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(REVIEW ARTICLE)

Nutritional and medical applications of spirulina

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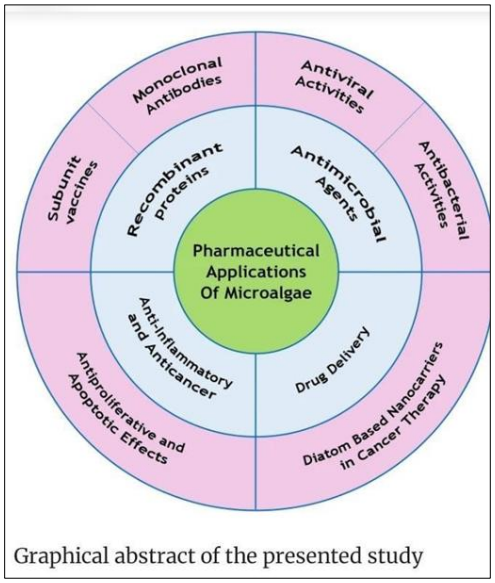
Abstract

Spirulina spp. and its processed forms are used in agriculture, food industry, pharmaceuticals, cosmetics, and medicine. Spirulina possesses various pharmacological effects, such as antimicrobial (including antiviral and antibacterial), anticancer, metalloprotective (prevention of heavy-metal poisoning against Cd, Pb, Fe, Hg), as well as immunostimulant and antioxidant properties due to its high levels of protein, polysaccharide, lipid, essential amino and fatty acids, dietary minerals and vitamins. This article provides an overview, presenting the fundamental biochemical makeup of the algae and then discusses its medicinal uses. Each application includes a description of the disease, how it causes damage, the specific content of Spirulina spp. for treatment, how it is used in vivo and/or in vitro, the factors involved in its therapeutic role, challenges faced, and benefits.

Keywords: Anticancer; Antimicrobial; Antioxidant; Chemical Composition; Immunostimulant; Metalloprotective; Spirulina

Graphical Abstract



Graphical abstract of the presented study

Pharmaceutical Application of Microalgae

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1. Introduction

Spirulina is the collective term for thread-like, multicellular, blue-green microalgae from two genera, Spirulina and Arthrospira, encompassing a total of 15 species. Spirulina platensis is the predominant and frequently utilized genus that has been thoroughly researched in various areas, particularly in the food industry and medicine. The chemical examination of Spirulina microalgae shows that it provides a rich supply of various macro and micronutrients. The abundance of protein, vitamins, essential amino acids, dietary minerals, and essential fatty acids in Spirulina contribute to its numerous health benefits. Possible health impacts include immune system regulation, cancer prevention, antioxidant properties, antiviral and antibacterial actions, as well as benefits against malnutrition, high cholesterol, obesity, diabetes, toxic exposure, allergies, radiation harm, and anemia 1Elsewhere, there has been a comprehensive presentation of the various health benefits of certain classes of algae and microalgae 2

Figure 1 Spirulina

This post highlights various biological attributes of Spirulina such as its abilities to fight cancer, combat microbes, protect against metals, act as an antioxidant, and boost the immune system. The chemical makeup of this microalga has been examined. New information regarding the medical benefits of Spirulina, not previously discussed in literature, is included, along with details on the safety and potential side effects of Spirulina.

Figure 2 Health Benefits of Spirulina

1.1. Chemical composition of spirulina

Essentially, Spirulina is made up of approximately 55-70% protein and 5-6% lipid (by weight of dried cell). This alga has a total lipid content of 1.5-2% polyunsaturated fatty acids (PUFAs). Spirulina spp. is abundant in linolenic acid (36% of total PUFAs), various vitamins (B1, B2, B3, B6, B9, B12, C, D, E), an array of minerals (K, Ca, Cr, Cu, Fe, Mg, Mn, P, Se, Na, Zn), pigments (including chlorophyll a, xanthophyll, betacarotene), and enzymes (such as lipase), as well as phycobiliproteins like C-phycocyanin and allophycocyanin [3] Hence, the biomass from this abundant source of elements is utilized as additives in various industries like agriculture, food, pharmaceuticals, and perfumery. Typically, the chemical properties of two microalgae species from the same category vary based on their source, cultivation conditions, harvesting time, and extraction method, despite their similar external appearance. The overall structure can be broken down like this (% of dry mass): Proteins: 50-70%; carbohydrates: 15-25%; lipids: 6-13%; nucleic acids: 4.2-6% and minerals: 2.2-4.8% [1,4,3]

1.2. Carbohydrates

The primary polymeric compound found in S. platensis is a branched polysaccharide that has a structure similar to glycogen. Large-sized anionic polysaccharides with antiviral and immunomodulation functions have been extracted from Spirulina [5]. The sections relating to Spirulina will cover the antiviral and immunomodulating properties of its polysaccharides. A fraction of sulfated polysaccharide with antiviral characteristics, known as calcium spirulan, has been thoroughly purified and found to consist of rhamnose, 3-O-methylrhamnose (acofriose), 2,3-di-O-methylrhamnose, 3-O-methylxylose, uronic acids, and sulfate [6,7]

1.3. Proteins

Spirulina's protein level ranges from 50-70% of its dried weight, surpassing that of meat, eggs, dried milk, grains, and soybeans. It provides all the essential amino acids, including leucine, valine, and isoleucine. Nevertheless, it appears to be lacking in methionine, cysteine, and lysine when compared to typical animal proteins like meat, eggs, or milk, although it surpasses all plant proteins, including those from legumes. Two key nutritional values are calculated for Spirulina as a substitute protein source: the protein efficiency ratio (PER) and net protein utilization (NPU). PER is determined by dividing an experimental animal's weight gain by the weight of reference proteins ingested, while NPU is the percentage of nitrogen retained when protein is the only limiting factor. The digestibility of protein in Spirulina is extremely high (83-90%), which is slightly lower compared to pure casein (95.1%) primarily because it does not contain cellulose walls. Therefore, cooking is not required to enhance the availability of proteins. Spirulina's NPU and PER values range from 53% to 92% and from 1.8 to 2.6, respectively. The PER values of casein, maize, rice, and wheat are 2.5, 1.23, 2.2, and 1.15 respectively as stated in references 2 and 3. The main protein components that have important positive health impacts are phycobiliproteins phycocyanin C and allophycocyanin, present at a ratio of around 10:1, and they contain linear tetrapyrrole prosthetic groups (phycocyanobilin) attached to certain cysteine residues of the proteins. Phycocyanins make up approximately 15-25% of the microalgae's dry weight [8]. Phycocyanins are a safe option for coloring non-acidic foods like chewing gum, confectionaries, and dairy products.

Phycocyanins are a safe natural option for coloring non-acidic foods like chewing gum, confectionaries, and dairy products [9,10]

The pigment phycocyanobilin (PCB) in Spirulina makes up 4.7% of the dried phycocyanin mass and effectively reduces NADPH oxidase activity by converting into phycocyanorubin. This similar compound to bilirubin hinders the function of the enzyme complex. PCB supplementation can be used to prevent and treat different diseases caused by NADPH oxidase overactivity like heart diseases, diabetes complications, metabolic syndrome, allergies, arthritis, cancer, Parkinson's, and Alzheimer's. Oral consumption can occur through whole Spirulina, phycocyanin protein, or isolated tetrapyrrole chromophore [11].

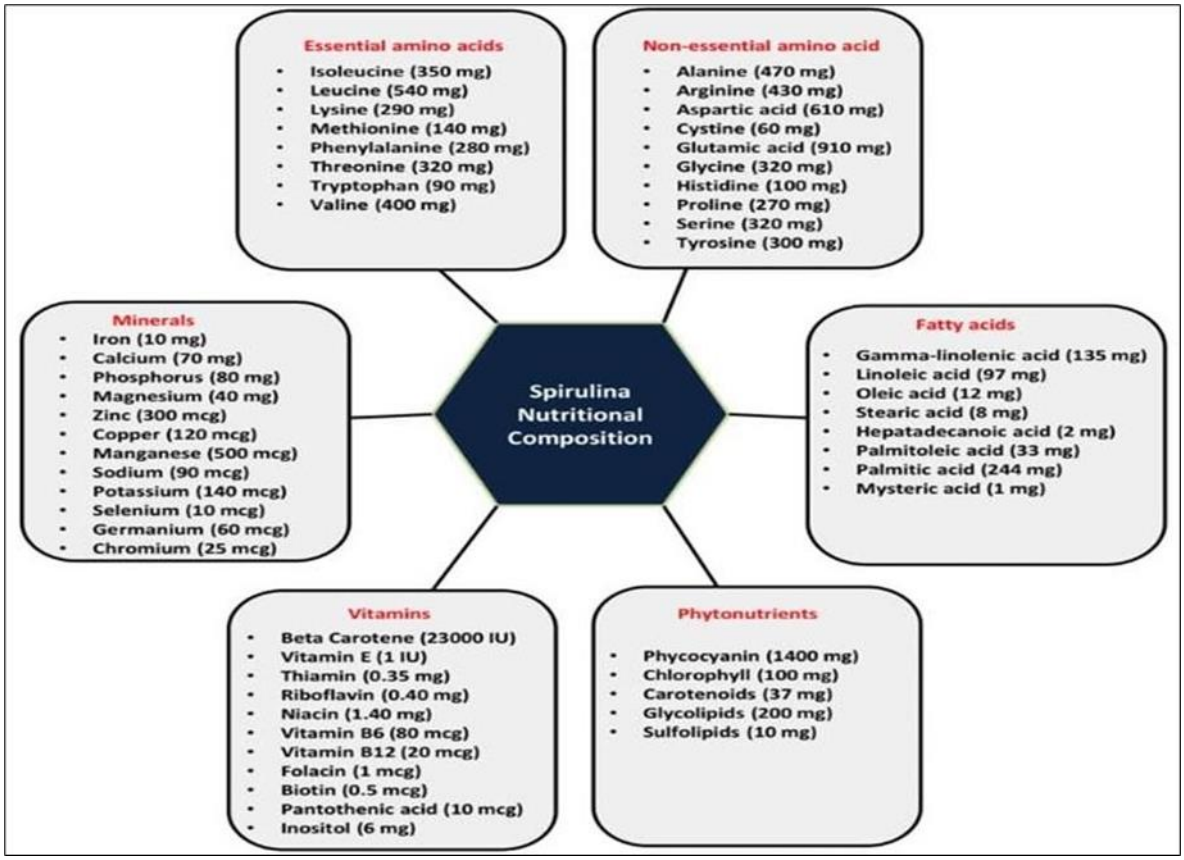

Figure 3 Spirulina Nutritional Composition

2. Lipids

Spirulina's lipids are divided into a saponifiable fraction (83%) and a non-saponifiable fraction (17%), which includes crucial pigments, paraffin, sterols, and terpene alcohol. Fatty acids (mainly -6) [12]make up half of all lipids, along with Cholesterol (< 0.1 mg/100 g of dried Spirulina mass) , a part of Spirulina's sterol fraction S. maxima and S. platensis have linolenic acid (GLA) in their fatty acids, with levels of 10-20% and 49%, respectively. Hence, following human milk and certain vegetable oils like evening primrose, borage, blackcurrant seed, and hemp oil, Spirulina can be seen as a reliable source of GLA. S. maxima also has unsaturated oleic and linoleic acids and saturated palmitic acid making up over 60% of its lipids.

Monogalactosyl- and sulfoquinovosyl-diacylglycerol, along with phosphatidylglycerol, account for around 2025% each of the lipids in Spirulina.

3. Minerals and vitamins

It is said that Spirulina is the most abundant natural source of vitamin B12, including its corrinoid forms, analogs, and provitamin A (carotene). Just 20g of this small algae provides the necessary amount of vitamins B1 (thiamine), B2 (riboflavin) and B3 (niacin) for the body [13]. While Spirulina does not serve the same unique functions as vitamin B12 in humans, it does not disrupt the metabolism of B12 in mammals. A highly sensitive microbiological test reveals that 36% of vitamin B12 molecules in Spirulina spp. are biologically active in humans . S. platensis contains the biologically active form of vitamin B12, methylcobalamin, at a concentration of 35-38 µg/100 g in dry Spirulina biomass [14].

Spirulina's high micronutrient levels, notably minerals like iron (0.58-1.8 g/kg), calcium (1.3-14 g/kg), phosphorus (6.7-9.0 g/kg), and potassium (6.4-15.4 g/kg), make it a beneficial nutritional supplement for vegetarians, acquired through absorbing these elements during growth. The mineral content of Spirulina varies depending on its source and the conditions in which it is cultured. Milk contains similar amounts of calcium, phosphorus, and magnesium. Spirulina is known for its high iron content, which is ten times greater than that of typical iron-rich foods. Spirulina iron is absorbed 60% better than ferrous sulphate found in iron supplements. Consuming Spirulina with excessive iodine (3 µg in 10g of

dried biomass) poses no danger to the consumer [15,16], as the European Food Safety Authority (EFSA) and Scientific Committee on Food (SCF) have set the upper safe limit for daily iodine intake for a 60kg adult at 600µg.

4. Anticancer effect of spirulina

Studies have shown that Spirulina may have a potential impact on preventing cancer. Certain natural or synthetic agents can prevent or reverse the carcinogenic process before cancer develops [16]. Grawish found that Spirulina extract has a tumor-suppressing effect on hamster cheek pouch mucosa by repairing damaged DNA. The unique polysaccharide contents of Spirulina can enhance endonuclease activity, leading to the repair of
DNA damage [17]

Research indicates a link between cancer and elevated prostaglandin (PG) levels [18]. Cox, also known as prostaglandin H synthase, is a dual-function enzyme responsible for producing prostaglandins using arachidonic acid as a substrate. Cox-1 and Cox-2 are two identified types of this dual-function enzyme, known as cyclooxygenase-1 and cyclooxygenase-2. Cox-1, acting as a constitutive enzyme, plays a role in upholding normal physiological functions and the PGs it generates help protect the body. Cox-2 is accountable for generating PGs at sites of inflammation and is an inducible form activated by mitogens, oncogenes, tumor promoters, and growth factors. Research demonstrated that the levels of Cox-2 were elevated in malignant tissues of colorectal cancer, as well as in human gastric and breast tumors, compared to Cox-1. S.platensis generates C-phycocyanin specifically to inhibit Cox-2. The reason for this inhibition is the shape and large size of phycocyanin (Fig. 1), which enables it to effectively attach to the active site of Cox2 Recent studies have demonstrated that S. platensis containing selenium was able to suppress the growth of MCF-7 human breast cancer cells .[19]

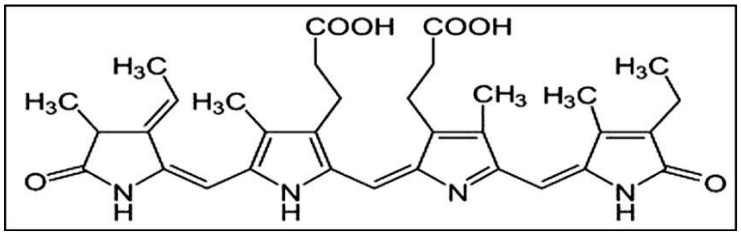

Figure 4 Structure of Phycocyanobilin

5. Structure of Phycocyanobilin

5.1. Antiviral activity of spirulina

The primary polymer found in S. platensis is a branched polysaccharide, having a structure that closely resembles glycogen. Large molecular weight anionic polysaccharides derived from Spirulina exhibit antiviral and immunomodulatory effects. A calcium spirulan, a type of sulphated polysaccharide with antiviral properties, has been thoroughly purified and found to contain rhamnose, acofriose, 3-O-methylxylose, 2,3-di-Omethylrhamnose, uronic acids, and sulphate [20]. A fraction of acidic polysaccharides extracted from S. platensis has been found to stimulate the production of Tumor Necrosis Factor-alpha (TNF-) in macrophages.

The protein phycocyanin, sulfated polysaccharide fractions, GLA, and certain sulfolipids are the most favorable components of Spirulina. The antiviral effect of Spirulina's sulfated polysaccharide is achieved by blocking the replication of several viruses including herpes simplex, human cytomegalovirus, influenza A, measles, mumps, human immunodeficiency, and white spot syndrome viruses . The range of calcium spirulan concentration needed to inhibit 50% of viral replication is 11.4-2600 µg/ml [21]. Spirulina is recognized for containing 2-5% sulfolipids, which specifically target DNA polymerase to combat the human immunodeficiency virus. A concentration of at least 24nM is needed to achieve 50% inhibition of the virus. Both the presence of the sulfonic acid group and the fatty acid ester chain play a major role in enhancing the level of inhibition[22]. A pigment called allophycocyanin, which is connected to a protein and extracted from S. platensis, demonstrated antiviral effects against enterovirus 71. This pigment suppresses half of the cytopathic effect induced by enterovirus 71, as well as viral plaque formation and viral-induced apoptosis, at concentrations ranging from 0.056 to 0.101 µM. Kaushik et al. [23] demonstrated that introducing allophycocyanin to the cells prior to viral exposure effectively inhibits enterovirus infection by disrupting virus adsorption and penetration.

5.2. Antibacterial activity of spirulina

The antimicrobial properties of Spirulina extracts collected with various solvents have been researched. [24] stated that the high concentration of -linolenic acid in the methanolic extract of S. platensis is responsible for its antimicrobial properties. The antimicrobial effects of Spirulina extract on various microorganisms were investigated by Mendiola et al. [25] including Staphylococcus aureus, Escherichia coli, Candida albicans, and Aspergillus Niger. The findings demonstrated that all Spirulina fractions obtained through supercritical fluid extraction were most effective in inhibiting the growth of C. albicans among all tested microorganisms. The antimicrobial effect might be due to the combined action of fatty acids [25] examined how different organic and aqueous extracts of S. platensis impact human pathogenic bacteria through agar-solid diffusion method. The water extract showed the highest antimicrobial activity against Klebsiella pneumoniae and the lowest against Proteus vulgaris. The acetone extract exhibited the greatest biological activity against Klebsiella pneumonia .

5.3. Heavy-metal poisoning activity of spirulina

Certain tissues are harmed by specific metals through the induction of oxidative stress. Antioxidants like GSH, SOD, and NO, which are compounds made internally, can safeguard aerobic organisms from free radicals. Several instances of Spirulina's protective effects against metal poisoning are provided in the upcoming [26]sections.

5.4. Cadmium induced poisoning

Cadmium leads to a reduction in cellular thiol which can disrupt the balance between pro-oxidant and antioxidant systems. Cadmium enhances the generation of reactive oxygen species (ROS) in tissues and hinders the function of certain enzymes in the antioxidative defense system. ROS, such as H2O2, O2 -, and OH radical, can be created and broken down by all organisms that require oxygen, and they can easily interact with certain biomolecules like lipids, proteins, lipoproteins, and DNA. The shield provided by S. platensis against cadmiuminduced oxidative stress may occur indirectly by boosting the activity of GSH peroxidase and superoxide dismutase, which are free radical scavengers, or directly by preventing lipid peroxidation and scavenging free radicals. The high levels of antioxidant components in S. platensis are responsible for these characteristics [27].

5.5. Lead induced poisoning

Lead poisoning results in alterations in bone marrow cell morphology, pathophysiological changes in tissues, and necrosis in proximal tubule cells. Moreover, it results in kidney dysfunction, changes in glomerular filtration rate, reduced sperm count, and alterations in the protein and lipid composition of the red blood cell membrane. Hb synthesis is inhibited later, resulting in decreased production of red blood cells and shorter lifespan of red cells. Spirulina demonstrated a protective effect in rats against changes in T lymphocyte, reticulocyte, red and white blood cell counts induced by cadmium and lead . Researchers have found that Spirulina could enhance iron and Hb metabolism in rats suffering from poisoning induced by Pb, Cd, Zn, and Hg This phenomenon is credited to the blue-green algae's ability to bind metals [28]

5.6. Iron induced toxicity

Iron is among the most crucial factors that lead to oxidative stress and deterioration of neuronal functions. Iron interactions with various cellular processes lead to oxidative stress and the creation of reactive oxygen species (ROS). Excessive iron levels also cause a substantial increase in the release of lactate dehydrogenase (LDH) as a result of cell death. Spirulina extract, particularly phycocyanin, boosts the cellular antioxidant enzymes (glutathione reductase and glutathione peroxidase), which help safeguard the body from the harmful impacts of ROS[29]

5.7. Mercuric choloride induced poisoning

Mercury results in numerous negative health impacts including renal, neurological, respiratory, dermatologic, immune, reproductive, and developmental issues. Mercuric chloride leads to a notable rise in lipid peroxidation, SGOT and SGPT levels, along with a decrease in the functions of reduced glutathione, superoxide dismutase, catalase, and glutathione-S-transferase in the liver. Spirulina boosts liver GSH level, SOD, CAT, and GST activity, acting as an antioxidant and lowering lipid peroxidation, which then leads to a decrease in serum transaminases SGOT & SGPT activity. Spirulina's ability to protect against metal toxicity may be linked to its rich supply of vitamin E, vitamin C, beta-carotene, superoxide dismutase enzyme, selenium, and the blue pigment phycocyanin [30]

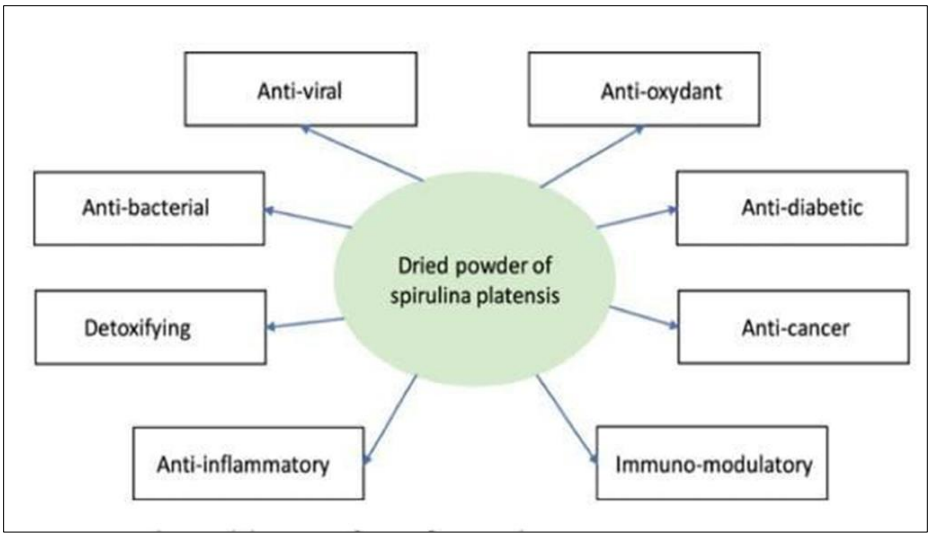

Figure 5 Dried Powder of Spirulina Platensis

6. Antioxidant activity of spirulina

Research studies have shown that Spirulina demonstrates antioxidant properties in both laboratory settings and in living organisms [31] The liver protective benefits of Spirulina against CCl4-induced toxicity stem from its ability to scavenge free radicals. These benefits are due to its rich levels of proteins, lipids, minerals (zinc, manganese, magnesium, and selenium), as well as several vitamins (beta carotene, riboflavin, cyanocobalamin, alfa-tocopherol, and alfa-lipoic acid).[32]

6.1. Metal-chelating activity is commonly utilized to assess the antioxidant activity of various natural products

Bermejo and colleagues (4) showed that the protein extract from S. platensis had strong antioxidant capabilities. Findings indicated that the protein extract from S. platensis was able to neutralize hydroxyl and peroxyl radicals and also demonstrated the ability to inhibit lipid peroxidation. S. platensis can effectively prevent oxidative stress in a living organism by scavenging these free radicals. An antioxidant can work in different ways: by stopping the creation of free radicals, by neutralizing existing free radicals, by preventing further damage from secondary radicals, or by reducing iron ions that trigger free radical formation.[33] found that Spirulina's chelating activity effectively blocked the formation of errozine–Fe2+ complex by acting as electron donors with antioxidant compounds. [26]

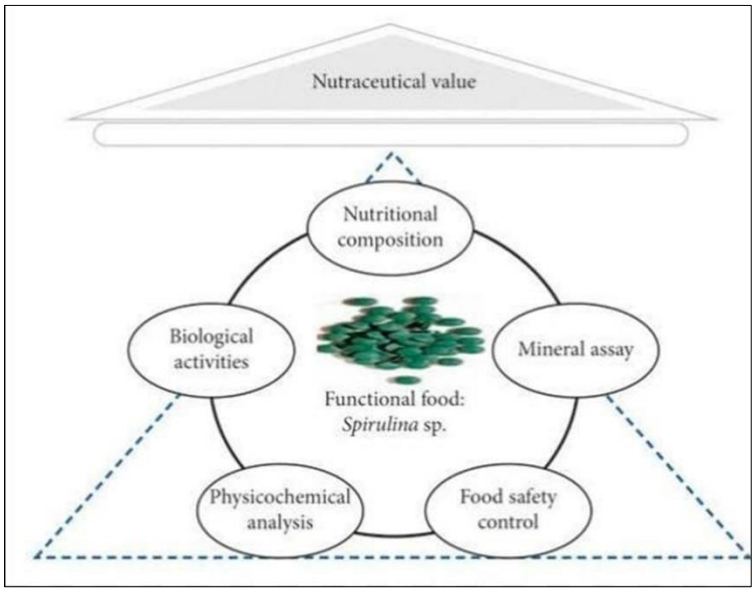

Figure 6 Nutraceutical Value

7. Immunostimulant effects of spirulina

Spirulina helps to boost antibody production, enhances the activity of peritoneal macrophages, and promotes the growth of spleen cells when exposed to Con A. The addition of Spirulina extract to cultured spleen cells increased the production of IL-1 and antibody [48]. Macrophages are the primary cells initially targeted by Spirulina. In myeloid cells, Spirulina has an additional impact on pathways for producing cytokines mediated by Toll-like receptors (TLR). Spirulina glycolipids act as Toll ligands to activate both TLR2 & 4 along with the cell wall skeleton of bacillus Calmette-Guerin (BCG) .[34]

examined how the dietary S. planeness affects the immune system of carp, Cyprinus carpio. The fish were given Spirulina as food and their non-specific defense mechanisms (phagocytosis and superoxide anion production) were tested on the 1st, 3rd, and 5th day. Spirulina boosts the ability of kidney phagocytic cells to respond and produce superoxide anions for a minimum of 5 days. The levels of IL-1 and TNF genes were also elevated in fish that were given Spirulina. There was a reduction in the manifestation of IL-10 gene. Additionally, there was a reduction in the levels of Aero monas hydrophilic in the liver and kidney of fish treated with Spirulina [35] Table 1 summarizes the antimicrobial (including antiviral and antibacterial), metalloprotective, and immunostimulant effects, as well as the antitumor and antioxidant activities of Spirulina.

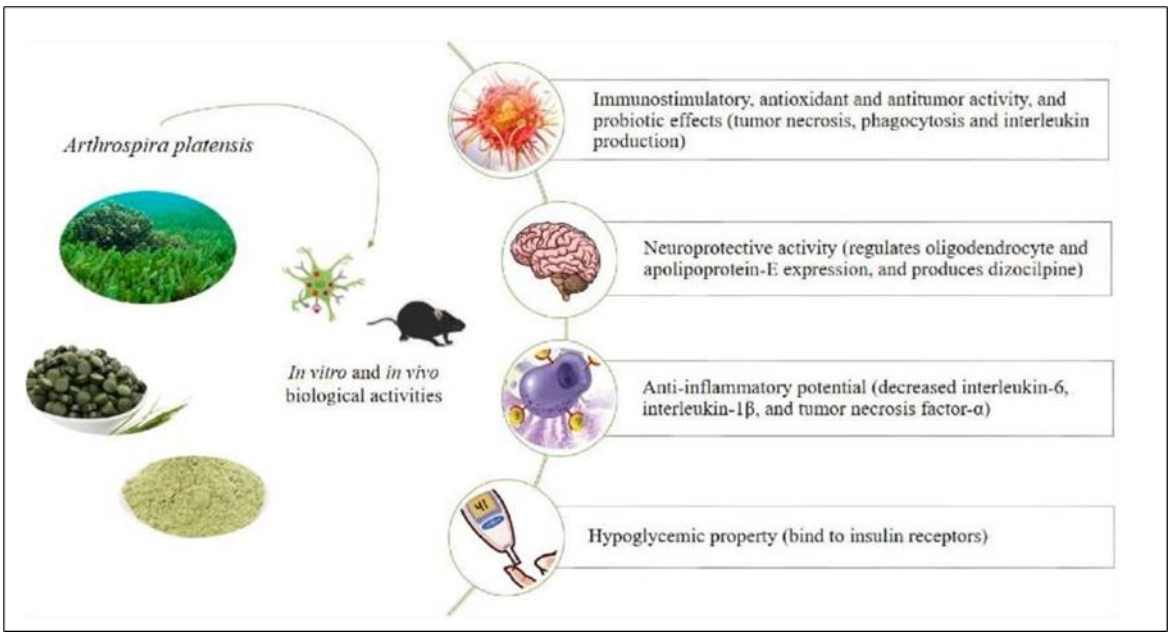

Figure 7 Some Studied Biological Effects of Spirulina Microalgae

Abbreviations

- PER is an acronym for Protein efficiency ratio.
- NPU stands for Net protein utilization.
- PCB stands for the pigment phycocyanobilin, also known as chromophore.
- NADPH is equivalent to Nicotinamide adenine dinucleotide phosphate.
- GLA is equal to -linolenic acid.
- EFSA stands for European Food Safety Authority.
- SCF stands for Scientific Committee on Food.
- PGs stands for Prostaglandins.
- Cox stands for Cyclooxygenase.
- TNF- is an abbreviation for Tumor Necrosis Factor-Alpha.
- GSH is an abbreviation for Glutathione.
- SOD stands for Superoxide dismutase.
- NO stands for Nitric oxide.
- ROS is an abbreviation for Reactive oxygen species.
- Hb stands for Hemoglobin.

- LDH stands for lactate dehydrogenase
- SGOT stands for Serum Glutamic Pyruvic Transaminase.
- SGPT stands for Serum glutamic pyruvic transminase.
- GSH is an acronym for Glutathione.
- SOD stands for Superoxide dismutase.
- CAT stands for Catalase.
- GST stands for Glutathione S-transferase.
- TNF stands for Tumor necrosis factor
- TLR stands for Toll-like receptors.
- BCG stands for Bacillus Calmette-Guerin.
- GRAS is an abbreviation for Generally recognized as safe.

8. Conclusion

In the 21st century, a lack of natural food consumption results in a shortage of vitamins and essential minerals in the human population. The cultivation of blue-green microalgae S. platensis provides an alternative method for adding protein, polyunsaturated fatty acids (-linolenic acid), vitamins, minerals, pigments, and enzymes to feed and food products. Spirulina exhibits various pharmacological properties including anticancer, antiviral, antibacterial, metalloprotective, antioxidant, and immunostimulant effects. The reasons behind Spirulina's abilities to fight cancer, viruses, and bacteria are its endonuclease content (which fixes DNA damage), calcium sulfated polysaccharide content (which hinders virus replication in lab settings), and its fatty acids (specifically high levels of -linolenic acid). Furthermore, Spirulina's ability to protect against metal damage may be due to the existence of beta-carotene, vitamins C and E, superoxide dismutase enzyme, selenium, and the blue pigment phycocyanin. Studies have also examined Spirulina's ability to stimulate the immune system. Certain experimental findings suggest that the most potential active components of Spirulina are phycocyanin, sulfated polysaccharide fractions, GLA, and specific sulfolipids. However, additional research is necessary to evaluate how effective Spirulina is as a potential source of pharmaceuticals and nutraceuticals.

Various pharmacological activities and diverse chemical composition have been documented for the microalgae. The conflicting findings could be due to variations in geographical source, harvesting time, characteristics of the aqueous medium, and genetic differences.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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