Plant Archives
Journal home page: www.plantarchives.org
DOI Url: https://doi.org/10.51470/PLANTARCHIVES.2021.v21.no1.177

SPIRULINA – A WONDER NUTRACEUTICAL AGAINST CANCER: A REVIEW

Kawalpreet Kaur[1] and Saranjeet Kaur[2]
[1]Department of Botany, Sri Guru Gobind Singh College, Sector 26, Chandigarh, India
[2]Post-Graduate Department of Zoology, Sri Guru Gobind Singh College, Sector 26, Chandigarh, India
*Email: kawalpreet38@gmail.com
saranjeet25@gmail.com

(Date of Receiving-20-01-2021; Date of Acceptance-31-03-2021)

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-phycocyanin 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 Oscillatoriaceae family (Karkos *et al.,* 2011; Thanh-Sang *et al.,* 2015; Ge *et al*; 2019). It grows naturally inmyriad 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 Svircev, 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), polyunsaturated 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. *Spirulina*is 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, hyperglycerolemia, 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 potent combo 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 Bcl-2 expression (Andrade and Costa, 2008). *In vitro* studies on human melanoma A375 cells by Chen and Wong (2008) proved that phycocyanin in a selenium-rich *Spirulina* extract is a potent antiproliferative agent. These studies suggest that new promising anticancer natural products from *Spirulina* are possible either enriched singly or in combination with others.

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[α]anthracene (DBMA)-induced hamster buccal pouch carcinogenesis. *Spirulina* also turned out to be an efficient radical scavenger in the latter.

Combined experimental models that comprised of both

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 pyrroles 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 with *Spirulina* 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 hepato cellular 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 P_{450} (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). Tetrapyrroles 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 F as 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 CD^{4+} 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[α]anthracene

IFN-γ– Interferon Gamma

NK – Natural Killer

IL – Interleukin

REFERENCES

Abd El-Hack, M.E.; Abdelnour, S.; Alagawany, M.; Abdo M.; Sakr, M.A.; Khafaga, A.F.; Mahgoub, S.A.; Elnesr, S.S. and Gebriel, M.G. (2018). Microalagae in modern cancer therapy: Current knowledge. *Biomedicine and Pharmacotherapy,* 111(2019): 42-50.

Akao, Y.; Ebihara, T.; Masuda, H.; Saeki, Y.; Akazawa, T.; Hazeki, K.; Hazeki, O.; Matsumoto, M. and Seya, T. (2009). Enhancement of antitumour natural killer cell activation by orally administered *Spirulina* extract in mice. *Cancer Science*, 100(8):1494-1501.

Andrade, M.R. and Costa, J.A. (2008). Outdoor and indoor cultivation of *Spirulina platensis* in the extreme south of Brazil. Zeitschrift fur Naturforschung C, *Journal of Biosciences*, 63(1-2): 85-90.

Bhatia, K.K.; Puri, S.; Kaur, R.; Ahluwalia, K.K. and Ahluwalia, A.S. (2016). Efficacy of *Spirulina* as Hepatoprotectant: A Review. *Vegetos – An International Journal of Plant Research*, 29: 129-136.

Cassidy, J.; Clarke, S.; Diaz-Rubio, E.; Scheithauer, W.; Figer, A.; Wong, R.; Koski, S.; Lichinitser, M.; Yang, T.S.; Rivera, F.; Couture, F.; Sirzen, F. and Saltz, L. (2008). Randomized phase III study of capecitabine plus oxaliplatin compared with fluorouracil/folinic acid plus oxaliplatin as first-line therapy for metastatic colorectal cancer. *Journal of Clinical Oncology*, 26(12): 2006-2012.

Chen, T. and Wong, Y.S. (2008). In vitro antioxidant and antiproliferative activities of selenium-containing phycocyanin from selenium-enriched *Spirulina platensis*. *Journal of Agriculture and Food Chemistry* 56(12): 4352-4358.

Czerwonka, A.; Kalawaj, K.; Slawinska-Brych, A.; Lemieszek, M.K.; Bartnik, M.; Wojtanowski, K.K.; Zdzisinska, B. and Rzeski, W. (2018). Anticancer effect of the water extract of a commercial *Spirulina* (*Arthrospira platensis*) product on the human lung cancer A549 cell line. *Biomedicine and Pharmacotherapy*, 106: 292-302.

Deng, R. and Chow, T.J. (2010). Hypolipidemic, antioxidant and anti-inflammatory activities of microalgae *Spirulina*. *Cardiovascular Therapeutics*, 28(4): e33-45.

Dillon, J.C.; Phuc, A.P. and Dubacq, J.P. (1995). Nutritional value of the alga *Spirulina*. World Review of Nutrition and Dietetics, 77: 32-46.

Gad, A.S.; Khadrawy, Y.A.; El-Nekeety, A.A.; Mohamed, S.R.; Hassan, N.S. and Abdel-Wahhab, M.A. (2011). Antioxidant activity and hepatoprotective effects of whey protein and *Spirulina* in rats. *Nutrition*, 27(5): 582-589.

Gantar, M. and Svircev, Z. (2008). Microalgae and cyanobacteria: food for thought. *Journal of Phycology*, 44(2): 260-268.

Ge, Y.; Kang, Y.K.; Dong, L.; Liu, L.H. and An, G.Y. (2019). The efficiacy of dietary *Spirulina* as an adjunct to chemotherapy to improve immune function and reduce myelosuppression in patients with malignant tumours. *Translational Cancer Research*, 8(4): 1065-1073.

Grawish, M.E. (2008). Effects of Spirulina platensis extract on Syrian hamster cheek pouch mucosa painted with 7,12-dimethylbenz[a]anthracene. Oral Oncology, 44(10):956-962.

Grawish, M.E.; Zaher, A.R.; Gaafar, A.I. and Nasif, W.A. (2010). Long-term effect of *Spirulina platensis* extract on DBMA-induced hamster buccal pouch carcinogenesis (immunohistochemical study). *Medical Oncology*, 27(1):20-28.

Hayashi, K.; Hayashi, T.; Maedaa, M. and Kojima, I. (1996). Calcium spirulan, an inhibitor of envelope virus replication, from a blue-green alga *Spirulina platensis*. Journal of Natural Products, 59(1): 83-87.

Ishii, K.; Katoch, T.; Okuwaki, Y.andHayashi, O. (1999). Influence of dietary Spirulina platensis on IgA level in human saliva. *Journal of Kagawa Nutrition University*, 30: 27-33.

Ismail, M.F.; Ali, D.A.; Fernando, A.; Abdraboh, M.E.; Gaur, R.L.; Ibrahim, W.M.; Raj, M.H.G.and Ouhtit, A. (2009).

Chemoprevention of rat liver toxicity and carcinogenesis by *Spirulina*. *International Journal of Biological Sciences*, 5(4): 377-387.

Kaji, T.; Fujiwara, Y.; Inomata, Y.; Hamada, C.; Yamamoto, C.; Shimada, S.; Lee, J.B. and Hayashi, T. (2002). Repair of wounded monolayers of cultured bovine aortic endothelial cells is inhibited by calcium spirulan, a novel sulphated polysaccharide isolated from *Spirulina platensis. Life Sciences*, 70(16): 1841-1848.

Karkos, P.D.; Leong, S.C.; Karkos, C.D.; Sivaji, N.andAssimakopoulos, D.A. (2011).*Spirulina* in clinical practice: Evidence-based human applications. *Evidence-based Complementary and Alternative Medicine*: e-CAM, 2011: 1-4.

Konickova, R.; Vankova, K.; Vanikova, J.; Vanova, K.; Muchova, L.; Subhanova, I.; Zadinova, M.; Zelenka, J.; Dvorak, A.; Kolar, M.; Strnad, H.; Rimpelova, S.; Ruml, T.; Wong, R.J. and Vitek, L. (2014). Anti-cancer effects of blue-green alga *Spirulina platensis*, a natural source of bilirubin-like tetrapyrrolic compounds. *Annals of Hepatology*, 13(2):273-283.

Kornhauser, A.; Wamer, W.andGiles, A.Jr. (1986). Protective effects of beta-carotene against psoralen photoxicity: relevance to protection against carcinogenesis. *Antimutagenesis and Anticarcinogenesis Mechanism*s, 39: 465-481.

Le, T.M.; Knulst, A.C.andRockmann, H. (2014). Anaphylaxis to *Spirulina* confirmed by skin prick test with ingredients of *Spirulina* tablets. Food and Chemical Toxicology, 74: 309-310.

Lisheng, L.; Baojiang, G.; Jihong, R.; Guangguan, Q.andBotang, W. (1991). Inhibitive effect and mechanism of polysaccharide of *Spirulina platensis* on transplanted tumour cells in mice. *Marine Sciences*, 1991(5): 33-38.

Mathew, B.; Sankaranarayanan, R.; Nair, P.P.; Varghese, C.; Somanathan, T.; Amma, B.P.; Amma, N.S.andNair, M.K. (1995). Evaluation of chemoprevention of oral cancer with *Spirulina fusiformis*. *Nutrition and Cancer*, 24(2): 197-202.

Medina, R.A.; Goeger, D.E.; Hills, P.; Mooberry, S.L.; Huang, N.; Romero, L.I.; Ortega-Barria, E.; Gerwick, W.H.and McPhail, K.L. (2008). Coibamide A, a potent antiproliferative cyclic depsipeptide from the Panamanian marine cyanobacterium *Leptolyngbya* sp. *Journal of the American Chemical Society*, 130(20): 6324-6325.

Mittal, A.; Kumar, P.V.; Banerjee, S.; Rao, A.R.andKumar, A. (1999). Modulatory potential of *Spirulina fusiformis* on carcinogen metabolizing enzymes in Swiss albino mice. *Phytotherapy Research*, 13(2):111-114.

Nuhu, A.A. (2013).*Spirulina* (*Arthrospira*): An important source of nutritional and medicinal compounds. *Journal of Marine Biology*, 2013(1): 1-8.

Ouhtit, A.; Gaur, R.L.; Abdraboh, M.; Ireland, S.K.; Rao, P.N.; Raj, S.G.; Al-Riyami, H.; Shanmuganathan, S.; Gupta, I.; Murthy, S.N.; Hollenbach, A.and Raj, M.H. (2013). Simultaneous inhibition of cell cycle, proliferation, survival, metastatic pathways and induction of apoptosis in breast cancer cells by a phytochemical super-cocktail: Genes that underpin its mode of action. *Journal of Cancer*, 4(9):703-715.

Ouhtit, A.; Ismail, M.F.; Othman, A.; Fernando, A.; Abdraboh, M.E.; El-Kott, A.F.; Azab, Y.A.; Abdeen, S.H.; Gaur, R.L.; Gupta, I.; Shanmuganathan, S.; Al-Farsi, Y.M.; Al-Riyami,H.andRaj, M.H.G. (2014). Chemoprevention of rat mammary carcinogenesis by *Spirulina*. *The American Journal of Pathology*, 184(1):296-303.

Palan, P.R.; Mikhail, M.S.; Basu, J.andRomney, S.L. (1992). Beta-carotene levels in exfoliated cervicovaginal epithelial cells in cervical intraepithelial neoplasia and cervical cancer. *American Journal of Obstetrics and Gynaecology*, 167(6):1899-1903.

Pang, Q.S.; Guo, B.J. and Ruan, J.H. (1988). Enhancement of endonuclease activity and repair of DNA synthesis by polysaccharide of *Spirulina platensis*. Yi Chuan Xue Bao, 15: 374-381.

Perchellet, J.P.; Perchellet, E.M.; Orten, D.K.andSchneider, B.A. (1986). Decreased ratio of reduced/oxidized glutathione in mouse epidermal cells treated with tumour promoters. *Carcinogenesis*, 7(3): 503-506.

Pilkington, K. and CAM-Cancer Consortium (2013).*Spirulina* (blue-green algae) CAM-Cancer Database National Information Center for Complementary and Alternative Medicine (NIFAB), http://www.cam-cancer.org/CAM-Summaries/Herbal-products/Spirulina-blue-green-algae Date of Access: 01-02-2020.

Pilkington, K. and CAM-Cancer Consortium (2019).*Spirulina* (blue-green algae) [online document], http://cam-cancer.org/en/spirulina. February 28, 2017. Date of Access: 01-02-2020.

Reddy, M.C.; Subhashini, J.; Mahipal, S.V.; Bhat, V.B.; Reddy, S.P.; Kiranmai, G.; Madyastha, K.M.and Reddanna, P. (2003). C-Phycocyanin, a selective cyclooxygenase-2 inhibitor, induces apoptosis in lipopolysaccharide-stimulated RAW 264.7 macrophages. *Biochemical and Biophysical Research Communications*, 304(2): 385-392.

Roy, K.R.; Arunasree, K.M.; Reddy, N.P.; Dheeraj, B.; Reddy, G.V.and Reddanna, P. (2007). Alteration of mitochondrial membrane potential by *Spirulina* platensis C-phycocyanin induces apoptosis in the doxorubicin-resistant human hepatocellular-carcinoma cell line HepG2. *Biotechnology and Applied Biochemistry*, 47(3): 159-167.

Schwartz, J. and Shklar, G. (1987). Regression of experimental hamster cancer by beta carotene and algae extracts. *Journal of Oral Maxillofacial Surgery*, 45(6):510-515.

Sharma, N. and Sharma, P. (2017). Industrial and biotechnological applications of algae: A review. *Journal of Advances in Plant Biology*, 1(1): 1-25.

Sharoba, A.M. (2014). Nutritional value of *Spirulina* and its use in the preparation of some complementary baby food formulas. *Journal of Agroalimentary Processes and*

Technologies, 20(4): 330-350.

Stavrovskaya, A.A. (2000). Cellular mechanisms of multidrug resistance of tumour cells. Biochemistry, 65(1): 95-106.

Tadros, M.G. and NASA (1988). Characterization of *Spirulina* Biomass for CELSS Diet Potential. NASA Contractor NCC 2-501. Date of Access: 23 February, 2020. URL: https://ntrs.nasa.gov/archive/nasa/casi.ntrs.nasa.gov/19890016190.pdf

Thanh-Sang, V.; Ngo, D.H. and Kim, S.K. (2015). Chapter 19 – Nutritional and Pharmaceutical Properties of Microalgal *Spirulina*. *Handbook of Marine Microalgae: Biotechnology Advances,* Pages 299-308.

Vadiraja, B.B.; Gaikwad, N.W.and Madyastha, K.M. (1998). Hepatoprotective effect of C-phycocyanin: Protection for carbon tetrachloride and R-(+)-pulegone-mediated hepatotoxicity in rats. *Biochemical and Biophysical Research Communications*, 249(2): 428-431.

Watanabe, F.; Katsura, H.; Takenaka, S.; Fujita, T.; Abe, K.; Tamura, Y.; Nakatsuka, T. and Nakano, Y. (1999). Pseudovitamin B12 is the predominant cobamide of an algal health food, spirulina tablets. *Journal of Agriculture and Food Chemistry,* 47(11): 4736-4741.

Website: 10 Health Benefits of *Spirulina*; Date of Access: 02-02-2020. URL Link: https://www.healthline.com/nutrition/10-proven-benefits-of-spirulina

Wells, M.L.; Potin, P.; Craigie, J.S.; Raven, J.A.; Merchant, S.S.; Helliwell, K.E.; Smith, A.G.; Camire, M.E. and Brawley, S.H. (2017). Algae as nutritional and functional food sources: revisiting our understanding. *Journal of Applied Phycology*, 29: 949-982.

Yogianti, F.; Kunisada, M.; Nakano, E.; Ono, R.; Sakumi, K.; Oka, S.; Nakabeppu, Y. and Nishigori, C. (2014). Inhibitory effects of dietary *Spirulina platensis* on UVB-induced skin inflammatory responses and carcinogenesis. *Journal of Investigative Dermatology*, 134: 2610-2619.

Zaid, A.A.A.; Hammad, D.M. and Sharaf, E.M. (2015). Antioxidant and anticancer activity of *Spirulina* water extracts. *International Journal of Pharmacology*, 11(7):846-851.

Zhang, H.Q.; Lin, A.P.; Sun, Y.and Deng, Y.M. (2001). Chemo- and radio-protective effects of polysaccharide of *Spirulina platensis* on haemopoietic system of mice and dogs. *Acta Pharmacologica Sinica*, 22(12):1121-1124.