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Spirulina (*Arthrospira platensis*)- a review on its pronounced bioactive properties and future applications in food technology and pharmaceutics

Akshay P.[1,3], Amruth P.[1,3], Rosemol Jacob M.[1,3], Preethy Treesa Paul[1,3], George Ninan[2], Suseela Mathew[1]
[1]Biochemistry and Nutrition Division, ICAR- Central Institute of Fisheries Technology, Kochi-682029, Kerala, India
[2]Fish Processing Division, ICAR- Central Institute of Fisheries Technology, Kochi-682029, Kerala, India
[3]Faculty of Marine Sciences, Cochin University of Science and Technology, Kochi-682022, Kerala, India

Abstract
Spirulina *(Arthrospira platensis)* is a photosynthetic aerobic unicellular organism found worldwide in marine and fresh waters realm. This cyanobacterium is a single cell protein with nutrient depot and bioactive compounds, commercialized world-wide as food, feed and source of several value-added products. Due to the pronounced functional and biological properties, they are used as a vital ingredient for the development of novel functional foods. They have wide spectrum of usage in the area of food technology, pharmaceutics and aquaculture. The current review presents the human clinical potential, bioactive, functional and health benefits of *A. platensis* to approach novel ideas for prospective advancements in research in the area of food technology, pharmaceutics and biomedicine.
Keywords*: Bioactive properties, functional food, health benefits, micro algae, spirulina*

INTRODUCTION
Spirulina (Fig. 1) is a filamentous micro alga, derives its name from the helical or spiral structure of its filaments and has a vast history of use as a dietary supplement (Karkos *et al*., 2011). *A. platensis* are devoid of cellulose cell walls and are easily digestible (Dillon *et al*., 1995) and are ideal for food technology applications. This microscopic alga is explored widely as a source of protein and vitamins, represents a chief staple human dietary supplement without any adverse effects. Despite the high protein composition, they serve as major sources of fatty acid like γ-linolenic acid, essential amino acids, vitamins, specifically vitamin $B_{12,}$ tocopherol and β-carotenes, minerals in particular iron and phenolic acids (Dillon *et al*., 1995; Karkos *et al*., 2011).

Figure1(a). Microscopic image of Spirulina,
(b). Culture of *A. Platensis* carried out in ICAR-CIFT laboratory, Cochin

In the food industry, compounds derived from *A. platensis* have the potential to be an active ingredient in the innovation of new functional foods. The bioactive peptides derived from them offer specific health benefits that include anti-oxidative, anti-microbial, anti-inflammatory, anti-hypertensive, anti-tumor, anti-obesity, immunomodulatory and probiotic properties as depicted in fig. 2. In this aspect, this article presents the existing information concerning the clinical potential, bioactive, functional properties and health benefits of *A. platensis* in humans to approach innovative ideas to researchers for prospective advancements in the area of food technology, pharmaceutics, biomedicine and aquaculture.

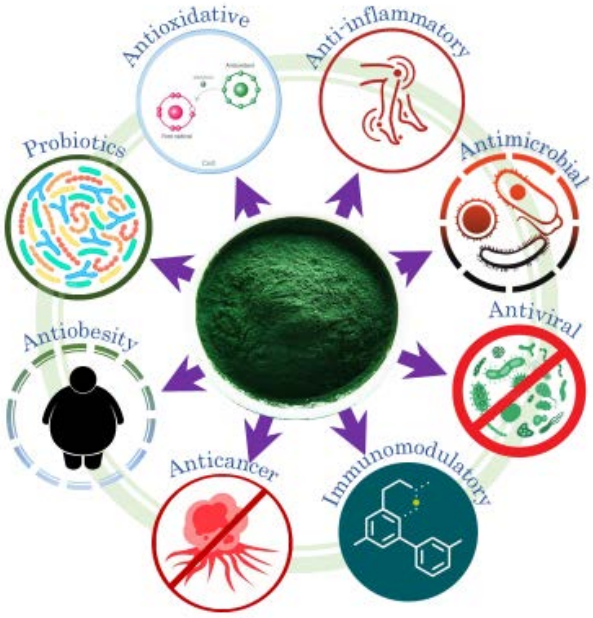


Fig 2. Bioactive Properties of *A. platensis*

The production of Spirulina at the industrial level has increased to a greater extent such that the product is being marketed and sold as a food supplement world-wide (da Rosa *et al.*, 2015). Albeit, few studies are carried out in regard to the bioactive efficacy of *A. platensis* in accordance with bioactive compounds derived from other marine organisms, it is very much relevant to identify the patterns, trends and research gaps to understand the potential benefits of *A. platensis*.

Application of *Arthrospira platensis* in the area of food

Historical records of the utilization of Spirulina in the diet of humans are numerous. It has been used as an everyday food for eras in Chad, famous in the local language as dihe and dry Spirulina cakes were prepared by Aztecs which was well-known locally as 'tecuitlatl' (Gantar and Svircev, 2018). In many countries like Germany, Holland, India, Japan, Mexico, Singapore, Spain, Switzerland, Taiwan and the United States, *A. platensis* is used as food material (Henrikson, 1994). It is incorporated as formulants in cosmetics, candies, appetizers and bread. (Henrikson, 1994). In recent years, Spirulina is added as a natural additive in animal feed for their healthy growth. Furthermore, in aquaculture, it is chosen as an economical, natural and healthy product that shows rapid growth performance. It is considered as one of the most sought-after ingredients for fish feed compared to other nutrients due to its high protein content and biocompatibility (Seyidoglu, 2017).

Bioactive prospects of *Arthrospira platensis* and future aspects

1. Antimicrobial Properties

The potential health impacts of Spirulina is well documented in several literatures. In a study conducted by Ozdemir *et al.* (2004), the volatile methanolic extracts isolated from *A. platensis* demonstrated an

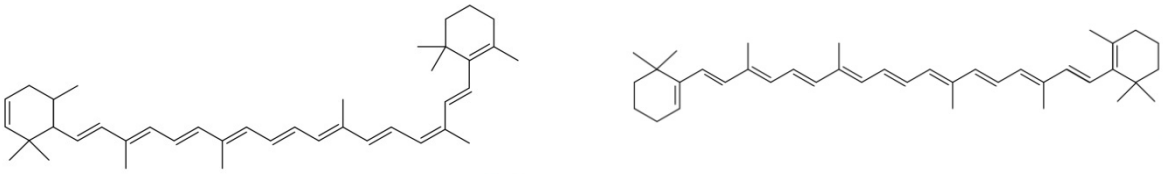
inhibitory effect on the growth of *S. epidermidis, S. faecalis and C. albicans*. In another study, the algal extract of *A. platensis* induced an antibacterial effect on *Staphylococcus aureus* and *Salmonella typhimurium* and observed growth arrest of the bacteria (Kumar *et al.*, 2011). Bancalari *et al*. (2020) confirmed the *in vitro* antimicrobial property of *A. platensis* against foodborne pathogens, *L. innocua, S. liquefaciens* and *P. fuorescens*. The inhibitory effect of methanolic and aqueous extracts of *A. Platensis* against foodborne pathogens, *Staphylococcus epidermis* and *Salmonella typhimurium* has been revealed by Challouf *et al*. (2011). Selenium nanoparticles synthesized with *A. platensis* exhibited potent antimicrobial activity against gram-negative bacteria and fungi which throws light into the future therapeutic applications of Spirulina (Abbas *et al*., 2021)

2. Antiviral Properties

The increasing morbidity and mortality rates in connection with the exposure and re-emergence of viral epidemics including COVID-19 and Nipah virus are major public health threats during this point of time. A novel effective therapy is the need of time to combat the same. Due to the effectiveness of natural products against viruses and their viability to act as antiviral drugs, there is a need to focus on the antiviral properties of natural products identified from plant sources to provide safe and effective drugs to control viral diseases in humans. Studies have proven that Spirulina possess the ability to impede the growth and proliferation of the virus. The ethanolic extract of Spirulina possess promising antiviral activity against enteric viruses (El-Baz *et al*., 2013). The researchers from Japan isolated sulphated polysaccharide from Spirulina later named Calcium Spirulan, which is found to be an antiviral agent that selectively constrains the virus penetration into host cells. A study conducted on human T-cell lines with water extracts of Spirulina shows inhibition to the replication of HIV-1 (Ayehunie *et al.*, 1998). When *A. platensis* biomass was added to the enriched nutrient agar, it produced an inhibitory effect on the multiplication of the bacteriophage in *Escherichia coli* (Gorobets *et al.*, 2002). The exopolysaccharides isolated from *A. Platensis* can act against koi herpesvirus which causes severe economic loss in carp culture farms (Reichert *et al*., 2017).

3. Antioxidant Properties

From several studies, it is demonstrated that carotenoid content in Spirulina extracts exhibits pronounced anti-oxidative properties. As a result of oxygen metabolization, free radicals are formed and they scavenge electrons from other molecules, results in cell and DNA damage leading to cancer. Antioxidants found in Spirulina incorporated foods are capable of neutralizing these free radicals and hence prevent the cell damage caused by them (Khan *et al.*, 2005). Some studies have revealed that food incorporated with Spirulina (carotenoids) lowers the risk of developing various cancers in humans (Khan *et al.*, 2005). *A. platensis* contains up to 2000 IU/g dry weight of β-carotene (Fig 3.) (Krinsky and Johnson, 2005*;* Ranga *et al.*, 2010; Mohan *et al.*, 2014). β-carotene has the ability to deactivate the free radicals that are responsible for cell damage. A study by National Cancer Institute, USA found that a daily intake of 6 mg β-carotene reducing the incidence of cancer, which can be met by 4 g daily intake of Spirulina (Ranga *et al.*, 2010).



(A) (B)

Figure 3. Molecular structure of two forms of β -carotene
A: *cis* β-carotene and **B**: *trans* β-carotene

Another major antioxidant found in Spirulina is phycocyanin (Fig 4.), which is a water soluble natural pigment that protects kidneys and liver at the time of detoxification, as well as activate the immune responses. Phycocyanin is often used as a dietary supplement and has a key role in the nourishment and well-being of humans as it contains most of the essential amino acids (Shih *et al.*, 2009). Phycocyanin also prevents neuronal

cell death by scavenging free radicals from damaged neurons, which can thus prevent the oxidative damage of DNA resulting from the free radicals (Rimbau *et al.*, 1999*;* Rimbau *et al.*, 2001). A recent study revealed the remarkable antioxidant property of food-grade phycocyanin extracted from Spirulina suggesting that it have a potential impact on human health upon consumption (Wu *et al.*, 2016).

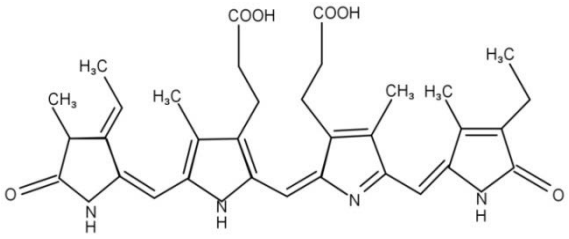


Figure 4. Molecular structure of C-phycocyanin

The scavenging activity of phycocyanobilin isolated from *A. platensis* inhibited the methyl linoleate peroxidation and the oxidation of phosphatidylcholine liposomes. (Hirata *et al.*, 2000*;* Wu *et al.*, 2016).

4. Anticancer Properties

The adverse effects that arise after cancer therapies remain dangerous than cancer. Exploring naturally available products (including Spirulina) are observed in reducing the after effects from chemotherapy and existing treatments. Various studies have validated the effectiveness of Spirulina in inhibiting various cancers by acting on immune system and DNA repair mechanism. A study conducted by Akao *et al*. (2009) stated that, hot water extract of *A. platensis* induces antitumor activity in rats by activating the natural killer (NK) cells and thereby limiting the spread of tumour cyst and subsequent damage of tissue. Spirulina are the repository of phycobiliproteins viz. C-phycocyanin, allophycocyanin and phycoerythrin which have bioactive properties against cancer. The phycocyanin isolated from *A. platensis* exhibited anticancer activity against squamous cell carcinoma (Schwartz *et al.*, 1987). In another study on water soluble polysaccharides isolated from Spirulina, enhanced repair activity of radiation damaged DNA and endonuclease activity were reported (Qishen et al., 1988). Studies performed on commercial Spirulina products developed from *A. Platensis* showed a significant reduction in the viability and effects of carcinoma, which was accompanied by arrest of the G1 phase of the cell cycle (Czerwonka *et al.*, 2018). Research by Salehzadeh *et al*. (2019) used *A. platensis* in the synthesis of Fe_3O_4/Ag nanocomposite and found its effectiveness in the inhibition of breast cancer. In human breast adenocarcinoma cell lines MDA-MB-231, the mitogen-activated protein kinase (MAPK) signalling pathway has been inhibited by C-phycocyanin purified from *A. platensis* revealing its anti-cancer effect (Jiang *et al*.,2018). In experimental mice, Markova *et al*., (2020) confirmed the capability of *A. platensis* in inhibiting the growth and proliferation of pancreatic cancer cells and recognised its angiogenic mechanisms.

5. Anti-inflammatory Properties

Inflammation is an immune response elicited by various elements including toxic compounds, pathogenic organisms and damaged cells leading to acute and/or chronic inflammatory responses in vital organs and biological systems, results in tissue damage or ailments. It is well-known that cyclooxygenase-2 (COX-2) is one of the major isoforms of enzymes associated with the inflammatory sites that produces prostaglandins (Fournier and Gordon, 2000). A study on human whole blood assay found that phycocyanin has the ability to suppress COX-2 significantly.

In an experimental model of colitis in rats, the anti-inflammatory effect of phycocyanin has been reported (González *et al*., 1999) and reduced activities of inflammatory markers *viz* IL-6, IL-1β, IL-1α and TNF were observed by the action of *A. platensis* (Abdel-Daim *et al.*, 2015). The anti-inflammatory effect of Spirulina was also studied in zymosan-induced arthritis in mice and it remarkably reduced the levels of zymosan-induced β-glucuronidase activity and the inflammatory reaction (Remirez *et al.*, 2002). These anti-inflammatory effects make Spirulina an effective candidate for the treatment of inflammation related disorders in animals and human

beings. Since most of these conclusions are drawn from animal studies, in order to fully validate the anti-inflammatory effects of Spirulina, further exploration is needed in human models.

6. Immunomodulatory Properties

The process in which immune responses is altered to the desired level is called immunomodulation and immunomodulators are the substances that are synthetic or biological in origin that can activate, regulate or hold down any aspect of the immune system (Kumar *et al.,* 2012). The extract obtained from Spirulina was found to have a vital role in stimulating NK cells in the immune system and this resulted in the enhanced phagocytic activity of macrophages. The aqueous extract also stimulates the production of cytokines and antibodies which activates and mobilizes the T and B cells (Schwartz & Shklar, 1987). An elaborate molecular mechanism of bioactivity of Spirulina derived C-phycocyanin in boosting immunomodulation was first reported by Hsiao *et al*., 2014. In murine macrophage cell lines, moderate stimulation of macrophages was observed in the presence of C-phycocyanin which increased the immunological activity of the cells (Chen *et al.,* 2014).

A progressive increase in the value of mean corpuscular hemoglobin (MCH) was observed in candidates supplemented with Spirulina, the MCH concentration was higher in males and older women appeared to benefit rapidly (Reboleira *et al.,* 2019). Dietary supplementation of *A. platensis* increased the hemolymph agglutination capacity and modulated the gene expression related to immunity in cyanobacteria fed shrimps (Pilotto *et al.,* 2019). Spirulina exerted its anti-inflammatory effects by providing relief to allergic rhinitis symptoms (Appel *et al*., 2018).

7. Anti-obesity and weight losing properties

According to the global nutrition report (2020), in India, 5.1% of women (18 years and more) and 2.7% of men suffers from obesity. The findings of Zeinalian *et al*. (2017) demonstrated that daily supplementation of *A. platensis* reduced the serum total cholesterol levels and appetite (Zeinalian *et al.,* 2017). The modulatory effects of *A. platensis* on anti-inflammatory pathways reduced triglyceride levels and helped in weight loss management (Yousefi *et al.,* 2018). The anti-obesity effects of Spirulina protein reduced glucose and total cholesterol levels and the modulation expressions of some key genes in the liver and brain helped in weight reduction (Zhao *et al.,* 2019). Spirulina protease hydrolyzate supplementation can directly affect lipid metabolism by influencing relational mRNA expression and by affecting the gut microbiome through HFD-induced lipid metabolism disorder in rats (Hua *et al.,* 2018).

8. Probiotic Properties

Probiotics are live microbial food with microorganisms that beneficially affect the host animal on consumption as a food supplement due to its prominent nutritional value. An *in vitro* study proved that the regular intake of Spirulina is anticipated to improve the growth of various strains of intestinal lactic acid bacteria (LAB) (Mazinani *et al.,* 2016). Celekli *et al*. (2019) identified that the addition of *A. platensis* has significantly increased the growth of probiotic bacteria such as *B. lactis, L. acidophilus, L. delbrueckii spp. bulgaricus* and *S. thermophilus* and the biochemical variables in comparison with the control after fermentation and within the storage. Another research demonstrated that the A. platensis biomass stimulated the growth of some starter cultures of LAB (Mocanu *et al.,* 2013).

CONCLUSION

Spirulina is reviewed as a superfood as it can reduce the detrimental impacts of malnutrition. *A. platensis* are excellent source of proteins, carbohydrates, essential fatty acids, vitamins, minerals especially calcium and potassium, carotenoids, chlorophyll and phycocyanin, which attributes pronounced biological functionality as depicted in figure 2. Despite, other properties including lipid lowering, suppression of fat deposition, prevention of tumor formation, enhancement of the immune system and the protective role to various organs makes Spirulina effective as a nutrient source as well as effective therapeutics. Spirulina pose wide application prospects in the area of aquaculture, food technology and pharmaceutics.

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