Int.J.Curr.Res.Aca.Rev.2022; 10(06): 89-100

EXCELLENT PUBLISHERS

International Journal of Current Research and Academic Review

ISSN: 2347-3215 (Online) Volume 10 Number 06 (June-2022)

Journal homepage: http://www.ijcrar.com

doi: https://doi.org/10.20546/ijcrar.2022.1006.008

Medical Application and Biochemical Mechanisms of *Spirulina platensis* for Human Benefit

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Abstract

Spirulina (Arthrospira) is considered as generally recognized as safe as a richest sources of organic nutrients without toxicological effects and it has been widely used in several countries. *Spirulina* contains good quality proteins, vitamins and minerals in addition to a wide variety of natural carotene and xanthophyll phytopigments. Many researchers studied the beneficial effects of *Spirulina* and reported its enhancing potential on its health benefits by improving general health as well as lowering the problems of different diseases like infilammation, diabetes, anaemia, hypertension and cardiovascular disorders by possessing some promising biological activities such as antitumor, antimicrobial, antiviral, anti-inflammatory, hypocholesterolemic, radio protective and metalloprotective effects. These pharmaceutical and medicinal properties of *Spirulina* could be attributed to some natural constituents such as phycocyanin, carotene, tocopherols, linolenic acid and phenolic compounds that had been shown to have strong antioxidant properties and powerful scavenging activities against Reactive Oxygen Species (ROS) like superoxide and H_2O_2 radicals. This review illustrates the beneficial effects of Arthrospira on human health with its specific mechanisms on its ability to protect the body physiological system against oxidative damage and source of potential pharmaceuticals based mainly on the highest levels of evidence available in the literature.

Article Info

Received: 06 May 2022
Accepted: 28 May 2022
Available Online: 20 June 2022

Keywords

Spirulina plantesis, Phycocyanin, Malnutrition, inflammation, antioxidants.

Introduction

Blue-green algae (cyanobacteria) are among the most primitive life forms on Earth; their cellular structure is a simple prokaryote (Saranraj and Sivasakthi, 2014), a diverse group of microorganisms that carry out photosynthesis by oxygen evolution using a mechanism very similar to that used by higher plants (Castro *et al.*, 2015). They have high morphological, physiological, and structural diversity necessary to adapt to a wide range of environmental parameters (Castro *et al.*, 2015). They share features with plants, as they have the ability to perform photosynthesis and they share features with primitive bacteria because they lack a plant cell wall. Interestingly, they also share characteristics of the animal kingdom as they contain on their cellular membrane complex sugars similar to glycogen (Saranraj and Sivasakthi, 2014).

Microalgae have received increasing attention due to the fact that they represent one of the most promising sources of compounds with biological activity that could be used as functional ingredients. Their balanced chemical composition (good quality proteins, balanced

fatty acid profiles, vitamins, antioxidants and minerals) and their interesting attributes can be applied in the formulation of novel food products (Ashraf, 2014). *S. platensis*is a microscopic and filamentous cyanobacterium that derives its name from the spiral or helical nature of its filaments (Radha and Chandra, 2018), an oxygenic photosynthetic bacterium represents an important staple diet in humans and has been used as a source of protein and vitamin supplement in humans without any significant side-effects (Karkos *et al.*, 2011). Hence *Spirulina* is of great interest as it offers the possibility of being used as a functional food and refers to those foods that have proven to aid specific body functions, yielding health-promoting properties and/or reduce the risk of disease beyond its nutritional functions (Ambrosi *et al.*, 2008). In the interest of developing novel more effective protein sources for preventing/reversing malnutrition, increasing attention has been turned to microalgae (Gabriela *et al.*, 2015). The aim of this review is to give an overall view of the nutritional properties and health benefits of *spirulina.*

Nutritional composition of Spirulina

Spirulina is the dried biomass of the cyanobacterium *Arthrospira platensis*, it has been widely used in several countries, it is considered GRAS (generally recognized as safe), without toxicological effects (Ashraf, 2014). *Spirulina*, has a unique blend of nutrients that no single source can provide and used as an important source of nutrients in the traditional diet of some populations of Africa and Mexico (Trung *et al.*, 2017). Its impressive protein content and its rapid growth in entirely mineral environments have attracted the attention of both researchers and industrialists alike. In terms of nutrition, *Spirulina* is a rich food source of macro- and micronutrients including high quality protein, iron, gama-linolenic acid, vitamins, minerals, sulfated polysaccharides and phycocanin (Gabriela *et al.*, 2015; Deasy *et al.*, 2019). It is composed of numerous antioxidants, including beta-carotene, phycocyanin, tocopherols, micronutrients, polyunsaturated fatty acids, particularly gamma-linolenic acid and phenolic compounds (DiNicolantonio *et al.*, 2020). *Spirulina* has a cell wall consisting of proteins, carbohydrates, and fats that are easily digested so that it has more nutritional content than other vegetable food sources (Deasy *et al.*, 2019). Therefore, Spirulina is potentially used as a functional food and supplements that are safe to consume in the right amount (Tang and Suter, 2011). Moreover, *Spirulina* has also proven to have good acceptance as of its organoleptic properties (thus making it a possible prospect for food or a nutrition supplement) and it has not exhibited neither acute nor chronic toxicities, making it safe for human consumption (Gabriela *et al.*, 2015).

Medical Application of *Spirulina* and its Mechanism

Spirulina is a low-cost nutritional supplement and has not been established to have any significant side effects (DiNicolantonio *et al.*, 2020) and dietary supplement, with an extremely wide range of alleged medical and health benefits (Ashraf, 2014). *Spirulina* has numerous medical advantages just as remedial significance, for example, insurance of the liver and kidneys, improvement of blood quality and anticipation of frailty, benefits for diabetes, decrease in circulatory strain, expulsion of substantial metals from the body, radioprotection, avoidance of liver and renal harmfulness, cancer prevention agent activity, safe security help in unfavorably susceptible responses (Kanojia *et al.*, 2019).

Clinical trials have shown that spirulina can serve as a supplementary cure for many diseases. It has been reported that consumption of Spirulina as diet supplement has health benefits in preventing or managing hypercholesterolemia, hyperglycerolemia, certain inflammatory diseases, allergies, cancer, environmental toxicant and drug-induced toxicities, viral infections, cardiovascular diseases, diabetes and other metabolic disease among others (Abeer *et al.*, 2015). Metabolic syndrome is currently on rise and dyslipidaemia and obesity are an integral component of Spirulina causation but also extends to its antiviral, anticancer, antioxidant, anti-diabetic, anti-inflammatory, hepatoprotective, cardioprotective and immunity boosting properties (DiNicolantonio *et al.*, 2020). Many studies have shown the effects of *Spirulina* that may result in significant therapeutic applications: an anti-cancer effect, a hypolipidemic effect, a protective effect against diabetes and obesity (Narmadha *et al.*, 2012; Ashraf, 2014), as well as positive effects against malnutrition, heavy metal/ chemical-induced toxicity, inflammatory allergic reactions, radiation damage and anemia (Hoseini *et al.*, 2013).

Effects of *Spirulina* on Malnutrition

Spirulina platensis gives a few huge and amazing medical advantages to malnourished kids, particularly the individuals who are under five years of age (Kanojia *et al.*, 2019). The protein constituents of *Arthrospira platensis* and its Vitamin-B complex give a significant

nourishing advancement in grown-ups and youngsters' eating regimen, since it supplies the attractive characteristics of beta carotene that can defeateye issue or eye sicknesses brought about by inadequacy of nutrient and propose to dietary prerequisite of β carotene which can help or counteract the eye infections of kids (Bob, 2010) It is the main nourishment source fusing huge measures of fundamental amino acids, gamma-linoleic-corrosive(GLA) and basic unsaturated fats, which helps to decide the whole hormonal framework (Kanojia *et al.,* 2019). *Spirulina platensis* assumes an incredible job in treating individuals who are experienced kwashiorkor (the ailment brought about by a protein- lacking eating routine in newborn children and youngsters). *Spirulina* protein is significantly more proficient and successful than some other protein sources like drain and milk powder. These *Spirulina* benefits considered as solid nourishment and diet with high dietary and therapeutic worth (Borchers *et al.,* 2009).

Roles of *Spirulina* in Antiviral activity

*Spirulin*a has strong antiviral activity due to presence of anti-bacterial and anti-mycotic substances that are isolated from *Spirulina platensis* through the therapeutic researches on it. Substances such as calcium spirulan (Ca-SP) from *A. platensis* hot water extract were found to be capable of inhibiting the infection and replication of several enveloped viruses *in vitro*, including the influenza A virus, the type 1 human immunodeficiency virus (HIV-1), the type 1 herpes simplex virus (HSV-1), the human cytomegalovirus, the measles virus, and the mumps virus (Chen *et al.,* 2016). The therapeutic evidence of the extract is reported to be over 100 and concentrations as low as 5-10 µg/ml evidently reduce the production of virus in any system and hence proveto be highly antiviral in activity (Kanojia *et al.,* 2019). *Spirulina* extract disrupts viral replication most effectively during early infection and targets hemagglutinin to inhibit influenza virus (by disrupting hemagglutination) (Chen *et al.,* 2016). Ingestion of *Spirulina* adds to the utilitarian safeguarding of the intestinal epithelium which acts as a first line of mucosal obstruction against diseases, restraint of humoralin susceptible reaction, cell interceded insusceptible reaction and TNF-alpha was seen in a portion subordinate way in mice (Kanojia *et al.,* 2019).

Braun-type lipoproteins from *A. platensis* ethanol extracts were also found to have immuno-stimulatory effects on monocytes and macrophage cells, and a recent study showed that they may activate innate immunity in mice to protect against the severe pathogenicity caused by influenza virus A (H1N1) (Pugh *et al.,* 2015). The red fluorescent protein allophycocyanin, purified from *A. platensis*, has been shown to inhibit EV71 RNA synthesis and viral plaque formation (Shih *et al.,* 2003).

And an aqueous extract of *A. platensis* also found to inhibit HIV-1 replication in human T-cells, peripheral blood mononuclear cells, and Langerhans cells (Chen *et al.,* 2016). These outcomes show fantastic in vitro restraint of HIV-1 infection both in human Lymphocyte lines and in human monocytes (Kanojia *et al.,* 2019).

Anti-cancer effects of *Spirulina*

Therapeutic alternatives originating from food or food supplements appear to be growing in popularity as "nutritional therapy" and are well studied for their chemo-preventive and chemotherapeutic effects (Ravi *et al.,* 2015). Over the last few decades, products from natural, non-synthetic origin have become increasingly important for the prevention and treatment of cancer due to the toxic side effects of many synthetic anti-cancer drugs. *Arthrospira platensis* (AP) is considered as one of the sources of such natural bioactive substances (Braune *et al.,* 2021) and it has cancer preventing effect because of its antioxidant properties; free radical scavenging properties, as it contains a number of natural pigments such as chlorophyll, beta-carotene, phycoerythrin and phycocyanin (Abeer *et al.,* 2015). Moreover, Spirulina contains a spectrum of natural mixed carotene and xanthophyll phytopigments that together with phycocyanin seem to be related to its antioxidant activity (Bermejo-Bescos *et al.,* 2008).

Phycocyanin (PC) is the main active ingredient of *Spirulina*, accumulating evidence suggests that PC has a potent anti-cancer effect on various cancer types (such as breast cancer, liver cancer, lung cancer, colon cancer, leukemia and bone marrow cancer) *in vitro* and *in vivo* (Braune *et al.,* 2021).

On the other hand, even high-dose PC treatment does not induce significant toxic symptoms or mortality in animal experiments (Liao *et al.,* 2016). Mechanistically, PC exerts its anti-cancer activity by induction of cell apoptosis reducing cell proliferation and migration and inducing apoptosis, as well as cell cycle arrest (Jiang *et al.,* 2019). Phycocyanin (PC) can penetrate the cell membrane and localized near mitochondria to induce apoptosis and necrosis via mitochondria-dependent intrinsic pathways (Braune *et al.,* 2021).

Scientific data indicated that Phycocyanin activates mitochondrial cytochrome c pathway by altering the Bcl-2/Bax ratio (Bcl-2, anti-apoptotic protein; Bax, pro-apoptotic protein; Bcl-2/Bax ratio represents the degree of apoptosis induction) (Braune *et al.,* 2021), activation of caspases and induction of poly (ADP-ribose) polymerase-1 (PARP-1) cleavage; might disable the immediate cellular response to DNA damages such as DNA excision repair (Subhashini *et al.,* 2004). After the supplementation of Phycocyanin to the tumor cells, remarkable morphological changes like cell shrinkage, formation of membrane blebs, nuclear and cytoplasmic condensation, endolytic cleavage of the DNA into small oligo-nucleosomal fragments, formation of apoptotic bodies, and micronuclei characteristic of apoptosis were observed (Oftedal *et al.,* 2010). Phycocyanin affects tumor cell invasion by lowering actin filaments to decrease the migration potential through inhibitions of cyclooxygenase 2 (COX-2), which converts arachidonic acid to prostaglandins and plays a key role in tumor progression and chemical resistance (Braune *et al.*, 2021). Prostaglandin-E2 is a tightly regulated product of COX-2, which promotes angiogenesis (Mizuno *et al.*, 2019), since COX-2 is positively correlated with tumor invasion, metastasis, and poor prognosis in non-small cell lung cancer (Braune *et al.,* 2021).

Phycocyanin down-regulates Matrix metallo-proteases (MMP-2 and MMP-9), which are required for the invasion into surrounding tissues and tumor metastasis (Jiang *et al.,* 2017). Furthermore, Phycocyanin down-regulates HIF-1, which associated with increased oxygen demand and angiogenesis as well as MCP-1 expression (which is positively correlated with metastatic prognosis in the tumor environment). This down-regulation also promoted MIP-1 expression (which plays a role in reducing angiogenesis) (Saini and Sanyal, 2014).

Wound healing Activity

Skin is one of the most vital organs that protect the body against external stress and pathogenic microorganisms. Immediately after a skin injury, a complex dynamic wound healing mechanism is initiated by a complex sequence of cellular, molecular, and biochemical processes with signaling cascade (Elbialy *et al.,* 2021). There is a seasonal and species-specific diversity in polysaccharides content in algae and worthwhile having constant high hydrophilicity completely fits the new concept of creating moist conditions for the treatment of wounds (Casillo *et al.,* 2018). Inspired progression has been developed to exploit the spirulina molecular mechanisms that regulate wound healing and the growth factors implicated in wound healing. Currently, a growing number of evidence propose that SP is involved in regulating the repair and healing of skin wound (Jung *et al.,* 2013).

Recent scientific evidence demonstrated that, the wounds treated with S*pirulina* improved much faster with healthy skin appearance by playing a role in rapid decrease in the wound size, accelerate burn healing with increasing production of collagen and subsequent collagen deposition and promote wound healing by enhancing collagen deposition(Elbialy *et al.,* 2021). Syarina *et al.*, (2015) reported that Spirulina aqueous extract enhanced migration of Human dermal fibroblast(HDF) cells and wound closure referring to the phytochemical profile of microalgae for the presence of multiple therapeutic compounds that are useful in chronic wound treatment (Syarina *et al.,* 2015). Also Jung *et al.,* (2013) reported that spirulina extract has potential wound healing promoting effect through its positive influence on fibroblasts viability and proliferation with enhanced wound closure of a human fibroblast (Jung *et al.,* 2013). In the same line Liu *et al.,* (2019) clarified that SP crude protein can promote proliferation and migration of human dermal fibroblasts although activation of the PI3K/Akt signaling pathway provides a possible application of spirulina crude protein (SPCP) in skin wound healing (Liu *et al.,* 2019).

Antioxidant activity of Spirulina

Antioxidants (carotenoids, flavonoids and related polyphenols, α-lipoic acid, glutathione etc.) help to protect the body against free radicals (Asieh *et al.,* 2016). *Spirulina platensis*, is considered as a valuable source of natural antioxidants, such as water-soluble phycocyanin pigments, carotenoids, and phenolic compounds, in addition to antioxidant enzymes, such as superoxide dismutase, catalase and peroxidase (Mahmoud *et al.*, 2021). NADPH oxidase (the enzyme complex that is the chief source of pathological oxidant stress in a wide range of health disorders) over activity in disorders had suggested that ample intakes of *Spirulina* may prevent and has therapeutic potential with respect to many vascular diseases (including atherogenesis, hypertension, and congestive heart failure), cancers, complications of diabetes, and a range of neurodegenerative, fibrotic, or inflammatory disorder (Ali and Saleh, 2012). The protective effects of Spirulina against CCl_4-induced liver toxicity are due to free radical scavenging. This observation is attributed to its high contents of proteins,

lipids, minerals (zinc, manganese, magnesium and selenium), and some vitamins (beta carotene, riboflavin, cyanocobalamin, alfa-tocopherol, and alfa-lipoic acid) (Hoseini *et al.,* 2013).

Eating foods rich in antioxidants such as carotenoids, phycocyanin, superoxide dismutase and vitamins C and E is another great way to help prevent cancer (Kalafati *et al.,* 2010). *Spirulina platensis* has found to have free radical scavenging properties and antioxidant activity, as it contains a number of natural pigments such as chlorophyll, beta-carotene, phycoerythrin and phycocyanin (Abeer *et al.,* 2015). *Spirulina* is a whole food with its beta-carotene in a naturally chelated food matrix and not only rich in beta-carotene, it contains other very important carotenoids like zeaxanthin and betacryptoxanthin as well as lesser known carotenoids such as myxoxanthophyll and echinenone (Ibañez *et al.,* 2012). Moreover, Spirulina contains a spectrum of natural mixed carotene and xanthophyll phytopigments that together with phycocyanin seem to be related to its antioxidant activity (Bermejo-Bescos *et al.,* 2008).

Chlorophyll derivatives such as pheophorbide*b* and pheophytin*b* have always been known as strong antioxidants (Asieh *et al.,* 2016). Carotenoids are vitally important antioxidants. Numerous studies have indicated that people whose diets contain a lot of foods rich in carotenoids lower their risk of developing various types of cancer (Khan *et al.,* 2005). Hoseini *et al.,* (2013) demonstrated that *S. platensis* protein extract possessed an excellent antioxidant activity. Results showed that the protein extract of *S. platensis* scavenged hydroxyl and peroxyl radicals and also had inhibitory activity against lipid peroxidation (Hoseini *et al.,* 2013). Scavenging of these free radicals by *S. platensis* can be an effective prevention for a living organism against oxidative stress.

An antioxidant can function either by inhibiting the processes that activate free radical formation (by intercepting the formation of the reactive radical species), or inhibiting free radical action (by scavenging the radical) or suppressing amplification of the radical damage (by further intercepting the attack of secondary-derived radicals on their biological components) or reducing iron ions which are known to catalyze many processes leading to the appearance of free radicals (by iron chelating properties) (Hoseini *et al.,* 2013). Hoseini *et al.,* (2013) reported that the chelating activity of Spirulina exhibited a strong inhibition of errozine–Fe2+ complex formation due to its antioxidant compounds as electron donors.

Effects of *Spirulina* against Hyperlipidemia, Diabetes and Weight loss

Lifestyle changes and medication are helpful measures for the control of obesity and diabetes. Keeping an adequate body weight, a healthy diet, and lifestyles with proper physical activity, remains a crucial part for the prevention and management of diabetes (Henry *et al.,* 2020). Hence, in recent decades, the efficacy of dietary supplements to reduce obesity and control diabetes has been studied.

The addition of functional foods to a low-energy diet has been proven to reduce blood pressure, body mass index (BMI), fasting blood glucose (FBS), body weight (BW), total cholesterol (TC), waist circumference (WC), triglyceride (TG), and low-density lipoprotein cholesterol (LDL-C) compared to a low-energy diet alone (Izadi *et al.,* 2018). Among functional foods, *spirulina* has been considered by various international health organizations as one of "the greatest food on earth" (Bohorquez-Medina *et al.,* 2021).

Spirulina has a high protein content with good digestibility index and well-balanced distribution of essential amino acids, with exceptionally significant levels of isoleucine, valine, and leucine, contains high levels of macronutrients, lipids (rich in polyunsaturated fatty acids, PUFAs), carbohydrates, and micronutrients, such as vitamins, minerals, and antioxidants.

Due to its high PUFA content compared to other protein sources, *spirulina* can be used in low-fat diets or hypercholesterolemia treatment (Bohorquez-Medina *et al.,* 2021). The main lipids found in Spirulina are γ-linolenic acid (18:3, n-6) from omega-6 family and palmitic acid (16:0) both known for their pharmaceutical potential to prevent cardiovascular diseases, hypercholesterolaemia and other disorders(Ragusa *et al.,* 2021).

Several clinical and preclinical trials have been conducted to test the benefits of *spirulina* on weight loss. Mansoreh and Laleh (2016) indicated that *Spirulina* prevented the lead acetate-induced significant changes on plasma and liver lipid levels and on the antioxidant status of the liver and kidney (Mansoreh and Laleh, 2016). The benefits of using *spirulina* have shown a significant reduction in body weight (BW), waist circumference (WC), body mass index (BMI), and body fat (BF), particularly in patients with obesity (Yousefi *et al.,* 2018).

Table.1 Nutritional profile of Spirulina Powder (composition by 100 g) (Gabriela *et al*., 2015)

Components	Amounts	Components	Amounts
Calories	373	**Vitamins**	
Total fat (g)	4.3	Vitamin A (β-carotene)	352.000 IU
Saturated fat	1.95	Vitamin K	1090 mcg
Polyunsaturated fat	1.93	Thiamine HCL (Vitamin B1)	0.5 mg
Monounsaturated fat Cholesterol	0.26	Rivoflavin (Vitamin B2)	4.53 mg
	< 0.1	Niacin (Vitamine B3)	14.9 mg
		Vitamin B6 (Pyridox. HCL)	0.96 mg
		Vitamin B12	162 mcg
Total carbohydrate (g)	17.8	**Minerals**	
Dietary fiber	7.7	Calcium	468 mg
Sugars	1.3	Iron	87.4 mg
Lactose	< 0.1	Phosphorus	961 mg
		Iodine	142 mcg
		Magnesium	319 mg
		Zinc	1.45 mg
		Selenium	25.5 mcg
		Cooper	0.47 mg
		Manganese	3.26 mg
		Chromium	<400 mcg
		Potassium	1,660 mg
		Sodium	641 mg
Protein		**Phytonutrients**	
Essential amino acids (mg)	1000	Phycocyanin	17.2%
Histidine	3500	Chlorophyll	1.2%
Isoleucine	5380	Superoxide dismutase (SOD)	531,000 IU
Leucine	2960	Gamma linolenic acid (GLA)	1080 mg
Lysine	1170	Total carotenoids	504 mg
Methionine	2750	β-carotene	211 mg
Phenylalanine	2860	Zeaxanthin	101 mg
Threonine	1090		
Tryptophan	3940		
Valine			
Non-essential amino acids (mg)			
Alanine	4590		
Arginine	4310		
Aspartic acid	5990		
Cystine	590		
Glutamic acid	9130		
Glycine	3130		
Proline	2380		
Serine	2760		
Tyrosine	2500		

Table.2 Therapeutically important compounds in *Spirulina* and their applications (Singh *et al*., 2020).

Name of compound	Properties
Ca-Sp (Calcium-Spirulan)	• Immunity enhancer, Anticancer • Antiviral Induces haematopoiesis
Sulpholipids	Antiviral
Beta-carotene	• Source of Vitamin A • Anticancer • Antioxidant
Cyanovirin-N	Antiviral
GLA (Gamma Linolenic Acid)	• Treatment of Arthritis • Anticancer • Fat-metabolism
Vitamin-E	Antioxidant
Phycocyanin	• Antioxidant, Anticancer • Immunity booster, Detoxifier • Antiviral, Induces Haematopoiesis

Table.3 Beneficial effects and mechanisms of action of Spirulina (Mayada *et al*., 2016)

Activities	Mechanisms
Antioxidant functions	Spirulina improve the antioxidant enzymes such as SOD, CAT, GSH, GSH-PX and reduce lipid peroxidation (MDA) as well as scavenging activity of free radicals.
Hepatoprotective effect	Spirulina reduce lipid peroxidation, decreased oxidative stress and apoptosis in the liver; prevent the chronic hepatitis from being complicated in to the hepatic cirrhosis.
Nephroprotective effect	Spirulina normalize the renal functions and histological structure.
Neuroprotective effect	Spirulina help in reducing cerebral infection and ischemic brain damage produced by toxic chemicals, lowering ROS, nitric oxide and lipid peroxidation, enhancing the locomotors functions and decreasing the morphological damage to the spinal cord
Hypoglycemic and hypolipidimic effect	Spirulina could lower the total lipid, cholesterol, triglycerides and glucose in blood and improve insulin resistance due to its antioxidant properties.
Antitumor effect	Spirulina could improve functions of NK-cells, down regulate proliferating cells PCNA and P53 expression and increase production of tumor necrosis factor (TNF-alpha) these effects could be attributed to antioxidant and immunomodulatory properties of spirulina.
Antigenotoxic effect	Spirulina prevent DNA damage, reduce the frequencies of micronucleus in bone marrow and activate cell nucleus enzyme.
Immunomodulating effect	Spirulina increased the phagocytic potential of macrophages, enhanced the activies of NK-cell and lysozyme and increased the production of antibodies, interferon gamma and cytosines Interleukins; IL-1, 4 and 17).
Anti-inflamatory effect	In addition to inhibition of colon inflammatory markers; MPO and PGE2 as well as proinflamatorycytosines (TNF-alpha and I-1beta, IL-6) with restoring the histological structure of colon by decreasing levels of lysosomal enzyme, tissue marker enzymes and glycoproteins.
Growth, productive and reproductive enhancer of animal and poultry	Spirulina could improve the growth, productive and reproductive performance of animal and poultry through improving feed intake, feed conversion, nutrient absorption and utilization body weight gain, carcass yield, egg weight, egg mass, egg component, egg quality as well as the fertility and hatchability rates.

Fig.1 Mechanisms of actions of Spirulina as an ant-cancer (Maria *et al.*, 2021)

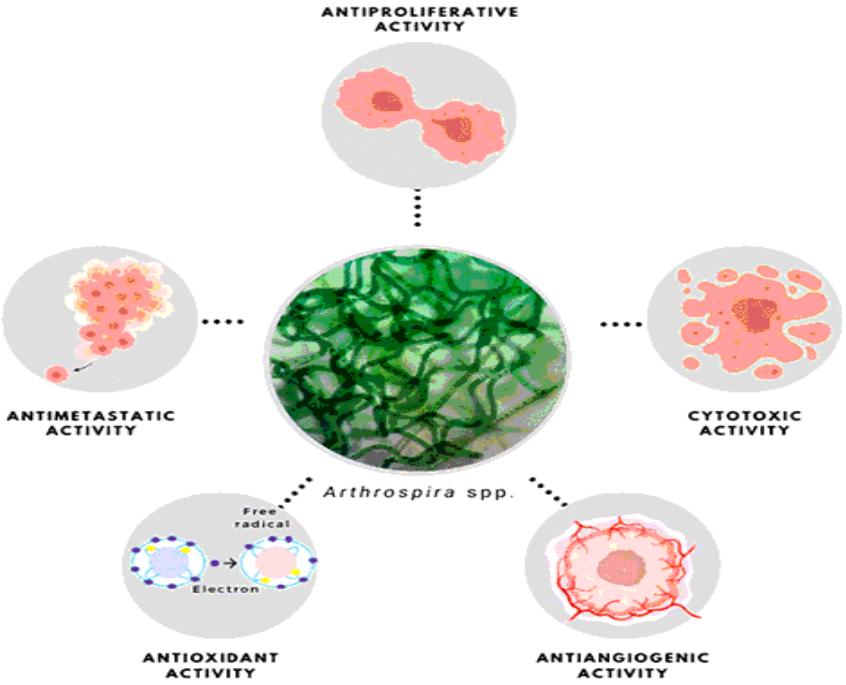
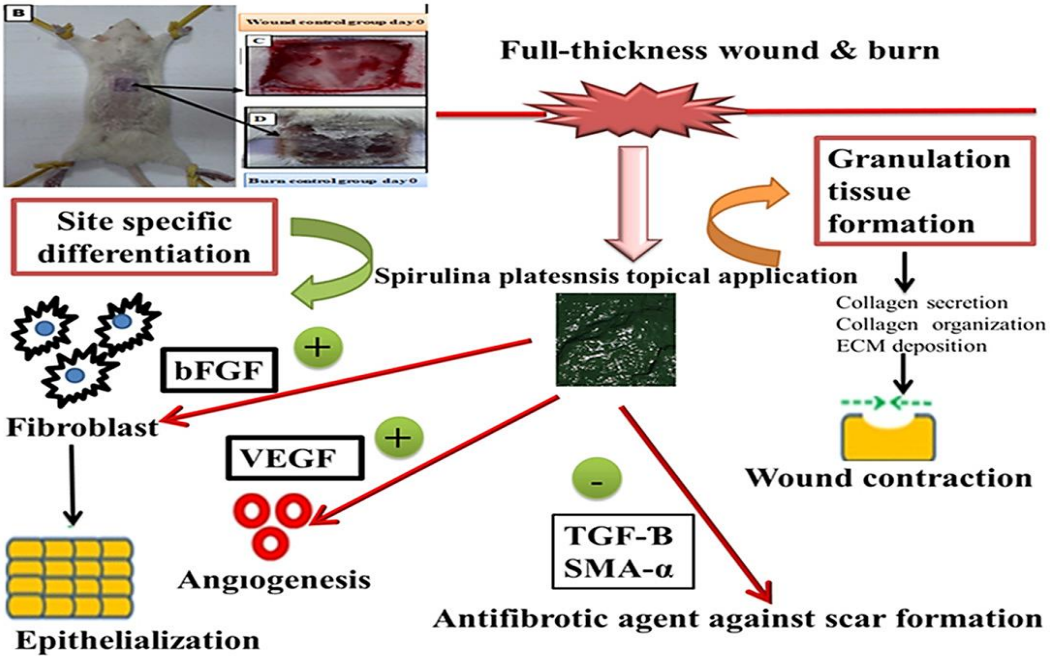


Fig.2 *Spirulina platensis* wound healing mechanism (Elbialy *et al*., 2021)



Similarly, the administration of *spirulina* has resulted in a significant reduction in fasting blood glucose (FBS), total cholesterol (TC), LDL-C, insulin, and very-low density lipoprotein cholesterol (VLDL-C) levels and a significant increase in high-density lipoprotein cholesterol (HDL–C) levels in patients with metabolic syndrome and related disorders (Hamedifard *et al.*, 2019). Decreases in blood pressure and plasma lipid concentrations, especially triacylglycerols and low density lipoprotein-cholesterol have been demonstrated as a result of oral consumption of *Spirulina*. It has also been shown to indirectly modify the total cholesterol and

high density lipoprotein cholesterol values and inhibits the intestinal absorption of dietary fat by inhibiting pancreatic lipase activity (Mansoreh and Laleh, 2016).

Anti-inflammatory effects of spirulina

Obesity has been closely linked to inflammation, hyperlipidaemia and insulin resistance (Shah *et al.*, 2008). This may be due to the fact that adipose tissue secretes numerous biologically active substances like adipokines and chemokines, which play an important role in inflammation and the development of atherosclerosis (Skrypnik *et al.*, 2017). The phycocyanin in spirulina contains a light-harvesting chromophore called phycocyanobilin, which is capable of inhibiting nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) oxidase, a significant source of oxidative stress in adipocytes playing a key role in inducing insulin resistance and shifting adipokine and cytokine production in hypertrophied adipocytes. Thus, by suppressing adipocyte oxidative stress, spirulina may lead to systemic anti-inflammatory and insulin-sensitising effects (Prokudina *et al.*, 2017; DiNicolantonio *et al.*, 2020).

Effects of Spirulina on Skin health

Having immune supporting phytochemicals make *Arthrospira platensis* such an attractive source for food, pharmaceutical and cosmetic industries (Macias-Sancho *et al.*, 2014). An enzyme, tyrosinase, play a vital role in the synthesis of melanin (crucial for preventing UV damage) and consequently for coloring hair, skin and eyes. This copper-containing metalloenzyme catalyzes the first two reactions of melanin synthesis, the hydroxylation of L-tyrosine to 3, 4-dihydroxyphenylalanine (L-DOPA) and the oxidation of L-DOPA to Dopaquinone. In addition to pigmentation of skin, hair and so on, tyrosinase also takes place in the browning of vegetables, the sclerotization of cuticle and the formation of neuromelanin that contributes to neurodegeneration associated with Parkinson's disease (Sahin, 2018). As a result of its key role in above mentioned processes (hyperpigmentation, neurodegeneration disorders, browning vegetables, etc) tyrosinase inhibitors have potential applications in cosmetics, medicine and agriculture (Si *et al.*, 2012). Widely used typical tyrosinase inhibitors exert their functions in two specified mechanisms; one of them is copper chelation within the active site and the other one is obstructing the substrate-enzyme interactions (Wang *et al.*, 2014). The use of most known inhibitor, hydroquinone, in cosmetic products is forbidden in European Union, as a result of the detailed investigations carried out (Akhtar *et al.*, 2015). The Japanese officials also spurred to ban the use of kojic acid in cosmetic products due to its carcinogenicity (Chen *et al.*, 2015). In this regard, owing to high toxicity, low stability, poor skin penetration, insufficient activity, and so on new tyrosinase inhibitors without side effects need to be identified.

Antioxidant defence of the skin is dependent on synergistic effects of different antioxidants like vitamins (Vit C, Vit E isoforms), nutrition and endogenous enzymes (superoxide dismutase: SOD and catalase, and GSH peroxidase: GPx) (Nege *et al.*, 2020). According to Gunes *et al.*, (2017), *S. platensis* is a microalga with high phycocyanin and the pigment phycocyanin has been largely used as a natural blue colourant in cosmetics (Gunes*et al.*, 2017).In this context, a recent trend is using *Spirulina* food supplements as “nutricosmetics” that not only help to prevent diseases and become healthier, but also they enhance the natural beauty of skin, nails and hair (Ragusa *et al.*, 2021).

This review highlights the health benefits of *Spirulina* with its specific mechanisms and the active chemicals as a source of potential pharmaceuticals. *Spirulina* has the capability to prevent cell damage through containing both enzymatic and non-enzymatic antioxidant defense system that counteract the biochemical abnormalities of different diseases.

The antioxidant activities of Spirulina could be also attributed to the presence of two main phycobiliproteins ingredients: phycocyanin and allophycocyanin that are acting mainly against superoxide radicals. *Spirulina* is reported to have a hepatoprotective, neuroprotective, nephroprotective and anti-diabetic potential through normalizing the level of antioxidant and glutathione metabolizing enzymes, managing hypercholesterolemia and hyperglycerolemia by lowering the contents of total lipid and triacylglycerol, lowering blood glucose level and improving insulin resistance.

Presence of phycocyanin and polysaccharides in high concentration gave the ability of *Spirulina* to inhibit carcinogenesis and protect DNA from damage and to exhibit a promising anti-inflammatory activity. Spirulina also found to possess an immunomodulatory effects by enhancing the functions of cells of the immune system, phagocytic and lysozyme activities and improving the hematological parameters. Also, further studies should

be done to evaluate the safety of Spirulina and its extracts in order to make new approach for considering their use in medicinal purposes and related application.

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How to cite this article:

Yiglet Mebrat. 2022. Medical Application and Biochemical Mechanisms of *Spirulina platensis* for Human Benefit. *Int.J.Curr.Res.Aca.Rev.* 10(06), 89-100. doi: https://doi.org/10.20546/ijcrar.2022.1006.008