ABSTRACT

Spirulina, a filamentous and spiral-shaped blue-green alga, contains an array of bioactive compounds and has emerged to be a nutraceutical. It has a unique blend of around 70 biologically active compounds which enhances its therapeutic significance. Its role against carcinogenesis can be attributed to its antioxidant and anti-inflammatory properties due to the presence of ingredients like C-Phycocyanin, β-Carotene, Calcium Spirulan, Linoleic and Linolenic acids. Spirulina extracts were shown to enhance endonuclease activity, DNA repair and induction of apoptosis in cells. Some studies also reported myelosuppression and enhanced immune function. Murine studies indicated there was a possibility of reversing the mechanism of carcinogenesis, particularly in oral, stomach, breast and skin cancers as well as in doxorubicin, cyclophosphamide and DBMA-induced tumours. Spirulina also appeared to reduce cardio-, nephro- and hepato-toxicity in rodents. The chemo and radioprotective effect of Spirulina was also observed in various carcinogenic human cell lines. The C-phytocyanin component was shown to induce apoptosis in HeLa cells in vitro. Commercially available Spirulina is administered as an adjunct to chemotherapy. The evidence of effectiveness of Spirulina in cancer is extremely limited as far as the clinical trials are concerned. The Spirulina studies conducted on various types of carcinogenesis show a degree of similitude but are in a haphazard state. The current anatomization is an attempt on part of the authors to coalesce all the contemporaneous data and create a systematic review.

Keywords: Spirulina, cancer, carcinogenesis, antioxidant, antitumour

INTRODUCTION

In recent years, Spirulina (Arthrospira) has gained the attention of the scientific and medical communities for its properties as a nutraceutical and as a potential source of pharmaceutical drugs. FDA and WHO have aptly called it as ‘Super Food’ or ‘Miracle from the Sea’ (Sharoba, 2014). Spirulina contains an array of bioactive chemicals and has emerged nutraceutical. It is a unique blend of numerous compounds of therapeutic significance. Its role in preventing carcinogenesis can be attributed to its various antioxidant ingredients (Bhatia et al., 2016). Cancer is one of the leading causes of death worldwide. In general, surgical resection is the first line of treatment in early cancers, while chemotherapy is used for treating advanced cancers. Although, modern research has come a long way in treating cancer, the success of chemotherapeutic drugs is limited by multidrug resistance and drug-induced adverse effects (Stavrovskaya, 2000). Conventional chemotherapeutic drugs often target non-specific cells other than cancer cells leading to challenges such as immuno- or myelosuppression (decreased production of blood cells), mucositis (inflammation of the lining of the digestive tract) and alopecia (hairloss), hence, deteriorating the quality of life for a cancer patient (Cassidy et al., 2008). This necessitates discontinuation of chemotherapy or alternate chemotherapy regimens. Immunotherapy and nanotherapy, although promising, are still in their budding stages. Therefore, there has been an upsurge in the field of modern medicine to identify anticancer agents from natural sources, which are effective and produce fewer side effects than the conventional chemotherapies. Plants, especially microalgae, have been an essential source of conventional and clinically valuable remedial preparations (Abd El-Hack et al., 2019). Although, their anti-oxidant properties have been well studied, the data on their anti-cancerous properties is scarce. Complementary and alternative medicine (CAM) encompasses the lifestyle choices where patients resort to plant-based therapeutic amalgams for cancer remission, with fewer or no side effects (Pilkington, 2013).

Spirulina is an unbranched, helicoidal, and filamentous blue-green alga or cyanobacterium belonging to Oscillatoriales family (Karkos et al., 2011; Thanh-Sang et al., 2015; Ge et al; 2019). It grows naturally in myriad of aquatic environments, viz., fresh, alkaline and saline, even in those with extremely high levels of pH (Karkos et al., 2011; Zaid et al; 2015). It is relatively easy to cultivate. The most extensively investigated species of Spirulina include: Spirulina platensis, S. maxima and S. fusiformis that are all edible. They come with high nutritional as well as potential therapeutic values (Deng and Chow, 2010). They are sold commercially under brand names: SBGA (Spirulina BGA), Spiralyne, Spiruline etc. They may be taken orally, as capsules, tablets, powder or as flakes either dried or freeze-dried form (Pilkington, 2013). Spirulina evolved as a bridge between bacteria and green plants. It has been in use as human food since ages. It was reported to be used during the Aztec Civilization (Dillon...
et al., 1995). It was also harvested as protein-rich food in Mexican, African, European and North American cultures (Gantar and Svirec, 2008). But its nutritional potential has been deciphered now due to the advent of modern scientific technology. It became particularly famous when it was endorsed by NASA and ESA, for cultivation and consumption by astronauts in long term space missions (Tadros and NASA, 1988; Zaid et al., 2015). It is being used as food supplement for the last 25 years without any undesirable side effects. *Spirulina* is easily digestible as it lacks cellulose cell walls (Dillon et al., 1995). *Spirulina* has a simple structure but complex composition. It is packed with nutrients of all cadres. These phytochemicals include: Essential amino acids (Methionine and Cysteine), lipophilic vitamins (A, E), hydrophilic vitamins (B1, B2, B3, B5, B6, B8, B9 and C), polysaturated fatty acids such as Eicosapentanoic Acid (EPA) and Docosahexanoic Acid (DHA), minerals (Ca, Fe, Cu, Zn, K, Mg, Mn, Se), phenolic acids, tocopherols and γ-linolenic acid (Kornhauser et al., 1986; Mathew et al., 1995; Abd El-Hack et al., 2019). *Spirulina*’s protein richness is well recognized. It is about 70% dry weight. The amino acid profile of *Spirulina* is comparable to that of an egg, as it contains almost all of the essential ones (Wells et al., 2017). As per the web report by healthline.com, the omega-6 and omega-3 fatty acids are in an approximately 1.5-1.0 ratio.

*Spirulina* is notably rich in unique sulphated polysaccharide, calcium spirulan (Ca-SP), which is reported to enhance DNA repair (Kaji et al., 2002; Pang et al., 1988). It inhibits *in vitro* replication of several enveloped viruses (Hayashi et al., 1996). Other polysaccharides of *Spirulina* such as Rhamnose and Glycogen are easily absorbed by human cells and facilitate release of energy (Karkos et al., 2011).

*Spirulina* may also favour the probiotic *Lactobacilli* in the intestine, enabling the production of Vitamin B6 (Karkos et al., 2011). It is often claimed that *Spirulina* contains vitamin B12, but this is false. It has pseudovitamin B12, which has not been shown to be effective in humans (Watanabe et al., 1999).

*Spirulina* is a complete health booster. Its free-radical scavenging property can be attributed to the presence of natural pigments such as β-carotene, chlorophyll, xanthophylls, phycoerythrin, phycocyanin and allophycocyanin (Gad et al., 2011). They may work individually or in synergy. *Spirulinais* a fantastic source of phycocyanin, a tetrapyrrolic compound, which gives *Spirulina* its blue-green colour and can protect against oxidative damage (Konickova et al., 2014). It can also lower total cholesterol, “bad” LDL cholesterol and triglycerides, while raising “good” HDL cholesterol, as reported by website healthline.com. Beta-carotene, a precursor of vitamin A, was reported to be responsible for anticancer effects (Karkos et al., 2011). In recent years, there has been an upsurge of interest in these biological antioxidants.

Beyond its rich nutritional content, *Spirulina* has been reported to show a wide array of therapeutic properties particularly alleviation of inflammation, oxidative and immune-stress, allergies, rhinitis, diabetes, diabetic nephropathy, hepatopathy, nephrotoxicity, hypercholesterolemia, hyperglycemia, drug-induced toxicities, viral infections, bacterial infections, cardiovascular diseases and cancer (Nuhu, 2013; Thanh-Sang et al., 2015; Bhatia et al., 2016). *Spirulina* seems to enhance immunity. It provides protection against toxic metals and harmful radiation (Zhang et al., 2001). *Spirulina* reduces lipid peroxidation, a key driver of many serious diseases, by reducing oxidative damage to the fatty structures (Nuhu, 2013).

Evidence for effectiveness of *Spirulina* in cancer is extremely limited. The studies carried out to check the efficacy of *Spirulina* against cancer have mostly been on either human cell lines or rodent models. So far, only one *in vivo* clinical study has been conducted on *Spirulina* with regard to cancer patients. It has been highly suggested that antioxidant and immune-modulating properties of *Spirulina* may be a potentcombo responsible for induction of apoptosis, tumour destruction and hence, cancer prevention.

**Spirulina and Cancer Cell Lines**

Numerous investigations supported the knowledge of the chemo-preventive properties of *Spirulina*. In a study by Czerwonka et al., (2018), *Spirulina* extract exerted a cytotoxic and anti-proliferative effect on non-small-cell lung carcinoma cell line, A549. It particularly inhibited progression of cell cycle towards G1 phase and induced apoptosis in these cells. *Spirulina* also showed cytotoxicity against colon carcinoma cell line HCT116 and hepatocellular carcinoma cell line HEPG2 (Zaid et al., 2015). In another study by Ismail et al., (2009) on HepG2, a liver cell line, *Spirulina* appeared to prevent carcinogenesis induced by dibutyl nitrosamine (DBN) precursors.

A selenium-enriched *Spirulina* extract inhibited the growth of MCF-7 breast cancer cells through induction of G1 cell cycle arrest and mitochondria-mediated apoptosis (Ouhtit et al., 2013). A phycocyanin-enriched *Spirulina* extract induced apoptosis in RAW264.7 macrophages through release of cytochrome c from mitochondria independently of Bel-2 expression (Andrade and Costa, 2008). *In vitro* studies on human melanoma A375 cells by Chen and coworkers (2010) demonstrated a beneficial role of *Spirulina* extract in the regression of cancer progression in 7, 12-dimethylbenz[a]anthracene (DBMA)-induced hamster buccal pouch carcinogenesis. *Spirulina* also turned out to be an efficient radical scavenger in the latter.

**Spirulina and Rodent Models**

Immuno histochemical studies by Grawish (2008) and coworkers (2010) demonstrated a beneficial role of *Spirulina* extract in the regression of cancer progression in 7, 12-dimethylbenz[a]anthracene (DBMA)-induced hamster buccal pouch carcinogenesis. *Spirulina* also turned out to be an efficient radical scavenger in the latter.
in vivo study on rodents and in vitro on cell lines were designed to check the efficacy of Spirulina-derived constituents. Ismail et al., (2009) conducted an in vivo study on DBN-induced hepatotoxicity and carcinogenesis in the rat liver and worked out the possible positive effects of Spirulina and the underlying molecular mechanisms on cell proliferation and apoptosis. Konickova et al., (2014) tested the effect of phycocyanobilin (PCB) and chlorophyllin on several human pancreatic cancer cell lines and xeno-transplanted nude mice. The former decreased the proliferation of experimental pancreatic cancer. It was also suggested that the intake of Spirulina might enhance the systemic pool of tetra pyroles in the body.

Spirulina and Clinical Trials

Although there were many animal and in vitro studies in the past, there was only one trial on human subjects. This study looked specifically at the effects of Spirulina on oral carcinogenesis, in particular leukoplakia (Mathew et al., 1995). This volunteer trial examined a cohort of 87 people from India with precancerous lesions – called oral submucosa fibrosis (OSMF) – in the mouth. The study exhibited the effects on the immune system reporting better response (improvement of lesions) to a year’s treatment than to placebo. When these people stopped taking Spirulina, almost half of them redeveloped lesions in the following year.

These reports were reminiscent of the antitumor functions of Spirulina, some of which would be derived from β-carotene and C-phycocyanin, the effective antioxidants (Kornhauser et al., 1986; Lisheng et al., 1991; Palan et al., 1992; and Schwartz and Shklar, 1987). Spirulina reduced myelosuppression and improved immune function after chemotherapy in patients with malignant tumours (Ge et al., 2019).

The Molecule Saga

In the immune histochemical study carried out against the human non-small-cell lung carcinoma A549 cell line by Czerwonka et al., (2018), Spirulina reduced phosphorylation of Akt and Rb proteins, reduced expression of cyclin D1 and CDK4 and increased the Bax to Bcl-2 ratio, a characteristic hallmark of apoptosis.

Ismail et al., (2009) noted high expression of both PCNA and p53 in the liver of DBN-treated rats. On Spirulina intake, both showed significantly reduced expression. This was also accompanied by increased p21 and decreased Rb expression, which could explain inhibition of cell proliferation in rats. In hepatocellular carcinoma cells HepG2, similar effects were reported by Ismail and group. They also noted increased expression of pro-apoptotic Bax and decreased expression of anti-apoptotic Bcl-2, suggesting the onset of apoptosis in the above cell line.

Phycocyanin of Spirulina was shown to inhibit cytochrome P450 (Vadiraja et al., 1998 and Mittal et al., 1999). It was followed by significant rise in hepatic glutathione S-transferase activity (Mittal et al., 1999). Tetrapyroles of Spirulina were reported to enhance glutathione redox status, known to be associated with inhibition of tumor formation (Perchellet et al., 1986).

Effect of Spirulina against DBMA-induced rat breast carcinogenesis was studied by Ouhtit et al., (2014). The reduced incidence of breast tumors was correlated to reduced expression of both Ki-67 and estrogen α. The increased and decreased expressions of Bax and Bcl-2, respectively, were seen in this case too. The induction of apoptosis by phycocyanin appears to follow a similar mechanism in both breast cancer MCF-7 cells (Ouhtit et al., 2014) and hepatocellular carcinoma HepG2 cells (Roy et al., 2007), most likely mediated by the p53-Bax-Bcl-2 pathway. Spirulina also seemed to desquamate the neoplastic cells in DBMA-treated rats, indicating eradication of the tumor.

Yogianti et al., (2014) investigated the antitumor effects of Spirulina extract against UV-B irradiation in the skin of Ogg1 knockout mice. The Ogg1 gene encodes for the repair enzyme for 8-oxo-7,8-dihydroguanine (8-oxoG). Spirulina inhibited the formation of skin tumors in these mice upon repetitive UV-B exposure through down regulation of various kinases, with p38 mitogen-activated protein kinase, in particular.

C-Phycocyanin, a selective cyclooxygenase-2 inhibitor, induced apoptosis in lipopolysaccharide-stimulated RAW 264.7 macrophages (Reddy et al., 2003). C-Phycocyanin also seemed to induce pathologic alteration and DNA fragmentation. It was reported to upregulate Fas and ICAM expression, down regulate expression of Bcl-2, as well as activation of caspases 2, 3, 4, 6, 8, 9, 10 in HeLa and MCF7 cell lines (Medina et al., 2008).

Immunological Aspect

Spirulina is claimed to have host of immune-stimulating effects owing to the presence of unique protein, sugar and lipid moieties. However, the exact molecular mechanisms responsible for these immune responses have not been deciphered yet.

Hot water extract of Spirulina when administered orally enhances NK activation in both adult humans and mice. It boosts immunity through cooperative action of IL-12 and IL-18 for NK-mediated IFN-γ production (Akao et al., 2009). As per Ishii et al., (1999), Spirulina might have a crucial role in developing mucosal immunity during oral cancer through increased IgA production. Spirulina seems to be a great adjunct to chemotherapy in improving immune function and in reducing myelosuppression in patients with malignant tumors (Ge et al., 2019).

Spirulina increases the production of cytokines that form a frontline of defense against viruses and cancer cells. It also seems to increase the production of tumor necrosis factor, interleukin (IL-2), and interferon, and causes CD4+ T-helper cell proliferation. It shows protective effect against toxicity related to various cytotoxic agents, such as doxorubicin-induced cardiotoxicity and cisplatin-induced nephrotoxicity (Pilkington, 2019). The effect of Spirulina on histamine production by mast cells is quite
well established, once again proving its anti-inflammatory nature (Karkos et al., 2011).

**Safety of Spirulina**

*Spirulina* has mostly been considered safe for human consumption through various toxicological studies except for a few. The latter claim the presence of microcystins in *Spirulina* that may cause hepatotoxicity, nephrotoxicity and neurotoxicity (Le et al., 2014; Sharma and Sharma, 2017; and Pilkington, 2019). As per them, in order to have toxin-free biomass of *Spirulina*, it has to be cultivated pure and should not be harvested from a polluted water source that contains toxic heavy metals. Reliable evidence on safety in pregnancy and breast-feeding is not available.

**CONCLUSION**

While more research is needed before any strong claims can be made, *Spirulina* may be one of the potential bio-candidates to be used as an adjunct in chemoprevention of cancer. It is the need of the hour to carry out further studies in order to fully understand the mechanisms underlying cell death caused by *Spirulina* in cancerous cells. Moreover, its excellent diversity of chemical constituents makes it a strong candidate for development of anti-cancer drugs. In a nutshell, *Spirulina* is an anti-cancer superfood worthy of an in-depth study.

**Abbreviations**

CAM – Complementary and Alternative Medicine  
NASA – National Aeronautics and Space Administration (USA)  
ESA – European Space Agency  
DBN – Dibutyl Nitrosamine  
DBMA – 7,12-dimethylbenz[a]anthracene  
IFN-γ – Interferon Gamma  
NK – Natural Killer  
IL – Interleukin

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