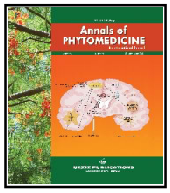
Annals of Phytomedicine 12(1): 79-92, 2023

DOI: http://dx.doi.org/10.54085/ap.2023.12.1.39

Annals of Phytomedicine: An International Journal
http://www.ukaazpublications.com/publications/index.php

Print ISSN : 2278-9839 Online ISSN : 2393-9885



Review Article : Open Access

Spirulina: A panacea for all human ailments

Divya Pingili◆, Archana Awasthi, Maryam Maqsood, K Sravya Devi, Patha Rasagna, Srinitha Bhagoji, Deepa N. Amminbavi and M. Bhagavan Raju

** Sri Venkateshwara College of Pharmacy, Madhapur-500081, Hyderabad, Telangana, India*

Article Info

Article history
Received 1 March 2023
Revised 20 April 2023
Accepted 21 April 2023
Published Online 30 June-2023

Keywords
Spirulina
Cynobacterium
Arthrospira
Phycocyanin
Phycocyanobilin
Phycobiloproteins

Abstract

In recent years, the idea of "superfoods" has interested people worldwide as most of them provide benefits irrespective of it being palliative or therapeutic. Spirulina is a cynobacterium of genus Arthrospira. Although unicellular, it is a storehouse of a great number of proteins, carbohydrates, vitamins, and essential nutrients. Spirulina is relatively easy to propagate considering it can be grown in both fresh water and wastewater, but only the former is implied for human use.

Spirulina basically steals the spotlight as it exerts antioxidant and anti-inflammatory properties due to phycocyanin, antiproliferative property due to phycocyanobilin (PCB), chlorophyllin, carotenoids, and polysaccharides, antianemic due to positive hematologic properties, immunomodulatory traits due to phenolics and phycocyanin, antihyperlipidemic potential due to polyunsaturated fatty acids (PUFA), and antihypertensive action due to phycobiloproteins in addition to low sodium value. Apart from these, it is also antimicrobial and aids in reversing the toxicity of some elements as well.The objective of this article is to present the efficacy of Spirulina in treating various human ailments and to project it as protecting agent of the human body.

This review presents Spirulina's great significance in treating various diseases. It can greatly affect the food, chemical, and pharmaceutical industries, provided its capacity is realized and popularized further in the near future.

1. Introduction

Spirulina is a unicellular, micro filamentouscyano bacterium of the genus Arthrospira which can be utilized in various facets of health maintenance, prevention and management of the disease; all with minimal side effects [Dillon *et al.,* 1995; Kay, 1991). Hence, it is of great importance to the food, chemical, and pharmaceutical industries (Volkmann *et al.,* 2008). Spirulina is rich in proteins (65%), carbohydrates (15%), lipids (6%), vitamins (0.75%) (especially B_{12}) and provitamin A (β-carotenes), essential minerals (8%), especially iron, magnesium and zinc (Ravi *et al.,* 2010). The reason it is hailed as a protein-rich source is that it contains all 8 essential amino acids namely: isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine; along with 10 non-essential amino acids. It is also a storehouse of other minerals like potassium, calcium, selenium, chromium, copper, manganese and sodium. Other carotenoids (apart from β-carotenes) include α-carotene, xanthophylls, cryptoxanthin, echinenone, zeaxanthin and lutein. Moreover, it is loaded with phenolic acids, γ-linolenic acid, chlorophyll, phycocyanin, tetrapyrroles and tocopherols. As *Spirulina*does not possess cellulose cell walls, most of it is assimilated by the consumer (85-95%) (Ravi *et al.,* 2010; Karko *et al.,* 2011).

Corresponding author: Dr. Divya Pingili
Sri Venkateshwara College of Pharmacy Madhapur-500081, Hyderabad, Telangana, India
E-mail: pingilidivya@gmail.com
Tel.: +91-9885223391

Spirulina is naturally an inhabitant of alkaline lakes of pH 11, usually high in sodium chloride and bicarbonates. Their commercial cultivation can be achieved in open reactors employing the use of both fresh water and wastewater. Yet, only the Spirulina cultivated under regulated conditions using fresh water is to be used for human consumption (Usharani *et al.,* 2012).

2. Cultivation of spirulina

Spirulina cultivation can be done in the presence of water with a wide variety of climatic conditions and environments, including tropical and subtropical climates, as well as open and closed environments. Spirulina growth necessitates a precise balance of chemicals and minerals. Throughout the cultivation cycle, the standard quality of water should be maintained (Ragaza *et al.,* 2020).

2.1 Conditions for spirulina cultural medium

- The concentration of sunlight should be between 20- 30 K luxfor optimal yield.
- The temperature has to be maintained between 30-35°C for optimum protein content, as well as a higher rate of production otherwise culture bleaching, occurs.
- pH levels should be between 8 and 11.
- Continuous oxygen supply is needed.
- Carbon dioxide and bicarbonate are required.

- Average water level in the pond or tank should be kept at 25 cm. Higher water levels in the tank can lead to difficulty in photosynthesis and algae development.
- Salt fertilizer (N, P, K, Na, Ca, Mg, Fe, S, *etc.*)

2.2 The cultural medium used in the cultivation process

- Crop-based organic substrates as a growth medium, such as molasses (Andrade *et al.,* 2007), cabbage extracts (Akhtar *et al*., 2015), sugarcane bagasse (Pelizer *et al.,* 2015), rice bran or other less expensive agricultural by-products (Ragaza *et al.,* 2020).
- Animal waste-based organic substrates as a growth medium, such as swine waste, Cattle waste (Mitchell *et al.,* 1998).
- Bio-digested poultry droppings and cow dung slurry obtained from biogas plants were cultivated in mud pots (Kumari *et al.,* 2020).
- Prawn hatchery wastewater mixed with seawater to make it cost-effective (Sandeep *et al.,* 2015).
- Wastewater (Volkmann *et al.,* 2008), Seawater (Leema *et al.,* 2013), and Industrial effluents (Amala *et al.,* 2013).
- A mineral water (Nguyet *et al.,* 2017)
- Zarrouk's medium: Replacement of potassium nitrate in Zarrouk's medium in place of sodium nitrate, is better for the growth performance and high yield of Spirulina (Zarrouk *et al.,* 1966).

2.3 Cultivation procedure

The pond water used for the cultivation process must be maintained with a proper pH level and the required amount of salt has to be added to make it alkaline. For commercial farming, a separate pond is required for seeding Spirulina. This reduces the need for regular purchases and allows the product to be sold to other farmers. The brief procedure for cultivating Spirulina is given in Figure 1. The amount of nutrients has to be checked throughout the process to improve the quality of the product. The harvesting time of production is determined by the concentration levels of algae and its color (Zhang *et al.,* 2015). The amount of Spirulina produced is primarily determined by the genus and species, exposure to light, temperature, pH, nutrient composition, CO_2 supply, and other factors (Lucie*et al.,* 2016).

Figure 1: Stages of Spirulina cultivation (Mathur*et al.,* 2018).

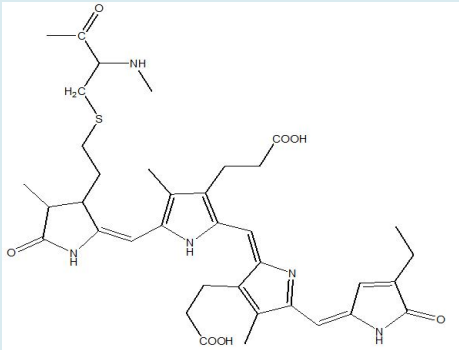
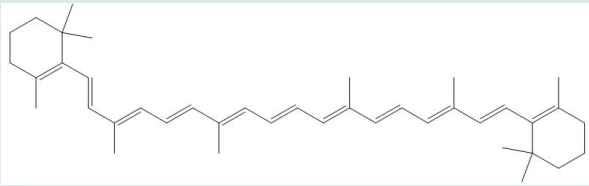
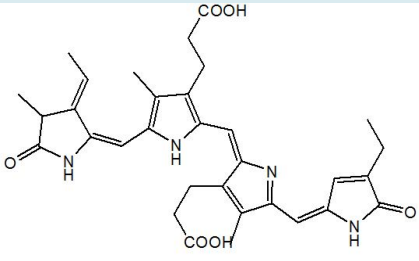
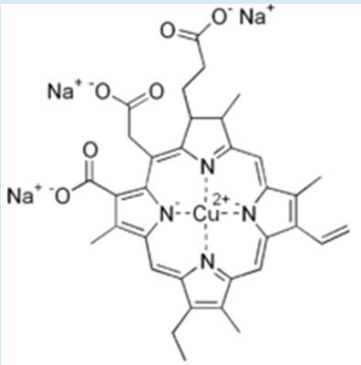
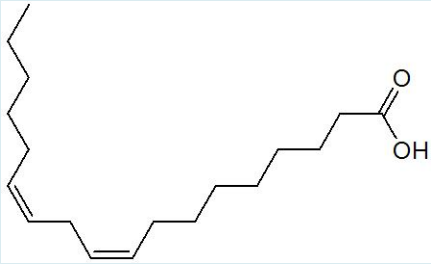
2.4 Other challenges in growing Spirulina

- Contamination should be avoided throughout the process.
- Insect breeding, foreign algae, and chemical contamination can all lead to decreased output.
- The presence of chlorine in the water leads to a decrease in production.
- Dried Spirulina powder should be stored immediately in an airtight container.
- The presence of mosquito larvae decreases production.
- Preservatives and additives are avoided.

3. Active chemical constituents of spirulina

Spirulina is said to possess a lot of active ingredients which can serve as a boon to the health of the people. It can be aptly designated as "Nature's wonder herb". In the pretext of the basic biochemical composition of Spirulina, it is found to contain 55-70% of protein with all essential amino acids in an amount higher than all standard plant proteins. It has precious amounts of polyunsaturated fatty acids (PUFA's) and vitamins like vitamin B_1, B_2, B_3, B_6, B_9, B_{12}, C, and D. It has a rich source of potassium, calcium, chromium, copper, iron, magnesium, manganese, phosphorous, selenium, sodium and zinc. Commercial Spirulina powder is found to contain 60% protein, 20% carbohydrates, 5% fats, 7% minerals, and 3-6% moisture and hence is considered a low-fat, low-calorie, and cholesterol-free source of protein. The active chemical constituents responsible for various pharmacological activities of Spirulina include phycocyanobilin, phycocyanin, β-carotene, chlorophyllin, linoleic acid, *etc.,* (Table 1) (Habib *et al.,* 2008).

Table1: Few important active constituents of Spirulina

Active constituents found in Spirulina	Structure
C-phycocyanin	
β-carotene	
Phycocyanobilin	
Chlorophyllin	
c-linolenic acid	

4. Pharmacological actions of Spirulina

Spirulina "The Food for Future" is bestowed with many pharmacological activities (Figure 2).

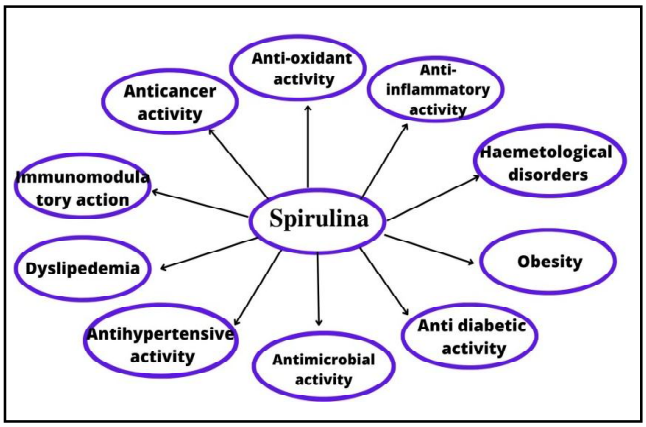


Figure 2: Various pharmacological activities of Spirulina.

4.1 Antioxidant activity

Antioxidants are majorly the substances that have been found to produce beneficial effects on our body by protecting it against the harmful effects of free radicals and thus have been found to play a role in some diseases which are generally associated with the formation of reactive oxygen species, which serves as one of the predisposing factors.

C-phycocyanin (Table 1) is one of the chief bile proteins that have been found to exist in *Spirulina platensis* that possess profound antioxidant and free radical eradicating properties (Karko *et al.,* 2011). This exhibits similar actions to that of bilirubin and biliverdin, the tetrapyrrolic antioxidants found in humans (Konickova *et al.,* 2014). Apart from this, Spirulina also contains β-carotene (Table 1) which also has good antioxidant and anti-inflammatory properties, which leads to a decrease in the incidence of cancers (Asghari *et al.,* 2016). Phycocyanin inhibits inflammatory mediators like tumor necrotic factor alpha (TNF-α), cyclooxygenase-2, and prostaglandin E2, which results in the decreased production of the same. Several pathways which mainly function by NF-Kβ, MAPK, p38, JNK, ERK ½ are restrained by the action of phycocyanin (Deng *et al.,* 2010).

Some of the active constituents in Spirulina were also found to be active against free radicals associated with some diseases explained below.

4.1.1 Sickle cell disease

Sickle cell disease is an inherited blood disorder. Nitric oxide loss and oxidative stress are the major causative factors for vascular abnormalities in sickle cell disease. Oxidative stress generates high levels of superoxide as it is associated with the changes in the NADPH activity and structural changes in the enzymes like nitric oxide synthase, and xanthine dehydrogenase (Figure 3). Phycocyanibilin, (Table 1) the key phytochemical of Spirulina mediates the inhibition of an enzyme NADPH oxidase which improves glutathione synthesis accompanied by an increase in the activity of antioxidant enzymes, thus establishing good control of oxidative stress in sickle cell disease. It can also be used as a part of FSAT (full spectrum antioxidant therapy) (Ravi *et al.,* 2010).

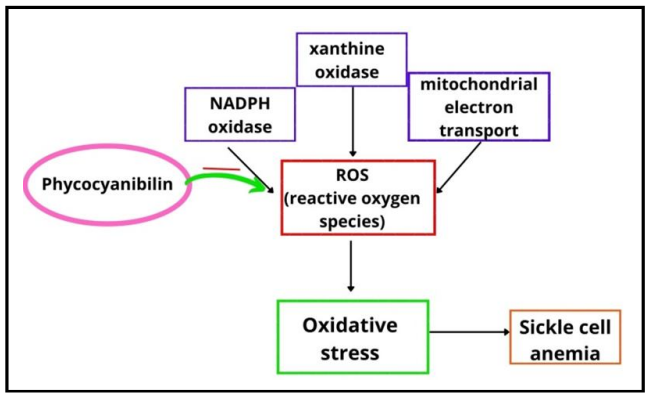


Figure 3: Role of phycocyanobilin in the management of sickle cell anemia.

4.1.2 Wound healing

Serving as a complete resource of chlorophyll, Spirulina exhibits promising wound healing effects. Chlorophyll has the ability to enhance tissue growth. Such activity leads to an increase in the rate of healing of wounds, hastens the growth of tissue, and decreases the severity of ulcers and oral sepsis (Asghari *et al.,* 2016).

4.1.3 Teratogenicity

Most of the abnormalities or malformations found in neonates can blame teratogenicity for their occurrence, one of their direct causes being an increase in free radical species. Thus, in order to establish the efficacy of Spirulina, a study was conducted on pregnant mice which showed a positive effect as an antioxidant. This was found to be dependent on the gradual dose administration that was done on the experimental animals (Ravi *et al.,* 2010).

4.1.4 Metal chelation

Spirulina's metal chelation properties, chiefly iron came into light when human neuroblastoma cells *in vitro* were exposed to toxic amounts of iron and then to Spirulina, which resulted in the reduction of iron-induced oxidative stress (Mohan *et al.,* 2014).

4.1.5 Miscellaneous

Apart from using the antioxidant property of Spirulina for therapeutic outcomes, it has also found an application as an antioxidant excipient in the formulation of nano-emulsions. All the nano-emulsions prepared as a part of the study possessed antioxidant activity, and electrostatic stability and their zeta potentials were below "30 mV (Costa *et al*., 2019). The lipid extracts from Spirulina species LEB18, exhibit good stabilizing action and act as biosurfactants. Spirulina is also efficient in providing symptomatic relief to free radical-related diseases like obstructive jaundice, diabetes, atherosclerosis, rheumatoid arthritis, recurrent aphthous stomatitis, cancer and also memory-related degenerative disorders (Ravi *et al.,* 2010; Mohan *et al*., 2014).

4.2 Anti-inflammatory activity

Inflammation is a localized physical condition wherein a part of the body becomes reddened, swollen and painful, mostly as a reaction to an injury or an infection. The major diseases characterized by the progress of inflammation have been found to be interlinked with the imbalance in nutrition and impaired immunity. Spirulina is proven to

inhibit various inflammatory pathways. The inflammatory pathway related to adipogenesis/lipogenesis can be suppressed by the administration of Spirulina. Spirulina promotes adipocyte differentiation/maturation by decreasing the stimulation of nuclear factor-mediated pathways which lowers the inflammatory conditions (Ku *et al.,* 2013). This wonder herb also decreases the HDAC2, 3 and 4 (Histone deacetylase) levels in macrophages (Pham *et al.,* 2016).

In the recent molecular mechanistic analysis, diminished production of inflammatory mediators like TNF-α, IL-1, IL-6, PGE2 and NO were noticed inthe administration of Spirulina which in turn suppressed the activities of COX-2 and iNOS (Abu-Taweel *et al.,* 2019).

4.3 Role of Spirulina in the diseases associated with inflammation

4.3.1 Hepatitis

Hepatitis, inflammation of the hepatocytes, is counteracted by *Spirulina platensis* (6.9%) in D-Galactosamine (D-GaIN) induced hepatotoxicity in rats. The 9% concentration of the same was found to elicit a similar effect in controlling hepatotoxicity as butylated hydroxyl toluene (BHT). In addition, it provides a protective effect when supplemented in the diet. A recent study indicated that patients with Hepatitis B virus showed lower qHBsAg with an improvement in their condition on supplementing with Spirulina (Clinical Trials. gov Identifier: NCT04718831).

4.3.2 Rheumatoid arthritis and colitis

The anti-inflammatory activity of Spirulina and its effective usage as a substitute for conventional NSAID (non-steroidal anti-inflammatory drug) therapy was revealed in an experiment conducted on a well-defined animal model for rheumatoid arthritis, adjuvant-induced rheumatoid arthritis in mice. This activity can be attributed to the chemical constituent phycocyanin present in Spirulina which significantly inhibits COX-2 selectively (Rasool *et al*., 2006). The chemical constituent phycocyanin also reduces myeloperoxidase (MPO) which is usually increased in ulcerative colitis.

4.3.3 Histamine related inflammation

Spirulina has been found to reduce the inflammation caused due to histamine. This cyanobacterium inhibits the release of histamine from mast cells, the production of which results in inflammation. It has also been found to inhibit arachidonic acid metabolism which ultimately inhibits prostaglandin synthesis (Nuhu *et al*., 2013). Increased expression of cyclic AMP further leading to inhibition of mast cell-mediatedimmediate-type hypersensitivity reactions while simultaneously inhibiting histamine was observed in mast cells of rats (Ravi *et al.,* 2010).

4.3.4 Periodontitis

Periodontitis is an inflammatory condition having sources of gram-negative bacterial organisms in plaque. Patients of periodontitis with the gingival condition as a complication, show reduced symptoms upon Spirulina treatment. Spirulina was applied for the treatment of Oral Submucous Fibrosis (OSMF) at 500 mg concentration twice a day. In comparison to betamethasone 4 mg/ml over a period of three months showed positive results in mouth opening, burning sensation and tongue protrusion. This efficiency can be owed to the presence of β-carotene, phenolic acid, tocopherol, and micronutrient content in Spirulina. Moreover, no side effects were observed (Desai *et al.,* 2017).

Inflammatory conditions attributed to microbial invasions, bacterial pathogens are recognized *via* receptors of the innate immune system like Toll-like receptors (TLRs) that are expressed in tissue-resident macrophages and stimulate the generation of inflammatory cytokines (*e.g.*, TNF-α, IL-1β, and IL-6), chemokines and PGE2 (Arulselvan *et al.,* 2016). These mediators and the complement system mediators are reduced by Spirulina, a natural product. Spirulina is a good antioxidant as well, this combined effect results in improved intestinal mucosal barrier function by reducing translocation of bacteria and endotoxin, resulting in reduced endotoxemia (Ravi *et al.,* 2010).

4.4 Anticancer activity

Spirulina forms a great choice for the novel management therapies of cancer as it has more weightage on the curative side of the intended therapy than on the palliative side. This is quite evident from its acceptance in dealing with various types of cancers.

4.4.1 Lung cancer

As of recent studies, lung cancer (LC) and respiratory tract cancers are the most common causes of cancer deaths among males and females in developed countries. There are many predisposing risk factors which make a person prone to LC such as tobacco smoking, air pollution, and exposure to carcinogens such as radon, asbestos, arsenic, silica, and polycyclic aromatic hydrocarbons. These factors are counteracted by the consumption of "chemo preventive agents" such as Spirulina and its derivatives (Czerwonka *et al.,* 2018).

In the case of human lung cancer A549, Spirulina shows anti-proliferative activity against A549 cells in a concentration-dependent manner. This action was achieved by cell cycle arrest in the G1 phase, the introduction of morphological changes in the tumor cells which leads to cell apoptosis, necrosis, cytoplasm swelling, thedisintegration of cell membranes, vacuolization and lysis. This culminates in a decrease of cancer cell count. Contrary to the drawback of conventional chemotherapeutic agents which usually do more harm than heal, the beneficial trait of Spirulina extracts is that it does not target normal fully functioning cells of the body (Czerwonka *et al.,* 2018).

4.4.2 Oral cancer

The wonder drug Spirulina was found to be very effective in treating oral cancers. The total tumor elimination was found in 30% of the animals receiving the extracts of Spirulina and Dunaliella extracts, while partial tumor regression was found in the remaining 70% of the animals. The control group showed no tumor regression.

In the clinical trials, 1g/day of Spirulina for chemoprevention of oral cancer was administered in patients with oral leukoplakia in whichthick, white patches form on the tongue and the lining of the mouth. It is effective in this case as well (Mohan *et al.,* 2014).

4.4.3 Pancreatic, hepatic and breast cancers

Spirulina exhibits antiproliferative activity in treating pancreatic, hepatic and breast cancers. This is due to presence of phycocyanobilin (PCB) and chlorophyllin, a derivative of chlorophyll a. When tested on human pancreatic cancer cell lines, within three days of treatment initiation, there was a decrease in the production of reactive oxygen

species in mitochondria. These factors in turn reduce the complexity of cancer by inducing mitochondrial-mediated apoptotic pathways (Konickova *et al.,* 2014).

The antioxidant and anticarcinogenic activity associated with tetrapyrroles of Spirulina has successfully inhibited the cancer cell multiplication within 24 h, accompanied by increased expression of the p53, BAX (pro-apoptotic gene) genes and reduced BcL-2 expression. This results in apoptosis.

Effects of Spirulina were studied in breast cancer cell lines at a dose of 800 mg/kg. It was elucidated that the expression of genes coding IL-4 and IL-10 was decreased, while the genes encoding IL-17, TNF-α and IFN-γ were markedly increased when treated with Spirulina. These findings imply that Spirulina induces tumoricidal effects *in-vivo* by increasing the production of inflammatory mediators TNF-α and IFN-γ.

The synergistic effect of selenium and phycocyanin complex (Se-PC) in Spirulina results in much stronger antioxidant activity which is capable of scavenging ABTS, DPPH and superoxide radicals. This complex also has protective effects on healthy RBCs against hydrogen peroxide-induced oxidative DNA damage. It also displays chemo preventive activity by acting as a potent anti-proliferating agent against human melanoma A375 cells and human breast adenocarcinoma MCF-27 cells (Kalafati *et al.,* 2010).

4.4.4 Acute myeloid leukemia

The Kasumi-1 cell line is an intensively investigated model system of acute myeloid leukemia. Administration of Spirulina extract obtained with 70% ethanol showed profound cytotoxicity in K562 and Kasumi-1 cell lines. This extract exhibits almost the same potency as that of cyclophosphamide, an alkylating chemotherapeutic agent employed in the treatment of cancer. This is attributed to the presence of phytopigments such as carotenoids, chlorophyll, phycocyanin and some polysaccharides. Phycocyanin possesses notable action against the growth of cancer cells (Hernande *et al.,* 2017).

4.4.5 Anaemia and haematologic disorders

The state of pregnancy requires optimum supplementation of iron and folic acid, the deficiency of which leads to anaemia. In such a case, it will lead to complications like preeclampsia, low birth weight, premature births and in severe cases, post-partum mortality. Supplementation of Spirulina to patients with these pre-existing risk factors leads to improvement in haemoglobin levels. To add to its credit, 1-2 g of Spirulina per day, for 3 to 6 months will eliminate both anaemia and also the chance of occurrence of stunted growth due to intra-uterine undernutrition.

Thalassemia is a genetic hematologic disorder resulting in impaired production of haemoglobin chains. This in turn leads to iron deposition in various tissues such as the heart, risking the occurrence of cardiomyopathy. Spirulina when used in this condition acts as a cardioprotective agent due to its antioxidant and metal chelating properties. It causes iron removal from the body due to its good chelation property. Spirulina in conjugation with amlodipine, a calcium channel blocker, further enhances the clearance of iron, regulating the iron levels in the body and decreasing the cardiac iron overload (Haggar *et al.,* 2018).

4.5 Arsenic poisoning

Arsenic poisoning is seen majorly in areas where people consume water contaminated with high amounts of arsenic. If arsenic poisoning occurs over a brief period of time vomiting, abdominal pain, encephalopathy, and watery diarrhoea that contain blood are predisposed. When in a group of 41 patients with chronic arsenic poisoning, a therapy of Spirulina extract (250 mg) along with zinc (2 mg) BID for 16 weeks was given, and the levels of arsenic showed significant changes (Misbahuddin *et al*., 2006).

Arsenic poisoning by pollutants or other contaminants is conventionally treated with drugs or antidotes that may lead to side effects or adverse drug reactions. Spirulina being a natural product is safer and more effective compared to these. Also due to its high antioxidants, mainly phycocyanin, its effect on metabolism and virtually zero per cent toxicity, it can also be considered as a co-adjuvant agent as it may exhibit a synergistic effect together with other drugs (Martinez-Galero *et al.,* 2016).

Spirulina also aids in the removal of nitrates and phosphates and hence can be employed in reducing their specific concentrations as well (Lodi *et al.,* 2003).

4.6 Immunomodulation

The presence of active compounds such as phenolics, phycocyanins and polysaccharides renders Spirulina an active antioxidant, anti-inflammatory and immunostimulating agent. The main mechanism by which Spirulina affects immunity is by enhancing the phagocytic activity of macrophages resulting in the accumulation of natural killer (NK) cells in tissues, by antibody and cytokine stimulation, activation and mobilization of T and B lymphocytes.

The constituents of Spirulina have been found to be more effective in innate immunity, enhancing the activity of natural killer cells, macrophages and neutrophils. Immulina, the high molecular weight polysaccharide found in Spirulina, elicits immunostimulatory activity. This effect is achieved by increased IL-1β and TNF-α expression and by stimulating nuclear factor kappa-β (NF-kB) pathway. It also stimulates COX-2 and Th-1 cells (Ravi *et al.,* 2010).

The studies have pointed out the importance of Spirulina in enhancing mucosal immunity by up surging the levels in human saliva. In the cases relating to diminished immunity due to nutritional deficiencies, Spirulina may provide adequate nutrient supplementation to activate or modulate the host immune system (Karko *et al.,* 2011).

In specific scenarios, where a delayed type of hypersensitivity reaction (Type IV) is induced in mice, the administration of *Spirulina fusiformis* in a dose of 400-800 mg/kg showed a reduction in hypersensitivity reactions, TNF-α production and immune response. A concentration-dependent decrease in T lymphocyte production is also seen *in vitro*. Immunosenescence, which refers to the gradual deterioration of the immunity of a person bought on by the natural ageing process; can also be improved by the administration of Sprirulina as a prophylactic therapy (Wu *et al.,* 2016).

4.7 Allergic rhinitis

Allergic rhinitis, also known as Hay fever, is an allergic response causing itchy, watery eyes, sneezing and other symptoms. This has been known to affect 10-25% of the population (Cemal *et al*., 2008). A lot of studies carried out on experimental models suggest the use

of Spirulina in reducing the inflammation caused by rhinitis. Spirulina has been found to significantly inhibit the release of histamine which is usually increased in allergic reactions (Yang *et al*., 1997).

This was further confirmed when Spirulina (0.001 to 10 µg/ml) dose-dependently inhibited the histamine release from rat peritoneal mast cells (RPMC) in drug-induced allergic reactions (Kim *et al.,* 1998).

The mechanism behind this is a decrease in the levels of cytokines namely IL-4, interferon-c, and interleukin which is brought about by Spirulina as a result of which the use of Spirulina in lowering allergic rhinitis has been stressed upon. Clinical presentations like nasal discharge, sneezing, nasal congestion, and itching have been ameliorated upon the usage of Spirulina. It has also been established that Spirulina is effective and tolerable compared to conventional treatments (Cingi *et al.,* 2008).

4.8 Dyslipidemia

Dyslipidemia is characterized by abnormally elevated cholesterol levels or fats (lipids) in the blood. It is considered one of the major health complications for the majority of the population.

A study conducted earlier has shown that Spirulina when administered in patients shows no significant increase in high-density lipoprotein (HDL) but the beneficial reduction of low-density lipoprotein (LDL) cholesterol was observed after 8 weeks of treatment. The atherogenic effect, leading to atherosclerosis had also declined. It reduces the amount of low-density lipoproteins by reducing their oxidation. Thus, Spirulina supplementation also has positive effects on total plasma lipids (Huang *et al.,* 2018).

Spirulina acts by inhibiting the absorption of cholesterol in the intestine, increases the concentration of lipoprotein lipase and promotes lipoprotein disintegration. The presence of polyunsaturated fatty acids in Spirulina is responsible for its anti-lipidemic activity (Szulinska *et al.,* 2017). The presence of 5-6% c-linolenic acid in Spirulina is effective in lowering plasma cholesterol levels. The c-linolenic acid (more active) is obtained from linolenic acid (less active) after ingestion by the action of the enzyme delta-6-desaturase. After its conversion, it acts on the increased lipid levels and reduces them (Ramamoorthy *et al.,* 1996).

4.8.1 Fatty liver

When Spirulina has been initiated at an approximate dose of 2 g/day for 2 months, it reduces serum aspartate aminotransferase, TG, and TC. This points out the hepatic protective activity of Spirulina (by decreasing the liver lipid profile). Thus, it can be trusted to produce good effects onhypercholestemia and decrease the risk of fatty liver. Hence, it also has positive effects on non-alcoholic fatty liver disease (NAFLD) (Szulinska *et al.,* 2017).

Another study has shown that Spirulina administration during high fat-induced NAFLD modifies the hepatic expression of miR-21, miR-34a and miR-122 and their target genes HPB1 (The hPB1 gene is located on chromosome 3p21, where some of the tumor suppressor genes have been mapped), SIRT1, and SREBP -1c, respectively. This shows the efficacy of Spirulina as an antisteatite supplement (Oriquat *et al.,* 2018).

4.8.2 Atherosclerosis

The initiation and propagation of atherosclerosis, which is a complication of dyslipidemia, can be reduced by the administration of Spirulina which thus reduces the risk of related cardiovascular diseases (Cheong *et al.,* 2010).

4.8.3 Metabolic syndrome

Spirulina when administered in metabolic syndrome, decreases dyslipidemia and also ameliorates the visceral adipose tissue macrophages. This effect was found to be prominent in mice, hence it may pass as a safe supplement in the treatment of metabolic syndrome (Fujimoto *et al.,* 2012).

4.8.4 Ischemic heart disease

Spirulina when administered to IHD patients showed a notable decrease in blood TC, TG, and LDL. A healthy increase in HDL levels was also noted (Ramamoorthy *et al.,* 1996).

4.9 Anti-hypertensive activity

Hypertension is defined as blood pressure above 140/90 mmHg and is considered severe if the pressure is above 180/120. Eventually, it has the risk of developing into severe cardiovascular disease.

Earlier studies have proved that *Spirulina maxima* showed a positive effect on maintaining lipids all the while reducing systolic and diastolic blood pressure.

In experimental specimens with pre eclampsia showing increased systolic BP, GTT, and vascular contractility, Spirulina was shown to have anti-hypertensive action. This action is mainly due to the phycobiliproteins present in it, which decrease systolic blood pressure and re-establish other suppressed enzymatic functions. Hence, this can preclude the risk posed by fetoplacental ischemia and therefore can be employed as prophylaxis therapy in high-risk patients.

The high potassium, and low sodium composition of Spirulina, have positive effects on blood pressure. It has been proposed that C-phycocyanin inhibits platelet aggregation and coagulation by blocking calcium channels and mediating free radicals released by the platelets (Hsiao *et al.,* 2005).

An angiotensin 1-converting enzyme (ACE) inhibitory peptide Ile-Gln-Pro was extracted from the alcalase digests of *Spirulina platensis* by gel filtration chromatography and RP-HPLC. The extracted peptide was successful in showing resistance to the degradative actions of the gastrointestinal proteases. The isolation of this compound reinstates the potency of Spirulina in the treatment of hypertension (Lu *et al.,* 2010).

4.10 Antimicrobial activity

4.10.1 Antiviral activity

Calcium spirulan, a sulfated polysaccharide component found in Spirulina has been credited with antiviral properties. The presence of this component is responsible for the inhibition of the replication of several viruses like CMV, mumps, Influenza A, HIV-1, and measles in human T-cells, mononuclear cells, and Langerhans cells (Ravi *et al.,* 2010; Hayashi *et al*., 1996). Spirulina also activates macrophages and the T and B cells. Sulfolipids derived from Spirulina have also proved effective against HIV.

The advantage of using natural products in treating certain viral infections is that they can be further taken advantage of by immunomodulatory techniques; even when the infection is already established (Karko *et al*., 2011).

4.10.2 Antibacterial activity

0.1% Spirulina was found to enhance bacterial resistance as shown by the production of phagocytotic cells, like heterophils, thrombocytes, macrophages, and monocytes chicks. The microalgal cultures of *Spirulina platensis* have displayed significant antibacterial activity against mainly six Vibrio strains: *V. parahaemolyticus,V. anguillarum, V. splendidus, V. scophthalmi, V. alginolyticus, and V. lentus* (Kokou *et al.,* 2012). Antibacterial activity against *Streptococcus pyogenes* or *Staphylococcus aureus* was shown by phycobiliproteins obtained from *Spirulina fusiformis*. C-phycocyanin from *Spirulina platensis* also inhibits some resistant bacteria like *E.coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, and Staphylococcus aureus*. Spirulina is also responsive toward tetanus toxoid (TT) (Sarada *et al.,* 2011).

4.10.3 Antifungal activity

Candida species of yeasts are the main cause of many fungal infections afflicting mankind today, the major one being *Candida albicans*. The water extract of *Spirulina platensis* is active against 22 strains of candida species. It exhibits fungicidal activity and may promise early eradication of infection (Antonella *et al.,* 2017). Administration of Spirulina also brings about changes in cytokine production and leukocyte proliferation (Ravi *et al.,* 2010), hence can be used as an alternate therapy in fungal invasions (Antonella *et al.,* 2017). Apart from these, the general immune boosting capacity of Spirulina can be trusted to provide protection to the body from minor and general infections.

4.11 Muscle strength and endurance

Muscle fatigue is characterized by tiredness and inability to gain muscle which is usually due to exercise-induced oxidation. *Spirulina platensis,* being a protein-rich supplement with easy digestibility due to the absence of cellulose, is a good choice for a body-building food. It also contains many essential non-toxic amino acids which aid in muscle enhancement. Spirulina enhances the functions of LDH (lactate dehydrogenase) in the sarcoplasm of skeletal muscles. Along with this, it reduces exercise-induced oxidative stress by exhibiting its antioxidant property (Lu *et al.,* 2006). Spirulina treatment for a period of 8 weeks is effective in enhancing isometric muscle endurance and strength (Sandhu *et al.,* 2010).

4.12 Diabetes

Diabetes is a group of diseases that result in excess blood glucose and may lead to complications if not controlled.

The blood sugar lowering the capacity of Spirulina may be attributed to its antioxidant activity, which helps in ameliorating diabetic conditions. The Spirulina supplementation (5%) in alloxan-induced diabetic rats led to a decrease in fasting blood glucose and an increase in glycogen levels. When compared with an insulin dose of 0.5 IU/rat for a period of 21 days, Spirulina was observed to be more potent than insulin. Hence, it could be used as a successful supplement in the management of diabetes (Gargouri *et al.,* 2016).

A similar study that compared the effects of EPO (erythropoietin) and Spirulina in rats concluded that Spirulina is still more effective in relieving diabetic symptoms than EPO. The major changes observed were a decrease in glucose and NO while increase in insulin, SOD (superoxide dismutase), and CAT (catalase). Histologically, the condition of pancreatic cells (β cells-islets of Langerhans) and acinar cells was improved (Desouki *et al.,* 2015).

Spirulina in doses of 2 g/day for 2 months supplied to diabetic rats increases hexokinase activity and decreases the glucose-6-phosphatase activity. This along with NADPH oxidation leads to an increase in glucose utilization by liver cells. Therefore, leading to a reduction in fasting, post-prandial blood glucose, and HbA1c levels. Interestingly, *Spirulina platensis* attenuates pyruvate carboxylase, and pro-apoptotic genes as well, thereby acting as an anti-apoptotic agent. By reducing activation of the MAPK pathway (Mitogen-Activated Protein Kinase) in hepatic cells and inducing repair of the damaged hepatic cells and pancreatic β cells, it has proved itself as an effective anti-diabetic agent.

When another batch of diabetic rats was treated with metformin (200 mg/kg) and Spirulina (250 or 500 or 750 mg/kg) for 30 days, Spirulina amplified the HFD/STZ-induced elevation of fasting blood glucose, insulin and liver enzymes. Spirulina successfully corrected the disrupted serum lipid profile and the impaired anti-inflammatory effect by inducing changes in TNF-α and adiponectin. Spirulina also reduced the expression of hepatic sterol regulatory element binding protein-1c (SREBP-1c) proving its lipotropic nature. Furthermore, Spirulina improved the hepatic mitochondrial biogenesis signaling pathway by promoting the increase of peroxisome proliferator-activated receptor-gamma coactivator-1α (PGC-1α), mitochondrial transcription factor A (Tfam) and mitochondrial DNA (mtDNA) levels. The results concluded that the highest dose of Spirulina showed almost the same potency as that of metformin (Oriquat *et al.,* 2019). Another similar study also came to the conclusion that Spirulina is safer and of equal effectiveness when compared to metformin (Alam *et al.,* 2016).

Spirulina maximus can be used as prophylaxis for fatty liver in diabetic subjects as it reduces hepatic risks as well (Rodríguez *et al.,* 2001).

4.13 Obesity

Obesity is a condition in which excess body fat gets accumulated to such an extent that it may have a negative impact on health. Spirulina when given to obese patients significantly reduces the risk of obesity-related hypertension by successfully improving lipid profile, insulin sensitivity and total antioxidant status of their bodies. This gradually results in a decrease in total body weight (Szulinska *et al.*, 2017).

Effective weight management in obese patients can be successfully done by Spirulina intake (500 mg*4 Spirulina tabs with a restricted calorie diet) as it results in a reduction of body weight and circumference, body fat and BMI thus, effectively ameliorating anthropometric measurements and obesity-induced metabolic disorders. On a molecular level, reduced quantities of triglycerides and C-reactive proteins were observed (Yousefi *et al.,* 2018).

Thus, Spirulina supplementation in obese patients is indeed very beneficial for accelerated weight reduction and optimum weight management.

4.14 Nutritional deficiencies

Malnutrition is a widespread condition seen due to the lack of sufficient nutrients in the body. This is also a major obstacle the country as a whole needs to tackle. The nutrient-enriched food supplement Spirulina is a very promising alternative at this junction time. The following are the major constituents of Spirulina that make it a supplement of superior nutritional value (Table 2).

Table 2: Major constituents of Spirulina (Ravi *et al.*, 2010)

Nutrient	% Composition	Details
Protein	65	All 8 essential amino acids: isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophane and valine. 10 non-essential amino acids: alanine, arginine, aspartic acid, cysteine, glutamic acid, glycine, histidine, proline, serine, tyrosine.
Carbohydrates	15	
Lipids	6	Gamma-linolenic acid (GLA), alpha-linolenic acid (ALA), linolenic acid (LA), stearodonic acid (SDA), ecosapentanoic acid (EPA), docosahexanoic acid (DHA), and arachidonic acid (AA).
Vitamins	0.75	Thiamine (B1), riboflavin B2), niacin (B3), pyridoxine(B6), folic acid (B9), cyanacobalamin (B12), biotin (B7), vitamin D, pantothenic acid (B5), vitamin E (tocopherol), inositol.
Minerals	8	Potassium, calcium, chromium, copper, iron, magnesium, manganese, phosphorus, selenium, sodium and zinc.
Carotenoids	346 mg/100 g	Alpha-carotene, beta-carotene, xanthophylls, cryptoxanthine, echinenone, zeaxanthin and lutein.
Other pigments		Chlorophyll, phycocyanin, porphyrin, phycoerythrin, tetrapyrrole, and phytonadione.
Moisture	3.80	

Positive improvement of β-carotenes, albumin, prealbumin, protein, and haemoglobin after Spirulina supplementation was observed. 1g/ day of Spirulina when used in a trial to treat children suffering from chronic vitamin A deficiency reduced the incidence of visual symptoms in them drastically, from 80% to 10% (Mishra *et al.,* 2014).

When supplied in adequate quantities to the body, Spirulina can hope to eradicate deficiency disorders like anemia, marasmus, rickets, kwashiorkor, folate insufficiency, or nervous system injury. Four commercially available preparations of Spirulina and zinc namely: BioSpirulina, Spiru Complex, Spiru Zinc, and Zink Spirulina+acerola, are of great importance as well.Thus, fortifying the body with Spirulina's nutrients can help the population achieve a good nutritional balance.

4.15 Toxicity

4.15.1 Neurotoxicity

Spirulina due to its antioxidant and anti-inflammatory characteristics has been proven effective in reducing the inflammation brought on as a consequence of neurodegenerative disorders like Parkinson's disease (PD). Usually, an increase in microglial activation in the substantianigra pars compacta (SNpc) occurs due to a decrease in tyrosine hydroxylase (TH) positive cells. This may present itself as neurotoxicity at any stage of the disease. Spirulina reverses this effect and also induces MHCII expression, decreases microglial activation, and increases expression of the fractalkine receptor or neurotactin (CX3CR1) on microglia. Thus, it exhibits neuroprotective action (Pabon *et al.,* 2012).

Additionally, Spirulina also retards neurological damage in ageing animals, ALS, and decreases the damage caused by strokes, which furthermore increases its importance in preventing Ischemic brain damage (Wang *et al.,* 2005).

4.15.2 Nephrotoxicity

In a study where rats with cisplatin-induced nephrotoxicity were treated with Spirulina, they showed that superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase were increased and lipid peroxidation was decreased due to Spirulina pretreatment regimen thus, protecting the rats from cisplatin-induced nephrotoxicity. The elevated levels of plasma urea, creatinine, urinary beta-NAG, plasma and kidney tissue MDA, and subsequent tissue toxicity were significantly attenuated by Spirulina (Mohan *et al.,* 2006).

Another similar chemotherapeutic drug, cyclophosphamide also induces urotoxicity and hemorrhagic cystitis. Due to the induction of modulation in levels of malondialdehyde (MAD) and glutathione, Spirulina effectively reduces urotoxicity. This is also attributed to its antioxidant and antiapoptotic nature. This can be effectively put to use when in pursuit of reducing adverse drug reactions.

4.15.3 Ovarian toxicity/dysfunction

In a female mice model consisting of monosodium glutamate (MSG) induced ovarian dysfunction, the administration of *Spirulina platensis* upregulated the ovarian antioxidant mRNA genes, glutathione peroxidase, SOD, and CAT. This resulted in an improvement in the levels of sex hormone content and ovarian enzymatic antioxidants. An overall recuperation in ovarian tissue alteration was observed. Hence, Spirulina reduces ovarian dysfunction symptoms (Abdel *et al.,* 2018).

4.16 Anti-pyretic

Spirulina platensis in comparison with *Spirulina lonar* was found to be more effective in reducing the body temperature as it works as a potent antipyretic agent in doses of 2 or 4 mg/kg administered to a batch of rats with Brewer's yeast-induced pyrexia, involving readings taken every 8 h indicating a dose-dependent relationship (Somchit *et al.,* 2014).

4.17 Radioprotective nature

Spirulina promotes the growth of hematopoietic stem cells and progenitor cells and promotes effective differentiation of the same after lethal Co-c radiation. Due to this nature, it can be utilized to relieve the side effects of chemo and radiotherapy which are commonly used in cancer treatment (Subhashini *et al.,* 2004).

One of the polysaccharides of *Spirulina platensis* displays radioprotective effects against γ-ray-induced bone marrow damage in dogs and mice (Zhang *et al.,* 2001). C-phycocyanin from Spirulina is responsible for selectively stimulating the lymphocyte antioxidant defense mechanisms in human subjects. It also protects the γ-ray-irradiated bone marrow from the harmful effects of radiation, by reducing the bioavailability of bionuclides due to their antioxidant nature (Young *et al.,* 2016).

5. Recent advances

5.1 Biofuel production

A recent move towards using Spirulina for environmentally friendly alternatives was to use it to produce bioethanol by applying the process of simultaneous saccharification and fermentation (SSF) of Spirulina sp. LEB 18. By subjecting the biomass and corn starch to fermentation, we obtain biopeptides from bioethanol residue, with the enzymatic activity of a protease (Figure 4). This prospect of bioethanol production using Spirulina brings forward a shift towards the concept of biorefinery with promising products as, when the biopeptides from bioethanol residue were evaluated, they were found to be high in antioxidant potential. This, points toward its applicability to nutraceuticals and the food industry (Astolfi *et al.,* 2019).

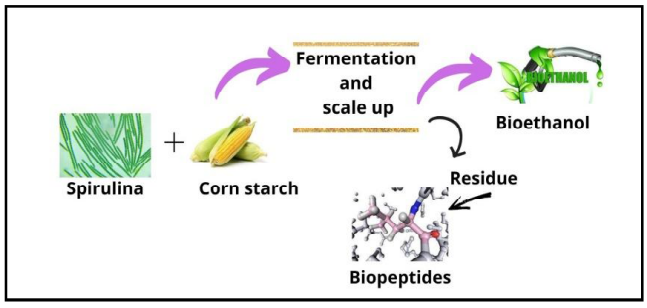


Figure 4: Biofuel production from Spirulina (Astolfi *et al.,* 2019).

5.2 Enhancing cardiovascular fitness

Another recent advance involving the implementation of Spirulina comes to light when a study was conducted with fifty-two young sedentary men with a BMI indicative of an overweight body who were inducted into an RCT which studied the efficacy of combining a systemic physical exercise with either *Spirulina maxima* or a placebo supplement given at 4.5 gms/day. The subject's BMI, lipid profiles and maximum oxygen uptake were measured before and after the proposed intervention. It leads to the conclusion that Spirulina maxima supplementation exhibited an optimistic synergism compared to placebo when paired with exercise. Beneficial effects were noted in terms of body composition and cardiovascular fitness. This could hold a significant value in today's busy lifestyles due to which young people are prone to develop NCDs (non-communicable diseases) (*Hernandez et al.,* 2018).

6. Outlook

Spirulina and all its derivative products present themselves as a potential modern solution to a huge number of human ailments that present a challenge in today's world. With antioxidant, anti-inflammatory, anti-malignant, hematologic, immunomodulatory, antiallergic, antilipidemic, antihypertensive, antimicrobic, antidiabetic, nutrient replenishing, antipyretic and radioprotective potential, it can contribute towards the development of pharmaceutical research sector in its favour. This in turn will enable product formulations for the nutraceutical industry.

7. Conclusion

The purpose of our review was to bring out awareness about a "superfood" that might just be the reason why drug developers find solutions to ailments that affect mankind today. The excellent nutritional value, health benefits, and wide range of applications made us choose this particular cyanobacterium. Being an all-in-one source of vitamins, antioxidants, and proteins, they are also promising candidates for anti-inflammatory, antiviral, and antineoplastic biomolecules.The testing pandemic times saw a lot of us, medical as well as non-medical specialties, look for an answer to increasing immunity without the use of synthetic drugs. Reviewing the various aspects of what this algal biomass has to offer us, we would like to address different viewpoints corresponding to the fields of use, while deducing their justifications.

Acknowledgments

The support from the Department of Pharmaceutical Chemistry and Pharmacognosyof Sri Venkateshwara College of Pharmacy is gratefully acknowledged.

List of abbreviations

ABTS - 2,2-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)

ACE - Angiotensin 1-converting enzyme

ALS - Amyotrophic lateral sclerosis

Beta-NAG - N acetyl beta glucosamidase

BHT - Butylated hydroxyl toluene

BMI - Body mass index

BP - Blood pressure

CAT - Catalase

CMV - Cytomegalovirus

COX-2 - Cyclooxygenase 2

D-GaIN - D-Galactosamine

DNA - Deoxyribonucleic acid

DPPH - 2,2-diphenyl-1-picrylhydrazyl

EPO - Erythropoetin

ERK - Extracellular signal regulated kinase

FSAT - Full spectrum antioxidant therapy

GTT - Glucose tolerance test

HBsAg - Heapatitis B surface antigen

HDAC - Histone deactylase

HDL - High-density lipoprotein

HFD/STZ - High fat diet/streptozotocin

HIV-1 - Human immunodeficiency virus

IHD - Ischemic heart disease

IL - Interleukin

iNOS - Inducible nitric oxide synthase

JNK - c-Jun-N-terminal kinase

LC - Lung cancer

LDH - Lactate dehydrogenase

LDL - Low-density lipoprotein

MAD - Malondialdehyde

MAPK - Mitogen activated protein kinase

MDA - 2,3-methylenedioxyamphetamine

MHCII - Major histocompatibility molecule

mRNA - Messenger ribonucleic acid

MSG - Monosodium glutamate

mtDNA - Mitochondrial DNA

NADPH - Nicotinamide adenine dinucleotide phosphate

NAFLD - Non-alcoholic fatty liver disease

NCDs - Non-communicable diseases

NF-Kα - Nuclear Factor Kappa-κα

NK - Natural killer

NO - Nitric oxide

NSAID - Non-steroidal anti-inflammatory drug

OSMF - Oral submucous fibrosis

PCB - Phycocyanobilin

PD - Parkinson's disease

PGC-1γ - Peroxisome proliferator-activated receptor-gamma coactivator-1γ

PGE2 - Prostaglandin E2

PGE2 - Prostaglandin E2

PUFA - Poly unsaturated fatty acids

RBC - Red blood cells

RCT - Randomized controlled trial

RP-HPLC - Reverse phase high performance liquid chromatography

RPMC - Rat peritoneal mast cells

Se-PC - Selenium and phycocyanin complex

SNpc - Substantianigra pars compacta

SOD - Superoxide dismutase

SREBP-1c - Sterol regulatory element binding protein-1c

SSF - Simultaneous saccharification and fermentation

TC - Total cholesterol

Tfam - Mitochondrial transcription factor A

TG - Triglycerides

TH - Tyrosine hydroxylase

Th-1 - T-helper cells

TLRs - Toll-like receptors

TNF-α - Tumor necrotic factor alpha

TT - Tetanus toxoid

Conflict of interest

The authors declare no conflicts of interest relevant to this article.

References

Abu-Taweel, G.M. (2019). Spirulina consumption effectively reduces anti-inflammatory and pain-related infectious diseases. J. Infect. Public Health, **16**:231-34.

Alam, A.; Siddiqui, M.A.; Quamri, A.; Fatima, S. and Roqaiya, M. (2016). Efficacy of spirulina (Tahlab) in patients of type 2 diabetes mellitus (Ziabetus Shakri). A randomized controlled trial. Journal of Diabetes and Metabolis, **7**:10

Andrade, M.R. and Costa, J.A.V. (2007). Mixotrophic cultivation of microalga Spirulina platensis using molasses as organic substrate.Aquaculture, **2**(64):130-134.

Akhtar, N.; Ahmed, M.; Hossain, A.; Jahan, M. and Akhter, H. (2015). Growth response of *Spirulina platensis* (Nordst) Geitler, in cabbage extract and antibacterial activities in different culture media. Bangladesh Journal of Scientific and Industrial Research, **49**(4):205-210.

Amala, K. and Ramanathan, N. (2013). Comparative studies on the production of *Spirulina platensis* on the standard and newly formulated alternative medium. Science Park, **1**(1):1-10.

Asghari, A.; Fazilati, M.; Latifi, A.; Salavati, H. and Choopani, A. (2016). A review on antioxidant properties of Spirulina. Journal of Applied Biotechnology Reports, **3**(1):345-351.

Arulselvan, P.; Fard, M.T.; Tan, W.S.; Gothai, S.; Fakurazi, S.; Norhaizan, M.E. and Kumar, S.S. (2016). Role of antioxidants and natural products in inflammation.Oxidative Medicine and Cellular Longevity, pp:5276130.

Astolfi, L.; Angela, Rempel Alan, Cavanhi, A.F. and Vítor,and Alves, M. (2019). Simultaneous saccharification and fermentation of Spirulina sp. and corn starch for the production of bioethanol and obtaining biopeptides with high antioxidant activity. Bioresource Technology, **301**:122698.

Abdel Aziem, S.H.; Abd El-Kader, H.A.M.; Ibrahim, F.M.; Sharaf, H.A. and El Makawy, A.I. (2018). Evaluation of the alleviative role of *Chlorella vulgaris* and *Spirulina platensis* extract against ovarian dysfunctions induced by monosodium glutamate in mice. J. Genet. Eng. Biotechnol., **16**(2):653-660.

Costa, A.M.; Bueno, K.T.A.; Centeno, A.P. and Costa, J.A.V. (2019). The antioxidant activity of nanoemulsions based on lipids and peptides from Spirulina sp. LEB18 LWT.Food Science and Technology, **99**:173-178.

Clinical Trials. gov Identifier: NCT04718831: Spirulina (FEM-102) Supplement to chronic hepatitis B patients [Internet]. Clinical trials. gov. Available from: https://clinicaltrials.gov/ct2/show/NCT 04718831.

Czerwonka, A.; Kaawaj.K.; Sawińska Brych, A.; Lemieszek, M.K.; Bartnik, M.; Wojtanowski, K.K.; Zdzisińska, B. and Rzeski, W. (2018). Anticancer effect of the water extract of a commercial Spirulina (*Arthrospira platensis*) product on the human lung cancer A549 cell line. Biomed Pharmacother., **106**:292-302.

Cingi, C.; Conk-Dalay, M.; Cakli, H. and Bal, C. (2008). The effects of Spirulina on allergic rhinitis. Eur. Arch. Otorhinolaryngol, **265**(10):1219-1223.

Cingi, C.; Conk-Dalay, M.; Cakli, H.; Bal, C.; Yang, H.N.; Lee, E.H. and Kim, H.M. (1997). *Spirulina platensis* inhibits anaphylactic reaction. Life Science, **61**:1237-1244.

Cheong, S.H.; Kim, M.Y.; Sok, D.E.; Hwang, S.Y.; Kim, J.H.; Kim, H.R.; Lee, J.H.; Kim, Y.B. and Kim, M.R. (2010). *Spirulina prevents* atherosclerosis by reducing hypercholesterolemia in rabbits fed a high-cholesterol diet. J. Nutr. Sci. Vitaminol (Tokyo). **56**(1):34-40.

Dillon, J.C.; Phuc, A.P. and Dubacq, J.P. (1995). Nutritional value of the alga Spirulina. World Review of Nutrition and Dietetics,**77**:32-46.

Deng, R. and Chow, T.J. (2010). Hypolipidemic, antioxidant, and anti-inflammatory activities of microalgae Spirulina. Cardiovascular Therapeutics, **28**(4):33-45.

Desai, K.M.; Hallikerimath, S. and Kale, A. (2017). Spirulina: An emerging treatment modality for the management of oral submucous fibrosis. International Journal of Oral Care and Research, **5**(4):328-331.

Desouki, G.A.; Tabl, K.K.; Abdel-Aziz, E.; Salim, N. and Nazeeh. (2015). Improvement in beta-islets of langerhans in alloxan-induced diabetic rats by erythropoietin and Spirulina. The Journal of Basic and Applied Zoology, **71**:20-31.

Fujimoto, M.; Tsuneyama, K.; Fujimoto, T.; Selmi, C.; Gershwin, M.E. and Shimada, Y. (2012). Spirulina improves non-alcoholic steatohepatitis, visceral fat macrophage aggregation, and serum leptin in a mouse model of metabolic syndrome. Dig. Liver Dis., **44**(9):767-74.

Gargouri, M.; Magné, C. and El-Feki. (2016). Hyperglycemia, oxidative stress, liver damage and dysfunction in alloxan-induced diabetic rat are prevented by Spirulina supplementation. Nutrition Research, **36**(11):1255-1268.

Habib, M.A.B.; Parvin, M.; Huntington, T.C. and Hasan, M.R. (2008). A review on culture, production and use of Spirulina as food for humans and feeds for domestic animals and fish. FAO Fisheries and Aquaculture Circular.No. 1034. Rome, FAO. pp:33.

Hernande.F.; Yohana, F.; Khandual, Sanghamitra, and López, R. (2017). Cytotoxic effect of *Spirulina platensis* extracts on human acute leukemia Kasumi-1 and chronic myelogenousleukemia K-562 cell lines. Asian Pacific Journal of Tropical Biomedicine, **7**:14-19.

Haggar, E.l.; Sahar,El-Shanshory, Mohamed, Elshafey, Rasha, Dabour and Mohamed (2018). Decreasing cardiac iron overload with Amlodipine and Spirulina in children with α-thalassemia. Pediatric Hematology Oncology Journal, **3**:10.

Huang, H.; Liao, D.; Pu, R. and Cui, Y. (2018). Quantifying the effects of Spirulina supplementation on plasma lipid and glucose concentrations, body weight, and blood pressure. Diabetes Metab. Syndr. Obes., **11**:729-742.

Hsiao, G; Chou, P.H.; Shen, M.Y.; Chou, D.S.; Lin, C.H. and Sheu, J.R. (2005).C-phycocyanin, a very potent and novel platetel aggregation inhibitor from *Spirulina platensis*. J. Agric. Food Chem. **53**(20):7734-7740.

Hayashi, K.; Hayashi, T.; Maedaa, M. and Kojima I (1996). Calcium Spirulina, an inhibitor of envelope virus replication, from a blue-green alga *Spirulina platensis*. Journal of Natural Products, **59**:83-7.

Hernandez-Lepe, M.A.; Lopez-Diaz, J. A.; Juarez oropeza, M.A.; Hernandez Toress, R.P.; Wall Medrano, A. and Raos Jimenez, A. (2018). Effect of Arthrospira maxima supplementation and a systematic physical exercise programo the body composition and cardiorespiratory program on the body composition and cardio respiratory fitness of overweight or obese subjects: A double-blind, randomized and cross over controlled trial. Mar. Drugs, **16**:364.

Kay, R.A. (1991). Microalgae as food and supplement.Critical Reviews in Food Science and Nutrition, **30**(6):555-573.

Karko, P.D.; Leong, S.C.; Karkos, C.D.; Sivaji, N. and Assimakopoulos, D.A. (2011). Spirulina in clinical practice: Evidence-based human applications. Evid-Based Complementary Alternative Medicine, pp:531053.

Kumari, J. (2020). Cultivation of Spirulina using biogas spent slurries as substrates. Journal of Xi'an University of Architecture and Technology, **12**:1452-1458.

Konickova, R.; Vankova, K.; Vanikova, J.; Vanova, K. and Muchova, L.(2014). Anti-cancer effects blue-green alga *Spirulina platensis*, a natural source of bilirubin-like tetrapyrrolic compounds. Annals of Hepatology, **13**:273-283.

Ku, C.S.; Pham, T.X.; Park, Y.; Kim, B.; Shin, M.S.; Kang, I. and Lee, J. (2013). Edible blue-green algae reduce the production of pro-inflammatory cytokines by inhibiting NF-κB pathway in macrophages and splenocytes. Biochim. Biophys. Acta., **1830**(4):2981-8.

Kalafati, M.; Jamurtas, A.Z. and Nikolaidis, M.G. (2010). Ergogenic and antioxidant effects of Spirulina supplementation in humans. Med. Sci. Sports Exerc., **42**(1):142-151.

Kim, H.M.; Lee, E.H.; Cho, H.H. and Moon, Y.H. (1998). Inhibitory effect of mast cell-mediated immediate-type allergic reactions in rats by Spirulina. Biochem. Pharmacol., **55**(7):1071-1076.

Kokou, F.; Makridis, P.; Kentouri, M. and Divanach, P. (2012). Antibacterial activity in microalgae cultures. Aquaculture Research, **43**(10):1520-1527.

Leema, J.M.; Kirubagaran, R.; Vinithkumar, N.V.; Dheenan, P.S. and Karthikayulu, S. (2013). High-value pigment production from Arthrospira (*Spirulina*) platensis cultures in seawater. Bioresource Technology, **101**:9221-9227.

Lucie, Novoves, Zapataa, Anastasia, K.M.; Zabolotneya, Jeffrey, B.; Atwood and Matthew. (2016). Optimizing microalgae cultivation and wastewater treatment in large-scale offshore photobioreactors. Algal Research, **18**:86-94.

Lodi, A.; Binaghi, L.; Solisio, C.; Converti, A. and Del Borghi, M. (2003). Nitrate and phosphate removal by *Spirulina platensis*. J. Ind. Microbiol Biotechnol., **30**(11):656-60.

Lu, J.; Ren, D.F.; Xue, Y.L.; Sawano, Y.; Miyakawa, T. and Tanokura, M. (2010). Isolation of an antihypertensive peptide from alcalasedigest of *Spirulina platensis*. J. Agric. Food Chem., **58**(12):7166-7171.

Lu, H.K.; Hsieh, C.C.; Hsu, J.J.; Yang, Y.K. and Chou, H.N. (2006). Preventive effects of *Spirulina platensis* on skeletal muscle damage under exercise-induced oxidative stress. Eur. J. Appl. Physiol., **98**(2):220-226.

Mathur, M. (2018). Bioactive molecules of spirulina: A Food Supplement. Reference Series in Phytochemistry. Springer.

Mitchell, S.A. and Richmond, A. (1988). Optimization of a growth medium for Spirulina based on cattle waste. Biological Wastes, **25**(1):41-50.

Mohan, A.; Misra, N.; Srivastav, D.; Umapathy, D. and Kumar, S. (2014). Spirulina-The Nature's Wonder: A review. Scholars Journal of Applied Medical Sciences, **2**(4C):1334-1339.

Misbahuddin, M.1.; Islam, A.Z.; Khandker, S.; Ifthaker-Al-Mahmud, Islam, N. and Anjumanara. (2006). Efficacy of spirulina extract plus zinc in patients of chronic arsenic poisoning: A randomized placebo-controlled study. Clinical Toxicology (Philadelphia). Review, **44**(2):135-141

Martínez Galero, E.; Pérez Pastén, R.; Perez Juarez, A.; Fabila Castillo, L.; Gutiérrez-Salmeán, G. and Chamorro, G. (2016). Preclinical antitoxic properties of Spirulina (Arthrospira). Review, **8:**1345-1353.

Mishra, P.; Singh, V.P. and Prasad, S.M. (2014). Spirulina and its nutritional importance: A possible approach for development of functional food. Biochemistry and Pharmacology, **3**:e171.

Mohan, I.K.; Khan, M.; Shobha, J.C.; Naidu, M.U.; Prayag, A.; Kuppusamy, P. and Kutala, V.K.(2006). Protection against cisplatin-induced nephrotoxicity by Spirulina in rats. Cancer Chemotherapy and Pharmacology, **58**(6):802-808.

Nguyet, V.T.; Kim, D.D.; Chuyen, N.H. and Tam, V.T.T. (2017). Experimental cultivation of *Spirulina platensis* using my an mineral water, thuathien hue province. Vietnam Journal of Science and Technology, **55**(5):548-556.

Nuhu, A.A. (2013). Spirulina (Arthrospira): An important source of nutritional and medicinal compounds. Journal of Marine Biology, **20**:1-8.

Oriquat, G.A. (2018). Therapeutic effects of Spirulina against experimentally-induced non-alcoholic fatty liver in rats may involve miR-21, -34a and -122. Meta Gene, **18**:115-121.

Pelizer, L.H.; Carvalho, J.C.M. and Moraes, O. (2015). Protein production by *Arthrospira* (Spirulina) *platensis* in solid-state cultivation using sugarcane bagasse as support. Biotechnology Reports, **5**:70-76.

Pham, T.X and Lee, J.Y. (2016). Anti-inflammatory effect of *Spirulina platensis* in macrophages is beneficial for adipocyte differentiation and maturation by inhibiting nuclear factor-αB Pathway in 3T3-L1 Adipocytes. Journal of Medicinal Food, **19**(6):535-542.

Pabon, M.M.; Jernberg, J.N.; Morganti, J.; Contreras, J.; Hudson, C.E.; Klein, R.L. and Bickford, P.C. (2012). A Spirulina-enhanced diet provides neuroprotection in an α-synuclein model of Parkinson's disease. PLoS One, **7**(9):e45256.

Ravi, M.; De, S.L.; Azharuddin, S. and Paul, S.F.D. (2010). The beneficial effects of Spirulina focus on its immunomodulatory and antioxidant properties, Nutrition and Dietary Supplements, **2:**73-83.

Ragaza, Janice, A.J.; Hossain, M.D.; Sakhawat Kristen, M.A.; Velasquez, Stephanie, F. and Kumar Vikas. (2020). A review on Spirulina: Alternative media for cultivation and nutritive value as an aquafeed. Reviews in Aquaculture, pp:12439.

Rasool, M.; Sabina, E.P. and Lavanya, B. (2006). Anti-inflammatory effect of *Spirulina fusiformis* on adjuvant-induced arthritis in mice. Biological and Pharmaceutical Bulletin, **29**(12):2483-2487.

Ramamoorthy, A. and Premakumari, S. (1996). Effect of supplementation of Spirulina on hypercholesterolemic patients. Journal of Food Science and Technology, **33**:124-127

Rodríguez Hernández, A.; Blé Castillo, J.L.; Juárez Oropeza, M.A. and Díaz-Zagoya, J.C. (2001). *Spirulina maxima* prevents fatty liver formation in CD-1 male and female mice with experimental diabetes. Life Science, **69**(9):1029-1037.

Sandeep, K.P.; Shukla, S.P.; Vennila, A.; Purushothaman, C.S. and Manjulekshmi, N. (2015). Cultivation of *Spirulina* (Arthrospira) *platensis* in the low-cost seawater-based medium for extraction of value-added pigments. Indian J. Mar. Sci., **44**:3.

Szulinska, M.; Gibas-Dorna, M.; Miller Kasprzak, E.; Suliburska, J.; Miczke, A.; Walczak-Ga³ezewska, M.; Stelmach-Mardas, M.; Walkowiak, J. and Bogdanski, P. (2017). *Spirulina maxim*a improves insulin sensitivity, lipid profile, and total antioxidant status in obese patients with well-treated hypertension: A randomized double-blind placebo-controlled study. Eur. Rev. Med. Pharmacol. Sci., **10:**2473-2481.

Somchit, M.N.; Mohamed, N.A.; Ahmad, Z.; Zakaria, Z.A.; Shamsuddin, L.; Omar-Fauzee, M.S. and Kadir, A.A. (2014). Anti-inflammatory and anti-pyretic properties of *Spirulina platensis* and *Spirulina lonar* : A comparative study. Review, **27**(5):1277-80.

Subhashini, J.; Mahipal, S.V.; Reddy, M.C.; Rachamallu, A. and Reddanna, P. (2004). Molecular mechanisms in C-Phycocyanin induced apoptosis in human chronic myeloid leukemia cell line-K562. Biochem. Pharmacol., **68**(3):453-462.

Sandhu, J.; Shenoy, S. and Dheera Ibnosina, B. (2010). Efficacy of Spirulina supplementation on isometric strength and isometric endurance of quadriceps in trained and untrained individuals: A comparative study. Journal of Medicine and Biomedical Sciences, **2**:79-86.

Sarada, D.V.L.; Kumar, C.S. and Rengasamy, R. (2011). Purified C-phycocyanin from *Spirulina platensis* (Nordstedt) Geitler: A novel and potent agent against drug resistant bacteria.World Journal of Microbiology and Biotechnology, **27**:779-783.

Usharani, G.; Saranraj, P. and Kanchana, D. (2012). Spirulina cultivation: A review. International Journal of Pharmaceutical and Biological Archives, **3**(6):1327-1341.

Volkmann, H.; Imianovsky, U.; Jorge, L.B.; Oliveira, Sant. and Anna. (2008). Cultivation of *Arthrospira* (Spirulina) *platensis* in desalinated wastewater and salinated synthetic medium: Protein content and amino acid profile. Braz. J. Microbiol., **39**(1):98-101.

Wu, Q.; Liu, L., Miron, A.; Klímová, B.; Wan, D. and Kuèa, K. (2016) The antioxidant, immunomodulatory, and anti-inflammatory activities of Spirulina: An overview. Arch. Toxicol., **90**(8):1817-1840.

Wang, Y.; Chang, C.F.; Chou, J.; Chen, H.L.; Deng, X.; Harvey, B.K.; Cadet, J.L. and Bickford, P.C. (2005). Dietary supplementation with blueberries, spinach, or Spirulina reduces ischemic brain damage. Exp. Neurol., **193**(1):75-84.

Yang, H.N.; Lee, E.H. and Kim, H.M. (1997). *Spirulina platensis* inhibits anaphylactic reaction. Life Sci. [Internet], **61**(13):1237-44.

Yousefi, R.; Mottaghi, A. and Saidpour, A. (2018). *Spirulina platensis* effectively ameliorates anthropometric measurements and obesity-related metabolic disorders in obese or overweight healthy individuals: A randomized controlled trial. Complement Therapeutic Medicine, **40:**106-112.

Young, O.; Fernando, I.P.S. and Jeon, Y.J. (2016). Potential applications of radioprotective phytochemicals from marine algae.The Korean Society of Phycology-Algae, **31**(4):403-414.

Zarrouk, C. (1966). Contribution a l'etude d'une cyanophycee. Influence de divers' facteurs physiques et chimiques sur lacroissance et la photosynthesis de *Spirulina maxima*. Universite de Paris, Paris, France.

Zhang, L.; Chen, L.; Wang, J.; Chen, Y.; Gao, X. and Zhang, Z. (2015). Attached is cultivation for improving the biomass productivity of *Spirulina platensis*. Bioresource Technology, **181**:136-142.

Zhang, H.Q.; Lin, A.P.; Sun, Y. and Deng, Y.M. (2001). Chemo-and radio-protective effects of polysaccharide of *Spirulina platensis* on hemopoietic system of mice and dogs. Acta. Pharmacol. Sin., **22**:1121-1124.

Citation **Divya Pingili, Archana Awasthi, Maryam Maqsood, K. Sravya Devi, Patha Rasagna, Srinitha Bhagoji, Deepa N. Amminbavi and M. Bhagavan Raju (2023). Spirulina: A panacea for all human ailments. Ann. Phytomed., 12(1):79-92. http://dx.doi.org/10.54085/ap.2023.12.1.39.**