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Review Article

The Numerous and Varied Applications of Spirulina in Medical Practice

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Abstract

Spirulina is a cyanobacteria (blue-green alga) rich in vital nutrients, having tremendous potential as a "future food". The utility of algae is not limited to providing nutrition. Specific alga can perform the following functions: immunomodulator, anti-allergic, cleanses the body of toxins, antitumor, anti-inflammatory, antiviral, and abstergent (cleansing the body of toxins). Spirulina has been a vital dietary component for humans for millennia. The United Nations recognizes Spirulina as a potential defense against malnutrition. The current evidence in support of Spirulina points towards perfoming further research regarding the promising applications of Spirulina. These organisms are a rich source of bioactive compounds and, thus, should be considered as an alternative and supplementary therapy—albeit with scientific support and evidence-based studies. The revolution in functional foods continues as the incidence of lifestyle-related diseases is increasing. The most notable experiments have been conducted in studying Spirulina*'s effect on* metabolic disorders, revealing its ability to reduce cholesterol, triglycerides, and blood glucose. Also, Spirulina has particular applications in cancer research, protecting against the adverse effects of specific chemotherapeutic agents. Microalgae can also form special supplements for vegetarians, offsetting the absence of protein in the vegan diet.

Nevertheless, Spirulina also has a negative side and potential adverse effects. Self-medication with Spirulina supplements can lead to unwanted complications if a person is taking immunosuppressants or anticoagulants concomitantly or suffering from autoimmune diseases. Children and pregnant women should avoid these products until more applicable data are obtained. Also, some people may have an inherent allergy to algal products.

Keywords: *Cyanobacteria; Diabetes Mellitus; Functional Food; Hypertension; Metabolic Syndrome; Microalgae; Nutritional Supplement; Phytochemicals; Phytosterols; Pseudovitamin; Zoochemical*

Abbreviations

Ca-SP: Calcium Spirulan; FDA**:** US Food and Drug Administration; GRAS: Generally Recognized Safe; HIV-1: Human Immunodeficiency Virus Type 1; HSV-1: Herpes Simplex Virus Type 1; PBR: Photbioreactor; w/w: Weight In Weight

Introduction

During previous world wars, food scarcity was prevalent across the globe. Seaweed and algae were used as food for animals, soldiers, and war-affected civilians [1]. Throughout history, due to various natural calamities or socio-political circumstances, humans struggled against hunger and malnutrition. However, in recent times, food has not remained merely a substance to satisfy hunger. A balanced diet is a mantra for a healthy life, which has paved the way for natural food supplements and additives. Microalgae have been part of the human diet for eons, although some of the tiniest organisms living on Earth. Marine life has been used as both food and medicine by human ancestors. Notably, Hippocrates grasped the antibiotic effects of certain sponges.

Early researchers deciphered Spirulina's rich blend of microalgae nutrients, and soon afterward, this knowledge spread rapidly and widely. The most extensively researched microalgae in the food and nutrition industry are Spirulina (*Arthrospira platensis*) and Chlorella. Currently, these microalgae and their extracts are an integral part of the supplementary diet, having gained extensive popularity and acceptance due to their associated health benefits. Spirulina, formerly known as *Arthrospira,* is a cyanobacterium of a spiral or helical filamentous morphology.

These planktonic cyanobacteria are blue-green algae—reported in 1519 by Herman Cortez (Spanish conquistador) [2,3]. While visiting Lake Texcoco in the valley of Mexico, Cortez found that the Aztecs ate it as a staple food [4]. Morphologically, these are free-floating filaments with an open left-hand helix. The species that received the most significant attention and are commonly studied are *Arthrospira platensis*, *Arthrospira maxima*, and *Arthrospira fusiformis*. The dried biomass of *A. platensis* is called Spirulina.

However, distinctions exist between the genus Spirulina and *Arthrospira*. In 1852, Stizenberger coined the term *"Arthrospira*" because the alga is septate. In 1892, Gomont found an aseptate form, and finally, in 1932, both forms were considered together and termed Spirulina by Geitler. Since then, Spirulina has become the popular and well-accepted term Arthrospira [5].

As a food supplement, Spirulina was reportedly used in 1520, when *S. maxima* was harvested from Lake Texcoco (Mexico City), dried, and consumed. Much later, in 1940, Pierre Dangeard mentioned a "dihe" cake eaten by the African Kanembu tribe [6]. He also noted that flamingos survived by ingesting this blue-green algae. Otto Warburg is known for growing algae, primarily for research purposes, by studying photosynthesis through his cultivation of the microalgae Chlorella.

After World War II, the United Nations addressed hunger and malnutrition, directing and encouraging dynamic research. Spirulina was deemed a "wonderful food source" by the International Association of Applied Microbiology. In the mid-1960s, the botanist Jean Leonard found that "dihe" is composed of Spirulina, resulting in numerous algae studies. In 1966, Spirulina mass production was established. Since the 1970s, Spirulina-producing factories have been built in about thirty countries cultivating, harvesting, and producing various forms of algae [7].

Discussion

Spirulina is a well-known name in the health and food industry due to its noted nutritional value. As a dietary supplement, it is rich in protein, vitamins, minerals (such as iron, calcium, magnesium, manganese, phosphorus, and sodium zinc), and phenolic acids (tocopher-

ols and γ-linolenic acid) [8,9]. Notably, however, Spirulina lacks vitamin B12; instead, it contains pseudovitamin B12, inactive in humans. Thus, it cannot be consumed for the sole purpose of supplementing active vitamin B12.

Unlike other protein sources, such as yeast, Spirulina does not have cellulose cell walls, making it easy to digest. Also, it is relatively straightforward to produce and preserve and does not require special treatment to ensure the release of its protein content. Under controlled conditions, it is grown in the highly alkaline outdoor water, containing high carbonate and bicarbonate [4]. The countries that commercially produce these microalgae are Thailand, the United States, Africa, China, and Chile. These locations are favorable due to their proximity to the ocean and the abundance of freshwater. Due to its preferred geographical location, Western Kenya is one of Spirulina's natural growth centers [10].

Experimentally, Spirulina can be grown in culture media, such as Zarrouk's, Rao's, CFTIR, OFERR, and revised media [11]. Open ponds are worked for large-scale harvesting, but in areas where environmental conditions are unfavorable, photobioreactors (PBRs) are utilized for Spirulina growth and production [12].

The most popular and favorable medium is the Zarrouk medium due to the high biomass productivity; however, the downside is the high cost. Researchers have been striving to reduce the cost of mass production by investigating alternative culture media and developing newer and more resultant PBRs [13].

Global recognition

In 1992, the WHO declared Spirulina the "best food for the future" and recommended its use to confront malnutrition in children [14]. Spirulina has been listed as generally recognized safe (GRAS) by the US Food and Drug Administration (FDA), making it readily available in health food stores as a dietary supplement [15].

Spirulina is sold in the form of health drinks, powders, capsules, and tablets. In some countries (the United States, Japan, Taiwan, India, Singapore, Germany, Spain, Switzerland, and Holland), Spirulina is incorporated in and sold as candies and bread (Spirulina powder is added). The FDA and the European Union also allow the algal extract as coloring agents in candies and chewing gums [16]. NASA and the European Space Agency recommend Spirulina as a food supplement for extended space travel [17]. Furthermore, the cosmetic industry promotes Spirulina, adding the extract to creams, masks, tonics, and shampoos [18].

Spirulina as a functional food

Functional foods are enhanced dietary products consumed as food or beverages. They have been proven to be safe, providing numerous health benefits [19]. By applying biotechnology, food can be made functional by increasing its concentration or adding or removing a particular component while increasing its bioavailability.

Functional foods differ from nutraceuticals, derived from food but used in pills, potions, and liquids. Functional foods can be fruits, vegetables, fiber-enriched grains, or beverages—and can be of animal origins, such as dairy products, fish, and meat.

Functional foods can be modified products (with the addition of phytochemicals or zoochemical) and whole, unmodified products (the types that are inherently rich in physiologically active compounds, such as alpha-linolenic acid, soluble fibers, and mono and polyunsaturated fatty acids). Spirulina is presented as a nutraceutical in powder, capsules, and tablets [20]—being first introduced as such in Japan in the 1980s. Spirulina is considered highly nutritious and known to aid in specific bodily functions.

The concept of functional food has gradually been integrated into mainstream medicine, and now it is a recognized category of alternative treatment and adjuvant therapy for many chronic diseases.

The International Food Information Council and the International Life Sciences Institute of North America define functional foods as products that provide essential nutrition and physiological components for enhanced health benefits [21]. Thus, functional foods are included in the diet of individuals at specific health risk and those suffering from such conditions, like cardiovascular disease, metabolic syndrome, diabetes mellitus, and other chronic diseases. The healthful and restorative diet and lifestyle modifications constitute alternative approaches for preventing physiological risks and treating or ameliorating specific conditions.

Microalgae are added in the manufacture of many food products, such as puddings, cakes, and biscuits. For example, Spirulina is used to fortify biscuits that benefit malnourished people. Loaves of bread, biscuits, and chocolates are popular throughout the world. Hence, these foods are commonly Spirulina-fortified, being accepted and adopted quickly by consumers. For example, a 2% w/w addition of Spirulina to biscuits and chocolate has provides adequate amounts of amino acids to children and infants [22].

However, Spirulina's integration with food must be performed under controlled conditions. The moisture content of the resultant food should be less than 9%. Spirulina over-drying can lead to its disintegration. Thus, manufacturers must take particular care when packaging such foods and recommend the proper storage procedures and conditions, which affect the humidity (water content) of the product. The risk of contamination prevails in all steps from harvesting, drying, and packaging. If not appropriately supervised, microorganisms (yeasts, *E. coli,* and *Staphylococcus*) can contaminate the biomass [23].

Spirulina's application in metabolic disorders (metabolic syndrome and diabetes mellitus) and hypertension

Phytosterols, present in Spirulina's cell membrane, lower blood cholesterol. These are also claimed to be antiatherogenic, immune-boosting, and anti-inflammatory [24]. A six-week oral supplement (4.5 g/day) of Spirulina decreased triglycerides and low-density lipoprotein while reducing systolic and diastolic blood pressures [25]. Regarding type 2 diabetes mellitus, a study by Parikh., et al. (2001) reported a significant reduction in HbA1c level after a two-month supplementation program (2 g/day). The researchers also found a significant reduction in the monitered atherogenic indices [26].

Spirulina's hypolipidemic effect is well recognized. Nagaoka., *et al*. (2005) found that C-phycocyanin—a protein that aids in photosynthesis and is found in platensis species and other seaweeds—inhibits jejunal cholesterol absorption and reabsorbs ileal bile acids [27]. It also inhibits platelet aggregation, thus reducing the formation of atherothrombotic plaques. Dose-dependent inhibition of pancreatic lipase is reportedly due to a glycolipid constituent of algae, which causes a decrease in plasma triglycerides [28]. Spirulina is a promising antihypertensive agent [29].

A systematic review based on eight human studies found evidence of Spirulina's lipid-lowering and antioxidant effects [30]. Moreover, another meta-analysis of twelve human studies reported the following: Spirulina supplementation (1g up to 19g per day) reduces low-density lipoprotein cholesterol, triglycerides, very-low-density lipoprotein cholesterol, fasting blood glucose, and diastolic blood pressure [31]. Clinical trials have found that Spirulina supports weight loss. A restricted diet and Spirulina supplementation (2g per day) could reduce BMI, waist circumference, and body fat [32].

Spirulina as an antiviral agent

In an *in vitro* study by Hayashi., et al. (1996), a polysaccharide found in Spirulina *platensis,* called calcium spirulan (Ca-SP), showed antiviral properties against the human immunodeficiency virus type 1 (HIV-1) and herpes simplex virus type 1 (HSV-1). Also, Ca-SP inhibited virus-induced syncytium formation even at low concentrations while showing a much longer half-life in the blood [33].

Spirulina as an antimicrobial agent

Patel and Goyal (2013) discovered that alga methanol extract has antimicrobial properties against many bacterial and fungal species [34].

Spirulina as an anticancer agent

An extensive review by Siva (2015) collated numerous *in vivo* and *ex vivo* studies regarding Spirulina's anticancer and carcinopreventive properties [5]. An early study from 1988 showed that Spirulina extract eliminated tumors in hamsters. The extract was applied topically 3 times a week for 28 weeks, using 7,12-dimethylbenz[a]anthracene (DMBA) in mineral oil. This result spawned numerous trials investigating the anticancer benefits of algae. As reported in the human study of malignant oral lesions, by Mathew., et al. (1995), encouraging results were noted using *S. fusiformis* [35].

Spirulina as a adjuvant therapy

Spirulina can be used synergistically with the anti-diabetic, Rosiglitazone. This drug heightens the risk of osteoporosis in diabetic patients, which can be improved by the co-administration of Spirulina [36]. As an adjuvant to anticancer drugs, phycocyanin demonstrates exceptional promise. It hinders the cancer cell cycle, resulting in reduced dosages and enhancing the efficacy of chemotherapeutic drugs. Also, it can be utilized as a photosynthesizer in low-level laser therapies [37].

Spirulina as a an abstergent agent

Spirulina proved beneficial as a complementary agent in conjunction with the specific treatment and rehabilitation of victims of the Chernobyl (nuclear reactor) accident [38]. Furthermore, in another study among 270 radiated children, Mishra., et al. (2015) found that Spirlina lowered levels of radionucleotides after 5 grams-45 day supplementation [39].

Spirulina for improving skin and enhancing beauty

Spirulina exhibits anti-aging properties, providing nourishment for the skin. Antioxidants, beta carotene, and superoxide dismutase protect the skin from damage caused by UV radiation. Furthermore, high polyunsaturated fatty acids (alpha-linolenic acid) promote skin elasticity [40].

Spirulina as an anti-allergic agent

Nourollahian., et al. (2020) noted that Spirulina can be used as alternative medicine in allergic rhinitis. A randomized clinical trial found Spirulina superior to conventional cetirizine [47]. However, the report's authors highlighted that the required high dose (2 capsules daily; 2 grams) might lead to non-compliance among patients. A systemic review by Karkos., *et al*. (2007) concluded that algae dietary supplementation beneficially affects allergic rhinitis [48].

Spirulina in protein-energy malnutrition

In 1984, Spirulina was put forth as a promising nutrional source to prevent malnutrition and hunger**.** Fox (1985) encouraged French villagers to cultivate Spirulina and use it as a food supplement [49]. Spirulina was later extensively studied as a food source for treating protein-energy malnutrition in children. Spirulina is helpful in the nutritional rehabilitation of cancer patients and HIV-infected population [50].

Spirulina's miscellaneous roles

Many animal trials revealed additional beneficial properties of Spirulina, such as increased fertility [51], improved wound healing [52], protection against chemical-induced nephrotoxicity [53], and cardiotoxicity [54]. In an animal study by Wang., *et al*. (2007), the researchers reported Spirulina's neuroprotective effects (in cerebral ischemia) [55]. Table 1 summarizes the benefits and active components found in this microalgae (through which it exerts its favorable effects).

Health benefit	Relevant mechanisms of action
Anti-inflammatory [41]	Chromophore phycocyanobilin exhibits anti-inflammatory and antioxidant properties. It activates antioxidant enzymes, inhibits lipid peroxidation and DNA damage, and destroys free radicals.
Fights fatigue [4]	Specific constituents of Spirulina, such as polysaccharides (rhamnose and glycogen) and essential fat, are absorbed by cells and help in energy release. It helps form vitamin B6 by increasing Lactobacillus in the intestine, which also helps in energy release.
Anti-allergic [42]	Spirulina inhibits histamine release, reduces IL-4, and heightens IgA production. It also regulates T-helper cells in people with allergic rhinitis.
Antiviral [43]	The sulfated polysaccharide—calcium spirulan (Ca-Sp)—displays antiviral properties, inhibiting *in vitro* replication of specific viruses, such such as Herpes simplex type I, human cytomegalovirus, measles and mumps viruses, influenza A virus, and human immunodeficiency virus-1.
Lipid and cholesterol [25]	Spirulina lowers high-density lipoproteins and triglycerides while increasing low-density lipoproteins and decreasing triglycerides.
Antioxidant [44]	C-phycocyanin exerts antioxidant and free radical-scavenging properties. It induces apoptosis in RAW 264.7 macrophages stimulated by lipopolysaccharides. Other constituents, such as tocopherols and beta-carotene, deactivate the free radicles generated in body phycocyanins.
Antimicrobial [23]	Spirulina stimulates antimicrobial activity as shown by functional lipids (c-linolenic acid) and an antibiotically active fatty acid. Lipids destroy microorganisms by disintegrating cellular membranes.
Obesity/weight loss [17]	Spirulina reduces macrophage infiltration into visceral fat, prevents hepatic fat accumulation, reduces oxidative stress, improves insulin sensitivity, and satiety.
Anemia [18]	C-phycocyanin encourages hematopoiesis and erythropoietin. Its essential amino acids, folic acids, vitamin B12, and iron also prompt erythropoiesis.
Hepatoprotective [45]	In NAFLD, AST decreases, and ALT levels increases.
Increases exercise-induced health benefits [46]	Spirulina neutralizes reactive oxygen species formed during high-intensity exercises, increases aerobic exercise performance, decreases carbohydrate oxidation, increases fat oxidation, and lowers lipid peroxidation.

Table 1: *Various health benefits of Spirulina and relevant mechanisms of action.*

Spirulina in the industrial sector

Extracellular production of Spirulina promotes the growth of lactic acid bacteria, such as Lactobacillus and streptococcus. These bacteria are essential components of probiotics, comprising a significant part of the food industry. Spirulina augments the growth and sustainability of specific organisms, such as *Lactobacillus acidophilus*, *Lactobacillus bulgaricus*, *Lactobacillus casei,* and *Streptococcus thermophilus* [56]. Thus, industries and science laboratories are thriving and reaping the financial rewards of Spirulina. This distinctive microalga is added to fish and animal feed—also enhancing milk production and boosting immunity as well as increasing nutritional quality [5].

Precautions regarding Spirulina

Dietary supplements help produce a healthier population, but safety concerns cannot be ignored. Functional foods, such as Spirulina, contain numerous beneficial elements for the human body within optimal—but not excessive—levels. Also, the risk of toxicity, drug interactions, and differences in the innate physiological construct of individuals must be acknowledged and considered when recommending or consuming this and other algal supplements. Spirulina may interfere with the blood clotting process. Patients taking anticoagulants

are not recommended this supplement; however, it has potential as an antithrombotic agent but only in clear cases [57]. In contrast, some studies have reported no effect of Spirulina on clotting time [58].

In phenylketonuria, there is an accumulation of phenylalanine. Spirulina further aggravates this sequella as the alga contains phenylalanine. Bernstein., *et al*. (2011) reported that people who already have an allergenic condition are more likely to be allergic to cyanobacteria [59]. Lee., *et al*. (2007) discovered a Spirulina allergy by a skin prick test in a 17-year-old male who had an anaphylactic reaction after consuming a Spirulina tablet [60].

If Spirulina's cultivation is not controlled, it can accumulate trace elements from the soil. Common minerals that contaminate the alga are lead, mercury, cadmium, and arsenic. These minerals find their way through agricultural soils containing pesticides and fertilizers. Cyanobacteria, such as Spirulina, excrete hydroxamate chelating agents that act as carrier molecules and increase the level of trace metals in the body. Beyond a tolerable limit, these elements are highly toxic. Thus, strict contaminant monitoring is imperative regarding these products [61].

Some cancer patients prefer complementary and alternative therapies to ease their pain and improve their quality of life. However, Spirulina has been found to inhibit the metabolism of bendamustine, a chemotherapeutic agent [62]. Thus, a qualified doctor's advice must be sought and considered before opting for such supplements. Table 2 lists the drug interactions, contraindications, and conditions under which Spirulina ingestion should be monitored.

Interferes in the process of blood clot formation, so it should not be taken in conjunction with anticoagulants [57].
Anaphylaxis must be ruled out before prescription [63].
Carries the risk of toxic elements.
May cause insomnia and gastrointestinal issues [64].
Individuals taking immunosuppressant, antihypertensive, and lipid-lowering drugs should exercise caution [56].
Precaution must be maintained during pregnancy and mothers who breastfeed due to the risk of transmitting toxic contaminants to their neonates [65].
Individuals with autoimmune disorders may show exacerbation because Spirulina stimulates the immune system [65].
'Possibly unsafe' for children due to the possibility of contaminants in algae [65].
Antagonizes immunosuppressive agents, so they should not be co-administered [65].
Avoid taking with herbs and supplements that lower blood glucose or slow blood clotting [65].
Limits the body's ability to absorb iron, so it should be avoided with iron supplements [65].
Cancer patients should be cautious, as it inhibits particular cancer-drug metabolism [66].

Table 2: *Circumstances that require careful administration of Spirulina supplementation.*

Conclusion

Due to ongoing research that has reported encouraging findings, Spirulina as a food supplement has gained immense popularity. Various companies manufacture and sell algae-based products and distribute them globally. Spirulina, in various forms, has become a part of the human diet and nutrition. However, the functional food industry needs to focus on the safety and efficacy of these products, which can only be possible through robust scientific experiments.

The effect of Spirulina on the food industry and its impact on human health should be presented in a more unified manner. Currently, numerous animal-based studies have shown the benefits that need to be corroborated by conducting human trials. Scientific, evidence-

based validation is of utmost importance. Notably, specific side effects of Spirulina and possible drug interactions are severe and should not be overlooked.

Conflict of Interest Statement

The authors declare that this paper was written without any commercial or financial relationship that could be construed as a potential conflict of interest.

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