

## ANTIVIRAL PROPERTIES OF CYANOBACTERIUM, *SPIRULINA* *PLATENSIS*-A REVIEW

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### ABSTRACT

Virus means poison and harmful to all forms of life. Viruses are acellular and obligate intracellular parasite cause viral infection in host cell. Viral diseases are observed in all living organisms including plant, animal and human. Carcinogenic viruses and other disease causative viruses including Chickengunya virus Dengue virus, SARS-CoV, HIV, Swine flu, Influenza virus, Herpes simplex virus, Human papilloma virus, oncornaviruses such as HTLV I and HTLV II are most important viruses spread disease worldwide. Some viruses are emerging, infectious, contagious. Prevention of virus transmission is important and is possible some extent by taking some important measures like creating awareness on transmission and pathology. Viruses are spread widely by many factors like environmental factors, contaminated, water, food, infected vector, person to person and to animals.

Resistance to the drug by host and virus is becoming one of the major problem in treatment with chemical drugs. To overcome this, one of the alternative ways is identifying biological compounds in the development of antiviral drugs and they are natural products especially from plants and algae. Natural products are effective against many viruses and act as antiviral drugs. Therefore, there is a need to focus on antiviral activities of natural products identified from plants to provide safe, lowest and effective drugs to control viral diseases of human. In the present study reviewed some of the important studies on the antiviral activities of microalgae *Spirulina platensis*.

**KEYWORDS:** *Spirulina platensis*, Antiviral, Virus, Phycocyanin, Polysaccharides, Ca-SP

### INTRODUCTION

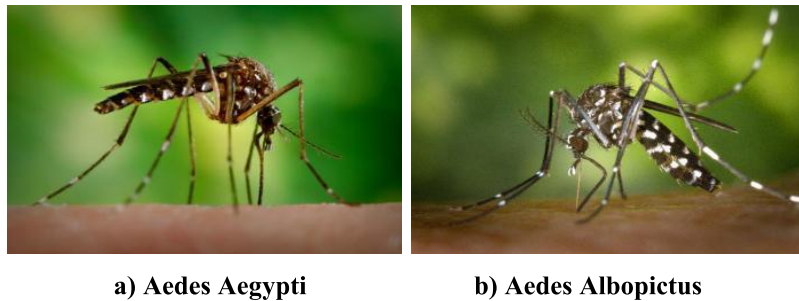
Human disease- causative infectious organisms or pathogens and way of spread from one person to person, animals, vector and environmental conditions (Table-1) was reported clearly (Louise *et al.*, 2001; Cleverland *et al.*, 2001; WHO, 1996; 2013). Early detection of emerging infectious diseases and outbreaks in human and animal is crucial to the effective surveillance (Jo Halliday *et al.*, 2013). Microbes both bacteria and virus lowers the quality of life and environment. Many emerging viruses cause disease in human and also in animals. Humans infecting virus species are nearly 219 and cause disease (Mark Whoolhouse *et al.*, 2012). International Committee on Taxonomy of Viruses (ICTV) updated the list of viruses. Many emerging disease in human and also in animals caused by pathogens, microbes including viruses spread worldwide (Figure 1).

**Table 1: Human Disease- Causative Infectious Organisms and Consisted of Pathogens and Way of Spread**

S No	Infectious Pathogens: Total No: 1415 Species	No. Sp.S	Among These		Transmitted & Pathogenic to	Pathogen Transmission	
						Way of Spread	%
1	Bacteria and rickettsia	538	zoonotic	868 (61%)	animals and humans	Person to-person	65
2	Fungi	307	Emerging	175	human	food/water/soil	22
3	Helminths	287	(Louise <i>et al.</i> , 2001) 1415 Species		humans	insect/vector	13

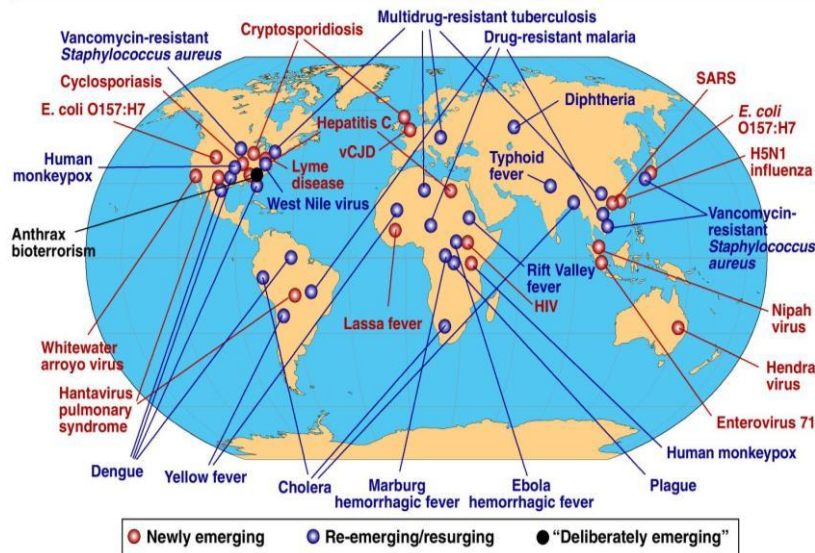
**Table 1: Contd.,**

4	Viruses and prions	217	374 Sp.s	domestic carnivores	directly from animal	<1
5	Protozoa	66	616 Sp.s	Livestock	(WHO, 1996).	
6 Ref	(Louise <i>et al.</i> , 2001).		(Cleverland <i>et al.</i> , 2001).		Food/insects environment	(WHO, 2013).



**Figure 1: Mosquito Vectors of Viruses (CDC:www.cdc.gov)**

Transmission of disease causative agents by vectors especially mosquitoes contribute more. For example, Chikungunya virus (CHIKV), Dengue virus (DENV: Kazuya *et al.*, 2013) and many other disease causative pathogens are carried by infected mosquitoes to healthy person and avoiding mosquito bites is the key to avoid chikungunya, Dengue fever and spread of many diseases.



**Figure 2: Emerging and Re-Emerging Infectious Diseases of Microbial Organisms: Examples (Clifton, & Lacy (2007)**

People with a deficiency or an excess intake of nutrients must be balanced and need to lead healthy life (Gardner and Halwell, 2000). United Nations sources says that malnutrition and lack of key vitamins and minerals leading to impairment of physical and intellectual development (D.von der Weid, 2000; UNICEF, 2012). Food production, fresh water supply, bioenergy and adaptation to climate change are an essential to meet global requirements (FAO, 2009; 2012). This may be achieved to some extent from blue green algae, including *Spirulina platensis*. The results showed that *Spirulina platensis* is a good food with therapeutic agents.

In addition to *Spirulina* and its potential health effects, such as antibacterial, antioxidant, anticancer, immunomodulation and antiviral activities, some of the other positive effects also observed against some disorders like malnutrition, diabetes, hyperlipidemia, inflammatory allergic reactions, obesity, anemia, heavy metal/chemical-induced

toxicity and radiation damage but further larger trials are essential (Falquet, 1997; Belay, 2002; Gershwin and Belay, 2008; Karkos *et al.*, 2008; Archana Kulshrestha *et al.*, 2008; Henrikson, 2009; Capelli and Cysewski, 2010; Deng and Chow, 2010; Soheili and Khosravi-Darani, 2011; Theodore G. Sotiroidis & Georgios T. Sotiroidis, 2013; Rakhi Bajpai Dixit & Suseela, 2013). Olivier Pignolet, *et al.*, (2013) Studied about antiviral properties of Cyanobacteria

*Spirulina* contains highest protein, essential amino acids, carbohydrates, essential fatty acids, minerals, vitamins, pigments. The three major bioactive components of *Spirulina*, biliprotein pigment Phycocyanin, sulfated polysaccharides and gamma linolenic acid play significant roles in improving human body functions. New experimental evidences support immunomodulation, potential health benefits and antiviral effects of *Spirulina* supplementation are mainly due to its chemical composition (Theodore G. Sotiroidis and Georgios T. Sotiroidis, 2013).

### Antiviral Properties

The discovery of potent antiviral compounds extracts from blue green algae, including *Spirulina platensis* studied by researchers at the National Cancer Institute (NCI), USA. The NCI research group screened for antiviral compounds. They screened about 600 strains of cultured cyanobacteria representing some 300 species and 10% of the cultures produced substances caused significant antiviral effect by reducing cytopathic effects induced by viral infections (Patterson *et al.*, 1989). The potent virus inhibitors against several enveloped viruses are acidic polysaccharides such as calcium spirulan (Ca-SP) from *Spirulina platensis* and also other microalgae compounds like nostoflan from *Nostoc flagelliforme*, and a fucoidan from the sporophyll of *Undaria pinnatifida* (Hayashi, 2008). The acidic polysaccharide named as nostoflan of *Nostoc flagelliforme* exhibits potent virucidal activity against herpes simplex virus-1 (Kenji, *et al.* (2005). The synergistic antiviral effects on influenza A virus was confirmed *in vitro* as well as *in vivo* by administering compounds such as fucoidan or nostoflan with oseltamivir phosphate (Hayashi, 2008). *Microcystis ichthyoblabe* contains an ichthyopeptins A and B, two cyclic depsipeptides show antiviral activity against influenza A virus (Zainuddin, *et al.*, 2007).

**Table 2: Antiviral Properties of Cyanobacterium, *Spirulina platensis*: Examples**

S. No	Name of the Virus	Mechanism Involved	Compound Name	Author & Year	System
1	HSV -1	inhibited replication of HSV -1 and prolongs survival time of infected hamster	Water extract	Hayashi <i>et al.</i> ,1993	Hamster
2	HCMV, measles virus, mumps virus, HIV-1, influenza virus, HSV -1	Inhibits replication of several enveloped viruses	Ca-SP (calcium spirulan)	Hayashi <i>et al.</i> ,1996	<i>In vitro</i>
3	Viruses like HIV-1,HSV-1	Anti viral	Ca-SP	Hayashi <i>et al.</i> ,1996	<i>In vitro</i>
4	HIV -1	<ul style="list-style-type: none"> <li>Inhibits replication of HIV-1 in human T-cell lines, PBMC</li> <li>Inactivates HIV-1 infectivity</li> </ul>	Aqueous extract	Ayehunie <i>et al.</i> , 1998	<i>In vitro</i>
5	Enterovirus 71	Delays viral RVA synthesis; activates apoptosis	allophycocyanin	Shih <i>et al.</i> , 2003	<i>In vitro</i>
6	HSV-1	Anti HSV-1	sulphoquinovosyl diacylglycerol	Chirasuwan <i>et al.</i> ,2007;2009	<i>In vitro</i>
7	EBV	antiviral	Spirulina	Kok <i>et al.</i> , 2011	<i>In vitro</i>
8	Many enveloped viruses & HCV (hepatitis C)	Activates Interferon gamma; Blocks virus absorption	Spirulina supplement	Yakoot & Salem, 2012	<i>Clinical trial</i>

Table 2: Contd.,

9	Adenovirus type 40, HIV-1, HIV-2, influenza virus, HSV -1	Antiviral	Aqueous & methanol extracts, Sulfated polysaccharides	Singh <i>et al.</i> , 2011 Sayda <i>et al.</i> , 2012	<i>In vitro</i>
10	HIV	Immunostimulant	<i>Spirulina</i> supplement	Simpore <i>et al.</i> , 2005 Theodore G. Sotiroudis & Georgios T. Sotiroudis (2013).	<i>Human</i>

The aqueous extract and methanol extract of *Arthrospira maxima* showed antimicrobial- antibacterial activity against many bacterial organisms tested (Medina Jaritz *et al.*, 2011). No inhibition was observed for poliovirus-1 subacute sclerosing panencephalitis virus (SSPE), measles virus, vesicular stomatitis virus (VSV) and rotavirus SA-11. Herpesvirus infection was inhibited by inhibiting virus adsorption and penetration to the host cell (beginning of the viral cycle). The *S. maxima* extracts prepared from methanol-water (3:1) exhibits highest antiviral activity was detected (Hernández-Corona *et al.*, 2002). The sulfated polysaccharide, calcium spirulan (Ca-SP) isolated from a hot water extract of *Spirulina platensis* displays anticancer activity. The calcium spirulan (Ca-SP) consists of sulfate, calcium, glucose, fructose, mannose, galactose, rhamnose, ribose, xylose, glucuronic acid and galacturonic acid (Hayashi *et al.*, 1996). The extracts of cyanobacteria contains sulfated polysaccharides that prevents virus-cell attachment and fusion with host cells. The inhibition of the fusion between uninfected CD4+ lymphocytes and HIV-infected cells and thus greatly enhances viral infectivity (Feldmann *et al.*, 1999; Rahul Kunwar Singh *et al.*, 2011).

The water extract of *Spirulina platensis* inhibited the Herpes simplex virus type-1 (HSV-1) replication in HeLa cells (*in vitro*). The extract is not virucidal but interferes with the virus entry into host cells (Hiyashi *et al.*, 1993). The calcium Spirulan (Ca-Sp) a sulfated polysaccharide isolated from *Spirulina platensis* inhibits many virus replications and exhibits antiviral activity against the HSV-1, influenza virus, Human cytomegalovirus (HCMV), mumps virus, measles virus and human immunodeficiency virus type 1 (HIV-1) (Hayashi *et al.*, 1996) *Spirulina* acts as an antiviral agent (Armida Zúñiga-Estrada *et al.*, 2007; Simpore *et al.*, 2005).

The *in vitro* replication of HIV-I is inhibited significantly by the aqueous extract of *Spirulina platensis* by using human T-cell lines, peripheral blood mononuclear cells (PBMC) and Langerhans, blood mono nuclear cells The aqueous extracts of *S. platensis* possess antiretroviral activity (Ayenunie *et al.*, 1998). The studies on anti-HIV activity and anti-HSV-1 activity of Ca-Sp was observed by inhibiting syncytium formation induced by HIV and HSV-1 plaque yield reduction respectively (Table 2). The Ca-SP of *S. platensis* is a potent antiviral agent against both HSV-1 and HIV-1 and Ca-SP can be a therapeutic drug (Hayashi *et al.*, 1996).

The inhibitory effects on the herpes simplex virus type 1 (HSV -1) replication by performing structural modification of calcium spirulan (Ca- SP), a sulfated polysaccharide from *Spirulina platensis* (Lee *et al.*, 2001). The study made by Gorobets *et al.*, (2002) revealed that the addition of *S. platensis* on bacteriophage T4 (bacterial virus) produced an inhibiting or stimulating effect on the reproduction of the bacteriophage in *Escherichia coli* B cells. The biological activities of algal sulphated polysaccharides was studied extensively (Witvrouw & De Clerq, 1997; Zvyagimtseva *et al.*, 2000). The purified allophycocyanin of spirulina platensis exhibited anti- enterovirus 71 activity and neutralized the cytopathic effects induced by enterovirus 71. The allophycocyanin delays viral RNA synthesis and activates apoptosis in both human rhabdomyosarcoma cells and Afrin green monkey kidney cells (Shih *et al.*, 2003). The white spot syndrome caused by white spot syndrome virus (WSSV) in black tiger shrimp (*Penaeus monodon*) and thus causes economic loss.

The effect of a crude extract from *Spirulina platensis* on white spot syndrome virus (WSSV) both *in vitro* and in *Penaeus monodon* and inactivated WSSV significantly (Hemtanon *et al.*, 2005).

The antiviral activity studied by a microplate inhibition assay using several viruses. The hot water extract of *Spirulina maxima* inhibits many viruses including herpes simplex virus type 2 (HSV-2), HSV-1, human cytomegalovirus (HCMV) and Pseudorabies virus (PRV) (Hernández-Corona *et al.*, 2002). In Japan and Korea most people eat seaweed daily. The consumption of *Spirulina*, ranges from 3-13 g daily in Asia and Africa. The prevention of HIV infection and suppression of viral particles in infected ones was observed by regular consumption of dietary algae (Teas *et al.*, 2004).

The supplement of *Spirulina platensis* for undernourished children seems to normalize anaemia and causes weight gain in HIV-infected children, and even in HIV-negative undernourished children very quickly (Simpore *et al.*, 2005). The Ca-SP targets viral absorption/penetration and some replication stages of progeny viruses (Hayashi, 2008). And also Ca-SP showed potent and broad-spectrum of antiviral activity against HIV-1, HIV-2, influenza and a series of other enveloped viruses (Feldmann *et al.*, 1999; Rahul Kunwar Singh *et al.*, 2011). Kazuya *et al.*, (2013) studied inhibition of entry of Dengue virus by carbohydrate inhibitors.

The potent inhibitor of NADPH oxidase enzyme is chromophore -phycocyanobilin have versatile potential in the prevention and therapy of various diseases (McCarty, 2007; McCarty *et al.*, 2010). The methanol (MeOH) and water extracts of *Spirulina plantensis* were active against Adenovirus type 40 and reduces 50% and 23% respectively. The nontoxic concentrations for all the extracts were 2 mg/ml (Sayda M. Abdo *et al.*, 2012).

Water and nonpolar extracts of *Spirulina platensis* exhibited antiviral activity against HSV -1 (Chirasuwan, 2009). The water extract of algae displays antiviral activity due to presence of sulphated polysaccharides (Sayda *et al.*, 2010; Singh *et al.*, 2011). The microalgae like *Ankistrodesmus convolutus*, *Synechococcus elongates* and *Spirulina platensis* are active against Epstein Barr virus (EBV) in three Burkitt's lymphoma cell lines and a source of antiviral compound (Kok *et al.*, 2011). *Spirulina* is active against HIV-1, HIV -2, influenza virus and HSV (Singh, 2011, Sayda *et al.*, 2012). The water and methanol extracts of *Spirulina* could be good source as antiviral agent (Sayda *et al.*, 2012). Viral absorption / penetration and replication stages of progeny of several enveloped viruses blocked by the substances of *Spirulina platensis*, including HCV. Dietary supplementation of *spirulina* activates production of Interferon gamma (IFN - gamma), cytokines, NK cells, B cells and T cells of immune cells and thus stimulates immune response (Yakoot & Salem, 2012). The biochemical composition and topology of selected microalgae was reviewed by (Olivier Pignolet *et al.*, 2013). The protective effects blue-green algae against viral and bacterial infections, cancer, diabetes, allergies, hyperlipidemia and inflammation documented well (Ku *et al.*, 2013).

To assess potential health concerns of *Spirulina* the Dietary Supplements Information Expert Committee (DSI-EC) reviewed from the recent information, analyzed adverse effects reports. The DSI-EC concluded that *Spirulina* supplement is accepted as a safe food except in some conditions (Belay, 2002; Marles *et al.*, 2011; Theodore G. Sotiroudis and Georgios T. Sotiroudis, 2013).

From the above studies it is clear that in an alternative approaches, therapeutic use of algae and its products may contribute more to combat diseases caused by viruses.

## CONCLUSIONS

*Spirulina plantensis* contains many nutrients including protein pigments such as phycocyanin, allophycocyanin, phycoerythrin, chlorophyll and carotenoids, protein, aminoacids sulfolipids, polysaccharides, minerals and vitamins. Many

research results say that *Spirulina plantensis* can be used as therapeutic agent and also as antiviral agent.

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