Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(6), 1355-1365 | ISSN:2251-6727

From Algae to Antiviral an Auspicious Journey of Spirulina Over Decade: A Review

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(Received: 16 September 2024 Revised: 11 October 2024 Accepted: 04 November 2024)

KEYWORDS
Spirulina,
A. platensis,
A. maxima,
Antiviral properties,
Water extract,
Bioactive compounds,
Nutritional benefits.

ABSTRACT:

Viruses are ubiquitous parasites that pose significant global health threats, compounded by a shortage of effective antiviral treatments and increasing resistance. Spirulina, a blue-green algae, has gained attention as a natural antiviral drug due to its rich composition of bioactive compounds, including sulfated polysaccharides, phycocyanin, and gamma linolenic acid. This review examines the antiviral properties of Spirulina and its efficacy against various viruses such as HCV, SARS-CoV-2, HIV and HSV. Research indicates that Spirulina can inhibit viral replication, block viral entry, activate immune responses, and disrupt viral replication pathways. Notable studies demonstrate Spirulina's ability to suppress HIV-1 replication in human T-cell lines, obstruct HSV-2 adsorption and penetration, and activate interferon gamma to prevent HCV replication. Furthermore, Spirulina extracts have shown broad-spectrum antiviral effectiveness against viruses such as influenza A (H1N1) and Ebola. Recognized by the World Health Organization (WHO) as a "superfood" for its nutritional benefits, Spirulina also exhibits significant immune-stimulating effects, enhancing its potential as an antiviral agent. Its diverse antiviral mechanisms and safety profile suggest it is a valuable natural resource for developing antiviral therapies. Spirulina' s considerable antiviral properties, backed by multiple studies, highlight its potential as a biological resource for antiviral drug development. The findings emphasize the need for further research to explore its full potential in treating viral diseases. Spirulina's multifaceted antiviral mechanisms, coupled with its nutritional benefits, make it an intriguing candidate for future antiviral therapies and preventive healthcare strategies.

1. Introduction

Viruses are harmful parasites that can infect host cells and spread globally through various factors. Effective observation and prevention depend on the early discovery of developing outbreaks. There are 219 forms of known human viruses; the first was identified in 1901 and is known as yellow fever **[1].** The main obstacles to managing viral infections now are the lack of effective antiviral medications and treatment resistance in both the virus and the host. But Natural byproducts of microalgae may offer a different kind of therapeutic intervention to manage viral infections in humans **[2].**

Microalgae are among the most intriguing options for producing certain naturally occurring antiviral chemicals. Nine percent of marine biological substances are obtained from algae **[3,4]** and some of these products are made up of molecules that are not yet able to be replicated chemically **[5-8]**. Furthermore, microalgae

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JCHR (2024) 14(6), 1355-1365 | ISSN:2251-6727

may produce high chemical products and very high biomass levels without requiring a lot of energy **[9-11].** The 1980s pandemic saw the demonstration of antiviral properties by cyanobacteria like as Nostoc and Spirulina in the mid-1990s **[12,13]**. Spirulina, found in Japan and has been studied extensively for its antiviral qualities. It reduced the creation of viral proteins without impairing host cell processes **[14]**.

Spirulina has the highest concentration of essential amino acids, carbohydrates, essential fatty acids, minerals, vitamins, and pigments. Sulfated polysaccharides, gamma linolenic acid, phycocyanin, the biliprotein pigment, and spirulina are the three main bioactive components that contribute significantly to the enhancement of bodily functioning. The chemical makeup of spirulina is primarily responsible for its possible health benefits, antiviral properties, and immunomodulation, as shown by recent experimental findings.

2. SPIRULINA: A SUPER FOOD

Arthrospira platensis, a blue-green algae species, is the source of spirulina in lakes. The National Aeronautics and Space Administration (NASA) has urged astronauts to eat a modest amount of spirulina while in space, dubbing it a "superfood" by the World Health Organization (WHO)**[15].** The indigenous people of the Lake Chad region and the Aztec people of Mexico have been consuming spirulina for food and supplements for over a millennium. The Spirulina species are *Arthropsira platensis, A. laxissima , A. subsalsa , A. fusiformis , A, maxima , and A, lonar*. Of all the species, *A. platensis and A. maxima* are the most widely utilized, largely for medicinal and nutritional purposes **[16].**

Arthrospira platensis is distinguished by its blue-green hue, filamentous and spiral form, fresh slimy texture, and distinct earthy flavor and aroma. It is possible to identify and make use of this important cyanobacterium thanks to these characteristics as well as its visible forms in commercial preparations **[17].**

Arthrospira maxima is distinguished by its blue-green hue, filamentous and spiral form, fresh slimy texture, and distinct earthy flavor and aroma. A. platensis has many of these characteristics, with minor differences in coil tightness and filament size. *A. maxima* is a desirable cyanobacterium for industrial and nutritional purposes because of its almost similar growth characteristics and commercial forms **[18].**

Spirulina is a protein supplement that strengthens the immune system. Preliminary studies on healthy individuals show that spirulina increases the generation of cytokines such as interleukin (IL)-2, interferon, and tumour necrosis factor as well as the proliferation of CD4+ Thelper cells **[19,20].** Moreover, it seems to boost natural killer cell activity and cytotoxicity **[21].** When spirulina is taken with different cytotoxic medicines, animal studies have shown chemoprotective benefits **[22,23,24].** The potential of spirulina to provide protection against toxicity associated with several cytotoxic drugs, such as cardiotoxicity, nephrotoxicity, and hepatotoxicity, has been examined in a number of animal studies **[23].**

Table 1.1 Taxonomical classification of Spirulina

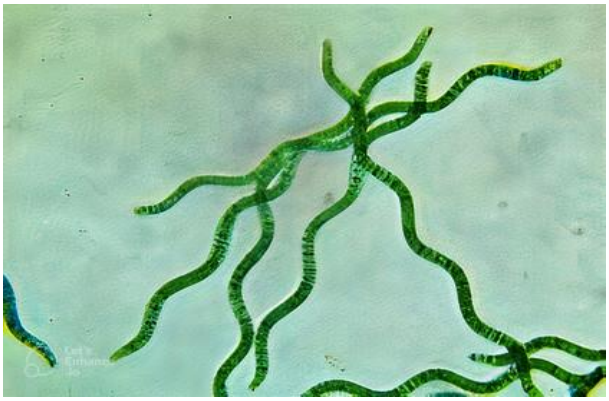

Fig 1.1 microscopic view of *Arthrospira maxima*

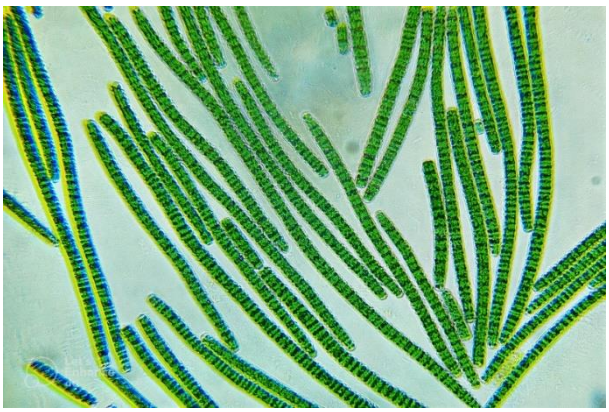

Fig 1.2 Microscopic view of *Arthrospira platensis*

It is a spiral-shaped, unicellular microalgae that thrives in alkaline environments, such as pH 10 to 12. For ages, people have used spirulina as a food source, particularly

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in famine-stricken regions of Africa, where local residents have been able to subsist for more than a month just on spirulina**[19].**

3. VIRAL PATHOLOGY:

Viruses are the tiniest and most prevalent non-cellular organisms on the planet**[25].**What distinguishes them from other living organisms is their ability to replicate exclusively within their cells. Given that viruses are made up of a protective protein shell called a capsid and a core of genetic material, either DNA or RNA **[26].**

Viral disease can spread through four pathogenic pathways: (1) virus implantation at the site of entry; (2) local replication; (3) diffusion to target organs (disease sites); and (4) propagation to places where the virus sheds into the environment. Factors influencing pathogenic pathways: (1) virus sensitivity to host defenses; (2) virus accessibility to tissue; and (3) virus vulnerability to cell growth. Low-virulence virus strains are more likely to propagate due to natural selection **[27,28].**

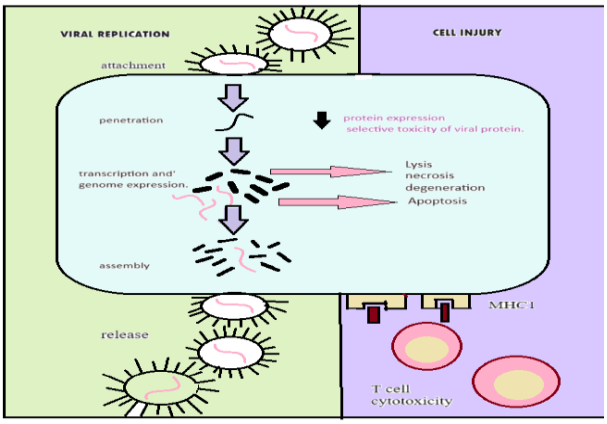

Fig 2.1 Viral Pathology

4. ANTI VIRAL PROPERTIES

Researchers at the National Cancer Institute (NCI) in the United States discovered potent antiviral chemicals in blue green algae, such as *Arthrospira platensis*. After examining 600 strains of cultivated cyanobacteria, 10% produced compounds that dramatically reduced cytopathic effects caused by viral infections **[29].** Numerous enveloped viruses have been demonstrated to be effectively inhibited by acidic polysaccharides, such as calcium spirulan from *Arthrospiraa platensis*, and microalgae compounds, such as nostoflan and fucoidan from *Undaria pinnatifida.*

Table 2.1 Antiviral properties of Cyanobacterium, *A.platensis* & *A.maxima*

Sl.NO	Type of the virus	Compound name	Mechanism involved	System	References
1.	Adenovirus type 7, Astrovirus type 1, Coxsackievirus B4, Rotavirus Wa strain, Adenovirus type 40.	Methanol extract	Virucidal	*In vitro*	[35][36]
2.	HIV-1	Water extract	Inhibit proliferation in human T-cell lines	*In vitro*	[37]

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3.	HSV-2	Methanol extract	Inhibit virus-host cell attachment and entry	*In vitro*	[31]
4.	HCV (Hepatitis c) & enveloped viruses	Spirulina supplement	Stimulate Interferon gamma production;halts viral replication	*Clinical trial*	[38]
5.	Enterovirus 71	Allophycocyanin	Hinder viral RNA synthesis; activate apoptosis	*In vitro*	[39]
6.	RSV/A2	Hot water extract	Inhibit RSV plaque formation	*In vitro*	[40]
7.	Influenza A (H1N1)	Cold water extract	Inhibit viral plaque formation	*In vitro*	[41]
8.	SARS-CoV-2	Hot water extract	Inhibit plaque formation of SARS-CoV-2 at the viral attachment stage	*In vitro*	[41][42]
9.	Ebolla virus	Hot water extract	Inhibit replication of ebola virus	*In vitro*	[41]
10.	HSV-2	Sulphoquinovosy-l-diacylglycerol	Inhibit viral replication and decrease plaque formation	*In vitro*	[43][44]
11.	EBV	Spirulina	Inhibit replication or activity of virus	*In vitro*	[45]

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12.	HIV&HSV-1	Ca-Sp (calcium spirulan)	Inhibit HIV & HSV-1 induced syncytium formation	*In vitro*	[46][47]
13.	HSV-1	Water extract	Inhibit replication and increase survival time of infected hamster	*Hamster*	[48]

Arthrospira maxima exhibited antimicrobial and antibacterial activity against a wide range of tested bacterial species in both its aqueous and methanol extracts **[30].** There was no discernible inhibition shown in the cases of poliovirus-1, vesicular stomatitis virus (VSV), or rotavirus SA-11, measles virus , subacute sclerosing panencephalitis virus (SSPE). Preventing the virus's attachment and entry into the host cell, which marks the beginning of the viral cycle, stopped the herpesvirus from spreading. Hernandez-Corona claims that the *A. maxima* extracts with a methanol-to-water (3:1) ratio exhibit the highest levels of antiviral activity **[31].**

Sulfated polysaccharide calcium spirulan (Ca-SP) was isolated from a hot water extract of *A. platensis* and has anticancer characteristics. Calcium spirulan (Ca-SP) is composed of sulfate , calcium, mannose, galactose ,glucose, fructose rhamnose, ribose, xylose, glucuronic acid, and galacturonic acid. **[32].**

Sulfated polysaccharides found in cyanobacteria extracts inhibit the adhesion and fusion of virus cells with host cells. the significant increase in viral infectiousness caused by the suppression of the fusion of HIV-positive cells and uninfected CD4+ lymphocytes **[33,34].**

Adenovirus types 7 and 40 were the subjects of a study that showed promising antiviral activity of *A.platensis* extract. *A.platensis* ethanol extract reduced adenovirus type 7 infectious units by 53.3% and adenovirus type 40 infectious units by 50% in vitro. These findings point to a possible virucidal activity of the extract against these strains of adenovirus. Furthermore, earlier studies have suggested that highly polar chemicals in Spirulina extracts could be involved in the antiviral action of the extracts against several viruses, including adenovirus types. All things considered, *A.platensis* exhibits promise as a natural substance with antiviral capabilities against adenoviruses**[35,36].**

The study also showed that *A. platensis* extract was effective against HIV type 1 as an antiviral. In instance, human T-cell lines and peripheral blood mononuclear cells showed reduced HIV-1 multiplication when exposed to *A. platensis* water extract. At concentrations of 0.3 to 1.2 µg/ml, the generation of viruses was reduced by around 50%. Furthermore, an inhibitory concentration (EC50) for cell growth range from 0.8 to 3.1 mg/ml was reported for the extract. These findings imply that Spirulina platensis holds promise as a natural antiviral medication that calls for more research against HIV-1. Specifically, it may be able to suppress the virus's replication**[37].**

The *A.platensis* extract's efficacy against HSV-2 was demonstrated in the respective experiment. Specifically, *A.maxima* methanol extract exhibited antiviral action against HSV-2, with an IC50 of 0.13 mg/ml and an EC50 of 6.9 mg/ml. The extract inhibited HSV-2 infection through interference with viral replication pathways, even in the absence of a direct virucidal action. As a result, the presence of highly polar compounds in spirulina extracts may enhance their antiviral efficacy against HSV-2. The research also showed how Spirulina extracts could be used as natural treatments for HSV-2 infections**[31].**

Hepatitis C virus (HCV) and other enveloped viruses have been shown to be effectively inhibited by spirulina. Spirulina supplements have been shown to activate interferon gamma, which inhibits HCV replication by preventing the virus from being absorbed. Furthermore, against a variety of enveloped viruses, including Human Influenza virus type -1&2 and influenza virus, spirulina has a broad-spectrum antiviral activity. Sulfated

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polysaccharides, which are present in spirulina extracts, are crucial for preventing virus cells from adhering to and fusing with host cells, which reduces the virus's infectiousness. The study's findings highlight spirulina's potential as an environmental asset for the creation of antiviral drugs that combat enveloped viruses like HCV**[38].**

Spirulina has demonstrated the capacity to halt the creation of viral RNA and cause enterovirus 71-infected cells to undergo apoptosis. *A.platensis* contains allophycocyanin, which exhibits anti-enterovirus 71 action by thwarting the virus's detrimental effects. These results imply that Spirulina may be a useful therapeutic alternative for infections caused by Enterovirus 71**[39].**

RSV strain A2 has been demonstrated to be highly susceptible to the antiviral effects of *Arthrospira maxima* hot water extract (AHWE). There was a substantial decrease in plaque formation (88.5% to 93.3%) indicating that AHWE successfully prevented RSV/A2 replication. AHWE's antiviral efficacy against RSV/A2 persisted even after being exposed to air for over four hours, suggesting that it has the potential to be a long-lasting antiviral drug. According to these findings, AHWE may prove to be a viable option for the creation of antiviral treatments that target RSV infections**[40].**

The reproduction of several influenza A virus strains, including H1N1, has been demonstrated to be inhibited by *Arthrospira platensis* cold water extract. Studies have also demonstrated that Arthrospira extract can act early in the course of infection to reduce the viral load in cells and improve the survival rate of mice infected with influenza. Additionally, it was discovered that the extract prevented several influenza virus strains, including those that are resistant to oseltamivir, from forming viral plaques. These results imply that *Arthrospira* extract has potential as an efficient antiviral agent against influenza A (H1N1) and other influenza virus strains**[41].**

Arthrospira maxima hot water extract (AHWE) has shown broad-spectrum antiviral efficacy, including against the COVID-19-causing SARS-CoV-2 virus. When the virus was attached, AHWE demonstrated a significant rate of inhibition (90% to 100%) on the production of SARS-CoV-2 plaques. Furthermore, AHWE's antiviral effectiveness persisted even after being outside for almost four hours. These findings highlight AHWE's potential role in combating COVID-19 and imply that it might be created as a workable broad-spectrum antiviral spray and SARS-CoV-2 therapy agent**[41][42].**

Anti-replication activities against the Ebola virus have been discovered in the *Arthrospira maxima* hot water extract (AHWE). It was stated that in experiments evaluating its antiviral effectiveness, AHWE inhibited the replication of the Ebola virus at 500 µg/ml.. Moreover, results from safety testing such as skin sensitivity, evaluation of skin irritation, and oral acute toxicity showed no safety issues with AHWE use. The findings indicate that AHWE may have the ability to stop the spread of the Ebola virus and other broad-spectrum viruses, underscoring its potential application as an antiviral treatment for Ebola virus infection **[41].**

Spirulina inhibits the Herpes simplex virus type 1 (HSV-1), hence lowering plaque development. Certain constituents of spirulina, like sulphoquinovosyl diacylglycerol, have anti-HSV-1 properties. These findings imply that spirulina might be a beneficial therapeutic substitute for the control of HSV-1 infections**[43][44].**

Spirulina's antiviral action against the Epstein Barr virus (EBV) suggests that it has the capacity to prevent the virus from replicating or acting as it would. Given that spirulina has demonstrated efficacy in battling EBV infections, this suggests that it may have potential as a treatment for EBV infections. To fully investigate spirulina's potential as a treatment for EBV infections, more investigation and clinical trials could be necessary **[45].**

Studies on the anti-HIV and anti-HSV-1 effects of Ca-Sp were discovered to suppress the formation of syncytiums induced by reductions in HSV-1 and HIV plaque yield, respectively. According to Hayashi *et al., A. platensis's* Ca-SP is a powerful antiviral agent that can be used as a therapeutic medication. It is effective against both HSV-1 and HIV-1**[32].** Herpes simplex virus type 1 (HSV-1) replication is inhibited by the structural modification of calcium spirulan (Ca-SP), a sulfated polysaccharide produced from *A. platensis* **[46].** According to a study by Gorobets et al. (2002), adding *A.platensis* to bacteriophage T4 (a bacterial virus) had an influence on the bacteriophage's ability to reproduce in Escherichia coli B cells, either promoting or inhibiting it**[47].**

The aqueous extract of *Arthrospira platensis* inhibited the in vitro growth of HSV-1 in HeLa cells. The virus is not killed by the extract, but it is kept from infecting host

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cells**[48].** Calcium Spirulan, also known as Ca-Sp, is a sulfated polysaccharide that is present in *Arthrospira platensis*. It possesses antiviral effects that help prevent the spread of HSV-1, influenza, HVMV, HIV and measles. Spirulina is an antiviral agent **[49][50].**

5. Discussion:

The promising antiviral properties of spirulina, especially *A.platensis* and *A.maxima* , derived from microalgae. The findings from various studies highlight the diverse mechanisms through which spirulina compounds exhibit antiviral response against a spectrum of viruses, including adenovirus, HSV-2, HCV, enterovirus 71, HIV-1, RSV, and influenza A virus strains. These mechanisms include inhibiting viral replication, blocking viral entry, activating immune responses, and interfering with viral replication pathways.

One allusion of the research is the potential of spirulina as a natural alternative for antiviral therapy. The documented antiviral efficacy of spirulina compounds, such as sulfated polysaccharides, suggests their utility in inhibiting viral infections and potentially reducing viral pathogenicity. This opens up avenues for exploring spirulina-based products as therapeutic supplements for managing viral infections and enhancing immune responses.

In addition, spirulina's immune-stimulating properties highlight its potential as a preventive as well as an antiviral medication for human health. Beyond its antiviral characteristics, spirulina's capacity to regulate immunological responses and inhibit viral replication indicates its wider range of health advantages.

Exhortation for future research include conducting more in-depth studies to elucidate the specific mechanisms of action of spirulina compounds against different viruses. Further exploration into the synergistic effects of spirulina with conventional antiviral medications could provide insights into potential combination therapies. Additionally, clinical trials to evaluate the safety and efficacy of spirulina-based products in treating viral infections in human subjects would be valuable for translating these findings into practical therapeutic interventions.

6. Conclusion:

The review demonstrates the potent antiviral qualities of spirulina, highlighting it as a potential natural resource for the creation of antiviral treatments. Spirulina, in particular *A.platensis* and *A.maxima*, has shown itself to be able to inhibit a variety of viruses, such as SARS-CoV-2, HSV-2, HCV, and HIV-1. Spirulina is an excellent option for upcoming antiviral therapies because of its broad-spectrum antiviral action and immune-stimulating properties.

Furthermore, Spirulina's potential goes beyond therapeutic use; its capacity to boost immune responses makes it a promising preventive health supplement. Its diverse bioactive components, including sulfated polysaccharides and phycocyanin, block viral replication and limit viral entry into host cells, providing a multimodal approach to viral control. These findings not only suggest an immediate application in antiviral medication research, but also open the door to adding Spirulina into preventative healthcare methods aiming at strengthening human immunological defence systems.

However, despite the promising results of in vitro and early-stage clinical investigations, further study is needed to completely understand the particular pathways by which Spirulina exerts its antiviral properties. Rigorous clinical trials are required to establish its efficacy and safety in humans, especially across a wider range of viral infections. Furthermore, investigating the synergistic potential of Spirulina with known antiviral medications may reveal new therapeutic combinations that improve treatment efficacy while reducing resistance.

In conclusion, Spirulina stands out as a wonderful natural medicine with enormous potential for treating and preventing viral infections. Its antiviral qualities, together with its nutritional and immune-boosting benefits, highlight the need for further research to fully realize its promise in treating viral infections and aiding worldwide public health efforts.

ABBREVIATIONS :

1. WHO – WORLD HEALTH ORGANIZATION
2. NASA – NATIONAL AERONAUTICS AND SPACE ADMINISTRATION

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3. DNA – DEOXY RIBONUCLEIC ACID
4. RNA – RIBOXYNUCLEIC ACID
5. NCI – NATIONAL CANCER INSTITUTE
6. HIV-1 – HUMAN IMMUNODEFICIENCY VIRUS TYPE 1
7. HSV-2 - HERPES SIMPLEX VIRUS TYPE 2
8. HSV-1 – HERPES SIMPLEX VIRUS TYPE 1
9. HCV – HEPATITIS C VIRUS
10. RSV/A2 – RESPIRATORY SYNCYTIAL VIRUS STRAIN A2
11. HIV-2 – HUMAN IMMUNODEFICIENCY VIRUS TYPE 2
12. AHWE - ARTHROSPIRA MAXIMA HOT WATER EXTRACT
13. EBV – EPSTEIN BARR VIRUS
14. VSV – VESICULAR STOMATITIS VIRUS
15. SSPE – SUBACUTE SCLEROSING PANENCEPHALITIS VIRUS
16. Ca-Sp – CALCIUM-SPIRULAN

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