Therapeutic Implications of Spirulina in ROS-Induced Cancer Progression

28

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Contents

Abstract

Health and environmental protective properties of spirulina have been investigated in many studies. Since it balances cytokines and other immune elements with the effect of contents that chemicals and other biological elements. It has some effects on immune system strengthening, antioxidant, antioxidative stress, anti-inflammatory, antibacterial, antiviral, antifungal, antidiabetic, antihypertensive and anticancer. When administered in appropriate dose, it decreases the reactive oxygen species (ROS) rates and reduces oxidative stress which contributes to cancer progression. Its effects against oxidative stress and beneficial effects in cancer prevention and cancer treatments have been investigated.

Keywords

Spirulina platensis · ROS · Free radical SP · Malnutrition SP · Heavy metal chelation spirulina · Spirulina cytotoxic anticancer · Antioxidant SP · SM

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Introduction

The nutritional, antimicrobial, antitoxic, heavy metal chelator, and environmental protective properties of spirulina (*Arthrospira platensis*) have been investigated (Dotto et al. 2013; Fang et al. 2011). It is a member of a type of algae group called blue green microalgae and cyanobacteria. Spirulina is used in health, environmental cleaning, and wastewater treatment with its high chlorophyll, various chemicals, and CO_2 and heavy metal fixation feature. Its production is very easy and cheap because its water and nutrient needs are very low. Because of its high protein and nutritional value, spirulina has also been used as animal feed to improve meat production and quality (Alberto et al. 2017). Its rich protein, fat, and vitamin contents have also been shown to have beneficial effects on malnutrition and cachexia (Siva Kiran et al. 2015). It has antioxidant effects against oxidative stress which contributes against chronic diseases and cancer.

What Is Spirulina?

Spirulina is one of the microalgae species, also called blue green algae. Although algae generally live in fresh waters and seas, there are also algae species that live on trees in hot spring waters, snow and ice, above and below ground, and in humid climates (Figs. 1 and 2). Algae are autotrophic microorganisms, and the most important feature that distinguishes them from other microorganisms is their ability to photosynthesize. They absorb the energy they get from sunlight and use this energy by converting the inorganic carbon dioxide (CO_2) that get from the water into carbohydrates. The algae give off oxygen during photosynthesis, which cleans the air. It has many varieties, contributing to a significant part of the natural smells and colors in the natural environment. Another important feature of blue-green algae is that they fix nitrogen in the air and soil. Blue-green algae in the soil are as important as bacteria for the ecological balance and the continuation of life. Because blue-green algae fix nitrogen, they increase the nitrogen and organic matter of the soil

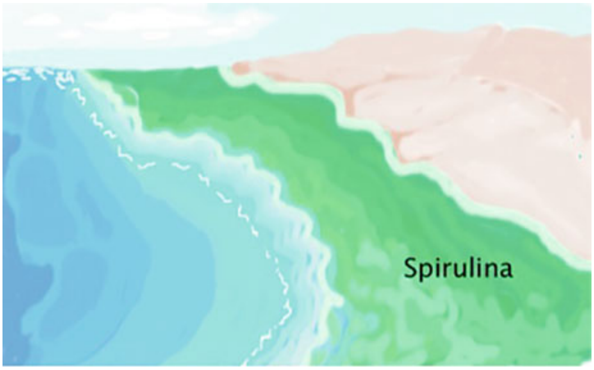

Fig. 1 Naturally grown spirulina (schematic illustration)

Fig. 2 Microscopic view of spiral-shaped spirulina (schematic illustration)

even when they die. Thus, soil fertility increases. Blue green algae are the only group with prokaryotic cell structure like bacteria. They are biologically interesting because of their abundant chlorophyll and mixed metabolism (Ciferri 1983).

Spirulina Species, Morphology, and Taxonomy

The three most important species of *Arthrospira*, also known as spirulina, are *Spirulina platensis* (SP), *Spirulina maxima* (SM), and *Spirulina fusiformis* (SF) (Table 1). *Spirulina* is a genus of cyanobacteria and has a filamentous, cylindrical, and multicellular structure (Fig. 2) (Ciferri 1983). Holmgren et al. reported that *Spirulina major* was a genus of *Arthrospira* due to the presence of cross walls and cellular septation in electron microscopy. Unbranched filamentous *Nostocales* and *Oscillatoriaceae* family traits were shown in *Spirulina* and *Arthrospira* (Homlgren et al. 1971).

Hintak described *Spirulina fusiformis* (SF), which also has a multicellular, filamentous, trichome structure formed by a fusiform single spirally twisted cell. *Spirulina fusiformis* did not have rotational motile structures such as flagella and heterocysts found in many other blue-green algae (Usharani et al. 2012; Hintak 1985).

SP is a filamentous, photoautotrophic, alkaliphilic cyanobacterium belonging to the *Oscillatoriaceae* family. It is abundant in environments rich in bicarbonate. It has an important place in the food, pharmaceutical, and cosmetic industries due to its rich protein and pigment source (Alberto et al. 2017).

Spirulina also known that cyanobacteria are a branch of bacteria that provide their energy through photosynthesis (Godlewska et al. 2019). Its name comes from the color cyanos, meaning blue. It is an important source of nitrogenous compounds in

Table 1 Naturally known species of Spirulina

Spirulina species	
Most known	*Spirulina platensis* *Spirulina maxima* *Spirulina fusiformis*
Lesser known	*Spirulina gessneri* *Spirulina condensata* *Spirulina flavovirens* *Spirulina major* *Spirulina minima* *Spirulina gracilis* Spirulina caldaria *Spirulina thermalis* *Spirulina laxa* *Spirulina bayannurensis* *Spirulina abbreviata* *Spirulina subsalsa* *Spirulina nodosa* *Spirulina agilis* *Spirulina gomontii* *Spirulina albida* *Spirulina baltica* *Spirulina rosea* *Spirulina schroederi* *Spirulina tenuis*

the sea. It is thought that cyanobacteria, which produce oxygen by photosynthesize with carbon dioxide, have an important role in the shaping and diversification of life on Earth and are one of the factors that led to the filling of the early Earth atmosphere with oxygen. Cyanobacteria also have important functions on chloroplasts and eukaryotic algae in plants (Ciferri 1983).

Spirulina is known as one of first photosynthetic organisms in nature (Dotto et al. 2013; Alberto et al. 2017; Olson 2006).

Production of Spirulina

Spirulina requires less water and soil compared to other field crops due to its rapid growth rate independent of climate (Alberto et al. 2017; Tanseem 1990; Ogawa and Teuri 1972). There is growth potential even on wastewater. It is a good source in terms of seawater production in very small areas. The tons of spirulina can be produced from the water surface in a short time (Dotto et al. 2013; Alberto et al. 2017; Ciferri 1983). It is found naturally in tropical regions with high alkalinity and rich in salt and bicarbonate (Alberto et al. 2017).

In their culture studies on spirulina, Ogawa and Terui tried to increase spirulina production in an environment free of different organic fertilizers and sodium chloride. In this way, they reported that *Spirulina subsalsa* and *Spirulina platensis* increased dry matter production by 5–30 percent (Gupta and Bajaj 1983). In a study by Nasima and his group, they used rice husk ash (RHA) and NaHCO3 l-1 as a carbon source in culture during *Spirulina* production. They showed that the growth rate obtained by adding 2 g of NaHCO3 l-1 to the culture per day was higher than that of adding 1 g of RHA l-1. However, the addition of RHA was preferred more because it was cheap (Nasima Akhtar et al. 1996). To achieve maximum *Spirulina* yield, a suitable environment must be provided. In the most ideal preferred environment, outdoor temperature is in the range of. 30–35 ° C. Temperature above 35 °C causes the cultures to bleach reducing production (Somasekaran 1987).

The optimum light intensity required for *Spirulina* generation was between 20 and 30 K lux. Subramanian and Jeejibai investigated the effects of different light qualities of *Spirulina* on the production of fusiformis, protein, and pigment synthesis in their studies and reported the results (Ogawa and Teuri 1970).

Vincent and Silvester reported that pH has a significant effect on the production of algae and their different physiological properties and nutritional values. They reported that pH *increases* and decreases have significant effects by changing the solubility of the carbon source and minerals in the culture. Spirulina production increases at high pH values such as 9 and 11, with an optimal pH of 9.5 (Vincent and Silvester 1979).

Spirulina Contents

Chlorophyll. Spirulina contains a high proportion of chlorophyll, especially chlorophyll a (Hoa Thi Hai et al. 2019; de Morais and Costa 2007; Savitskiy and Zorin 2002). It increases antioxidant capacity with the effect of phenolic contents like phytochemicals, phycobiliprotein, and C-phycocyanin (Riss et al. 2007; Muthuraman et al. 2009; Machu et al. 2015).

Phycocyanins. The most important and abundant chemical in its content are antioxidant phycocyanins with anti-inflammatory effects. The most important is c-phycocyanin (13.5–14.8 g). Other phycocyanins are allophycocyanin (2.3 g) and phycobiliproteins (1.1 g) (Table 2) (Riss et al. 2007; Banji et al. 2013; Bhat and Madyastha 2001; Chen and Wong 2008; Koníčková et al. 2014; Zhang et al. 2011). C-phycocyanin also contains heptadecane, a volatile component (Kim et al. 2013). Some polysaccharide content such as immolina has also gained importance due to its antioxidant and immunomodulatory effects (Tang et al. 2014; Grzanna et al. 2006).

Phenol content is 0.2–1.73 g and flavonoid content is 0.1–0.9 g (Machu et al. 2015; Abd El-Baky et al. 2009). It also contains a small amount of polysaccharide (0.2–12.5 g) (Tang et al. 2014; Grzanna et al. 2006).

Spirulina has high nutritional values due to the contents such as proteins, fats, minerals, and vitamins (Table 2) (Simpore et al. 2006; Bensehaila et al. 2015).

If we consider *Spirulina* as a vegetable, the amount of protein (60–70%) contained in 1 gram of *Spirulina* is equal to that of approximately 1 kg of other vegetables. Moreover, the amino acid composition of *Spirulina* protein is even

Table 2 Most beneficial pigmented chemicals in spirulina content

Pigmented contents of spirulina	Chemicals	Effects
Phycobiliproteins	Phycocyanin	Antioxidant, antiviral, antibacterial, antidiabetic, anti-inflammatory, immune modulator, anticancer
	Phycocyanorubin	
	Phycocyanobilin	
	Phycoerythrin	
Chlorophylls	Chlorophyl a	Oxygen enhancer, blood builder, energy balancer, antioxidant, immune modulator, anticancer
	Chlorophyl b	
	Chlorophyl c	
	Chlorophyl d	
	Chlorophyl f	
Carotenoids	β-Carotene	Antioxidative stress, repairer of DNA damage, energy balancer
	Cryptoxanthin	
	Zeaxanthin	

Table 3 Protein and amino acid content in 100 g of spirulina

Contents of protein and amino acids	Amount of contents (g)
Proteins	35.4–70.0
Amino acids	
Glutamate	7.0–7.3
Leucine	5.9–8.4
Aspartate	5.2–6.0
Lysine	2.6–4.6
Tyrosine	2.6–3.4
Phenylalanine	2.6–4.1
Methionine	1.3–2.7
Total	100

higher than that of soybean, and it is among the best in the plant world (Siva Kiran et al. 2015) (Table 3).

Spirulina is rich in palmitic acid (25.8–44.9%), gamma-linoleic acid (17.1–40.1%), and other ingredients like linoleic acid (11.1–12.0%), oleic acid (10.1–16.6%), palmitoleic acid (2.3–3.8 %), and stearic acid (1.7–2.2%). Its content of carbohydrates and crude fiber is low (carbohydrates 14.0–19.0 g and crude fiber 3.0–7.0 g). The most important thing for our nutrition is that it contains calcium (120–900 mg), magnesium (330 mg), iron (273.2–787.0 mg), and potassium (2.0–2.6 g), much more intense than other foods. Other important minerals are sodium (1.5–2.2 g) and phosphorus (1.3–2.2 g), which constitute an important part of its content. Tocopherol (vitamin E, 0.4–9.8 g), carotenoids (vitamin A, 0.3–2.6 g), especially B vitamins (B12 5.7–38.5 μg, B2 3.0–4.6 mg, B6 0.5–0.8 mg, niacin (B3) 13–15 mg), and folic acid (0.05–9.92 mg) are also rich (Siva Kiran et al. 2015; Simpore et al. 2006; Bensehaila et al. 2015).

Kumar and Singh conducted studies to enrich the cobalt and iodine content of spirulina and showed that there could be a 3.98-fold increase in the amount of cobalt bound to proteins and a 1.25-fold increase in iodine intake. They also carried out biochemical studies to determine the sugars and enzyme ratios in spirulina. In these studies, it was reported that total water-soluble sugars were higher than acid-soluble sugars (7.31%) (Kumar and Singh 1992). Powder spirulina contains 480 mg of iron Kg-1. It contains higher iron content in wet algae (15–20 percent) than dried algae (8–10 percent) (Kumar and Singh 1992). The powder and dissolved in water forms of spirulina are shown in Figs. 3 and 4 (Figs. 3 and 4). Spirulina purified the C15H18NO8 molecule from *platensis* (Fig. 5).

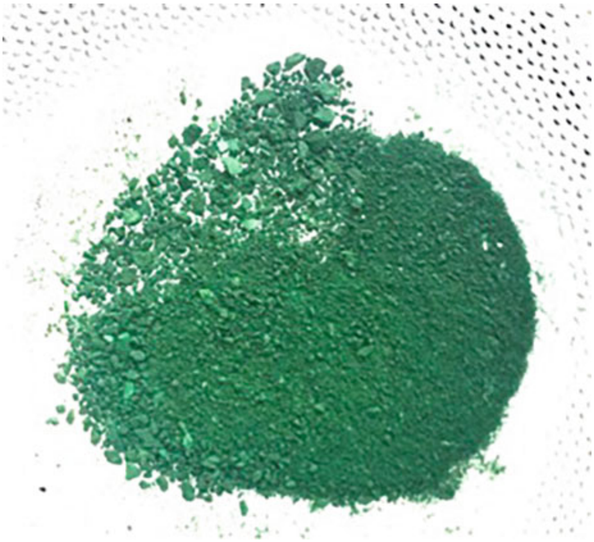

Fig. 3 The powder form of spirulina

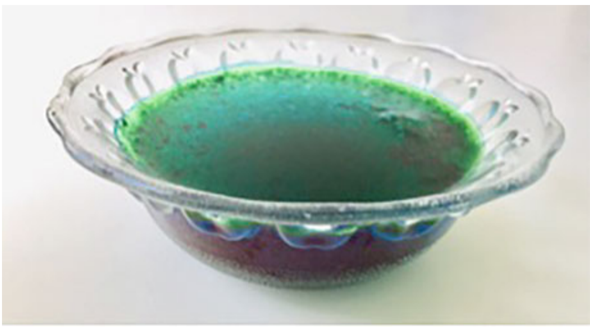

Fig. 4 The dissolved form of spirulina in water

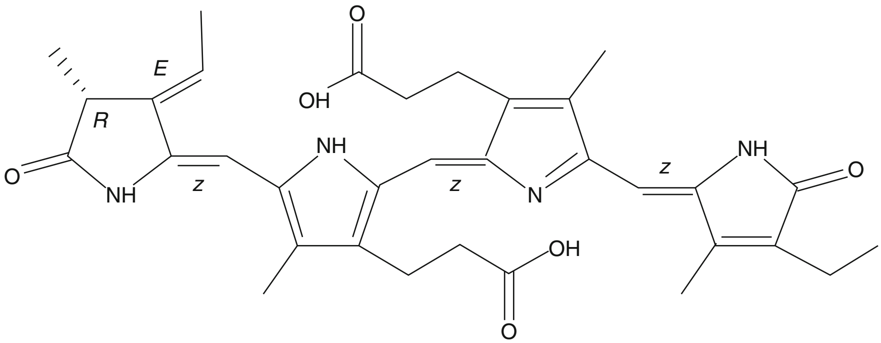

Fig. 5 Chemical formula of spirulina

Where Spirulina Is Used?

Spirulina is used in wastewater treatment, increasing the oxygen ratio in the air with its features such as CO_2 fixation. The increase in CO_2 in the atmosphere leads to global warming with the greenhouse effect. In the opinion of the Intergovernmental Panel on Climate Change (IPCC), about 10–15% of the gases emitted from coal used as fuel is CO_2. Since microalgae and cyanobacteria use this gas as a carbon source during their production, they can reduce the CO_2 concentration in the atmosphere (Hoa Thi Hai et al. 2019; de Morais and Costa 2007; Singh et al. 2016). They contribute to the purification process by living in symbiosis with bacteria in the stabilization pools of treatment plants. During this process, they should be kept in a certain balance as their excessive reproduction can cause problems. Especially when they reproduce too much, their biggest drawback is clogging the sand filters (Singh et al. 2016; Ignacio de et al. 2010; Rangsayator et al. 2002). Cyanobacterium (*Spirulina platensis*) was combined with other microalgae, and its effects on biodegradation and reducing carbon, nitrogen, and phosphorus levels were investigated by symbiosis with activated sludge bacteria in wastewater. For this purpose, pig house wastewater was diluted four and eight times and used because they are known to be very dirty. Microalgae increased the oxygen production rates in wastewater from 116 to 133 mgO (2)/L (Ignacio de et al. 2010).

Another study showed significant reduction of pollution in wastewater with a method called phycoremediation (Rangsayator et al. 2002). Since *Spirulina* absorbs toxic substances, products produced for purification purposes should not be used as a supplement.

Beneficial Effects of Spirulina on Health

Antitoxic, Heavy Metal Chelating Properties

Cadmium, mercury, lead, and arsenic, which are heavy metals, are toxic heavy metals that pose the most risks to the environment and health. In the scientific literature, a total of 58 preclinical studies reveal that *Spirulina* attenuates experimentally induced heavy metal toxicity (Sanjib 2020). Spirulina has been shown to reduce the toxic effects of arsenic, mercury chloride, chromium, cadmium, and metals such as fluoride and iron (Banji et al. 2013; El-Desoky et al. 2013; Elshazly et al. 2015; Karadeniz et al. 2009; Bermejo-Bescós et al. 2008) and carbon tetrachloride, insecticide deltamethrin, and tilmicosin (Kepekçi et al. 2013; Abdel-Daim et al. 2016; Ibrahim and Abdel-Daim 2015). In a study, the contribution of SP to the negativities of sodium fluoride-induced thyroid functions and neurological development in the offspring of pregnant rats was investigated. It was observed that the addition of SP decreased the toxic effects by reducing the serum fluoride levels. Thyroid hormone improvement was observed in the changes due to excess serum fluorine. It has been reported that as a result of the decrease in oxidative stress and the increase in antioxidant capacity, the damage of Purkinje cells is also prevented which is important in the conduction of the heart muscle (Banji et al. 2013).

In another study, the protective effects of *Spirulina platensis* on oxidative damage caused by mercury(II) chloride (HgCl) in testicles of Wistar albino rats were investigated. After inducing oxidative stress with a single dose of HgCl (5 mg/kg, subcutaneous), antioxidant biomarkers such as superoxide dismutase (SOD), catalase, glutathione, and mercury levels in the testis were measured. In addition, after HgCl application, damage was determined by histopathological examination and sperm count, etc. It was observed that the toxicity caused by HgCl decreased especially with the application of 300 mg/kg *Spirulina* in animals. It was reported that histopathological changes of sperm abnormalities and disorders decreased with SP with increased antioxidant biomarkers and reduced mercury accumulation in the testis (El-Desoky et al. 2013).

The protective effect of SP against nephrotoxicity caused by chromium metal was investigated. *Spirulina platensis* (300 mg/kg) and a concentration of 520 mg/l were administered via drinking water to rats. Sodium dichromate dihydrate (SDD) was given as a chromium source. It has been reported that as a result of chromium application, there is an increase in blood urea and creatinine levels, together with a decrease in catalase activity and glutathione levels in kidney tissue. When *Spirulina* is given together with Cr, increased antioxidants and restoration were detected in kidney functions (Elshazly et al. 2015).

Cadmium is an environmental and industrial cumulative pollutant with toxic effects on the liver and many organs. In a study on rats, SP and *Panax ginseng* were given together to reduce the toxic effect of cadmium. After a 1-month application, an increase was observed in malondialdehyde (MDA) and reduced glutathione (GSH), SOD, and nitric oxide (NO) levels (Karadeniz et al. 2009).

The efficacy of SP was investigated with its protean extract and biliprotein phycocyanin in reducing iron-induced neurotoxicity. Iron is one of the most important agents that cause neurotoxicity due to oxidative stress. It has been shown that protein extract of SP can reduce cell death mediated by free radicals with high antioxidant activity. It has been said that spirulina can be used in neurodegenerative diseases such as Alzheimer's or Parkinson's caused by free radicals (Bermejo-Bescós et al. 2008).

Hypolipidemic Hypoglycemic Effects

Spirulina shows hypolipidemic effects by increasing lipoprotein lipase activity and hypoglycemic effects by increasing insulin secretion (Muthuraman et al. 2009; Torres-Duran et al. 2007a). The effect of *Spirulina platensis* in diabetic rats was investigated. A significant antidiabetic effect was demonstrated as a result of marinated *Spirulina platensis* given orally for 30 days (Muthuraman et al. 2009).

Antimicrobial Effects

Antiviral

Calcium spirulan (Ca-SP) which is one of the sulfated polysaccharides is a potent antiviral agent against both HIV-1 and HSV-1 (Hernández-Corona et al. 2002; Hayashi et al. 1993; Gustafson et al. 1989). In HIV-infected patients, increases in T-helper lymphocytes (CD4) in parallel with the decrease in viral load with spirulina consumption have been reported. In HIV infection the reductions in glucose or HOMA-IR (homeostatic model assessment for insulin resistance) were seen with *Spirulina* supplementation (Ngo-Matip et al. 2015). One study reported that calcium spirulan (Ca-SP) which is one of the *Spirulina* contents has antiviral activity against HIV at certain doses (Hayashi et al. 1996).

Antibacterial

SP can inhibit the growth of some Gram-positive bacteria and Gram-negative (*Pseudomonas aeruginosa*, *Escherichia coli*, and *Proteus vulgaris*) bacteria, including *Bacillus subtilis*, *Bacillus pumilus*, and *Staphylococcus aureus*, by producing extracellular metabolites with antibacterial activity (Ozdemir et al. 2004).

Spirulina is also used in the synthesis of gold nanoparticles showing antibacterial action against Gram-positive bacteria (Uma Suganya et al. 2015).

El-Sheekh et al. purified a molecule of C15H18NO8, an antimicrobial compound, from *Spirulina platensis*. The extract was found to be effective with this compound at concentrations against Gram-negative bacteria *Pseudomonas aeruginosa* with MIC = 85 μg/ml, against *Candida albicans* with MIC = 30 μg/ml, and against Gram-positive *Bacillus subtilis* with MIC = 60 μg/ml. (El-Sheekh et al. 2014).

Probiotic

It can also treat metabolic syndrome by preventing dysbiosis and inflammation with its probiotic enhancing and antimicrobial effects in intestines (Riss et al. 2007; Bhowmik et al. 2009). It has also been shown that the extracellular products of *Spirulina* can increase the in vitro growth of probiotic lactic acid bacteria such as *Lactobacillus* and *Bifidobacterium*. These effects are reported to occur with nitrogenous substances and free amino acids and phenolic compounds in *Spirulina*. The quality of fermented milk products can be increased due to the chemicals and compounds in *Spirulina*. It appears to be even more effective than probiotics in the treatment of intestinal dysbiosis. SP has been shown to reduce *Bifidobacterium* and increase *Clostridium irregulare* in the intestines. It is known that intestinal microbiota and normal anaerobic bacterial balance are disrupted in inflammatory bowel disease (IBD) and other bowel diseases (Rasmussen et al. 2009).

Nutritional Supplement

Malnutrition is an important problem that affects both morbidity and mortality. For the rehabilitation of malnourished children, public health, nutritionists, and other related health branches should work in synergy (Alberto et al. 2017). Beneficial effects have also been demonstrated in malnutrition and cachexia (Siva Kiran et al. 2015).

Spirulina is used as a nutritional support in humans and animals and in babies (Alberto et al. 2017; Siva Kiran et al. 2015; Jin et al. 2020). Spirulina has high nutritional values due to the its contents of proteins, fats, minerals, and vitamins (Simpore et al. 2006; Bensehaila et al. 2015). Spirulina is added to some foods such as baby foods, biscuits, and yoghurt in order to increase their nutritional values (Sharoba 2014; El Baky et al. 2015).

In a study of 60 low-middle-income girls aged 7–9 years old, 1 g of Spirulina was added to the diet of one group and Spirulina not added to diet of the other group 5 days a week for a period of 2 months. Hemoglobin (Hb), erythrocyte (RBC) count, and "Raven's colored progressive matrices" were used to assess intellectual status before and after supplementation. Significant improvement was observed in both hematological and intellectual findings in the spirulina-supplemented group (Sachdeva et al. 2004).

It has been shown that 2 g of spirulina supplements can increase the levels of elements such as iron, calcium, magnesium, copper, and vitamins such as B6, B12, and folic acid, which are necessary for hemopoiesis (Kaur et al. 2009).

In a study weight gain was detected with the addition of SP, in HIV-infected children. All children had a decrease in the level of anemia, although slightly less in HIV-infected children (63.6% improvement). When they examined the lactation performance of mothers fed food supplemented with *Spirulina platensis* in their study, they showed that milk composition improved in terms of protein, fat, and lactose (Chung et al. 1978).

Antihypertensive

Spirulina has shown the effect of lowering plasma lipid concentrations and blood pressure in several studies (Torres-Duran et al. 2007a; Torres-Duran et al. 2007b; Miczke et al. 2016; Lu et al. 2011). In one clinical study, patients were given 4.5 g/day *Spirulina maxima* (SM) orally for 6 weeks. In this study, the volunteers did not change their dietary habits or lifestyles to demonstrate the SM effect more clearly. The triglyceride, lipids, blood pressure values, and body anthropometric values were measured before and after the study. When the results were compared, it was shown that there was no significant change in glucose and AST values but significant change in triglyceride, total cholesterol, and HDL-C at the end of the study, Approximately 10 mm Hg decreases were detected in systolic and diastolic pressures, and the difference was found to be significant ($p < 0.01$) (Torres-Duran et al. 2007b).

There are few clinical studies evaluating the effect of SM consumption in patients with blood pressure. Miczke et al. showed that blood pressure values returned to normal in 36% of patients and partial response was obtained in 50% who received 2 g/day SM. The antihypertensive effect of SM has been reported to be due to the C-phycocyanin and antihypertensive peptides it contains, which increase the expression of endothelial nitric oxide synthase (Miczke et al. 2016). Other antihypertensive chemicals are also said to contribute to this effect by inhibiting angiotensin-converting enzyme (ACE) such as tripeptide Ile-Gln-Pro (IQP) (Lu et al. 2011).

In Cancer Treatment

It has been used as a cancer preventer, by reducing the side effects while increasing the efficacy of the treatment. Manoj et al. reported that spirulina can be used in cancer prophylaxis (Wan et al. 2016; Manoj et al. 1992).

An experimental model of pancreatic cancer has demonstrated dose-dependent antiproliferative and antioxidative effects (10–125 μmol/L) of chlorophylls (chlorophyll a/b, chlorophyllin and pheophytin a). Chlorophylls bind tightly to carcinogenic substances such as heme and aflatoxin in the intestinal lumen and prevent their absorption. Dietary chlorophyll was shown to reduce the risk of colon cancer in a clinical study in the Netherlands (Kateřina et al. 2018).

Spirulina also showed complete response in 45% of patients when used 1 g/day for 12 months against oral carcinogenesis. Mishima et al. showed that the calcium spirulan (Ca-SP) compound of spirulina can reduce lung metastasis. Phycocyanin, the active integrin of spirulina, has been used successfully to reduce edema and inflammation due to cancer (Mishima et al. 1998).

Sonodynamic and Photodynamic Therapy (PDT) in Cancer

Recent studies showed to chlorin 6 (Ce6) which using SDT and PDT agent produced by chlorophylls which included Spirulina and other plants (Wan et al. 2016).

The chlorines that make up the chlorophylls are a class of tetrapyrrole chemicals produced from plants and spirulina. In photodynamic therapy, cytotoxicity was demonstrated that agents such as Ce6 obtained from spirulina act as photosensitizers by absorbing phototoxic red spectrum light (Hoa Thi Hai et al. 2019; Wan et al. 2016).

Since Ce6 and its derivatives obtained from chlorophyll of SP accumulate more in tumors than in normal cells, cytotoxicity is not observed in normal cells. It can absorb more red light at a wavelength of 670 nm. Ce6-mediated PDT has been used successfully in certain types of cancer, such as cervical cancer, colon cancer, and leukemia (Hoa Thi Hai et al. 2019; Wan et al. 2016).

Radioprotector Effects

In a case report study, it was reported that in a patient with relapsed vulvar cancer who had previously received radiotherapy, a 2nd series of low-dose radiotherapy (total 24 Gy in 12 fractions with 200 cGy daily fraction) and 750 mg of spirulina given twice a day gave a complete response in the tumor. It has been suggested that while spirulina reduces possible side effects by protecting from radiation, it can also increase cytotoxicity by sensitizing the tumor to radiation (Kiziltan et al. 2015).

The radiation protective effects of spirulina were demonstrated in a study of bone marrow cells on rats (Qishen et al. 1989).

Effects of Antioxidant and Anti-reactive Oxygen Species (ROS)

ROS

ROS are highly reactive chemical molecules formed as a result of electron affinity of oxygen (O_2). ROS chemicals such as peroxides, superoxide, singlet O_2 hydroxyl radical, and alpha-oxygen act on various signaling pathways by participating in important chemical reactions in the body (Qishen et al. 1989). While ROS exerts beneficial effects at low levels in normal cells, excessive production of ROS can oxidize certain cellular components, causing irreversible damage to DNA. This suggests that it has a dual role, occurring at different levels of ROS. Exposure to environmental factors such as excessive exercise and excessive heat, cold, light, and drought may significantly increase ROS levels. ROS can cause carcinogenesis by damaging proteins, lipids, and DNA in cells (Devasagayam et al. 2004). The sum of these harmful effects is known as oxidative stress.

ROS and Cancer

ROS-related stress increases in cancer cells due to mitochondrial dysfunction and increased metabolic activity.

During the excessive proliferation and progression of tumors, excessive amounts of ROS may be formed, and this may cause the process to accelerate with a vicious circle. The damage of excess ROS produced by cells can be prevented by increasing NADPH production. The increase in NADPH and the increase in antioxidants such as decreased glutathione (GSH) and thioredoxin (TRX) reduce the harmful effects of ROS (Gupta et al. 2012).

In cancer cells, B cells activated by ROS production cause inflammation, invasion, and angiogenesis by activating transcription factors such as nuclear factor kappa-light chain enhancer (NF-κB), hypoxia-inducible factor-1α (HIF-1α), and activator protein-1 (AP-1) (Edreva 2005). ROS-associated oxidation of DNA is one of the main causes of mutations.

ROS and Cancer Progression

There is an uncontrolled proliferation in cancer cells with the oxidative stress effect of exogenous and endogenous ROS. While normal levels of ROS protect cells against cancer by apoptosis, a moderate increase in ROS can lead to mutation, carcinogenesis, and proliferation. Excessive increase in ROS sometimes leads to cytotoxicity or rapid progression (Edreva 2005; Ramsey and Sharpless 2006).

ROS and Cytotoxic Effects

A cancer cell can die by apoptosis, necrosis, and autophagy. A moderate increase in ROS further increases apoptosis, while excessive ROS levels usually cause necrosis and autophagy. Necrosis and autophagy may reduce the viability of the tumor while reducing oxygen leading to excessive proliferation.

Spirulina has an antioxidant defense system that eliminates reactive oxygen species (ROS) that can damage cells by inducing oxidative stress. Since this antioxidant system reduces most of the oxidized forms through photosynthesis, the antioxidant property in spirulina extract is associated with some phycobiliproteins such as C-phycocyanin and allophycocyanin. Despite these pharmacological benefits, the molecular mechanisms for the antioxidant effects of Spirulina are mostly unknown (Devasagayam et al. 2004; Gupta et al. 2012; Edreva 2005; Ramsey and Sharpless 2006).

Antioxidant Effects of Spirulina on Cancer

It increases antioxidant capacity with the effects of chemical contents like phycobiliprotein, C-phycocyanin, carotenoids, and phenolic phytochemicals (Riss et al. 2007; Muthuraman et al. 2009; Machu et al. 2015; Woo et al. 2018). In a study, the enriched effects of spirulina and phycocyanin, which has a chemical content with chromophore properties, both without bound selenium (Se) and bound with Se, were investigated on the production of superoxide anions and nicotine adenine dinucleotide phosphate hydrogen (NADPH) oxidase. Se-rich phycocyanin (Se-PC), spirulina (SP), or Se-rich spirulina (SeSP) contained 0.4 microg Se per 100 g body weight. It was observed that Se-PC increased 42% more antioxidant capacity of plasma. In all groups average protective effect of 87% on liver glutathione peroxidase levels and 56% on superoxide dismutase levels was observed (Ogawa and Teuri 1970; Riss et al. 2007). High-performance liquid chromatography (HPLC) analysis in another study showed epicatechin to be the most abundant phenolic compound in SP and cyanobacteria (Bhat and Madyastha 2001).

In another study, it was reported that both selenium and phycocyanin showed strong chemopreventive effects against cancer. In vitro antioxidant and antiproliferative properties of selenium-enriched phycocyanin (Se-PC) were investigated. The antioxidant activity of Se-PC has been reported that analysis using four different free radical scavenging assays to show that Se-PC is a stronger antioxidant than phycocyanin on free radical activity. By applying the comet test, PC shows dose-dependent protective effects against H_2O_2-induced oxidative DNA damage in erythrocytes. It was also reported in this study that Se-PC showed antiproliferative activity against human melanoma A375 and human breast carcinoma MCF-7 cells. The study also showed that the antiproliferative effects of Se-PC in these cell lines are caused by apoptosis induction, increase in sub-G1 cell populations, and increase in DNA fragmentation. The study has been reported that depletion of mitochondrial membrane potential plays a role in Se-PC-induced apoptosis (Chen and Wong 2008).

In another study, higher antioxidant activities of selenium-enriched allophycocyanin (APC) were reported. In this study, Se-APC showed a stronger antioxidant effect than APC by reducing free radicals. The effects of free radicals such as malondialdehyde glutathione peroxidase and reductase enzyme were reduced by Se-APC. Intracellular ROS levels were also reduced by Se-APC (Zhang et al. 2011).

Phycocyanobilin, one of the ingredients of spirulina, is converted to phycocyanorubin by biliverdin reductase. In the human body, phycocyanorubin formed by the intake of spirulina is reduced to bilirubin, which has antioxidant effects. Contrary to popular belief, bilirubin has been shown to have beneficial effects on cancer and cardiovascular and autoimmune diseases caused by oxidative stress. A study of hyperbilirubinemic patients with Gilbert syndrome showed a reduced risk of colon cancer (McCarty 2007). However, spirulina does not increase bilirubin above normal levels. Oxidative stress due to ROS is also reduced with increased hem oxygenase effect (Vitek and Schwertner 2007). The possible anti-proliferative and potent ROS-reducing effects of chlorophyll, another important ingredient of spirulina, may also reduce cancer progression (Kumar et al. 2001).

In one study on calcium spirulan (Ca-SP) isolated from spirulina effects investigated on B16-BL6 melanoma and colon 26 M3.1 cancer cells. When Ca-SP was applied together with Matrigel/fibronectin-coated filters, it significantly inhibited the expected tumor invasion to Matrigel and laminin substrates. Its effect on fibronectin was not demonstrated. It also reduced the degradation of heparan sulfate by Ca-SP heparanase. It has been reported that experimental lung metastasis is prevented by injection of 100 microg Ca-SP of B16-BL6 cells (Mishima et al. 1998).

In addition to these effects, SP reduces oxidative stress via decreasing to nitric oxide (NO) and malondialdehyde (MDA), which are oxidative stress markers with increasing superoxide dismutase (SOD), which reduces the effect of these radicals. A reduction in redox peroxidation marker or an increase in antioxidant enzyme TAS, GSH, or vitamin C have been reported with 7.5 g/day for 3 weeks using of SP (Lu et al. 2006).

Total antioxidant status (TAS), antioxidants such as vitamin C, GSH, SOD, lipid peroxidation markers such as MDA, and peroxides (ROOH)] were used to determine the redox status. Cytokines and natural killer (NK) which are cytotoxic activity markers were used for immune functions. Spirulina used on healthy subjects showed no change in NK, natural killer T cells (NKT), and T cell rates, unlike on pathological subjects (Lu et al. 2006).

In the study of Abdel-Daim et al. (Abdel-Daim et al. 2016), a decrease in serum proinflammatory cytokine tumor necrosis factor-alpha (TNF-α) and cyclooxygenase-2 (COX) was demonstrated after administration of *Spirulina platensis* powder (Abdel-Daim et al. 2016). A significant increase in the production of interleukin-12 (IL-12) was also reported with the effect of NK cells. It shows anti-inflammatory and antioxidant effects by using phenolic antioxidants and C-phycocyanin, Nrf2, and NF-κB pathways (Wu et al. 2016). Spirulina also contains heptadecane, a volatile component that reduces NF-κB activity which increases inflammation and cancer progression (Dotto et al. 2013; Fang et al. 2011; Alberto et al. 2017; Kim et al. 2013).

It has been reported that antibody production is increased in mice fed with *Spirulina platensis*. Spirulina is said to strengthen the immune system by stimulating macrophage functions, phagocytes, and immunoglobins which reduce cancer progression (Grzanna et al. 2006).

Side Effects

Dietary Supplements Information Expert Committee (DSI-EC) has classified spirulina as "generally recognized as safe" (GRAS) (Wan et al. 2016). Nonserious side effects such as insomnia and stomach problems may rarely occur in those using spirulina (Marles et al. 2011). A very few rare serious adverse events have been reported in individuals taking spirulina 3 g daily for 1 month (Mazokopakis et al. 2008; Petrus et al. 2010). These side effects may also be due to products produced in filthy environments or derived from spirulina sources grown. Because spirulina absorbs toxic substances, the products used must be produced in environments that do not contain toxic substances. Although side effects are rare, caution should be exercised when administering spirulina to patients using certain immunosuppressant and antihypertensive and lipid-lowering drugs, especially those containing substrates of cytochrome P450 enzymes.

Conclusion

Spirulina can reduce the progression of cancer due to ROS by increasing antioxidant and capacity with very different chemicals in its flavonoid, pigmented, and phenolic contents. Some chelating, anti-inflammatory, antiviral, antibacterial, antidiabetic, and tissue and organ protective effects of spirulina also contribute to the reduction of cancer progression with its antioxidant and anti-ROS effects.

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