spirulina plantensis* which is believed to be the first form of plant life on earth (nearly 3.5 billion years old). It is a spiral shaped blue green algae, a 100 % natural fresh water micro plant. It is regarded as “future food” because it has a blend of nutrients. It is also grown in artificial ponds; utilize sunlight and inorganic nutrients to produce high quality food. Spirulina has a long history of safe usage. The Aztecs consumed spirulina in Mexico over five centuries ago. For the past 20 years, millions of people around the world have used spirulina as a food supplement to their diets [4].

It was reported that *Spirulina plantensis* was harvested from the Lake Texcoco, dried and sold for human consumption in a Tenochtitlán market.2 (Sánchez et al., 2003). It is still being used as food by the Kanembu tribe in the Lake Chad area of the Republic of Chad where it is sold as dried bread called “dihe” [5].

Spirulina –Approved by both FDA and WHO as healthy food.

Spirulina became famous after it was used by NASA as a dietary supplement for astronauts. The safety of Spirulina has been well established. NASA found it to be an excellent, compact space food for astronauts (1kg. of Spirulina is equivalent to 1000 kgs. of assorted vegetables) [6].

Spirulina has been approved as “safe food” with no toxicological effects and has received GRAS (Generally

Recognized as Safe) certification with a daily consumption of 5-10 grams [7].

Spirulina is an ideal food and dietary supplement for the 21st century by the Food and Agriculture Organization (FAO) of the United Nations [8].

Spirulina – Source of complete Protein and Micronutrients

Nutritional analysis of Spirulina indicates that it is an excellent source of some macro and Micronutrients. (Table-1) It has the highest protein content among the natural foods (65%) : far more than animals and fish flesh (15-25 %) soya bean (35%), whole milk (3%), dried milk (35%) eggs (121%) and grains (8-14%) or peanuts (25%). Protein contents of Spirulina show very high digestibility (83-90% as compared to 95.1% for pure casein) due to lack of cellulose walls.

Source of Natural Vitamins

Vitamins and minerals are the essential components of our diet. Vitamins in the natural foods, such as vegetables and spirulina are chelated with natural components of food, like protein, carbohydrates and lipids. The human body recognizes the entire complex as food and completely assimilates the same.

Spirulina is a rich source of natural bio-chelated vitamins, containing all B-complex vitamins - B1, Vitamin B2, Vitamin B3, and Vitamin B6 and beta carotene. The beta-carotene content in spirulina is several times higher than that of carrots. It also contains vitamin E, folic acid, biotin, inositol and pantothenic acid.

Source of Bio-chelated minerals

Spirulina also contains good amount of bio-chelated calcium, magnesium, manganese, potassium, copper, zinc and selenium. It is a good source of bio chelated iron. It is believed that the natural pigment phycocyanin found in spirulina forms a soluble complex with iron and other minerals making them easily absorbable and resulting in a higher bioavailability studies show that iron from spirulina is 60% better absorbed than ferrous sulphate.

TABLE: 1

COMPOSITION		VITAMINS mg/100g	
Protein	60-65%	Vitamin B1 (Thiamine)	2.5-5.5
Carbohydrates	9-16%	Vitamin B2 (Riboflavin)	4.0-6.5
Fats	5-6%	Vitamin B3 (Niacin)	4.0-7.5
Minerals	5-8%	Vitamin B6 (Pyridoxine)	2.0-3.5
Fiber	8-10%	Vitamin B9 (Folic acid)	0.05-0.25
ESSENTIAL AMINO ACIDS g/100g		Vitamin B12 (Cyanocobalamin)	0.07-0.20
		Vitamin E	10.0-18.0
		Vitamin K	1.5-2.0
		MINERALS mg/100g	
Isoleucine	3.0-4.0	Iron	60-75
Leucine	4.0-5.5	Calcium	400-550
Lysine	3.0-5.5	Magnesium	400-650
Methionine	2.0-6.0	Zinc	2.0-4.0
Phenylalanine	2.5-4.0	Copper	1.0-2.0
Threonine	1.5-4.0	Sodium	500-700
Tryptophan	1.0-2.0	Potassium	1300-1500
Valine	1.5-5.0	Phosphorus	800-1000
ANTIOXIDANT PIGMENTS mg/100g		Manganese	2.0-4.0
		Chromium	0.2-0.3
		ESSENTIAL FATTY ACIDS g/100g	
Total Carotenoids	400-500	Palmitic acid	1.0-2.0
Carotenes	170-260	Linoleic acid	0.5-0.9
Chlorophyll	1100-1500	GLA	1.0-1.5
Phycocyanin	11000-15000		

Spirulina and Essential fatty acids

Humans require a dietary source of polyunsaturated fatty acids. Spirulina has only 4 to 7% lipids. It has a high content of GLA, 1-1.5% of the dry weight, and is the only source of GLA apart from mother's milk and the oil of evening primrose. It has potent anti-inflammatory activity.

Spirulina and Antioxidant Phyto pigments

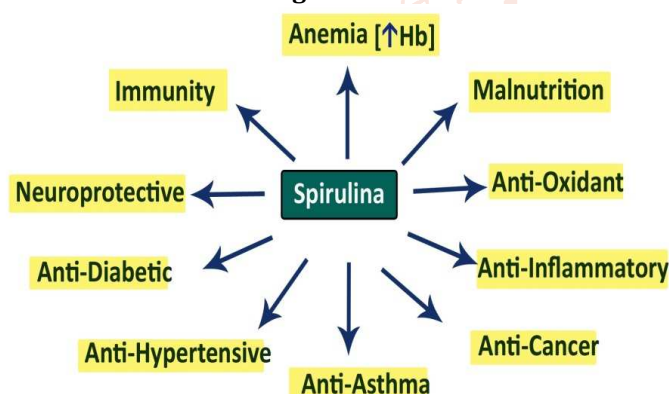
Spirulina has several important natural pigments of which are important to the human health. Carotenoids make up to 0.37% of spirulina biomass. Spirulina is 1.1% of chlorophyll level than any other plants. Chlorophyll is referred to as green blood, because it is similar to the haemoglobin molecule in human blood.

Phycocyanin comprises up to 16% of the total dry weight of the spirulina bio-mass. C-Phycocyanin molecule has an antioxidant activity, which regulates immunity and protects the organism against oxidative stress.

THERAPEUTIC ROLE OF SPIRULINA

Spirulina, popularly known as super food, which is to promote physical health, improve defense mechanisms of the body and enhance longevity. Clinical trials have showed that spirulina has antioxidant[9], anti-inflammatory[10], immuno modulating[11], anticancer[12], anti-diabetic[13], hypolipidemic activity[14], hepato protective[15], anti-obesity[16], antihypertensive[16], property and anti-allergic[17].

Figure: 1 Therapeutic Role of Spirulina on Children Health and Age Related Diseases



SPIRULINA ON ANEMIA AND MALNUTRITION

Spirulina is proposed that it can sustainably contribute to alleviating malnutrition because it is rich in various nutrients, is easy to produce, and can be added to many traditional foods [18].

Several clinical research Spirulina has been shown to be effective in treating anemia in infant, children, pregnant women [19, 20, and 21], malnutrition in adults [22], and growth faltering in children who are malnourished [23]. Apart from contributing the required iron, Spirulina also supplies folic acid and vitamin 12 – needed by anemic persons – making it a wholesome nutritional support. Morbidity from infectious diseases increases in iron-deficient populations. U. Mani et al [24] reported that supplementation of 5 gram spirulina to 20 anemic girl improved blood hemoglobin levels. Another clinical research from the University of California at Davis, Davis [25] reported that spirulina improves anemia status and immune function, particularly in senior citizens. Spirulina contains

various nutrients such as protein, beta-carotene, iron and vitamin B, which are usually deficient in undernourished populations[26]

SPIRULINA AND ANTIOXIDANT

Respiratory viral infections are, in general, associated with cytokine production, inflammation, cell death, and other pathophysiological processes, which could be link with a redox imbalance or oxidative stress. Oxidative stress generally occurs due to an imbalance between free radical, i.e., pro-oxidant content (hydrogen peroxide, superoxide, hydroxyl radical, alkoxyl and peroxy radicals) and anti-oxidant (both enzymatic and non-enzymatic) response system of body. This pro-oxidant/anti-oxidant balance is necessary for proper body functioning. Spirulina is packed with potent antioxidant and anti-inflammatory agents notably phycocyanin and β -carotene and vitamin E which act as a supportive therapeutic approach in treatment of viral infection. Phycocyanin has the ability to scavenge free radicals, including alkoxyl, hydroxyl and peroxy radicals [9,10]. It eases the inflammation caused during viral attack by lowering oxidative stress and eliminating harmful free radicals from the body. Kalafati et al 2020[27] reported that spirulina supplementation reduces oxidative stress and improve antioxidant level in human. The active compound phycocyanin, gamma linoleic acid, vitamin E and beta carotene found in spirulina are attributed to the antioxidant and anti-inflammatory.

SPIRULINA IMMUNITY

Spirulina is an effective immune modulator. It strengthens both innate and specific immunity. Spirulina as a dietary supplement had been found to exhibit many immune-stimulating and antiviral activities. It had been found to activate macrophages, NK cells, T cells, B cells, and to stimulate the production of Interferon gamma (IFN- γ) and other cytokines.

Spirulina accelerates production of the humoral system (antibodies and cytokines), allowing it to better protect against invading germs. The cellular immune system includes T-cells, Macrophages, B-cells and the anti-cancer Natural Killer cells. These cells circulate in the blood and are especially rich in body organs like the liver, spleen, thymus, lymph nodes, adenoids, tonsils and bone marrow. Spirulina up-regulates these key cells and organs, improving their ability to function in spite of stresses from environmental toxins and infectious agents

A clinical study from Osaka Medical Center for Cancer and Cardiovascular Diseases, Japan concluded that Administration of Spirulina to volunteers (age of 40 -65) potentiate the immune system leading to suppression of cancer development and viral infection. The researcher found that subjects given the Spirulina extract had higher levels of natural killer cells interferon gamma and more potent production of interleukin-12p40. The bioactive antioxidant compound phycocyanin in spirulina is attributed the immune modulatory activity [28].

IMMULINA is a high-molecular-weight polysaccharide extract from spirulina plantensis. Denmark researchers found that supplementation of immulina enhanced the blood immune markers, tumor necrosis factor alpha, interferon gamma, and interleukin-6 in healthy volunteers when tested at both 8 and 14 days of continuous consumption. This

finding also indicates an age dependent temporary temporary enhancement of adaptive immune responses [29].

ANTIVIRAL ACTIVITY

Natural substances isolated from *Spirulina platensis* had been found to be potent inhibitors against several enveloped viruses by blocking viral absorption/penetration and some replication stages of progeny viruses after penetration into cells. The Antiviral and immunostimulatory properties of *S. platensis* preparations were elicited through increased mobilization of macrophages, cytokine production, antibodies generation, accumulation of NK cells, and mobilization of B and T cells [30, 31].

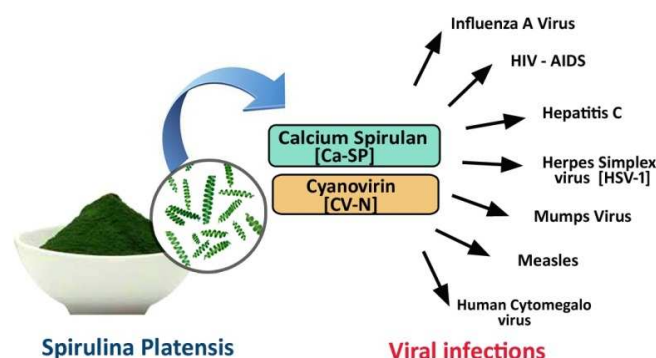
Calcium spirulan (Ca-SP) – Antiviral 624olysaccharide

Japanese scientists discovered a novel sulfated polysaccharide anti-viral compound in *Spirulina* called Calcium spirulan (Ca-SP)[31]. Recent structural analysis of Ca-SP-derived oligosaccharides using electrospray ionization mass spectrometry indicated that Ca-SP was composed of two types of disaccharide repeating units, O-rhamnosyl-acofriose and O-hexuronosyl-rhamnose (aldobiuronic acid).5) When calcium ion (Ca²⁺) of Ca-SP was exchanged with sodium ion (Na⁺), the sodium salt (Na-SP) showed comparably potent anti-HSV-1 activity to that of Ca-SP, while removal of Ca²⁺ and desulfation remarkably reduced its antiviral activity.3) Thus, metal cation binding with anionic sites such as sulfate groups was suggested to play an important role in exerting antiviral activity. Ca-SP was found to inhibit the replication of several enveloped viruses including Herpes simplex virus type 1, human cytomegalovirus, measles virus, mumps virus, influenza A virus, and HIV-1 by inhibition of viral penetration into target cells without host toxicity [31].

Cyanovirin-N (CV-N) – Antiviral Carbohydrate-binding agent (CBAs)

In addition to Calcium spirulan (Ca-SP), other antiviral agent named Cyanovirin-N (CV-N), has been isolated from *spirulina*. Cyanovirin-N (CV-N), a novel Carbohydrate-binding agent (CBAs) that inhibits HIV-I and other enveloped viral particles. It has been reported that Cyanovirin-N (CV-N) has multiple antiviral activity blocking of human immunodeficiency virus type 1 gp120 interaction with CD4 and coreceptor and inhibition of diverse enveloped viruses [32]. According to review published in Antiviral chemistry & chemotherapy by Balzarini (2007) [33] reported that the Carbohydrate-binding agent (CBAs) may be suitable antiviral agent for coronavirus infections.

Figure:2 Antiviral Activity of Calcium Spirulan [Ca-SP] and Cyanovirin [CV-N] of Spirulina On Human Viruses - Based on Clinical and Preclinical research



SPIRULINA AND HIV

Acquired immunodeficiency syndrome (AIDS) is a chronic, potentially life-threatening condition caused by the human immunodeficiency virus (HIV). By damaging your immune system, HIV interferes with your body's ability to fight infection and disease. HIV is a sexually transmitted infection (STI). Calcium Spirulan was found to be a superior antiviral to dextran sulfate indicating that Calcium Spirulan is a potent antiviral agent against both HIV-1 and HSV-1. The researchers concluded that Calcium Spirulan can be a candidate agent for an anti-HIV therapeutic drug that might overcome the disadvantages observed in many sulfated polysaccharides [31].

A major tribal group in Chad, the Kanemba, eats *Spirulina* every day, consuming between 3 to 13 grams per day. The researchers drew a correlation between the use of *Spirulina* in Chad and the low incidence of HIV/AIDS, concluding that the regular consumption of *Spirulina* could help prevent HIV infection and decrease viral loading of those infected (34). A large number of human clinical trials have been showed the therapeutic antiviral activity of *spirulina* supplementation in patients with HIV (35, 36, and 37).

SPIRULINA AND HEPATITIS

Infection with hepatitis C virus (HCV), an enveloped virus that belongs to the Flaviviridae family of positive-strand RNA viruses, is a major cause of chronic liver disease. WHO estimated that about 170 million people, (3% of the world's population), are infected with HCV and 3-4 million persons are newly infected each year. According to a pilot randomized study suggested a therapeutically feasible potential for *Spirulina platensis* in chronic HCV patients. Carbohydrate-binding agent (CBAs) present in could be considered as prime drug leads for the treatment of chronic viral infections such as HCV by preventing viral entry into target cells. CBAs may also have the potential to prevent HCV/HIV transmission. A pilot randomized, comparative clinical trial from Green Clinic and Research Centre, Egypt showed the anti-hepatitis activity of *Spirulina* supplementation [38].

HOW TO TAKE THE SUPER FOOD SPIRULINA

Researchers have proved that daily intake of 1-5 gms *Spirulina* powder can help in maintaining nutritional fitness in human body. Commercially, *Spirulina* can be found in health food stores and is sold mainly as a dietary supplement in the form of powder, tablets and health drink. As a food supplements, *Spirulina* (1 to 2 grams for children and 3 to 5 gram for adult) can be taken daily. The most popular way to enjoy it at home is to add it to your favorite fruit or vegetable juice in a blender and sprinkle on vegetable salads. It provides quick energy and nourishment between meals or in place of a meal. Taken in an empty stomach is also favorable. *Spirulina* based value added products such as candies, chewing gums, biscuits, chocolates; ice-cram and jam are available in the market worldwide.

CONCLUSION

Viral infection including Covid 19 is strongly associated with Macro and Micro nutrient deficiency, inflammation, oxidative stress along with respiratory complication. *Spirulina* is a micro alga which has an amazing potential to play a major role in Therapeutics. Cultivation of *Spirulina* is very economical. It is rich in micro and macro nutrients a human

body requires and packed with immuno modulating, antioxidant, anti-inflammatory, antiviral agents which act as a supportive therapeutic approach in treatment of viral infection. A number of clinical and preclinical researches exhibited potent antiviral activity of Spirulina against several enveloped viruses including influenza A virus, HIV-1, hepatitis C, herpes simplex virus type 1, human cytomegalovirus, measles virus, and mumps virus. Calcium spirulan (Ca-SP) and Cyanovirin-N (CV-N) are novel antiviral compound in spirulina which can be consider as an alternative therapeutic candidate for the treatment of Covid-19.

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