

ANTICANCER PROPERTIES OF BLUE GREEN ALGAE *SPIRULINA PLATENSIS* – A REVIEW

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ABSTRACT

Many public health problems are caused by infectious agents like microbial organisms including virus, bacteria and fungi, life style and environmental factors. The most dreadful diseases like tuberculosis, diabetes, many viral infections, heart diseases and cancer are causing human deaths worldwide. Cancer is a complex, multistep process and multi-factorial in origin. Cancer causing agents called carcinogens transform a normal cell to tumor or cancerous cell. Life style, food habits, job factors, environmental factors and hereditary mutations plays major role in carcinogenesis. Consumption of Tobacco products, chewing of betel nut, Alcohol, high dietary fat, red meat, imbalanced diet, canned and preserved food, deep fried and junk food, Cigar smoking, exposure to smoke contents of cigarette, radiation for a longer period, lack of adequate physical activity, are main causes of tumorigenesis and increase in rate of cancer incidences.

Persons working in cement factory, welding works, wood works are more susceptible to transformation and development of tumor. Biological microorganisms such as bacteria and viral infections also contribute nearly 19% of cancers. Chemical drugs used in the treatment or cancer therapy are leading to side effects. Therefore, there is a need to develop safe, effective and novel drugs. Research findings of earlier studies indicate that the *Spirulina platensis* exhibits clinical significance especially anticancer activity.

KEYWORDS: Anticancer, Phycocyanin, Spirulina, Chemoprevention, Phycobiliproteins, Antitumor, Cancer

INTRODUCTION

Mutations, alterations at chromosomal, DNA and gene level take place due to various molecular mechanisms such as aberrations, gene translocation, gene amplification, gene insertion, gene deletion and Involvement of proto-oncogenes, oncogenes and tumor suppressor genes and their products also contributes more in carcinogenesis. They cause DNA damage leading to produce either high amount or hyperactive oncoproteins. Carcinogenic factors induce loss of function of TSG and gain of function of proto-oncogenes and oncogenes results transformation. Cell signaling process mediated by oncoproteins or TSG proteins causes loss of control on DNA replication, cell growth, cell proliferation and apoptosis. Normal cell signaling cascade is disrupted by several carcinogenic mediators leading to neoplasm. Tumor cells invade through blood into various parts of body, metastasis leading to cancer or malignancy. Angiogenesis process helps tumor cells to survive by providing required nutrients. Impairment of apoptosis makes cell immortal.

The cancer occurrence and annual report on cancer in the USA is provided every year in collaboration with the National Cancer Institute (NCI), American Cancer Society (ASC), North American Association of Central Cancer registries (NAACCR) and Centers for Disease Control and prevention (CDC). The cancer incidences are increased worldwide (Christie Eheman, *et al.*,2012). Mostly all forms of cancers 80- 90% are caused by environmental factors (Damodar *et al.*, 2011).The cell mediated immunity is affected due to the physiological aging of human immune system leading to the cancer development and then infections (Clifford 2000). The death caused by all types of human cancer is to

be associated with nutrition and diet (Doll and Peto, 1981; World cancer research fund, National Academy of sciences (NAS, NRC.1989).

Treatment methods are associated with side effects and moreover cost effective. In case of radiation therapy, normal cells also die due to lack of specificity over cancer cells. Radiation fails in recognition of normal cells from abnormal cells. Therefore, researchers are focusing on identification and development of new diagnostic devices, safe and potential, natural cancer drugs. Most of the medicinal plants and their products are the natural source of therapeutic agents.

The vegetables and fruits containing antioxidants vitamin C, E, β -Carotene and they are having role in protecting from different forms of cancers. Herbs and spices like garlic also contribute as an anticancer agent (Ranjani and Ayya Raju, 2012).

Natural compounds isolated from plants are having multiple uses with clinical significance such as immunomodulatory, hypoglycemic, antioxidant, anti-inflammatory, antimicrobial, antibacterial, antiviral, chemopreventive and anticancer properties. The microalgae applications mainly for biodiesel production but also in the fields of food, feed, therapeutics and cosmetics in future increased significantly (Olivier Pignolet *et al.*, 2013).

The pharmaceutical importance of bioactivities of cyanobacterium including antiproliferative, antitumor, antifungal, antibacterial, antimalarial, antiviral, antimycotics, cytotoxicity, multi-drug resistance reversers and immunosuppressive agents (Jalaja Kumari *et al.* , 2011; Rakhi Bajpai Dixit & M. R. Suseela (2013). Blue green algae, *Spirulina* display antitumor activity against many cancers both in human and animal systems.

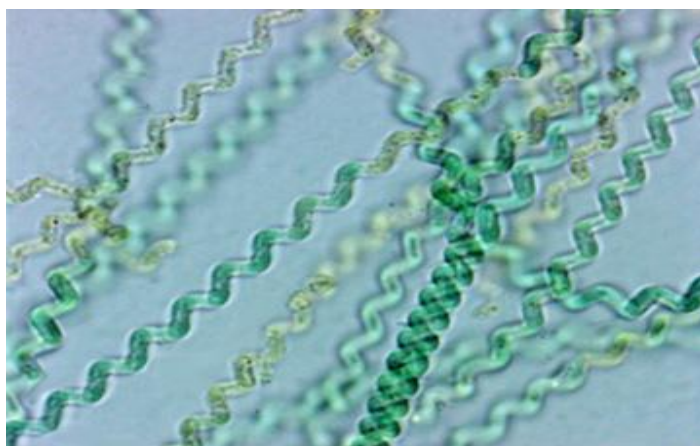


Figure 1: Filamentous Structure of Cyanobacterium, *Spirulina platensis* (from: fmp.conncoll.edu/ Available Online; <http://www.spirulinasource.com/library/health-library/>)

Cyanobacterium, *Spirulina platensis* is a microbial, photosynthetic filamentous algae possessing potential clinical importance (figure 1). In this context, *Spirulina platensis* is also one of the important ‘super food’ with pharmaceutical and nutraceutical properties. *Spirulina* contains many bioactive compounds with therapeutic activity including antitumor property. *Spirulina platensis* contains approximately 65% of proteins, 20% of carbohydrates, 7% of minerals, 5% of lipids and 3% of moisture (Table.1). *Spirulina platensis* possesses with many active biomolecules such as glycolipids, polysaccharides, pigment proteins and aminoacids.

The cancer treatment therapies causing side effects and are most dangerous than cancer. In the preventive or treatment methods using natural products, help avoiding side effects. From the available literature suggests that *Spirulina* may protect from various types of cancers via it acts on immune system, repair of DNA, antioxidant property. Available literature says further research is required.

Table 1: Nutritional Profile of Cyanobacterium, *Spirulina* Powder (Taken from Online; <http://www.spirulinaresource.com/library/health-library/>)

Chemical Composition %		Physical Properties		Pigments
Protein	60-65	Appearance	Fine powder	Chlorophyll <i>a</i>
Carbohydrates	15-20	Colour	Blue green	c-phycoyanin (C-PC)
Lipids	4-5	Odor and taste	Mild like weed	Allophycocyanin (APC)
Minerals	6-7	Particle size	64 mesh through	Phycocerythrin (PE)
Moisture	2-3	Digestibility	83 - 84%	Carotenes, Betacarotene xanthophyll

Anticancer Properties of *Spirulina platensis*

In recent research, scientists are focusing on utilizing natural products in conventional cancer treatment (Blaylock, 2000). Recent advances in research helps in development of various novel anticancer agents. Several natural products and their synthetic derivatives of marine organisms are identified as anticancer drugs (Luke Simmons et al., 2005). The antioxidant properties of various forms of algae and their anti-inflammatory, antinociceptive, and anti-cancer effects were reviewed by Jin-Ching Lee *et al.*, (2013). An inhibitory effect of *Spirulina* algae on oral carcinogenesis evaluated that the chemopreventive effect of *Spirulina fusiformis* in reversing oral leukoplakia in pan tobacco chewers in Kerala, India (Babu, *et al.*, 1995). In kerala, Mathew *et al.*, (1995), studied the effect of *spirulina* supplementation on human, who (use) pan tobacco chewers with oral leukoplakia and observed that regression of lesions.

Constituents of *spirulina* may be responsible for this (table: 2). Not only in developing countries, even in the developed countries also tobacco use is the cause of cancer and incidence of 30% of cancer was observed. And tobacco has significant influence on lung and oral cancer (Garrison and Somer, 1995). Studies made by Chen and Zang (1995) says that the 1,2-dimethyl hydrazine (DMH) under aberrant crypts in the rat colon was reduced by *Spirulina*. Intravenous injection of Radachlorin, obtained significant to full tumor regression. Radachlorin is a photosensitizer, isolated from *S. platensis* (Privalov *et al.*, 2002).

The enhanced antitumor activity of natural killer (NK) cells in rats by the hot-water extract of *S. platensis* (Akao, *et al.*, 2009). *S. platensis* extract causes cancer regression of squamous cell carcinoma progression induced by 0.5% of 7, 12- dimethylbenz[a]anthracene (DMBA) of male golden Syrian hamsters (Grawish, *et al.*, 2011). The ultrasonic extraction of *Spirulina maxima* exhibited potential anticancer activity. The extract is effective against different types of human cancer cell lines such as lung (A549), liver (Hep3B), stomach (AGS) and breast (MCF-7) cell lines (Sung-Ho Oh *et al.*, 2010). Karkos *et al.*, (2011) that the *Spirulina platensis* is having anticancer properties are may be due to two important activities and they are antioxidant and immune-modulation activities. *Spirulina (Arthrospira)* shows antitumor, anticancer and antimicrobial (antibacterial, antifungal, and antiviral) activities via the production of valuable products, phycobiliproteins including c-phycoyanin (C-PC), phycocyanobilin, allophycocyanin (APC). (Abdulmumin A. Nuhu, 2013).

Table 2: Anticancer Properties of *Spirulina platensis*

S No	Author & Year	Name of the Cancer	Mechanism	Name of the Compound / Extract	Experimental Organism
1	DIC, Japan, 1982,	Liver	Anticancer	Phycocyanin	mice
2	Schwartz et al., 1987	Oral –squamous cell carcinoma	cytotoxic and cytostatic activity	<i>Spirulina</i> Phycocyanin	Human and hamster
3	Schwartz and Shklar, 1987	Squamous cell carcinoma (DMBA induced)	Total tumor regression	<i>Spirulina</i> Dunaliella Extract	Hamster
4	Schwartz et al., 1988	Oral buccal pouches tumor	Immune response	<i>Spirulina</i> Dunaliella Extract-administration orally	Hamster
5	Lisheng et al., 1991	Hepatoma	Inhibited proliferation of absctic hepatoma cells	<i>Spirulina</i> Polysaccharide extract	Mice

Table 2: Contd.,

6	Hayashi et al., 1993	HeLa cells	Cytotoxic	Water extract	<i>In vitro</i>
7	Chen and Zhang, 1995	Colon (Dimethylhydrazine: DMH)	The no. of aberrant crypts reduced significantly	Whole <i>Spirulina</i> feed	Rats
8	Babu, et al., 1995; Mathew et al., 1995	oral leukoplakia	Combined antioxidant and immune modulation	<i>Spirulina</i> supplementation	Human
9	Mishima et al., 1998	Lung cancer	Marked decrease of lung cancer; anti-heparanase activity inhibits metastasis and invasion	Ca- Spirulan (Ca - SP 's)	Mice
10	Liu et al., 2000	Leukemia	Inhibited growth of K562 leukemia cells	<i>Spirulina</i> C-Phycocyanin	Mice
	Li et al., 2006	caspase dependent apoptosis	HeLa cells	C-phycocyanin (C-PC)	<i>In vitro</i>
11	Chen and Wong, 2008	human melanoma A375 cells and human breast adenocarcinoma MCF-7 cells	Apoptosis and antiproliferative agent	selenium-containing phycocyanin (Se-PC)	<i>In vitro</i>
12	Akao, et al., 2009	B16 melanoma	natural killer (NK) cells dependent tumoricidal activity	Hot water extract	Human, mice
12	Sung-Ho Oh et al., 2010	Lung, liver, stomach and breast cell lines	Not known	<i>Spirulina Maxima</i> ultrasonic extraction	<i>In vitro</i>
13	Grawish, et al., 2011	squamous cell carcinoma induced by 0.5% of 7, 12-dimethylbenz[a]anthracene (DMBA)	Tumor regression	<i>Spirulina platensis</i> extract	Hamsters
14	Parages, et al., 2012	B16 melanoma cells - Indirectly helps in oral cancers	production of macrophage - tumor necrosis factor- α (TNF- α)	Polysaccharides from <i>S. platensis</i>	<i>In vitro</i>

β - Carotene

Green and yellow vegetables are important foods for good health. One of the most well known important natural anti-cancer substances is beta carotene NCI, USA and as known antioxidant. Spinach and Kale with their dark green leaves, broccoli, carrots, cantaloupes, squash, papayas and pumpkin all contain this important substance. *Spirulina* is very rich in beta-carotene (Harald W. Tietze, 2004). Beta carotene significantly inhibits the formation of squamous cell carcinoma (Schwartz., et al 1986). *Spirulina*, Dunaliella algae prevents tumor development. Studies related to use of beta carotene on animals indicating that a smaller but statistically significant reduction in tumor number and size (Schwartz, et al., 1988; Annapurna et al., 1991).

Polysaccharides

The water soluble polysaccharides isolated from *Spirulina* enhanced both the repair activity of radiation damaged DNA excision unscheduled DNA synthesis and exhibited enhanced activity of endonuclease significantly (Qishen, et al., 1988). The polysaccharides isolated from *Spirulina platensis* extract inhibited DNA synthesis of sarcoma 180 and ascetic hepatoma cells and inhibited the proliferation of ascitic hepatoma cells of mice (murine model) (Lisheng et al., 1991).

Calisium spirulina (Ca-SP) is a polysaccharide of *Spirulina platensis* inhibited tumor invasion and metastasis caused decrease of lung tumor colonization of B16-BL6 cells in a spontaneous lung metastasis model (Mishima *et al.*, 1998). The polysaccharide and phycocyanin obtained from *Porphyra yezoensis* are useful in the treatment of human cancers (Lu-Xi Zhang *et al.*, 2011). The presence of acidic polysaccharides from *A. platensis* was observed that the high amount of production of macrophage - tumor necrosis factor- α (TNF- α) dependent tumoricidal activity. (Parages, *et al.*, 2012). The suppression of glioma cell (murine RSV-M) growth by complex polysaccharides from *Spirulina* via partial regulation of interleukin-17 production and downregulating angiogenesis (Kawanishi, *et al.*, 2013). The selenium nanoparticles (SeNPs) with *Spirulina* polysaccharides (SPS) named SPS-SeNPs may be a potential candidate against human cancers as a chemopreventive and chemotherapeutic agent (Fang Yang *et al.*, 2012).

Phycocyanin (PC)

Spirulina platensis possessing phycobiliproteins like C-PC, APC and PE and they are biologically active in phycobilisome. Oral administration of PC of *Spirulina* cause increase in the survival rate of mice with live tumor cells (Dainippon Ink and chemical Inc. (DIC) 1983). The phycocyanin isolated from *Spirulina platensis* exhibited anticancer activity against squamous cell carcinoma (Schwartz *et al.*, 1987). The effect of *Spirulina* and *Dunaliella* extract on oral cancers in hamster. From Schwartz and Shklar (1987) studies observed that the regression of tumor induced by DMBA (dimethylbenz (a)-athracine)-induced squamous cell carcinoma in hamster. The oral administration of *Spirulina* and *Dunaliella* extract prevented tumor development in hamster, due to immune response algae extract prevents cancer development and destroys developing malignant cells and algae extract is not toxic to normal cells. The inhibition of growth and cell viability of human leukemia K562 cells by C-phycocyanin (C-PC) isolated from *Spirulina platensis* and due to involvement of different types of mechanisms (Liu *et al.*, 2000).

C- phycocyanins (C-PC) is a major biliproteins of *Spirulina platensis* has radical scavenging and antioxidant properties. C-PC is a inhibitor of cox - 2 (cyclooxygenase - 2), induces apoptosis (*in vitro*) and exhibits anti inflammatory and anticancer properties (Reddy *et al.*, 2003). The increased phycocyanin of *S. platensis* induces apoptosis by the expression of CD59 proteins in HeLa cells (Li *et al.*, 2005). The C-PC induces apoptosis in HeLa cells by activating apoptosis enzymes, caspases 2, 3, 4, 6, 8, 9, and caspase - 10. The release of cytochrome c from the mitochondria into the cytosol related to apoptosis in C-PC-treated HeLa cells *in vitro* also. Cell shrinkage, membrane blebbing, microvilli loss, chromatin margination and condensation into dense granules or blocks which suggests that C-PC- caspase-dependent apoptosis (Li, *et al.*, 2006). The PC of *Spirulina platensis* has potential cancer chemopreventive property. The purified selenium-containing phycocyanin (Se-PC) from selenium-enriched *Spirulina platensis* was identified as a potent antiproliferative agent on human melanoma A375 cells and human breast adenocarcinoma MCF-7 cells. The Se-PC induces apoptosis by accumulation of sub-G1 cells, and nuclear condensation, DNA fragmentation in both A375 and MCF-7 cells (Chen and Wong, 2008).

Spirulina platensis - Hematopoiesis

Drugs and its components display potential effect on immune system and immune response and it contributes some extent in treating diseases and killing of cancerous cells. Therefore, the role of *Spirulina platensis* and its components in enhancing the efficiency of immune response is important in treatments and prevention of diseases including cancer to be considered along with anticancer properties of *Spirulina platensis*. The purified polysaccharides and c-phycocyanin of *Spirulina platensis* influence the proliferation and differentiation of committed hematopoietic progenitor cell and can lower the anemic degree of mice (Zang Chengwu *et al.*, 1994). *Spirulina platensis* enhances the immune response by activating

macrophage functions, IL - I production, phagocytosis and particularly by primary response (Hayashi *et al.*, 1994). *Spirulina platensis* extract showed that it enhancing the disease resistance, macrophage phagocytic function and chicken macrophage functions (in-vitro).

Spirulina platensis enhances functions of selected effector cells of immune system of chicken. The available data suggesting that the *Spirulina platensis* exposure improves chickens immune performance without adversely affecting other performance characteristic. The whole cells of blue green algae, *Spirulina platensis* and its lipopolysaccharides were shown to stimulate production of macro and microglobulin antibodies in rabbits (Besednova *et al.*, 1979). *Spirulina* lowers the amount of Ig E in the blood and reduces allergies in the body which in turn normalizes (Evets, *et al.*, 1994). The results obtained by Baojiang *et al.*, (1994) demonstrate that the polysaccharides isolated from *Spirulina platensis* can improve both the specific humoral immunity and the non-specific cellular immunity. The whole *Spirulina platensis* cell extracts were found to enhance immunity by increasing phagocytic activity in animals (Portoni *et al.*, 1996).

CONCLUSIONS

Spirulina platensis is rich with nutrients and active components. *Spirulina platensis* is a super food. The research results of scientists shown that *spirulina* extracts and *Spirulina* and its constituents has role in reducing and preventing different forms of cancers.

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