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Spirulina and Its Role in Immune System: A Review

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ABSTRACT

Spirulina is a high quality source of proteins, pigments, minerals, vitamins. It has special properties in food and drug industries. It's role proved to potentiate the immune system leading for prevent of cancer development, viral infection, inflammatory, allergy and immunodeficiency, increase activity of macrophages, stimulating the production of antibodies and cytokines, activation of B and T cells and immune modulation effect. In addition Spirulina supplements have a greater effect on innate immunity by improving the activity of NK cells. Spirulina can be a healthy and functional diet with potential impacts on immunity, thus the effect of food containing it should be evaluated in the future. Aim of this review is exhibit knowledge regarding the character of this microalga in human immune system.

Keywords: Spirulina, Immune system, Antioxidant, Antibodies

INTRODUCTION

There is interest in using antioxidants because it protects cells and tissues from oxidative damage and free radical [1]. In the mid-1980s, extensive research and development efforts have been made to develop nutritious and functional foods for the prevention and management of various diseases [2-5]. Spirulina look at as the most prophylactic and healing nutritional requirements in this century [6]. It has superiority protein, minerals (K, Ca, Mg, Fe, Zn, Na), vitamins, particularly vitamin B12 and pro-vitamin (β-carotene), polyunsaturated fatty acids and other bioactive as molecules Include phenolic acids, tocopherols and γ-linoleic acid [7,8]. The unfamiliar or questionable activities of immune modulatory function of Spirulina were first determined by scientific observation in mice since 1994 [9]. Spirulina is produced in a widespread and make commercial as a dietary supplement for treatment of malnutrition and modulating immune functions, as well as increase a range of diseases [10]. Including obesity, hyperlipidemia, protection against some cancers, enhancement of the immune system, increment of intestinal lactobacilli, and decrease of nephrotoxicity by heavy metals and drugs, radiation protection [11]. Moreover, Spirulina contain many functional bioactive ingredients with antioxidant and anti-inflammatory, including phenolic phytochemicals [12,13] and the phycobiliprotein c-phycocyanin [14]. Therefore, purpose of this review aimed to evaluate the possibility that Spirulina could be an immune system activation, antioxidant and immunomodulation functional food on human evidences.

BIOLOGICAL AND MEDICAL APPLICATIONS

Spirulina is considered as one prophylactic and healing nutritional component in this century [6] due to its nutrient profile non-significant side effects [7] and therapeutic properties [15,16]. Earlier, due to plant pigments and its ability to photosynthesis, it was classified in the plant category. Later on the basis of biochemical properties, physiology and genetic understanding of the new, they were classified as realm of bacteria [17]. In fact, Spirulina is recognized for its high protein content (60-70% by dry weight) as well as vitamins, minerals, essential fatty acids and other nutrients [18-20]. Recent analyze indicate that blue-green alga is named as *Spirulina platensis* **(Figure 1)**, may have a variety of health benefits and therapeutic properties and it has antioxidant and anti-inflammatory role

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[21]. Clinical tests have testified that Spirulina can serve as a supplementary for many diseases. Capsules of Spirulina showed effective in lowering blood lipids level and in decreasing white blood cells after radiotherapy and chemotherapy, as well as improving immunological function. [22,23]. It is a potential therapeutic material for oxidative stress-induced disorders [24]. Clinic trial suggest that Spirulina has certain therapeutic effects such as reduction in blood cholesterol, protection against some cancers, enhancement of the immune system, growth of intestinal lactobacilli, decrease of nephrotoxicity by heavy metals and medicines, radiation protection, fall of hyperlipidemia and fatness [11]. Also Spirulina pills and capsules, there are too pastries, blocks and Spirulina containing chocolate bars, sold as health food. Other products are applied for weight loss and as an aid for quitting drug-addictions [25]. Spirulina has got no side effects and is non-toxic in nature.

Figure 1. Microscopic view of Spirulina.

EFFECTS ANTIOXIDANT, ANTI-INFLAMMATORY AND IMMUNOSTIMULATING OF SPIRULINA

Immune systems are defense against pathogenic organisms such as bacteria, viruses, cancer cells and parasites and against a complex series of compounds that are distinguish as “foreign” or “non-self”. Cells or molecule recognized as non-self is attacked by immune system cells and the antibodies they produce. The immune system is a complex system that involves specific cells that interconnect with each other via chemical messengers called cytokines. Therefore, impairment of the immune system has far-reaching consequences in the body. The close connection between oxidative stress and life-style diseases is evident. Oxidative stress is in fact defined by the loss of balance between high levels of oxidation and antioxidant systems in the body. It not only causes problems such as DNA oxidative damage and lipid peroxidation, but is associated with physiological imbalance and intracellular signal transduction tuning [26]. Foods that increase blood cholesterol levels also affect the expression of antioxidant enzymes [27,28], while free radicals caused by oxidative stress have been damaged to cells and tissues and possibly lead to cancer and cardiovascular damage [29,30]. Spirulina has high Functional compounds values and lip soluble antioxidants **(Table 1)** [12-14,31-33]. The anti-inflammatory effects of Spirulina are due to its antioxidant activity. Most recently Abdel-Daim et al. [34] using *Spirulina platensis* powder (500 and 1000 mg/kg) for an hour prior to the injection of delta methrin (15 mg/kg) in mice observed a significant reduction of the pro inflammatory cytokine tumor necrosis factor-alpha (TNF-α) in serum and at the same time an improvement of oxidative stress markers (malondialdehyde (MDA), nitric oxide (NO), superoxide dismutase (SOD), catalase (CAT), reduced glutathione (GSH) and glutathione peroxidase (GPX)) in hepatic, renal, and brain tissues [34]. Carotenoids are also important antioxidants and it has been shown that the risk of developing types of cancer in the diet rich in carotenoids has been reduced [2]. C-phycocyanin is a major Bili protein source of Spirulina which has antioxidant and radical breakdown properties [35]. Phycocyanin may prevent cancer by scavenging DNA damaging agents such as peroxynitrite [36]. Also induced apoptosis of human chronic myeloid leukemia cell line-k562 [37]. Spirulina also contains phenolic acids, tocopherols and ß-carotene, all of which have anti-antioxidant properties [38].

Table 1. Functional compounds of Spirulina.

	Content in 100 g	The effects *in vitro* and in animal models	References
Functional Compounds			
Carotenoids	0.3-2.6 g	Antioxidant, Anti-inflammatory	[12,13]
Total phenol	0.20-1.73 g		
Flavonoids	0.1-0.9 g		
Phycocyanins			
C-Phycocyanin	13.5-14.8 g	Antioxidant, Anti-inflammatory	[14-31]
Allophycocyanin	2.3 g		
Phycobiliproteins	1.1 g		
Polysaccharides	0.2-12.5 g	Immunostimulating	[32,33]

SPIRULINA EFFECT ON COMPLEMENT SAFETY INDICATORS

The complement system consists of more than 35 types of serum proteins that have a very close and controlled relationship with each other and other immune system molecules. 9 of their main components are named from C-1 to C-9 and these compounds play a key role in innate and acquired immunity [39]. The most important biological tasks of the complement system include eliminating microorganisms through involvement in phagocytosis processes, inflammatory reactions, immunization complexes and induction and improvement of antibody responses [40]. In the experiment, the Spirulina algae were added to the fish diet. The results of the experiment showed that the levels of C3 and C4 complements in fish with diet containing 10% Spirulina were higher than the control group and showed a significant difference ($P<0.05$) with the control group [41]. Regarding the effect of Spirulina on the complement based on genotype, the level of C3 increased significantly after 16 weeks ($P<0.05$) even after placebo supplementation. However, in all groups the level of C3 after the addition of Spirulina was unchanged, after the use of Spirulina supplementation or placebo, the level of ($P<0.05$) C3 was only altered in people with genotype A and G. There was major Spirulina supplementation effect on C3 level ($P<0.01$) and also MCP-1 genotype × treatment for C3 ($P<0.05$) [42]. Therefore, the use of Spirulina as a safety stimulant improves the physiological response in the disease.

ANTI-CANCER EFFECTS OF ALGA SPIRULINA

In many tumors, there are NK, T cells and activated macrophages around the tumor which among these cells, T-cell lymphocytes shapes the most effective response. Spontaneous immune responses are very weak to suppress tumor growth, although the immune system detects abnormal proteins in tumor cells as tumor antigens. To overcome this problem, a variety of adjuvants, including toll-like receptor (TLR) ligands, are investigated to potentiate antitumor immunity [43]. Cytokines and Th17 cell produced IL-17, which plays a very important role in tumor progression in mice and humans. IL-6 and IL-23 are vital cytokines for the differentiation and proliferation of Th17 cells Studies have shown that Spirulina LPS (Bacterial lipopolysaccharides) is a very weak inducer of IL-6 and IL-23 and a strong anti-cancer immune suppression with suppression IL-17 induction by increasing IFN-γ production through the TLR4 pathway [44,45]. Spirulina as well as its tetrapyrrolic components showed a significant decrease in the promotion of pancreatic cancer. PCB (phycocyanobilin) Available in Spirulina has a structural similarity to bilirubin, which is a potent antioxidant. Indeed, Bilirubin's anticancer action is related to its effects on the mitochondria and the internal signal of the cell [46]. This condition supports the role of chemotherapy [47]. To the rats with liver cancer were given phycocyanin and it was observed that their survival rates have increased significantly. Phycocyanin probably has hematopoietic function that can increase the number of thymocytes, which in turn increases the body's natural resistance to cancer, bleeding, ulcers and other diseases [48,49]. It has been shown that phycocyanin to cause apoptosis in tumor cells through the production of ROS and reduce the Adjusting the expression of Bcl-2. Phycocyanin is also known as an anti-apoptotic molecule [50], as well as through inducing cytochrome c release from mitochondria into the cytosol and PARP cleavage [51].

Anti-viral effects of Spirulina

Many researchers have tried to find practical and efficient antiviral foods within natural resources. Initially, almost four decades ago, the effects of polysaccharide from seaweed on the virus replication were reported [52]. Hayashi et al. [48] reported the anti HSV-1 activity of aqueous extracts from *S. platensis*. Spirulina polysaccharides inhibit replication of several enveloped viruses such as herpes simplex virus,

influenza virus, measles virus, mumps virus, human cytomegalovirus and HIV-1 [53-56]. Three compounds of Spirulina, which include Ca-Sp, Cyanovirin-N and sulpholipid, have antiviral activity in HIV [54-56]. Ca-Sp and Cynovirin-N appear to interfere with the host cell in the first stage of the viral cycle, while sulpholipid interfere with reverse transcription of HIV-RNA **(Figure 2)** [56]. Thus extracts may become useful therapeutics that could help AIDS patient's longer normal lives. Moreover, when HIV-infected or HIV-negative undernourished children and HIV-infected adults were treated with Spirulina supplementation, clinical improvement was always detected, including weight increase, improvement of hematological parameters and decrease in the HIV viral load [57-59].

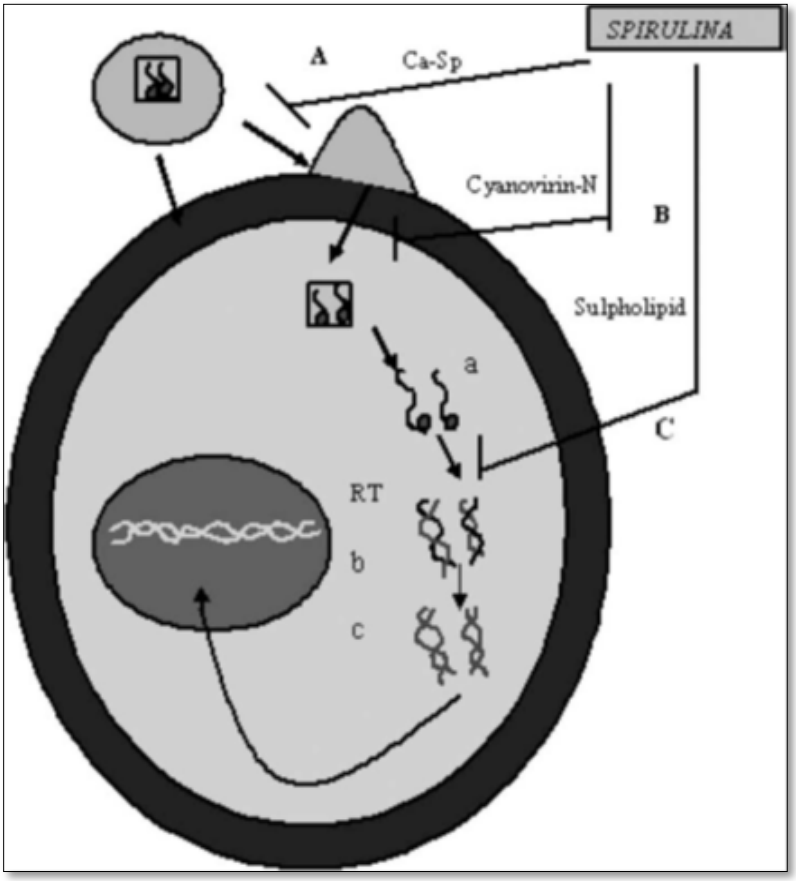

Figure 2. Spirulina effects on HIV virus to target cell.
Ca-Sp Interacts between viral epitopes and host cell receptor. Cyanovirin-N has inhibitory activity during fusion. Sulpholipid interfere in the reverse transcription of HIV-RNA (RT: Reverse Transcriptase; a: HIV-ssRNA with RT; b: RNA-DNA hybrid; c: ds DNA)

ALLERGY, RHINITIS AND IMMUNOMODULATION

Spirulina inhibits the release of histamine from mast cells and shows anti-inflammatory properties [60,61]. In a randomized clinical trial [62], individuals with allergic rhinitis were fed daily with placebo or Spirulina for 12 weeks. The levels of cytokines (IL4, IFN-γ and IL-2) that are important in regulating immunoglobulin (IgE) mediated allergy as well as the level of peripheral blood mononuclear cells were measured before and after feeding with Spirulina. The study showed that high dose of Spirulina significantly reduced IL-4 levels by 32%, demonstrating the protective effects of this microalga toward allergic rhinitis [63]. In another study in Turkey, in order to evaluate the efficacy and tolerability of Spirulina against placebo, treatment for patients with allergic rhinitis was performed. This study showed that taking Spirulina compared to placebo ($P<0.001$), significantly improved symptoms and physical findings such as sneezing, nasal discharge, congestion and itching [64]. The above studies suggest that Spirulina can modulate the immune system by covering nutritional deficiencies [65]. Each of the four symptoms that were compared and evaluated for the use of Spirulina with placebo showed a significant improvement in each of the symptoms. For example, at the start of the study there was no significant difference in mean baseline values of both symptoms and physical findings of both groups (p more than 0.05 which mean non-significant correlation). The placebo group rated symptoms at 2.84, standard deviation 0.37 and the Spirulina group at 2.74, SD 0.45) After 21 weeks, the

sneeze score of the placebo group was 1.91 (SD 0.52) and that of the Spirulina group was 0.58 (SD 0.50) ($p<0.001$). For nasal discharge, congestion and itching also documented similar results. If after 21 weeks in both groups occur improvements, may be due to the change of seasons or placebo effect. However, when directly comparing the data of the Spirulina group with the placebo group, they showed a large and steady improvement, which showed no symptoms until the end of the study. Perhaps the best and most interesting point in the study is the high level of satisfaction with the use of Spirulina versus the placebo group for treatment. At the end of the study, all the patients were asked to rate their state of symptoms on a scale of zero to ten with zero being no relief. The placebo group graded their experience at 3.54 (+/- 1.37) while the Spirulina group applauded with a 7.44 (+/- 0.89: p less than 0.001). In addition, the patients that took Spirulina rated their satisfaction as 7.21 (+/- 2.01), while the placebo group rated their experience as 3.54 (+/- 1.37) (p less than 0.001) [64]. As expressed by these researchers, Spirulina may be a "clinically effective" option for allergic rhinitis and is worthy of further study to investigate its mechanism.

EFFECTS AGAINST TOXICITIES FROM HEAVY METALS AND OTHER COMPOUNDS

Heavy metals such as cadmium, lead, mercury, copper, nickel and chromium are in the list of priority hazardous pollutants. Contact with heavy metals can cause neurological disorders, cellular aging, liver and kidney failure and carcinogenesis [66]. The liver is one of the organs affected by lead toxicity. On the other hand, the liver is one of the main organs for the storage and detoxification of poisoning with heavy metals [67]. In one study, the effect of spiroinema supplementation on lead-induced liver damage in rats was as follows. The activities of alanine transaminae (ALT) and aspartate transaminae (AST) are indicators of hepatotoxicity [68]. Lead toxicity significantly decreased at the level of the glutathione (GSH) and superoxide dismutase (SOD) and also significantly increased at malondialdehyde (MDA) and nitric oxide (NO) levels. Rats treated with spirulina supplementation showed a high level of GSH and produce SOD and a decrease in MDA and NO, indicating the antioxidant role of Spirulina. This may be due to the proposed role of GSH in the active excretion of lead by bile by binding to the thiol group of GSH, which is subsequently repelled. Reducing GSH levels can lead to oxidative stress and MDA increase [69,70]. Yaman et al. [71] in a trial with high mercury dosage in the mice, rising blood urea nitrogen (BUN) and serum creatinine, both of which are acute nephritis, increased 30% of Spirulina to their diet, resulting in a significant improvement in decrease BUN and serum creatinine levels. This was because of the presence of phycocyanine in the presence of Spirulina antioxidants. In recent years, some of its properties, such as protection against Arsenic toxicity, have been approved. While the added medicinal properties should be proven [72]. Also radiation protection by Spirulina can be attributed to phytopigments that include carotenoids, chlorophyll and phycocyanin [73].

CONCLUSION

Spirulina products buildup both the humoral and cellular of the immune system and possess anti-allergic properties by inducing IgA antibody and phycocyanin and decrease of IL4 inhibit release of histamine and functions as anti-inflammatory compound. Furthermore, Spirulina improves oxidative stress markers and NK activity in healthy subjects and CD4+ count in HIV+ patients. Previous studies indicate that some antioxidant and immunological markers are sensitive to stimuli that affect the mood of the individual. In this context different species of Spirulina, possibly having different biological effects, showed different suitability. Therefore, the study of the relationship between liking and markers of antioxidant and immune status should be measured in human's studies. As a final point, clearly this safe food makes available nutritional support for optimum health and the multifunctional role of Spirulina in ideal natural drug with immense therapeutic properties.

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