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The Therapeutic Potential of *Spirulina* to Combat COVID-19 Infection

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MANY countries and labs are currently looking for a COVID-19 vaccine but have yet to explore it. Many species of *Spirulina* contain significant active compounds such as sulfated polysaccharides, phenols, phycobiliproteins, and calcium spirulan with inhibition activity against replication of viruses, especially influenza A (H1N1), HCV, and HIV viral infection. As there is no vaccine was approved against COVID-19, the potential of using *Spirulina* as antiviral and an immune agent has been tested for many viruses, and this encourages using the *Spirulina* as a whole amount or its extract for immunization against COVID-19, the causative pathogen of Coronavirus disease. The present article discusses some of the important studies on the therapeutic antiviral activities of the cyanobacterium *Spirulina platensis*.

Keywords: Calcium spirulan, COVID-19, *Spirulina*, Sulphated polysaccharides.

The world is currently facing a challenge when it comes to overcome the COVID-19 pandemic. Till now, no vaccine has been succeeded in providing the human body with the required immunization against this virus. However, there is a gleam of hope in using the cyanophycean filamentous species *Spirulina* as a dietary supplement previously approved by NASA for astronauts on space missions (Tadros, 1988). It has the potential of clinical applications to treat many diseases, and it has been used as anticancer, antiviral, and anti-allergic (Karkos et al., 2011). The advantage of introducing *Spirulina* in medicinal applications has been proven in many medical cases, that it was used to defeat many viruses such as influenza A (H1N1) virus (Pugh et al., 2015; Chen et al., 2016), chronic hepatitis C virus (Yakoot & Salem, 2012; Elshanshory et al., 2020), HIV (Ngo-Matip et al., 2015), enterovirus 71-induced apoptosis (Shih et al., 2003), herpes simplex virus (HSV) type (Hayashi et al., 1996a, b; Mader et al., 2016).

Several research studies recommended that *Spirulina* can be a potential alternate therapy against virus diseases due to the possible synergistic effect of many bioactive compounds present in the whole cell or the extract (Zhou et al., 2020). The viruses, especially coronavirus, are resistant to chemical

drugs, and there is a must for researchers to explore alternative biological compounds extracted from some algae, including cyanophytes, or other natural products that can act as protective agents against viruses. *Spirulina* has many healing properties and positive effects on the body. In addition to its detoxifying effect, it also has many benefits for gut health, blood pressure, blood cholesterol levels, hair, skin, antioxidant, and anticancer (Shao et al., 2019; Singh et al., 2020). *Spirulina* also contains a high content of nutrients, a powerful antioxidant, and anti-inflammatory properties. It includes vitamins B1, B2, and B3, iron, magnesium, and potassium. Several bioactive compounds derived from *Spirulina* have been recognized, including proteins, essential amino acids (EAAs), carbohydrates, essential fatty acids, minerals, vitamins, pigments, and gamma linolenic acid with their remarkable antimicrobial and antiviral (El-Baz et al., 2013; El-Sheekh et al., 2014a; Daoud & Soliman, 2015), improving human body functions (Ramakrishnan, 2013). The United Nations confirmed that malnutrition and lack of key vitamins and minerals lead to impairment of physical and intellectual development (UNICEF, 2012). Therefore, the dual role of *Spirulina* as a food supplement and therapeutics against virus infection is important (El-Sheekh et al., 2014b).

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Emerging or re-emerging of pandemic viral diseases is the most critical situation human could face. During the last decades, the number of antiviral products that have been approved for clinical trials has been jumped tremendously from 5 to more than 30 drugs (Ismail et al., 2020; Pereira & Critchley, 2020). Many studies have confirmed the antiviral activity of *Spirulina* extracts (Table 1). In that context, a sulfated polysaccharide, namely, calcium spirulan (Ca-SP), was extracted for the first time from *S. platensis* found to have antiviral bioactivity (Hayashi et al., 1996a). Several studies showed that using calcium spirulan (Ca-SP) could inhibit the replication of several enveloped viruses, including influenza A virus, Herpes simplex virus, human cytomegalovirus, measles virus, mumps virus, and HIV-1 (Hayashi et al., 1996a). Hayashi et al. (1996b) confirmed the selective ability of (Ca-SP) to inhibit the penetration of viral molecules into host cells. Therefore, (Ca-SP) has been introduced to the medical market as a good antiviral candidate due to its low anticoagulant activity, long half-life in the blood, also it proved to be dose-dependent, without any stimulation of viral replication at low concentrations. Rahman et al. (2006) compared two antiviral candidate products, cidofovir, and *S. platensis* extract, using infected pathogen-free

Litopenaeus vannamei juveniles. Substantially hindered mortality in white spot syndrome virus (WSSV) infected shrimp treated with cidofovir, whereas shrimp supplied with *Spirulina* showed delayed clinical signs for 12hrs; however, the cumulative mortality at the end of the experiment has not been affected. *Spirulina* has been claimed to have the potential to increase the body's interferon type 1 response defeating RNA viruses, including the flu and the coronavirus (McCarty & DiNicolantonio, 2020). A pigment fraction, namely phycocyanobilin (PCB) mimics bilirubin extracted from *Spirulina*, has been found to mimic NADPH oxidase inhibiting activity, which in turn blocks the key reproduction mechanism of RNA viruses human body (McCarty, 2007; Zheng et al., 2013; McCarty & DiNicolantonio, 2020). PCB, a biliverdin metabolite, was shown to mimic the NADPH oxidase inhibiting the activity of unconjugated bilirubin, likely because of its conversion to phycocyanorubin, which is structurally comparable to bilirubin (Romay et al., 2003; Zheng et al., 2013). Thus, this could explain the antioxidant and anti-inflammatory effects recorded when phycocyanin or PCB are administered in rodent models of human pathology (Romay et al., 2003; McCarty & DiNicolantonio, 2020).

TABLE 1. Antiviral activity of specific compounds from cyanobacteria, showing the wide range of antiviral activity of *Spirulina* sp.

Organisms	Compounds	Virus	Reference
<i>Nostoc ellipsosporum</i>	Cyanovirin-N Da-1	Human immunodeficiency virus HIV-1 and HIV-2 and Simian Immunodeficiency Virus SIV fusion, replication and RNA-dependent DNA polymerase activity of the viral RT	(Boyd et al., 1996) (Pereira et al., 2004)
<i>Calothrix gracilis</i>	Methanol extract	Influenza A virus	(Zainuddin et al., 2002)
<i>Arthrospira platensis</i>	Calcium spirulan	Herpes Simplex HSV-1 replication; Measles replication; Mumps replication; Influenza replication; Polio replication; Coxsackie replication; HIV-1 replication; Human Cytomegalovirus HCMV replication.	(Hayashi et al., 1996b)
<i>Spirulina maxima</i>	Methanol extract	Herpes simplex virus type 2	(Corona et al., 2002)
<i>Spirulina platensis</i>	<i>Spirulina platensis</i> mediated Au-NPs	Herpes simplex (HSV-1)	(El-Sheekh et al., 2020)
<i>Arthrospira platensis</i>	Methanol extracts	Coxsackievirus B3 (CVB3) and rotavirus (RV)	(Deyab et al., 2020)
<i>Spirulina</i> sp.	Spirulan	HIV-1 and HIV-2 (inhibit reverse transcriptase) HSV, influenza	(Singh et al., 2011)
<i>Spirulina platensis</i>	Allophycocyanin	Enterovirus 71	(Shih et al., 2003)
<i>Spirulina platensis</i>	Water-soluble extract	Herpes Simplex HSV-1	(Hayashi et al., 1993)

Considering the results obtained from other studies on other viral diseases, including coronaviruses, it could be cautiously suggested that *Spirulina* extract could represent a gleam of hope as a therapeutic agent for COVID-19, which for sure needs further and extended clinical investigation.

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Conflict of Interest: Authors declare that there is no conflict of interest.

Authors contribution: Mostafa El-Sheekh: Conceptualization, Investigation, Methodology, Validation, Writing - original draft. Abd El-Fatah Abomohra: Data curation, Writing - review & edit.

Ethical approval: This article does not contain any studies with animals performed by any of the authors.

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الاحتمالات العلاجية للـسبيرولينا لمكافحة عدوى فيروس كورونا

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تبحث العديد من الدول والمختبرات حاليًا عن لقاح لفيروس كورونا ولكن لم تستكشفه بعد. تحتوي العديد من أنواع السبيرولينا على مركبات نشطة مهمة مثل السكريات الكبريتية والفينولات والبروتينات النباتية وسبيرولان الكالسيوم والتي لها نشاط تثبيطي ضد تكاثر الفيروسات، وخاصة الأنفلونزا (H1N1) والفيروسات الكبدية (HCV) وفيروس نقص المناعة البشرية (HIV). ونظرًا لعدم وجود لقاح تم اعتماده ضد فيروس كورونا (COVID-19) فقد تم اختبار إمكانية استخدام سبيرولينا كمضاد للفيروسات وعامل مناعي للعديد من الفيروسات، وهذا يشجع على استخدام سبيرولينا ككل أو مستخلصه للتحصين ضد فيروس كورونا (COVID-19). يناقش هذا المقال بعض الدراسات الهامة حول الأنشطة العلاجية المضادة للفيروسات من البكتيريا الزرقاء سبيرولينا بـلاتنيسيس.