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Review Article

Spirulina Miscellany: Medicinal Benefits and Adverse Effects of Spirulina

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Abstract

The nutritional and health benefits of Spirulina have been known for thousands of years. Spirulina has been grown and harvested by ancient cultures since written history, and likely before. Much anecdotal evidence has been put forth, and more recently, evidence-based scientific research confirms many of Spriluina's nutritional and health benefits. However, such benefits are far-reaching (and only recently researched). In the commercial exuberance surrounding Spirulina, sparse research regarding any potential toxicity or adverse effects has been undertaken. This review—as a miscellany—highlights notable benefits, potential toxicity, and adverse effects in the human consumption of Spirulina. It is hoped that this review will provide the reader, especially those new to Spirulina, with an introduction and overview regarding the benefits and detriments of Spirulina, which will act as a springboard to more in-depth research regarding Spirulina as a vital nutritional and medicinal source for humans—needed now more than ever.

Keywords: *Anemia; Anti-Inflammatory; Blood Pressure; Cancer; COVID-19; Diabetes; Immunomodulation; Longevity; Plasma Lipids; ROS; SARS-CoV-2; Skin*

Abbreviations

ACE: Angiotensin-Converting Enzyme; BMI: Body Mass Index; C-PC: C-phycocyanin; COVID-19: Coronavirus Disease 2019; CVD: Cardiovascular Disease; ERK: Extracellular Signal-Regulated Kinase; GPX: Glutathione Peroxidase; GPX-Se; Selenium-Dependent Glutathione Peroxidase; GR: Glutathione Reductase; Hb: Hemoglobin; HbA-1c; Glycosylated Hemoglobin; IQP: Ile-Gln-Pro; MDA: Malondialdehyde; NO: Nitric Oxide; PI3K: Phosphoinositide-3-Kinase; ROS: Reactive Oxygen Species; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; SPC; *S. platensis* Concentrate; TNF: Tumor Necrosis Factor

Introduction

Spirulina platensis and *S. maxima* are rich in nutrition, void of toxicity, and have therapeutic benefits. Thus, they are a frequent study topic for the pharmaceutical and food industries. Spirulina contains several primary and secondary health-promoting metabolites. Growing evidence suggests its health-promoting properties (e.g., antioxidant, anti-inflammatory, antiviral, and antibacterial activities, antitumor effects, and positive effects against diabetes, hyperlipidemia, and obesity).

Discussion

Anemia

Spirulina has a high iron concentration of approximately 28.5–100 mg, which is 58 times that of spinach and 18 times that of meat [1,2]. A 100 g portion of Spirulina can provide 158% of the daily iron requirement. The cell wall of Spirulina is made up of mucopolysaccharides instead of cellulose, facilitating up to 85%–95% better absorption than powdered milk containing lactic acid [1].

Consuming Spirulina for 6 weeks has been shown to increase hemoglobin (Hb) levels, reducing anemia by 60% [3]. Adding Spirulina to iron supplementation demonstrates a significant effect in alleviating pregnancy anemia by boosting the Hb levels. Spirulina supplementation increases the size and number of red blood cells in elderly patients, regardless of their diet [3].

In study by Thaakur and Pushpakumari (2007), Spirulina supplementation restored total erythrocyte count, leukocyte count, and Hb content [4]. An evidence-based study by De M., *et al*. (2011) demonstrated that the addition of Spirulina to iron-folic acid or folic acid supplementation was associated with more profound improvements in Northeast Indian tribal populations with nutritional anemia [5].

Anti-inflammatory effect

Evidence supports the antioxidant and anti-inflammatory effects of Spirulina or its extracts. Treatment with Spirulina protected the activities of cellular antioxidant enzymes, including glutathione peroxidase (GPX), selenium-dependent glutathione peroxidase (GPX-Se), and oxidized glutathione reductase (GR), indicating its antioxidant effects [6]. Following supplementation with Spirulina, functional neutrophils underwent a dose-dependent reduction in metabolic activity, suggesting its anti-inflammatory effects [7]. In rats treated with Spirulina, increased levels of proinflammatory cytokines in the cerebellum—including tumor necrosis factor (TNF), and malondialdehyde (MDA), and oxidative markers—were reversed [8]. It also resulted in considerable improvements in enzymatic and non-enzymatic antioxidants [9] and noticeable reductions in chromosomal damage and lipid peroxidation [10], as well as restored the activities of antioxidant enzymes superoxide dismutase, catalase, and glutathione-S-transferase [11].

Kim and Kim (2005) showed that Spirulina consumption for 8 weeks significantly decreased serum IL-6 levels and lymphocyte IL-6 production [12]. In a recent randomized, double-blind, placebo-controlled study involving 78 healthy elderly individuals, Spirulina supplementation (8 g/day for 16 weeks) promoted a significant increase in plasma IL-2 concentrations [13].

A similar effect was observed in patients with diabetes [14]. The plasma MDA level decreased significantly (from 2.57 to 1.85 μM/L, $p < 0.01$). At the end of the 12-week intervention period, no differences were observed between baseline and end TNF-alpha and IL-6 levels [14].

Spirulina can alleviate allergic rhinitis through its anti-inflammatory and antioxidant properties, as evidenced in human clinical studies involving allergies [15,16]. Sneezing, nasal congestion, and itching were significantly reduced in the Spirulina group compared with the placebo group. The potent antioxidant and anti-inflammatory properties of Spirulina are attributed to the active ingredients phycocyanin and beta-carotenes [17,18].

Blood pressure

The high antioxidant activity of Spirulina has drawn the attention of several clinical studies, which have examined its role in the prevention and treatment of cardiovascular diseases (CVDs). However, the results of these studies have been inconsistent. These studies were unable to analyze the precise effect of Spirulina consumption on CVDs systematically.

A pooled data analysis demonstrated that Spirulina consumption was associated with a considerable decrease in diastolic blood pressure [19]. In an *ex vivo* vessel model, the peptide fraction isolated from *S. platensis* showed direct endothelium-dependent vasodilation. This mechanism may be through a phosphoinositide-3-kinase (PI3K)/AKT (serine/threonine kinase AKT) pathway that converges on nitric oxide (NO) release [20]. Moreover, this peptide induced a significant reduction in blood pressure *in vivo* [20]. In a randomized, double-blind, placebo-controlled trial, treatment with *S. maxima* resulted in significant reductions in blood pressure in 40 Caucasian patients with hypertension (with no other CV risk factors) [21].

S. maxima (4.5 g/day, for 6 weeks) reduced systolic and diastolic BP irrespective of sex in a Mexican population (age, 18–65 years) [22]. Phycocyanin contributes to lowering BP by increasing the expression of endothelial nitric oxide synthase [23]. Substances, such as the tripeptide Ile-Gln-Pro (IQP) present in Spirulina, also showed antihypertensive activity by inhibiting angiotensin-converting enzymes [24].

Cancer

Regular consumption of phytochemicals can reduce the risk of certain cancers. Such phytochemicals are known as chemopreventive agents. Spirulina appears to be an advantageous chemopreventive agent. Spirulina extracts have demonstrated anticancer properties. The anticancer properties may be through its action on the immune system, a direct effect on DNA repair, and antioxidant protection against reactive oxygen species (ROS) generated during normal or abnormal metabolism and from toxic substances in the environment.

In Kerala, India, the first human study on its effect on cancer chemoprevention was in patients with oral leucoplakia (a precancerous lesion) in *pan* tobacco chewers. Discontinuation of Spirulina supplementation resulted in recurrent lesions in almost half of the subjects [25]. Spirulina extract inhibited the proliferation of A549 cancer cells, altered cell cycle, and plausibly inhibited apoptosis by reducing AKT/Rb phosphorylation and CDK4 expression that led to the arrest of the G1 phase cell cycle, as well as induction of apoptosis.

A549 lung adenocarcinoma cells were much more sensitive to the tested extract than normal skin fibroblasts, suggesting the role of Spirulina in lung cancer prevention [26]. In an experimental pancreatic cancer model, *S. platensis* and its tetrapyrrolic components substantially decreased cell proliferation (in part because of their potent antioxidant activity) and inhibited mitochondrial production of ROS and subsequent changes in intracellular redox status [27].

S. platensis extract produced anti-angiogenic effects on the PA-TU-8902 pancreatic cancer cells [28]. Spirulina-induced COX-2 inhibition reduced tumor growth and repressed angiogenesis. This application may also be helpful in the chemoprevention of various cancers [29,30]. Studies have attributed the algae's anticancer effect to its carotenoids, especially β-carotene, which has an effect similar to algal extract.

β-carotene found in Spirulina may also help protect the skin against the damaging effects of sunlight and prevent skin cancer [31]. Various polypeptides isolated from Spirulina have shown antiproliferative effects on specific cancer cells (HepG-2, MCF-7, SGC-7901, A549,

and HT-29), with IC50 values between < 31.25 and 336.57 µg/mL [32]. Other phytoconstituents of Spirulina (e.g. CaSp) also demonstrated inhibition of tumor invasion and metastasis [33].

In vivo and *in vitro* effects of CaSp suggest that its intravenous administration reduces lung metastasis of melanoma cells by inhibiting tumor invasion of the basement membrane [33]. The polysaccharide extract of *S. platensis* has the chemoprotective and radioprotective capability and could be a potential adjunct to cancer therapy. Furthermore, a combination of C-PC (a major phytoconstituent of Spirulina) and other drugs demonstrated anticancer potential (Table 1).

In combination with	Type of cancer and model	Effect
Piroxicam [34]	Colon carcinogenesis induced by 1,2-dimethylhydrazine dihydrochloride in rats	Reduced the number and size of tumors and increased the tumor inhibition rate compared with piroxicam monotherapy
Topotecan [35]	Prostate cancer (prostate cell line LNCaP)	
Doxorubicin [36]	Hepatocellular carcinoma cell line HepG2	Better antitumor effect and less toxic side effects than monotherapy

Table 1: *Anticancer effects of Spirulina.*

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease 2019 (COVID-19)

Bioactive compounds from Spirulina, such as angiotensin-converting enzyme (ACE) inhibitor peptides, phycobiliproteins, sulfated polysaccharides, and calcium Spirulan, can serve as antiviral agents. This plant-derived bioresource possesses natural ACE inhibitory peptides and can potentially be used to treat severe symptoms of lung trauma and inflammation associated with beta-coronavirus infection, including COVID-19.

Spirulina extracts suppress the activation of the NLRP3 inflammasome by inhibiting extracellular signal-regulated kinase (ERK) signaling, which plays a vital role in the innate immune response to pathogenic infections in macrophages. COVID-19 patients require post-treatment care due to the potential side effects associated with drug toxicity. As immune boosters, antiapoptotic agents, antioxidants, and immune stimulators, Spirulina and its extracts have extensive research supporting their use in such applications.

The use of Spirulina biomass or its active ingredients may be able to protect against drug-induced hepatotoxicity and immune suppression [37]. However, investigating these Spirulina-derived compounds to prevent SARS-CoV2 infection requires more extensive research.

Diabetes

Spirulina appears to be a most promising functional food in managing diabetes [14]. In a study by Park and Ahn (2007), Spirulina supplementation reduced mean fasting blood glucose from 105.1 mg/dL to 100.0 mg/dL in healthy elderly individuals with normal fasting blood glucose levels [38]. Similarly, Khan., *et al*. (2005) discovered that Spirulina-supplemented diets reduced fasting blood glucose levels, postprandial blood glucose levels, and glycosylated hemoglobin (HbA-1c) in patients with type-2 diabetes [39].

Kamalpreet., *et al*. (2008) found that blood glucose levels in the fasting and postprandial groups decreased by 16.3% and 12.5%, respectively, and 21.8% and 18.9%, respectively, in the 2-g group [40]. In addition, Spirulina improved C-peptide and plasma insulin [41].

Increased hexokinase activity in liver cells of rats treated with Spirulina suggested increased glucose uptake from the blood. Therefore, Spirulina produces high levels of NADP+, resulting in reduced lipogenesis, less oxidative stress, and lowering resistance levels to diabetes [41].

Immunomodulation

The ability of this dense alga to activate innate immune cells makes it one of the most potent immune system boosters available. Spirulina consistently improved immune function in mice, hamsters, chickens, cats, and fish studies. Additionally, Spirulina appears to enhance the body's ability to produce blood cells. Spirulina consumption improves the function of the spleen and thymus. and modulates the gut microbiota.

As Mao., *et al*. (2000) demonstrated, Spirulina increased IL-1β, IL-4, and IFN-γ production by human peripheral blood mononuclear cells [42]. Spirulina increases the activity of macrophages, T cells, and natural killer cells. Spirulina-fed mice exhibited immunomodulatory functions [43]. By administering Spirulina, allergic symptoms caused by shrimp extract were relieved by significantly increasing IgG1 and IgA compared to IgE levels [44].

Administration of *S. platensis* for 1 year resulted in a significant increase in total secretory IgA levels in saliva and protection against hay fever [45]. Spirulina increased the CD4 counts in patients with HIV-1 and reduced the viral loads [46]. It also suppressed Th2 cell differentiation mediated by inhibition of IL-4 production in patients with allergic rhinitis [15].

Longevity

Spirulina's C-phycocyanin (C-PC) is a pigment with potent antioxidant properties, while humans have long used it as a nutrient supplement. Furthermore, Spirulina is also rich in iron, manganese, zinc, copper, selenium, and chrome [47]. These nutrients help the body fight free radicals that damage molecules within the cells, improving the immune system against cancer [48].

As phycocyanin-rich Spirulina can support the body's natural cleansing process, it may help support the immune system. In studies evaluating the interaction between gut microbes and the host, Spirulina modulated the immune responses associated with aging [49]. Recent research has shown that Spirulina's antioxidant properties can increase the lifespan of people with Parkinson's disease [50].

Plasma lipid profile

The hypolipidemic effect of Spirulina or its extracts has been demonstrated in various animal models, including mice, rats, hamsters, and rabbits, and humans [51]. Spirulina has been shown to decrease BP in healthy, diabetic, and ischemic individuals and those with high cholesterol.

Park and Kim (2003) reported that total cholesterol, LDL cholesterol, and triglyceride levels in Korean elderly individuals improved after a 24-week supplementation with Spirulina [52]. Healthy individuals consuming Spirulina had a substantially lower total serum cholesterol and LDL level than their counterparts who did not take the supplement [22].

Furthermore, patients with type 2 diabetes receiving Spirulina supplementation had significantly lower plasma levels of triglycerides, total cholesterol, and LDL cholesterol [53]. The effect of 3 months of Spirulina treatment on total cholesterol, LDL, VLDL, triglycerides, and

HDL levels was significant in individuals with ischemic heart disease [54]. Two months of Spirulina consumption resulted in significant reductions in triglycerides, total cholesterol, free fatty acids, LDL, and VLDL in patients with type 2 diabetes [14].

Patients with hyperlipidemia and nephrotic syndrome also exhibited benefits from Spirulina consumption. Patients who received Spirulina supplementation for 2 months had decreased total serum cholesterol, LDL fraction, and triglyceride levels [55]. Spirulina clinical trials in humans have been conducted to investigate its therapeutic effects on the elderly population.

After 4 weeks of Spirulina supplementation, plasma concentrations of triglycerides, total cholesterol, and LDL fraction were reduced [52,56]. Spirulina consumption increased lipoprotein lipase and triglyceride lipase levels in the liver, indicating decreased hyperlipidemia [57]. However, the active ingredients in Spirulina responsible for hypolipidemic activity are yet to be identified.

Nagaoka S., *et al*. (2005) reported that *S. platensis* concentrate (SPC) could bind cholesterol metabolites and bile acids, decreasing cholesterol solubility [58]. They opined that phycocyanin might be the active ingredient responsible for the hypolipidemic properties of Spirulina.

Skincare

Antioxidants found in Spirulina may curb aging and reduce inflammation. Spirulina destroys free radicals, reducing the signs of skin aging and the development of wrinkles.

The results of a recent study by Liu P., *et al*. (2019) suggest that Spirulina may increase growth factors in dermal fibroblast cells, possibly contributing to skin tightening; however, the results of this study have to be confirmed by further research [59].

The antifungal activity of Spirulina may prevent candida skin infections. Spirulina was evaluated *in vitro* against 22 *Candida* strains in guinea pig uteruses. According to Marangoni A., *et al*. (2017), Spirulina can potentially treat *Candida* infections without topical antifungal agents [60].

Evidence supporting Spirulina's use for treating acne, psoriasis, eczema, or skin tightening is scarce. Nevertheless, due to its antioxidant and antimicrobial properties, Spirulina creams may be considered as a treatment for acne [61].

Spirulina helped reduce psoriasis in mice, improving the symptoms of eczema [62,63].

Weight loss management

Exercise and calorie restriction are the primary means of addressing obesity. Spirulina has been shown to aid in weight loss significantly. Clinical and preclinical studies have investigated the weight loss benefits of Spirulina.

In a recent investigation involving participants with a higher body mass index (BMI); > 25–40 kg/m^2), Yousefi., *et al*. (2018) reported that 2 g/day of Spirulina along with a calorie-deficit diet considerably reduced body weight, waist circumference, body fat, and BMI compared to placebo [64].

Zeinalian., *et al*. (2017) discovered that consuming 1g of Spirulina for 12 weeks decreases appetite, body weight, BMI, and total cholesterol [65].

Adverse effects

The safe consumption of Spirulina has been noted historically. Several animal studies support this benefical view. In rats, no teratogenicity was detected with Spirulina consumption in maternal and fetal studies [66]. Spirulina's effects were not affected by behavior, food intake, weight, health status, or clinical chemistry measurements.

The safety profile of Spirulina (in and of itself) has been posited by human clinical trials [67]. Nevertheless, a few reports cited safety concerns when used in humans. Spirulina grown in an open water source was reported to contain minimal amounts of mercury and heavy metals.

Consuming such Spirulina preparations can cause a buildup of mercury and heavy metals, contributing to toxic effects. In addition, consumers may be adversely affected by contamination by certain cyanobacterial species. For cyanobacterial food supplements, quality control has been recommended to avoid potential adverse effects in animals and humans, including Spirulina.

Spirulina supplements have contributed to adverse effects in very few human cases [47]. A case of rhabdomyolysis and the development of a mixed immunoblistering disorder with characteristic features of bullous pemphigoid and pemphigus foliaceus was reported in individual cases [47].

Conclusion

Based on its history as a food source and its favorable safety profile in animal studies, Spirulina is generally considered safe for human consumption—with rarely reported side effects. Nevertheless, a credible safety profile of Spirulina must be established in humans through additional clinical studies. In addition, Spirulina products must have strict quality control measures to prevent contamination during growth and processing.

Overall, data indicate that algae are a promising functional food supplement for human well-being and the prevention and treatment of various diseases. Spirulina supplementation can effectively control hyperglycemia and hypercholesterolemia, reducing CV risk in patients with type 2 diabetes. Also, Spirulina can help manage weight gain, facilitate the efficacy of anticancer agents, and serve as a potent antioxidant and anti-inflammatory agent to prevent specific diseases and improve longevity in humans.

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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