*REVIEW ARTICLE*

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# Spirulina maxima supplementation: benefits and limitations – results of latest studies

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## Abstract

**Introduction and Objective.** Clinical use of the blue-green algae Spirulina has gained attention due to its potential health benefits. While some research suggests promising outcomes, the overall evidence is still limited, and further rigorous clinical trials are needed to validate its therapeutic efficacy and safety profile. Despite the need for more research, Spirulina continues to be explored as a potential adjunctive therapy in holistic health approaches and dietary supplementation.

**Review Methods.** A search of the Pubmed, EMBASE, Cochrane Library, UpToDate databases was carried out using key words: 'spirulina' and 'spirulina supplementation' in order to find the latest publications.

**Brief description of the state of knowledge.** Spirulina is considered a nutrient-dense food source, abundant in vitamins, minerals, amino acids, and antioxidants. Research indicates potential health benefits, including immune system support, anti-inflammatory effects, improved lipid profiles, and antioxidant properties. Studies have also investigated Spirulina's potential role in managing conditions such as obesity, diabetes, cardiovascular diseases, allergies, and cancer. While some studies show promising results, further research is needed to fully understand its mechanisms of action, optimal dosage, and long-term effects on human health.

**Summary.** Despite limitations, numerous studies have explored the effectiveness and potential clinical uses of Spirulina in treating various diseases. Some randomized controlled trials and systematic reviews indicate that this alga could alleviate symptoms and potentially exhibit anti-cancer, antiviral, ant-inflammatory effects.

## Key words

dietary supplements, spirulina maxima, food supplements, antioxidant potential, nutrition awareness

## INTRODUCTION

*Spirulina* is the commercial name of cyanobacteria belonging to the order *Oscillatoriales*. It is widely used as a nutritional supplement rich in proteins, vitamins, minerals and other healing phytonutrients (Tab. 1.) [1, 2]. Numerous toxicological studies have confirmed the safety of consuming *Spirulina*, and it is now included in the list of substances recognized as safe by the US Food and Drug Administration (GRAS Notice No. GRN 000127) [3, 4].

This study investigates the clinical potential of Spirulina supplementation, aiming to comprehensively review the existing evidence and shed light on its therapeutic uses, by examining its impact on key health outcomes, including immune function, inflammation, cardiovascular health, metabolic disorders, and oxidative stress. Furthermore, the study explores the underlying mechanisms of action that contribute to *Spirulina's* claimed health benefits. Understanding the clinical potential of *Spirulina* can inform healthcare professionals, researchers, and consumers about its role in promoting health and preventing disease.

## OBJECTIVE

The aims of this review are 1) to outline the mechanisms of action, emphasize the potential impacts of this algae on human health, and discuss present as well as potential future clinical uses; 2) by synthesizing findings from numerous trials, to provide insights into the efficacy, safety, and potential limitations of *Spirulina* supplementation in clinical practice.

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**Table 1.** Composition of *Spirulina* extract powder formulations

| Description | Spirulina extract powder formulations | |
|---|---|---|
| Components | | |
| Phytonutrients | | g/100 g$^{-1}$ |
| • Phycocyanin | 12 | |
| • Chlorophyll-a | 1 | |
| • Cis beta – carotene | 0.073 | |
| • Trans beta – carotene | 0.26 | |
| Protein (total) | 31.8–63.8 | g/100 g |
| • Leucine | 4.94 | |
| • Valine | 3.51 | |
| • Isoleucine | 3.20 | |
| • Tryptophan | 0.93 | |
| • Methionine | 1.15 | |
| • Phenylalaline | 2.78 | |
| • Threonine | 2.97 | |
| • Lysine | 3.02 | |
| Carbohydrates (total) | 17.8–63.8 | g/100 g |
| Lipids | | g/100 g$^{-1}$ |
| • Oleic | 0.017 | |
| • Myristic | 0.041 | |
| • Arachidic | 0.048 | |
| • Palmitic | 2 | |
| • Gamma linolenic (GLA) | 1 | |
| Fibre | 0.88–6.13 | g/100 g |
| Minerals | | mg/100 g$^{-1}$ |
| • Zinc | 3 | |
| • Potassium | 1,400 | |
| • Sodium | 900 | |
| • Phosphorus | 800 | |
| • Manganese | 5 | |
| • Magnesium | 400 | |
| • Calcium | 700 | |
| • Copper | 1.2 | |
| • Iron | 100 | |
| Vitamins | | mg/100 g$^{-1}$ |
| • Carotene | 140 | |
| • Vitamin E | 100 | |
| • Vitamin K | 2.2 | |
| • Vitamin B1 | 3.5 | |
| • Vitamin B2 | 4 | |
| • Vitamin B3 | 14 | |
| • Vitamin B9 (folic acid) | 0.01 | |
| • Vitamin B12 | 0.32 | |
| Potential impurities | | |
| Heavy metals | | mg/1000g |
| Lead (Pb) | 0.029–0.165 | |
| Arsenic (As) | 0.011–0.05 | |
| Mercury (Hg) | <0.01–0.006 | |
| Cadmium (Cd) | 0.008–0.084 | |
| Pesticides | Not detected | |
| Aflatoxins | Not detected | |

## REVIEW METHOD

A search of the Pubmed, EMBASE, Cochrane Library, UpToDate databases was carried out using key words: 'spirulina' and 'spirulina supplementation' in order to find the latest publications.

**Hypertension.** According to World Health Organization (WHO) an estimated 1.28 billion adults aged 30–79 years worldwide have hypertension – a major cause of premature death globally. Among other complications, hypertension can cause myocardial infarction, heart failure, aneurysm, stroke, kidney problems, vision loss and dementia. Together with hypertriglyceridaemia, excess abdominal weight, low levels of HDL cholesterol, elevated blood sugar levels, it is a part of the metabolic syndrome [5]. The life-long risk of developing hypertension is estimated at 90%, and a correct non-pharmacological approach can be helpful in avoiding all its complications. Multiple clinical trials have been conducted concerning hypertension and *Spirulina* supplementation. As mentioned in the introduction, this microalga contains numerous bioactive compounds, among which several peptides showed anti-hypertensive effects. The tripeptide Ile-Gln-Pro given orally showed an inhibition of ACE, significantly decreasing the weighted systolic blood pressure (SBP) and diastolic blood pressure (DBP) in spontaneously hypertensive rats [6]. A blue pigment – phycocyanin has been reported to enhance the expression of endothelial nitric oxide synthase in the aorta under the stimulation of adiponectin [7, 8] contributing to the dilation of blood vessels. Miczke et al. [9] in their randomized double-blind placebo-controlled trial showed that a daily intake of 2.0 g of Hawaiian *Spirulina* for three months can significantly reduce systolic blood pressure in overweight hypertensive Caucasians. Administration of 8 g per day of *Spirulina* for 12 weeks showed a significant lowering effect on DBP ($p < 0.021$), and no significant effect on SBP in a study by Lee et al. [10] Consumption of 2.3g of *Spirulina* for two weeks did not have statistically significant impact on systolic and diastolic blood pressure in a study conducted by Jensen et al. However, the intake was correlated with a slight decrease in DBP [11]. Eight weeks of *Spirulina* supplementation by ulcerative colitis patients did not influence blood pressure values ($p>0.05$). The dosage in this study was relatively low (1.0g per day) [12].

According to the results of a meta-analysis conducted by Machowiec et al., both the dose and the duration of supplementation may be important in achieving the anti-hypertensive effect [13]. For example, studies in which the duration of *Spirulina* supplementation was below 12 weeks showed no significant changes in BP [11, 12].

**Obesity.** Highly processed foods, excessive caloric intake and lack of exercise, among other environmental, psychological, genetic and hormonal factors, contribute to the development of the disease that affects 1 in 8 people worldwide. In 2022, according to the WHO, 43% of adults were overweight and 16% were living with obesity [14]. Obesity is not only an aesthetic problem as it contributes to the occurrence of cardiovascular diseases, chronic respiratory diseases, diabetes, cancers, neurological disorders, digestive disorders, and more [14]. Adipose tissue secretes biologically-active substances, such as adipokine, leptin, resistin, several cytokines, adipsin and acylation-stimulating protein, angiotensinogen and plasminogen activator inhibitor-1. It also produces steroids hormones [15]. When it comes to their function, adipolin, an anti-inflammatory cytokine can be decreased in obesity and other pathological conditions associated with obesity [16]. Apelin inhibits lipolysis in adipocytes and is involved in angiogenesis in adipose tissue [17]. Ghrelin, known as the 'hunger hormone', plays a crucial role in glucose- and energy-homeostasis, cardioprotection, muscle atrophy, bone metabolism, and cancer [18]. Vascular endothelial growth factor (VEGF) is a potent angiogenic factor which is an important biomarker in obesity and obesity-related cancer

progression. Visceral fat accumulation leads to increase serum VEGF concentrations [19]. Also, in obese patients, the mineral status of the body is impaired including altered iron homeostasis [20].

Reducing calories, practicing healthier eating habits and engaging in more physical activity are the key to overcoming obesity, but poor compliance with lifestyle changes leads to failure in attempting to achieve optimum long-term weight loss. If lifestyle modification alone has not been effective, patients can use pharmacological treatments. However, in contrast to dietary supplements, anti-obesity drugs have side-effects. That is why recently some herbal supplements have been used as a strategy in weight management – among them *Spirulina*.

A reduction in macrophage infiltration into the visceral fat, prevention of hepatic fat accumulation, reduction in oxidative stress, improvement in insulin sensitivity and satiety, are some potential mechanisms that could explain the role of *Spirulina* in weight loss. Results of a study conducted by Szulinska et al. confirm that *Spirulina* supplementation (2g) considerably improved the ratio of total antioxidant status and insulin sensitivity. It also had a lowering effect on low-density lipoprotein cholesterol ($p<0.001$) and interleukin-6 concentration ($p=0.002$). The patients additionally decreased their body mass, body mass index ($p<0.001$) and waist circumference ($p = 0.002$) [21]. Mohammad et al. report that 'eight weeks of circuit resistance training and *Spirulina* supplementation (1g) can lead to reduced weight, apelin and FBS levels as well as increased concentrations of adipolin and ghrelin contents in overweight and obese men' [16]. Hernández-Lepe et al. also suggest that supplementation (4.5g) synergistically improves the effects of systematic exercise on body composition and cardiorespiratory fitness parameters during six weeks of treatment [22]. A study conducted by Zeinalian et al. reports that 1 g of *Spirulina Plantensis* daily for 12 weeks effectively helped in weight regulation and appetite reduction [19].

In conclusion, it seems that *Spirulina* supplementation significantly reduces body weight and is more effective especially for obese individuals. However, all the current studies have limitations, for example, small sample size, short duration of study, varied dose of supplementation, and lack of diversity in terms of gender and age. Therefore more studies are required.

**Hypertriglyceridaemia.** Hypertriglyceridaemia (HTG) is characterized by elevated fasting plasma triglyceride (TG) levels exceeding the 95th percentile for age and gender [23]. Hypertriglyceridaemia has been associated with an increased risk of cardiovascular disease and pancreatitis [24]. As mentioned before, elevated serum triglycerides is a valuable clinical marker of the metabolic syndrome. In meta-analysis of data from randomized controlled trials, Rahnama et al. [25], after examining 1,107 records, included and analyzed 20 studies concerning 1,067 subjects. Four trials lasted more than 12 weeks, and 16 had a treatment duration of 12 weeks or less. According to the researchers, only 4 studies were of good quality [19,26–28]. The combined findings suggested that the consumption of *Spirulina* led to a significant reduction in LDL-C levels, and considerable heterogeneity was observed among the studies. Variability in baseline BMI, study design, health status, and geographical location could account for this heterogeneity. Notably, the reduction effect of *Spirulina* was pronounced in studies with parallel designs. Additionally, *Spirulina* did not demonstrate a significant reduction in LDL-C levels among healthy, obese, NAFLD, and MetS participants in crossover-designed trials conducted in Iran, USA, The Netherlands, Korea, and Romania. Meta-regression analysis revealed that neither *Spirulina* dosage nor the duration of supplementation were the source of heterogeneity.

The blue-green *Spirulina* algae has the potential to notably increase HDL-C levels. The significant impact of *Arthrospira* was evident in studies with dosage less than 4 grams per day duration supplementation of less than 10 weeks, focusing on patients with T2DM, HIV, and HTN. There was also a notable decrease in the levels of triglycerides (TG). In research of fair quality, parallel designs and using intervention doses of less than 4 grams per day, demonstrated a significant reduction in TG levels due to *Spirulina*. Additionally, interventions involving *Spirulina* showed significant reductions in TG levels among patients with T2DM, HIV, HTN, and individuals with a baseline BMI less than 30 kg/m2.

Analysis of available randomized controlled trials (RCTs) also revealed that the consumption of *Spirulina* resulted in decreased concentrations of total cholesterol (TC), LDL-C, and TG, while increasing the levels of HDL-C. Additionally, a significant dose-response relationship was observed between *Spirulina* supplementation and plasma lipid profile concentrations. Moderate doses of the algae, approximately 4 grams per day, exhibited the most pronounced effect on HDL-C levels, whereas doses of 5 grams per day had the greatest impact on TG concentrations. Conversely, higher doses of *Spirulina*, around 10 grams per day, demonstrated the most significant effect on TC levels. Furthermore, the researchers concluded that the beneficial impact of *Spirulina* supplementation on improving lipid profile parameters exceeded the minimal clinically important difference (MCID), which is significant for healthcare professionals in clinical decision-making.

**Blood sugar levels, type 2 diabetes.** Type 2 diabetes is a prevalent metabolic disorder marked by persistent hyperglycaemia. This condition is linked to a decreased lifespan due to the heightened risk of heart disease, stroke, peripheral neuropathy, renal disease, blindness, and limb amputation. Presently, the most reliable indicators of elevated diabetes risk include high fasting plasma glucose, abnormal glucose tolerance test results, obesity, and signs of impaired insulin function. Despite the multitude of strategies proposed for improving or managing diabetes, the prevalence of this disease is rapidly escalating. This surge in incidence places a significant strain on healthcare system resources, resulting in substantial annual economic costs. Therefore, any feasible alternative, complementary, or supplementary therapy that could alleviate some of the economic and healthcare burdens, is of the utmost importance. Hatami et al. [29], in their study emphasizes that supplementation with *Spirulina* can lead to improvements in fasting blood sugar (FBS) levels as well as lipid profiles.

The current study synthesizes the available information from clinical trials, offering a deeper understanding of the effects of *Spirulina* supplementation on type 2 diabetes. *Spirulina*, being a natural functional agent, is generally considered a safe and cost-effective supplement that can positively impact metabolic abnormalities associated with

type 2 diabetes. The beneficial effects of *Spirulina* suggest it could serve as a valuable adjunct therapy alongside conventional medicine. Nevertheless, the findings of this study should be regarded as preliminary, and further research is warranted to validate the obtained results.

**Anti-inflammatory effects.** Inflammation – the body's defence mechanism against injuries and pathogens – serves to eliminate damaged cells and pathogens, thereby safeguarding the organism. Nevertheless, when inflammation becomes excessive, it can inadvertently harm healthy tissue cells while targeting pathogens. This can lead to the development of various inflammatory diseases and have negative effects on human health [30]. Studies have indicated that *Spirulina* enhances macrophage activity, promotes natural-killer (NK) cell proliferation, activates T-cells, and up-regulates key cells and organs of the immune system, thereby boosting their ability to combat infectious agents and environmental toxins. Various authors have reviewed the potential therapeutic uses of *Spirulina*, highlighting its immunomodulatory and anti-inflammatory properties [31–34]. Calella et al. [35] in their systematic review analyzed the anti-oxidant, anti-inflammatory and immunomodulatory effects of *Spirulina* in exercise and sport. The results obtained indicate the following: for athletes engaged in extensive sub-maximal endurance training, such as cyclists or runners, considering a daily supplementation of 6–7.5 grams might be beneficial for improving the redox status, fatigue tolerance, and haemoglobin levels. However, it seems that *Spirulina* supplementation does not enhance physical performance in power athletes. Most studies suggest no significant improvement in creatine kinase (CK) or delayed onset muscle soreness (DOMS), indicating no influence on muscle recovery. Nevertheless, a dosage of 5.7 grams per day of *Spirulina* appears to accelerate recovery after training or competitions in elite rugby players. Moreover, supplementation could potentially alleviate exercise-induced oxidative damage, inflammation, and muscle damage in elite athletes who fall short of the recommended intake of dietary anti-oxidants. It is speculated that *Spirulina* might protect athletes from immune dysfunction associated with intense exercise by maintaining lower levels of regulatory T cells (Tregs) in tissues, thus preventing their immunosuppressive effects and restoring immune balance. Nonetheless, the available evidence supporting the immune system benefits of *Spirulina* supplementation is currently limited.

**Dermatomyositis.** Dermatomyositis (DM) is an autoimmune condition impacting the skin, lungs, muscles, and other organs. The age of onset of DM demonstrates a bimodal distribution, with one peak typically occurring between ages 5–14 and another between 45–64 years. Although the precise causes and mechanisms of DM remain unclear, there is a consensus that it stems from an autoimmune attack on affected organs. Environmental factors, including medications, infections, exposure to ultraviolet (UV) radiation, and pollutants, may trigger DM in individuals with genetic susceptibility [36]. *Spirulina* has been found to boost the immune system, as demonstrated by research conducted both in laboratory settings and on living organisms. Recent epidemiological data indicate a potential association between *Spirulina* consumption and the development or worsening of pre-existing autoimmune skin conditions like dermatomyositis (DM). *Spirulina* has been shown to enhance the production of important inflammatory cytokines, such as TNFa and IFNb, and it can activate both the TLR4 and STING pathways in laboratory studies involving DM patients. These findings suggest a possible mechanism by which *Spirulina* usage could contribute to the onset or exacerbation of the disease in susceptible individuals [37–39].

**Anti-viral applications.** Hepatitis B virus (HBV) infection is considered one of the most significant infectious diseases globally, with more than 240 million individuals contracting the virus during their lifetimes. In patients with chronic hepatitis B (CHB), there is an increase in the concentration of HBV DNA in the serum, which serves as the primary risk factor for liver fibrosis. Persistent liver fibrosis can progress to cirrhosis, leading to symptomatic complications such as jaundice, ascites, variceal haemorrhage, and hepatic encephalopathy, and ultimately to the development of hepatocellular carcinoma (HCC).

A study conducted by Sheng-Jie Shiue et al. [40] aimed to investigate the effect of *Arthrospira* on reducing hepatitis B surface antigen (HBsAg) levels in CHB patients undergoing continuous nucleos(t)ide analogues (NA) therapy. Sixty CHB patients with undetectable HBV DNA levels, who had been receiving NA treatment for at least one year, were randomly assigned to three groups: a control group and two groups receiving oral *Arthrospira* at doses of three or six grams daily as add-on therapy. The patients were followed-up for six months. Additionally, an oral *Arthrospira*-diet was administered to mice to explore the potential immunological mechanisms of *Spirulina* against HBV. Over the six-month period, the mean quantitative HBsAg (qHBsAg) levels decreased in the group receiving oral *Arthrospira* add-on therapy. Notably, interferon gamma (IFN-γ) levels increased, while TNF-α, interleukin 6 (IL-6), hepatic fibrosis, and steatosis decreased in the add-on therapy groups. *Spirulina* may modulate IL-2- and TNF-α/IFNγ-mediated B and T cell activation to reduce HBsAg levels. Additionally, the algae shows promise in restoring immune tolerance and enhancing HBsAg seroclearance in CHB patients by promoting T, B, and NK cell activation.

**Animal studies.** After analyzing available studies conducted on animals, it is suspected that *Spirulina* has significantly more health benefits. Ekeuku et al. [41] examined the algae's influence on bone formation and in diabetic rats induced by streptozotocin (STZ), *Spirulina* enhanced bone formation, leading to improved bone strength and stiffness. The increased expression of osteocalcin, higher numbers of osteocytes/osteoblasts, and reduced levels of serum calcium and phosphorus all supported these findings. This implies that *Spirulina* might have the potential to prevent brittle bones associated with type 2 diabetes mellitus (T2DM), thereby reducing the risk of fractures.

A recent study by Chen et al., [42] in a nude mice model found that extracts derived from *Spirulina*, specifically phycocyanin, along with its purified forms – allophycocyanin and C-phycocyanin – could stop the movement and spread of endometrial cancer cells by affecting a signalling pathway in the body called TGFβ/SMAD4. This works by decreasing certain proteins in the cells, such as TGFβR1, Smad4, Snail, SLUG, TWIST1/2, and ZEB1, while increasing another protein – E-cadherin. It also involves reducing the levels of other

proteins like N-cadherin, vimentin, α-SMA, fibronectin, and TMEFF2. Ultimately, this process triggers the MET process, which helps to prevent the cancer cells from spreading further. These findings suggest that *Spirulina* phycocyanin extract, along with its purified forms allophycocyanin and C-phycocyanin, could be highly beneficial in treating metastatic endometrial cancer, offering potential for use in clinical settings.

The results obtained by Abu-Taweel et al. [43] showed that *Spirulina* significantly reduced swelling in the hind paws of the mice, caused by carrageenan, and decreased inflammation associated with cotton pellet-induced granuloma. Initial molecular studies revealed that *Spirulina* lowered the levels of inflammatory markers such as TNF-α, IL-1β, IL-6, PGE2, and NO, and inhibited the activities of COX-2 and iNOS. These results provide a solid base for understanding the anti-inflammatory and pain-relieving effects of *Spirulina* in various animal models.

Liu et al. [44] designed a study which implied that during treatment with phycocyanin, the levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in the blood plasma, significantly decreased. Further examination of tissue samples confirmed that phycocyanin provided protection against radiation-induced liver damage. Phycocyanin treatment also increased the mRNA expression of superoxide dismutase (SOD) and glutathione peroxidase (GSH-PX), while reducing the levels of reactive oxygen species (ROS) in the liver. Additionally, the expression of H2AX, a marker of DNA damage in mice, was significantly lower in the group receiving phycocyanin compared to the radiation-only group. In animal models, phycocyanin treatment notably increased the expression of NF-E2-related factor 2 (Nrf2) and downstream genes, such as heme oxygenase-1 (HO-1) and NAD(P)H quinone dehydrogenase 1 (NQO1). In conclusion, phycocyanin can mitigate oxidative stress caused by radiation by activating the Nrf2/HO-1 signaling pathway and reducing radiation-induced DNA damage, thereby serving as a protective agent against radiation-induced liver damage.

## SUMMARY

*Spirulina* has shown promising effects in preclinical and clinical studies. It has been associated with anti-hypertensive effects, weight loss, improvements in metabolic parameters, and has anti-inflammatory properties. Additionally, *Spirulina* may have positive impacts on such conditions as hypertriglyceridaemia, type 2 diabetes, and certain autoimmune diseases. Animal studies further suggest potential benefits in bone health, cancer prevention, and protection against liver damage. While *Spirulina* shows promise as a complementary therapy, more research is needed to confirm its efficacy and determine optimal dosages for specific health conditions.

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