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Spirulina, an FDA-approved functional food: Worth the hype?

Abdul Momin Rizwan Ahmad[1], Anosh Intikhab[2], Saira Zafar[3], Umar Farooq[1], Hassan Bin Usman Shah[4], Sajeela Akram[5], Juweria Abid[1], Zehra Parveen[1], Sehar Iqbal[6,*]

[1] Department of Nutrition & Dietetics, National University of Medical Sciences (NUMS), Rawalpindi, Pakistan
[2] Riphah International University, Islamabad, Pakistan
[3] Department of Public Health, Health Services Academy, Islamabad, Pakistan
[4] The Kirby Institute, University of New South Wales, Sydney, Australia
[5] Department of Human Nutrition & Dietetics, University of Chakwal, Chakwal, Pakistan
[6] College of Pharmacy, Al-Ain University, Abu Dhabi Campus, United Arab Emirates

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ABSTRACT

Spirulina, a blue-green microalga is an eminent functional food due to its unique nutritional and disease-mitigating properties. The main objective of this article is to present an overview of the nutritional composition of Spirulina. Along with its therapeutic potential and applications in the food industry. Studies included in this review have suggested spirulina to be a rich source of complete proteins, essential fatty acids (EFAs), vitamins, minerals and various bioactive compounds like carotenoids, chlorophyll, and xanthophylls. This makes Spirulina a promising functional food for the treatment of ailments like diabetes, cancer, cardiovascular disorders (CVDs), COVID-19, neuroinflammatory conditions and gut dysbiosis. Additionally, data from numerous studies suggest its use in food formulations, primarily in sports supplements, bakery products, beverages, dairy products, snack sources and confectionaries. It has also been used by the National Aeronautics and Space Association (NASA) for astronauts on space missions to the Moon and Mars. Furthermore, spirulina's use as a natural food additive possesses enormous potential for further research. Owing to its high nutritional profile and disease-fighting potential, it lends itself to numerous food formulations. Therefore, based on the findings of previous studies, further progress can be made considering spirulina's application in the food additive industry.

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Introduction

Consumer awareness regarding their dietary habits and its correlation with the potential onset of chronic ailments has increased remarkably in recent years (1). Resultantly, food industries are striving to maximize the use of algae-based products. Effectively using these eco-friendly extracts, containing ingredients that are both nutritious and beneficial for human health, to increase profits (2,3). In this regard, there is an ever-growing interest in the functional food market especially macro and micronutrients involving microalgae and fungi species(4). According to the Credence Research Market Analysis (2016), the global use of algae products particularly that of nutraceuticals, pharmaceuticals and fitness supplements will report an annual growth rate of 5.8% during the years 2017-2026 and is expected to reach more than USD 53 billion in the years to come (5).

Among microalgae, studies related to Spirulina have gained particular momentum in the past years(6). Spirulina is a blue-green alga found both in fresh and salt water. It was initially classified under the plant kingdom owing to its photosynthetic properties but later was placed into the bacteriological kingdom after detailed studies related to its genetic, physiological, and biochemical prototype(7). It is normally known to grow naturally in high salt alkaline water, mostly in tropical and subtropical areas of America, Mexico, Africa and Asia(8). Among its vast varieties, the most commonly studied are; Spirulina platensis (*Arthrospora platensis*), Spirulina maxima (*Arthrospora maxima*) and Spirulina fusiformis (*Arthrospora fusiformis*)(9).

Over the past decades, numerous studies have been carried out to study the nutritional and therapeutic potential of Spirulina(10–12). It is known to contain various functional compounds such as beta-carotene, phycocyanin, tocopherols, polyunsaturated fatty acids, particularly gamma-linolenic acid and phenolic compounds(13). Initially, the nutritional properties of Spirulina were recognized by various intergovernmental institutions to fight against malnutrition in 1970(14). In 1996, World Health Organization (WHO) declared spirulina to be the best food for the future owing to its rich protein and antioxidant properties (15). More recently, it also received the status of "Generally Recognized as Safe (GRAS)" by the United States USDA, when harvested under controlled conditions(16). Furthermore, spirulina has also been recognized and recommended by the National Aeronautics and Space Administration (NASA) and the European Space Agency (ESA) for food supplementation during long-term space travel(17). Since then, numerous clinical trials have been

* Corresponding author. Email: saheriqbal55@gmail.com

conducted for determining its vast nutritional benefits as a supplement(10,18–20).

This algae-based food makes a low-cost supplement, with numerous health benefits. It can be especially beneficial for Non-Communicable Diseases (NCDs) and metabolic syndrome on the rise in European and Asian regions(21). For instance, a meta-analysis of randomized control trials by Serbab et al. 2016, evaluated the effects of Spirulina supplementation on plasma lipid concentrations. A dose of 1-10g/day over 2-12 months period resulted in a significant reduction of total cholesterol(22). The therapeutic potential of spirulina extends to its antiviral, anticancer, anti-diabetic, anti-inflammatory, hepatoprotective, and immunity-boosting properties(23). Furthermore, studies also reported neuroprotective effects and benefits in age-related vascular dysfunction in murine models(24,25).

The above-mentioned facts indicate the need for evaluating the nutritional value of algae-based products like spirulina often known as a "superfood", although this term does not represent an official legal definition(26). Therefore, the objective of the current review is to give an overview of the nutritional composition of Spirulina along with its therapeutic potential and health benefits as a supplement and a natural food additive. Furthermore, safety concerns and future consideration regarding the administration and growth of this algae-based supplement will be discussed in this review.

Nutritional composition

Microalga like spirulina is a novel yet sustainable food source. These organisms can produce a large amount of high-biological value protein, long-chain polysaturated acids, carotenoids, vitamins, and phenolic compounds(27). Some studies show microalgae proteins to be competitive with commercial proteins used as an emulsifier for example whey protein and soy protein (28,29). Spirulina's protein content ranges between 65-70%. However, the maximum protein content reported to date is 59%(28). Its amino acid profile is considered a high-biological value protein. Additionally, it is also an opulent source of essential fats (e.g., gamma-linolenic acids). It also has an exceptionally high content of vitamin B12, beta-carotene, iron, calcium and phosphorus(29). The influence of wheat flour fortification with Spirulina in vitro protein digestion was observed by De Marco et al. According to this study, adding 5, 10 and 20g Spirulina increased the protein content of pasta to 15.4 g/100g, 18.0g/100g and 23.5g/100g respectively, but the protein digestibility decreased significantly from 80.9 % (pasta without Spirulina) to 55.5 % (pasta including 20 g 123 Spirulina/100 g) with increasing amounts of Spirulina(30).

Analysis of the fatty acid profile revealed considerable amounts of omega-6 fatty acids, in particular, linoleic acid, and gamma-linoleic acid (GLA) in Spirulina strains collected from Algeria and Haiti. Omega-6 fatty acids accounted for 23.1-24.5 % of total lipids, whereas a lower concentration of 10% of omega-6 fatty acids was found in the Spirulina powder from Chad. As a result, studies suggest consuming other healthful sources, such as nuts and seeds to meet daily dietary requirements (31). It is also a rich source of various micronutrients, for instance, vitamin E ranges from 2.8-12.5 mg/100g with higher concentrations in traditionally dried spirulina(32). Carcea et al. 2014, charted a drastic variation in folate content from 270-535µg/100 g dry weight. This marked difference in folate content could be due to the difference in processing techniques(32). Additionally, spirulina is a good source of vitamin B12, especially for vegans and vegetarians, with nutritional ranges between 127-244 µg/100g dry weight(33). Vitamin C presence was not detected in any study from different locations around Lake Chad, regardless of the techniques applied(34). The micronutrient content is generally reported to be higher for algae grown in fresh water(35). Besides vitamins and minerals, numerous bioactive compounds in Spirulina e.g., phenolic compounds, carotenoids, chlorophyll, lutein, and quercetin, etc. are shown in "Table 1."

Therapeutic potential

Heart health

During the past decades, reduction in total fat intake from saturated and trans fatty acids has been the focus of various national dietary recommendations to decrease the risk of atherosclerosis, coronary heart disease (CHD), hypertension and hyperlipidemia (36). Numerous studies including human and murine models have been conducted to study the lipid-lowering effect of spirulina up till now. Researchers in a study demonstrated the benefits of spirulina in forty hypertensive patients. When supplemented with 2g/day of spirulina versus placebo for 3 months, there was a significant reduction in Body Mass Index (BMI) (26.9±3.1 vs 25.0±2.7kg/m2, p=0.0032), systolic blood pressure (149±7mm Hg vs 143±9mm Hg, p=0.0023) and arterial stiffness index (7.2±0.6 vs 6.9±0.7 m/s, p<0.001),

Table 1. Biochemical analysis of *Arthrospira platensis* (Spirulina).

Bioactive Compound	Amount
Macronutrients	
Carbohydrates	15-25%
Proteins	60-70%
Lipids	6-12%
Fatty Acids	
Myristic Acid (C14),	46.07%,
Palmitic Acid (C16)	5.26%,
Oleic Acid (C18:1),	23.1-24.5%,
Omega3& 6	10%
Vitamins	
Folate,	270-535µg/100 g
VitB12,	127-244 µg/100 g
Vit E,	2.8-12.5 mg/100g
Vit A	29 µg/100 g
Minerals	
Calcium	1.68 mg/g
Manganese	0.19 µg/g
Iron	0.52 mg/g
Potassium	18.30 mg/g
Zinc	0.20 µg/g
Copper	0.30 µg/g
Molybdenum	0.30 µg/g
Phytopigments	
Carotenoids	0.551%
Chlorophyll	1.472%
Xanthophylls	0.271%
Phycocyanin	14.18%

thus proving beneficial cardiovascular effects (37). Certain Greek patients with dyslipidemia also demonstrated significant improvements using spirulina supplementation, a mean level of triglycerides (TGs) reduced by 16.3% ($p<0.0001$) (Low-Density Lipoprotein- Cholesterol) LDL-C by 10.1% ($p<0.0001$), (Total Cholesterol) TC by 8.9% ($p<0.0001$), (Non-High Density Lipoprotein- Cholesterol) non-HDL-C by 10.8% ($p<0.0001$) (38).

Gut health

Spirulina has a probiotic effect owing to its rich oligosaccharide composition, which can promote the growth of good gut microflora like Desulfovibrio, Eubacterium, Barnesiella, Bacteroides, and Flavonifractor(39). A recent study, observing the effect of spirulina dosage on colonic microbiota suggested a significant effect of dose-related modulation of spirulina i.e. low (1.5 g/kg) and high (3.0 g/kg) on gut/colonic microbial concentrations(40).

Weight loss and muscle strength

Obesity is one of the most prevalent public health issues around the globe(41). According to a 2016 global health report, more than 1.9 million adults were characterized as overweight, while 650 million were reported to be obese(42). Obesity is closely linked to inflammation, hyperlipidemia, and insulin resistance(43). Although caloric restriction and caloric deficit are the main concepts, recent studies have shown that spirulina supplementation, either in capsule or powder form, can help with weight loss (44). The phycocyanin in spirulina contains a light-harvesting chromophore called phycocyanobilin(45). This compound possesses an inhibitory effect towards nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) oxidase, a major source of oxidative stress in adipocytes, (46) which can potentially lead to insulin resistance. Spirulina supplementation can reduce oxidative stress in adipocyte tissues, resulting in controlled anti-inflammatory properties (44,45). Moreover, in addition, to weight loss, numerous studies have reported the effect of spirulina supplementation on strength and endurance during high-intensity strength training(46–48). Strength training is known to increase systemic oxygen consumption, causing excessive production of reactive oxygen species (ROS) thereby, promoting oxidative stress(52). One study conducted in this regard revealed that spirulina supplementation for 8 weeks was effective in increasing isometric muscle strength and isometric muscle endurance, proving it to be a good dietary strategy in sports nutrition(46).

Anti-cancer properties

In addition to its other health benefits, microalgae have been shown to improve the immune system and have anticancer properties (9). Several studies have been conducted that demonstrate its cancer-fighting properties in both animal and human studies(9,53–55). In vitro studies are suggestive of the fact that the unique polysaccharide of Spirulina enhances cell nucleus enzyme activity and DNA repair synthesis(49). Its applications in oncological treatments range from minimizing the risk of breast cancer to lung cancer. Spirulina significantly reduces cancer cell proliferation, accompanied by cell cycle inhibition in (Growth 1) G1 phase and the resulting morphological changes. Furthermore, it has been proved that there is no potential harm of spirulina on normal skin fibroblast function. This strong cancer-fighting property shows the efficacy of the supplements in the treatment of lung cancer(50). It also has a scavenging effect on the early stages of hepatocellular carcinoma (HCC). Spirulina inhibited structural and functional alterations of HCC, thereby improving survival rates by significantly decreasing the tumor marker (Alphafetoprotein) AFP and the count and size of liver nodules in HCC(51).

Diabetes control

Diabetes is one of the most prevalent metabolic conditions around the world, due to the toll it takes on the healthcare sector(52). Spirulina demonstrated glucose and lipid-modulating effects, indicating that it might have a diabetes control potential in both animal and human studies (60–62). A study conducted in 2017, on male subjects with non-insulin-dependent diabetes mellitus (NIDDM) suggested supplementation of 2g of Spirulina can improve nutrient adequacy and health status of male subjects(63). Numerous studies have reported increased oxidative stress present in diabetic subjects(64–66). The extreme production of reactive oxygen species (ROS) leads to excessive oxidative damage or potentially leads to Diabetic Neuropathy (DN) mainly due to the activation of protein kinase C, oxidative stress or production of advanced glycation end products (AGE) (67). Thus, any treatment that can stabilize oxygen metabolism and regulate it can lead to the reduction of symptoms. Therefore, supplementing spirulina with a diabetic diet can significantly reduce blood glucose levels and improve the lipid profile of type-2 diabetes mellites, (68) thereby reducing diabetic neuropathy (DN)(69). Diabetic patients usually exhibit lower levels of superoxide dismutase (SOD), catalase (CAT), and reduced glutathione (GSH) activity in hepatic and renal tissues. The roles of SOD, CAT, and GSH are increased in Spirulina-treated diabetic individuals(55). Administering the methanolic extract to experimental mice at doses of 15 and 10 mg/kg body weight resulted in hypoglycemic activity and improved the histological disorders of the liver and pancreas that are associated with diabetes(53). Studies suggest that this microalga should be incorporated into supplemental and medicinal products for treating diabetes and its related symptoms(72). An animal-based study revealed the mechanism of how Spirulina supplementation increased hexokinase activity while reducing glucose 6 phosphate activity, mice that were fed spirulina showed greater hexokinase activity, resulting in mice hepatocytes drawing in more glucose from the blood(54).

Covid-19 response

The global pandemic wreaked havoc around the globe, because of its high transmissibility and a drastic mortality rate of 0.5-1%(74). Before any vaccination discovery, several areas were explored to find better therapeutic remedies. In this regard microalgae were considered, mainly due to mounting evidence regarding its bioactive compounds for example, ACE inhibitor peptides, phycobiliproteins, sulfate polysaccharides, and calcium, that can serve as antiviral agents(75). These cyanobacterium-based nutraceuticals could be used as an immune booster to fight against the virus along with supplement vaccination(56). A recent study was successful in discovering the inhibitory effect of C-Phycocyanin of *Spirulina plantesis* on the nonstructural protein 12 (NSP12) required for replication of SARS-COVID (77). C-Phycocyanin specifically targets the active site of the main protein responsible for viral replication, thereby, minimizing potential complications(57).

Neuroprotective

Spirulina is known to contain a vast majority of nutritive and nonnutritive components known to provide health benefits to brain cells (20,78). It is evident from previous studies that spirulina can help reduce mental fatigue, protect the vascular walls of brain cells from endothelial damage, and regulate internal pressure, thereby reducing cerebrovascular conditions(20,58,59). *S. platensis* supplementation, especially during pregnancy and lactation, has shown beneficial neuroprotective effects against the negative implications of malnutrition and neurodegeneration(60). Furthermore, spirulina can be used as a supplementary therapy in malnourished, autistic and children with ADHD to improve motor, language, and cognitive skills, reinforcing a role in brain development and protective mechanisms (60–62). Some studies have also shown the anti-inflammatory and neuroprotective effects to be particularly useful in treating schizophrenia(84). A study by Haider et al. (2021) reported *S. platensis* administration could improve dizocilpine-induced behavioral deficits, regulate neurotransmission, and restore immune response dysfunction by effectively reducing cytokine production(63,64). Furthermore, an oral administration of 200mg/kg of C-phycocyanin, a phycobiliprotein extracted from S. platensis, improves the quality of life for individuals with Multiple Sclerosis (MS) by exhibiting a neuroprotective effect through the modulation of redox mechanism and myelination, demyelination involved in the disease occurrence(65).

Beyond earth: The space diet

Earth resource depletion especially in the past years due to crises like pandemics, droughts, floods, and other natural calamities, overpopulation, and food insecurity is a call for harnessing potentially new food and renewable energy sources to save the future of humanity. Such sources of energy could be effectively achieved through waste recycling, water conversation, reforestation, and industrial growth. Scientists have proven the possibility of humans traveling and living on other planets(66–68). Various studies have postulated the use of waste resources like microalgae or bacterium as a food source to sustain life, especially on Moon and Mars(69). Mars represents the strongest candidate, due to its proximity to Earth, suitable temperature (~−14 ◦C on average on the equator), and the day duration (~25 h). Additionally, the presence of atmospheric CO2 and water can be manipulated to sustain life(70). Considering these facts, the main space agencies, gathered in the International Space Exploration Coordination Group (ISECG), have listed manned missions to Mars as a target for the years to come(71). Therefore, astronauts can use it to sustain the space mission. In this regard, various ISRU (In Situ Resource Utilization) technologies can be used that rely on rock-weathering cyanobacteria which can photosynthetically convert Nitrogen (N_2) and carbon dioxide (CO_2), along with Sulphur, Phosphorus, Iron, and several micronutrients, available in the Mars atmosphere and the regolith, respectively, into newly formed edible biomass by relying on the water and the light available in-situ(72) Recently, a study conducted a comparative analysis of various customary and alternative food sources to non-biological synthesis (NBS) used recycled CO_2 for space missions. A closed loop food production system was considered efficient along with other promising alternatives (73)

Spirulina applications in the food industry

The demand for nutritious and innovative products is increasing day in and day out. Food derived from microalgae biomass and other microorganisms is now positioning itself in the market(74,75) Figure 1**.**

For instance, in Asia, it is now possible to buy crackers filled with spirulina (Lee Biscuits, Malaysia). Similarly, the USA recently launched microalgae products including Chia & Spirulina Roo'Bar (Roo Brands, Bulgaria) along with dried enriched spirulina soups, pasta, ice-creams and frozen yogurts(76,77). Spirulina is currently being commercialized in three main forms i.e., as food/supplement in baked goods, beverages, dairy products and as snacks. In the food/supplement category, it is vastly sold either as a capsule, tablet, or powdered form e.g., Dragon Superfoods Spirulina powder (Smart Organic, Germany). Similarly, it can be a widely usable source of baked goods considering their widespread use and consumption. Furthermore, its use in the beverage industry can be justified because of its convenience of use for all age groups and functional nutritional properties, for instance in sports or energy drinks and fruit smoothies(78,79). Thus, the use of microalgae as a coloring and flavoring agent is an untapped field that should be explored further(80).

Safety concerns and future considerations

Spirulina, a microalga when taken with diet, or through supplements can present a rich source of nutrients for example, calcium, iron, magnesium, potassium, vitamin C, phosphorus, and sodium. It possesses the potential to fight against cardiovascular disorders, diabetes, cancer, infections, and allergies, and support brain and gut health in addition to its other functions. However, there are still some looming threats regarding safety concerns regarding the presence of cytotoxins, heavy metals and pesticides in such microalgae organisms. Studies conducted in this regard report a concentration of 11µg aflatoxin A/g, in samples for human consumption indicating potential contamination for other anatoxin A-producing cyanobacteria(92). Due to spirulina's ability to accumulate heavy metals from water, it should be given special attention. Although heavy metal absorption like lead might be advan-

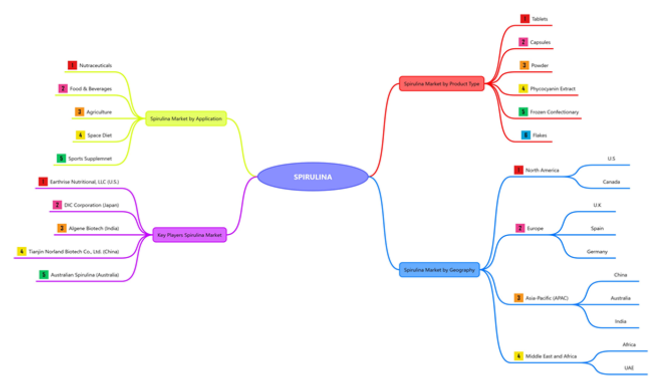

Figure 1. **Figure 1.** Applications of Spirulina in the food industry.

Table 2. Studies showing the application of Spirulina in the food industry.

Food Product	Country of origin	Use	Reference
Recovery Supplements, Sports Industry	USA, Germany	Strength, Recovery, Antioxidant activity, Shelf life.	81–84
Snacks	Malaysia, USA, Germany	Coloring Agent, Flavoring Agent, Nutritional Properties, Antioxidant activity	85,86
Beverages	USA	Physiochemical and Nutritional Properties, Antioxidant, and phenolic activity	9,87
Soups and Pastas	USA, Europe	Coloring and Flavoring Agent, Physiochemical and Nutritional Properties	76,77
Dairy Products	Ireland, USA	Stabilizing agent, Coloring Agent, Nutritional and Sensory Properties	88,89
Baked Goods	USA, Europe	Nutritional and Sensory Properties	90

tageous for clearing wastewater from lead, it can pose a significant threat to humans if its concentration goes up to 20 mg/L(93). Similarly, regulations for pesticide use and administration should be put into consideration to avoid the harmful effects of pesticides like benzalkonium chloride (BAC)-C16 and didecyldimethyl ammonium chloride C10, etc.(94).

The growing interest of consumers and industries alike leads to the development of research focused on functional food utilization, especially from plants and microorganisms. Spirulina being a rich source of proteins, healthy fats, micronutrients, and phytochemicals is a smart choice for the food industry. This review summarized the therapeutic potential of this microalga in the treatment of ailments like cardiovascular diseases (CVDs), diabetes, cancer, viruses, and allergies. Due to its anti-inflammatory, immunomodulatory, antihypertensive, neuroprotective, and nutritional properties, it can be added to various food formulations and supplements, widely available across the USA, Europe, and Asia. Based on these facts, further progress can be made in areas of the additive industry to maximize the use of microalgae as compared to synthetic chemical additives in food formulations, while not neglecting the safety concerns related to heavy metals and pesticide toxicity.

Conclusion

Spirulina, a microalga is a functional food source with a rich nutritional profile. Owing to its high nutritional profile, for example, complete protein, essential fatty acids, vitamins, minerals and bioactive compounds like carotenoids, chlorophyll and xanthophylls it lends itself to be one of the most convenient supplementary foods for product formulations. Up till now, it has been tested in various food productions, including sports supplements, bakery products, the dairy industry, snacks, and the beverage industry. Additionally, various animal and human studies across the globe have testified its therapeutic role in ailments like cardiovascular diseases (CVDs), cancer, neuroinflammatory conditions, diabetes, viral diseases, and allergies making this microalga a potential human ally. Additionally, as a sustainable food source for space missions, it indeed possesses an untapped potential for saving humanity.

Authors' contribution

Conceptualization: A.M.R.A and A.I..; Literature Search: A.I. and S.Z.; Writing Original Draft: A.I. and U.F.; Writing Critical Analysis: H.B.U.S. and S.A.; Review and Editing: J.A., Z.P. and A.I. Validation: S.I.

Conflict of interest

The authors declare no conflict of interest.

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