

Nutritional and Therapeutic Potential of *Spirulina*

Zakir Khan, Pratiksha Bhadouria and P.S. Bisen*

Department of Biotechnology, J.C. Bose Institute of Life Sciences, Bundelkhand University, Jhansi 284128, U.P., India

Abstract: *Spirulina*, a filamentous cyanobacterium, possesses diverse biological activities and nutritional significance due to high concentration of natural nutrients, having bio-modulatory and immuno-modulatory functions. Different *Spirulina* preparations influence immune system viz. increase phagocytic activity of macrophages, stimulating the production of antibodies and cytokines, increase accumulation of NK cells into tissue and activation and mobilization of T and B cells. *Spirulina* have also shown to perform regulatory role on lipid and carbohydrate metabolism by exhibiting glucose and lipid profile correcting activity in experimental animals and in diabetic patients. Preparations have been found to be active against several enveloped viruses including herpes virus, cytomegalovirus, influenza virus and HIV. They are capable to inhibit carcinogenesis due to anti-oxidant properties that protect tissues and also reduce toxicity of liver, kidney and testes.

Key Words: *Spirulina platensis*, Ca-Sp, Sulpholipid, Cyanovirin-N, Phycocyanin, Beta-carotene, HIV, Immunomodulatory.

INTRODUCTION

Spirulina, a planktonic blue green alga, is a traditional food of some Mexican and African people. They are one of the oldest forms of life growing in warm water alkaline volcanic lakes on earth for the last 3.5 billion years or so. The cellular structure of this alga is spiral shape and similar to that of a simple prokaryote. The most commonly used species of *Spirulina* for nutritional supplements are *Spirulina platensis* (*S. platensis*) and *Spirulina maxima*. This alga has a long history of use as a food and can grow in many places around the world [8]. The alga possesses an amazing ability to thrive in conditions much too harsh for other algae. Habitats with sufficient *Spirulina* growth include the Pacific Ocean near Japan and Hawaii, large fresh water lakes, including Lake Chad in Africa, Klamath Lake of North America, Lake Texcoco in Mexico, and Lake Titikaka in South America. It has a soft cell wall made of complex sugars and protein [2]. Increasing interest is being shown in *S. platensis* by commercial firms because of its global market potential. Several species contain very rich unusual nutritional profile and the bioavailability of various nutrients is very high. Moreover, *Spirulina* species exhibit anti-viral, anti-bacterial, anti-fungal, anti-parasite activities. *Spirulina* preparations contribute to preservation of resident intestinal microbial flora, especially *Lactobacillus* and *Bifidus* that's why it reduces potential problems from opportunistic pathogens like *E. coli*, and *Candida albicans* [46].

Millions of people eat *Spirulina* cultivated in scientifically designed algal farms. Current world production of *S. platensis* for human consumption is more than one thousands metric tons annually. The USA leads world production followed by Thailand, India, Japan and China. Several multinational companies cash the nutritive and therapeutic value of *Spirulina* and is marketed as different trademarks in the form of powder or tablets (Table 1). They are being used for

different purposes like weight loss, fitness, bodybuilding and wellness.

NUTRITIONAL VALUE

The *Spirulina* species contain significant amount of valuable proteins, indispensable amino acids, vitamins, beta-carotene, mineral substances, essential fatty acids, polysaccharides, glycolipids and sulpholipids etc [6-9, 45, 67]. The addition of *Spirulina* to the diet can give a wide range of vital nutrients. Certain features are common to all edible *Spirulina*. They are accepted as functional food, which are defined as products derived from natural sources, whose consumption is likely to benefit human health and enhance performance. *Spirulina* contains high level of various B vitamins, and minerals including calcium, iron, magnesium, manganese, potassium and zinc [6, 13]. They also act as a suitable matrix for biotechnological incorporation of new food trace element preparation. It is a good source essential fatty acid, gamma-linolenic acid (GLA) [9, 45]. 10 gm of *Spirulina* contains over 100mg of GLA [44, 57]. Protein contents of *Spirulina* are very good. It contains up to 70% protein of dry weight [11] which is ten times more than soybean and three times to that of beef protein. It provides full compliment of nine essential amino acids [7]. *Spirulina* is also known to contain high percentage of glycolipids and sulpholipids [30]. It contains 5-8% lipid, from which 40% are glycolipids and 2-5% are sulpholipids which is of great therapeutic value. *Spirulina* contains high amount of bioavailable vitamin B₁₂ and this is particularly important for vegetarians who often find it hard to get this nutrient in their diet [10, 67]. Pigment content including chlorophyll and beta-carotene and vitamin E level is also high [14]. Pigments, called phycobilins, include phycocyanin and allophycocyanin [13, 20, 39]. Phycobilins are similar in structure to bile pigments such as bilirubin. In *Spirulina* cell, phycobilins are attached to proteins; the phycobilin-protein complex called phycobiliprotein [4, 49]. Studies have shown that the nutrients of *Spirulina* are readily absorbed by the body and help to bring nutrient status up to normal level. This is especially true for minerals such as zinc and iron and vitamins

*Address correspondence to this author at the Department of Biotechnology, J.C. Bose Institute of Life Sciences, Bundelkhand University, Jhansi 284128, U.P., India; E-mail: psbisen@gmail.com

Table 1. Some Well Known Companies Marketing *Spirulina*

Name Industry/ Trading company	Product name
Lithose Food MAF Group Company Netherland	Parrys Spirulina
Cyanotech Corporation 73-4460 Queen Kaahumanu, Hwy, suit 102, Kailua, Hawaii 96740	Spirulina Pacifica
Kats Herbs 3206, N. Wisconsin, Racine, WI 53402	Spirulina Tablet (200 mg, 500mg) Spirulina Powder
Jiangsu Cibainian Nutrition Food Co. Ltd. New World Center, B Tower 40 floor, No.88, Zhujiang Road, Nanjing City, Jiangsu Province, China	Spirulina Powder (Mod. No. 100, 112, 114) Spirulina Tablet (Mod. No. 101, 108, 111, 113, 115)
Axem Agro, Food Pvt. Ltd. House 197, Road-1, New DOHS, Mohakhali, Dhaka-1206	Spirulina Energy Drink (200 ml pet bottle) Spirulina Energy Drink (Powder form in sachet pack) Spirulina Tablet (60's pet bottle) Spirulina-Garlic Cople (60's pet bottle)
Evolutionary Health Org. Ltd. P.O. Box 8036 New Polymouth, New Zealand	Organic Spirulina powder Organic Spirulina Tablet Premium Spirulina powder Premium Spirulina Tablet
IMPAG Cosmetic & Pharmaceutical Industry, Prits-Remy Str. 25, 63071, Offenbach, Germany	Spirucom
Nan Pao Pvt. Ltd. Taiwan	Spirulina Tablet (200mg, 500mg) Spirulina Powder
Source Naturals Rainbow light Division of Health Genetics Corp. 9429 Harding Avenue, Unit 12, Surfside, FL33154, USA	Hawaiian Spirulina
Nature's Way 149 Valleyview Drive, China	Chinese Species
Earthrise Nutritionals Inc. (Trading Company)	Spirulina Green Super Food For Life Spirulina Gold
Glenny's (Trading Company)	Spirulina Sunrise Bar
Nutrex	Spirulina Pacifica
GNC (Trading Company)	Fingerprinted Spirulina
Quindao Binhua Industry Co. Ltd. (Trading Company)	Spirulina Tablet Spirulina Powder
Biz Dimention Co. Ltd. (Trading Company)	Spirulina Capsule Spirulina Powder
The Wolfe Clinic (Trading Company)	Spirulina Microclusters

[25]. In rats, *Spirulina* appears to be effective in improving the iron status during pregnancy and lactation [29]. Due to easy bioavailability of nutrients including minerals, it may be a good choice for women during pregnancy and lactation. It is also beneficial for malnourished children [61]. The

WHO has described *Spirulina* as one of the greatest super foods on earth and NASA considers it as an excellent compact food for space travel, as small amount can provide a wide range of nutrients.

Spirulina used for the production of nutritional supplements is either grown in outdoor tanks or harvested from big bioreactors. Nutrient content depends on the location and environment in which the alga grows. Harvesting procedures may also influence the content of vitamins and antioxidants. Percentage of specific components of *Spirulina* can be increased or decreased according to need by growing under regulated growth conditions.

BIOLOGICAL ACTIVITIES OF SPIRULINA

There is no doubt that *Spirulina* is a highly acknowledged nutritious food. Beyond nutritional value, *Spirulina* species possess specific therapeutic properties. Certain species of *Spirulina* have shown to exhibit immunomodulating and biomodulating properties. *S. platensis* has a positive and regulatory effect on immune system. Studies indicated immuno enhancing properties of *S. platensis* in animals and humans. Administration of this alga improved immunological resistance in subjects with various types of cancer, AIDS and other viral diseases.

EFFECTS OF SPIRULINA ON INNATE IMMUNITY

Spirulina showed specific positive effects on innate immune functions and can affect the nonspecific immunity in several ways. Novel sulphated polysaccharides isolated from water extract of *Spirulina*, named as calcium-spirulan (Ca-Sp) showed immunomodulatory and anti-viral activities [36, 52].

Polysaccharides and phycocyanin from *Spirulina* increased immunity in mice by enhancing bone marrow reproduction, thymus growth, and spleen [16, 19, 53, 55, 69]. It was reported that *Spirulina* up-regulates key cells and organs of the immune system improving their ability to function in spite of stress from environmental toxins and infectious agents. Studies on animal models documented that phycocyanin of *Spirulina* stimulates hematopoiesis, especially erythropoiesis by inducing erythropoetin hormone (EPO). There is also evidence (Fig. 1-3) that c-phycocyanin and polysaccharides of *Spirulina* enhance white blood cell production [54, 55]. The percentage of phagocytic macrophages increased when cats were administered water-soluble extract of *S. platensis* [54]. Increased phagocytic activity was also observed in other animals such as mice and chicken [1, 17, 55]. The water-soluble extract of *S. platensis* induces secretion of interleukines such as IL-1 from peritoneal macrophages [17]. The activity of NK cells was also enhanced significantly [19]. Studies on chicken model showed increased tumoricidal activity of NK cells [54-56]. Further studies are needed to establish the exact biochemical mechanisms involved.

EFFECTS OF SPIRULINA ON SPECIFIC IMMUNITY

Experimental studies indicated that *Spirulina* products buildup both the humoral and cellular arms of the immune system Fig. 1-3 [55]. Lymphocytes are key players of specific immunity. *Spirulina* stimulates mobilization of lym-

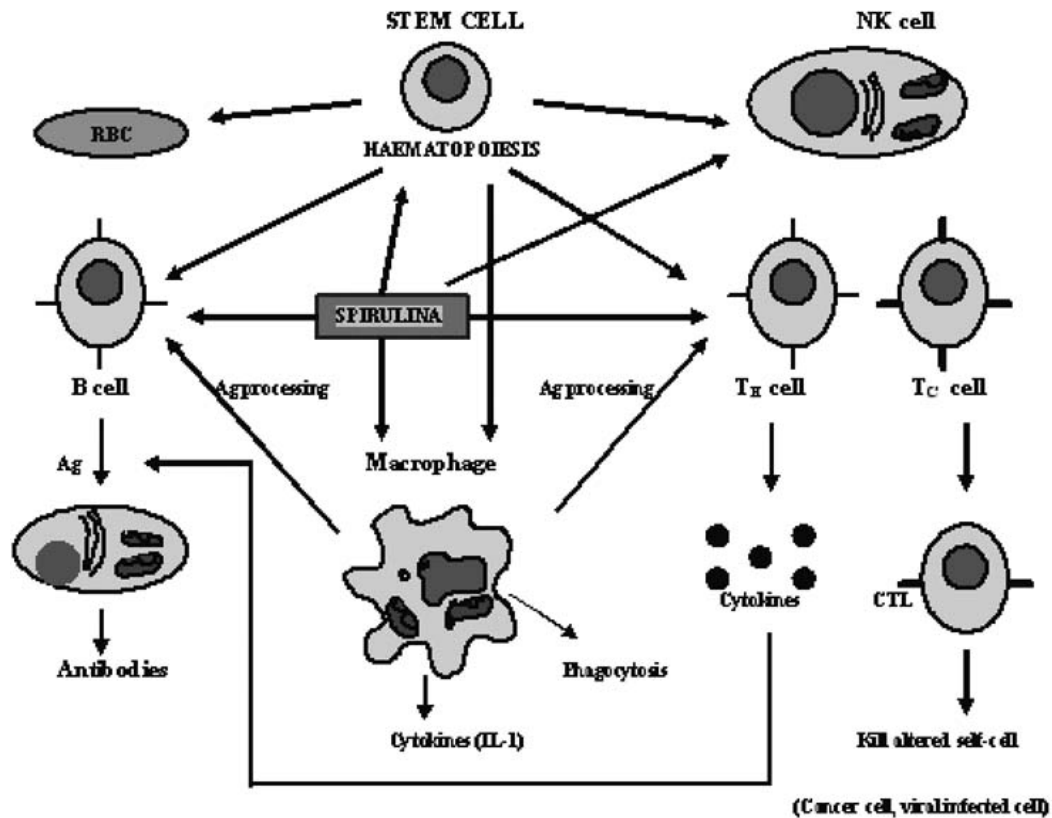


Fig. (1). Effects of spirulina on immune system. Spirulina enhance rate of production of RBCs and WBCs by enhancing hematopoiesis. Spirulina also shows direct effect on both innate and specific immunity. Spirulina activate macrophage and NK cells. Spirulina induce production of the antibodies. Spirulina also activate of T-cells.

phocytes and other immune cells into the blood [36]. It was found that when mice were fed with *Spirulina* there was a significant increase in splenic cells producing IgM antibody [22,23]. Addition of water extract of *Spirulina* also increased proliferation of spleen cells in culture. Several studies on animal model indicated increased production of specific classes of antibodies such as IgA and IgE [16, 44, 55]. It was observed that *Spirulina* possess anti-allergic properties by inducing IgA antibody against food allergens. Studies on rats suggested mast cell inhibiting functions of *Spirulina* [32, 68]. Further studies revealed that phycocyanin of *Spirulina* inhibit release of histamine and functions as anti-inflammatory compound [56]. Recently, it was observed that phycocyanin enhances mucosal immunity [43]. In a significant contrast to its positive role on immune system, the *Spirulina* products have been shown to exacerbate pre-existing autoimmune disease or precipitate autoimmune disease in persons genetically predisposed to such disorder [33]. In mice, it is found that *Spirulina* induces the expression of bcl-2 (an anti-apoptotic gene) in hematopoietic cells that may inhibit apoptosis [35].

ANTI-VIRAL EFFECTS OF *SPIRULINA*

Spirulina exhibits a potent broad-spectrum anti-viral activity. It protects human and monkey cells from viral infection in cell culture [17]. *Spirulina* polysaccharides inhibit

replication of several enveloped viruses including herpes simplex virus, influenza virus, measles virus, mumps virus, human cytomegalovirus and HIV-1 [18, 22, 23, 36]. Hamsters treated with water-soluble extract of *Spirulina* showed better recovery rates when infected with an otherwise lethal herpes virus. *Spirulina* inhibits herpes virus infection at the initial stage of viral cycle [18]. Allophycocyanin neutralizes the enterovirus 71 induced cytoplasmic effects in both human rhabdomyosarcoma cells and in African green monkey cells [63]. *Spirulina* extract can inhibit HIV-1 replication in human derived T-cell lines and in human peripheral blood mononuclear cells [36]. Three compounds of *Spirulina* viz., Ca-Sp, Cyanovirin-N, sulpholipid have shown to exhibit anti-HIV property [22, 23, 36]. However, the mechanism of anti-viral activities of these compounds is poorly understood. It is suggested that Ca-Sp and Cyanovirin-N selectively interfere at the initial stage of viral cycle to the host cells [22, 23, 36]; whereas sulpholipid interferes in the reverse transcription of HIV-RNA (Fig. 2) [36]. Thus *Spirulina* extracts may become useful therapeutics that could help AIDS patients to lead longer normal lives.

ANTI-CANCER PROPERTIES OF *SPIRULINA*

Spirulina preparations have shown to exhibit anticancer activity in a number of experimental models. *Spirulina-Dunalilla* extract significantly reduced the rate of tumor de-

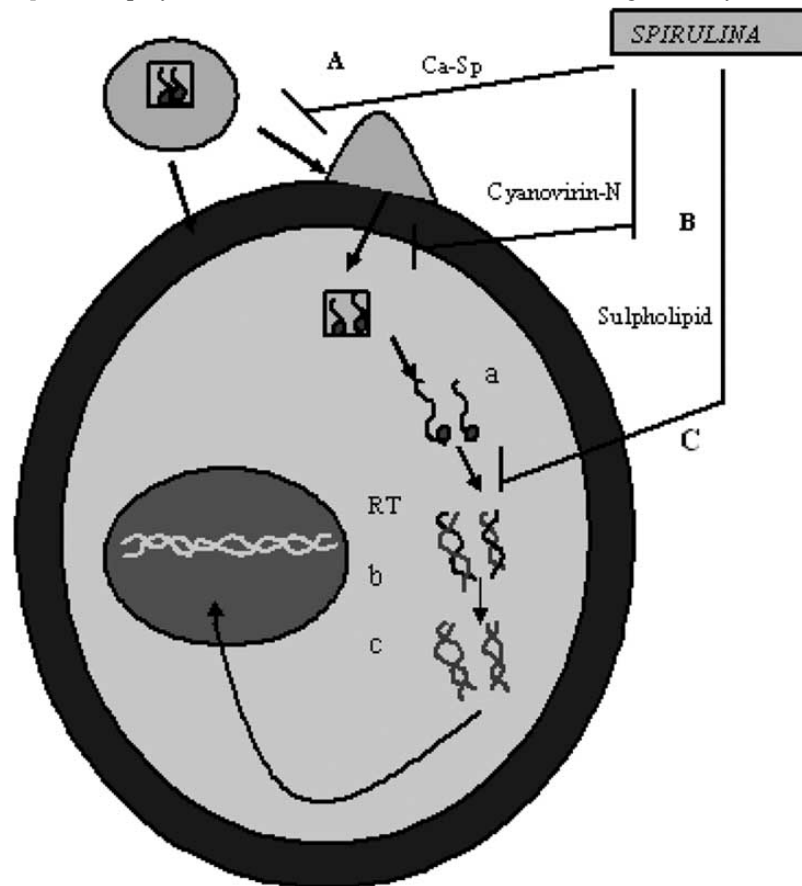


Fig. (2). Effects of spirulina preparations on HIV infection to Target cell. Ca-Sp selectively interferes in the interaction of viral epitopes and host cell receptor. Cyanovirin-N shows inhibitory activity during fusion. Sulpholipid interfere in the reverse transcription of HIV-RNA. (RT = Reverse Transcriptase, a = HIV-ssRNA with RT, b = RNA-DNA hybrid, c = ds DNA).

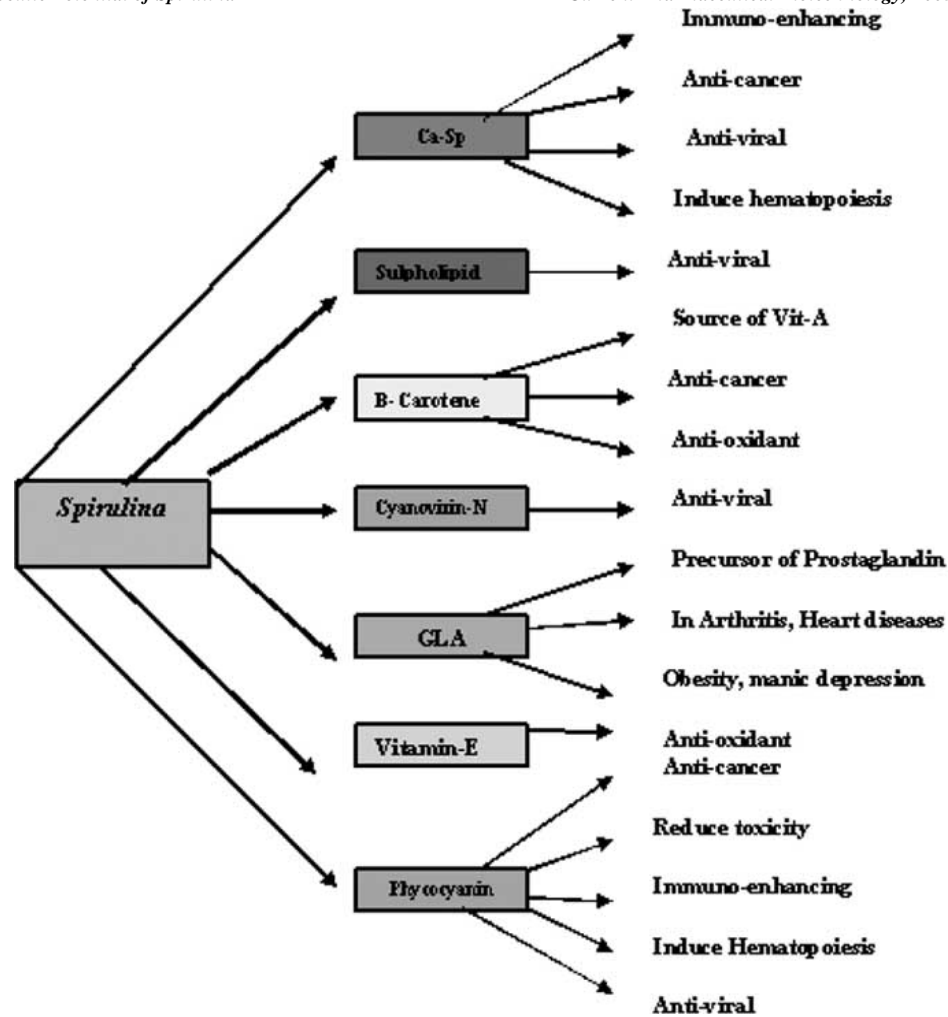


Fig. (3). Therapeutically important compounds of spirulina and its effect.

velopment in hamster buccal pouch [60] and a significant recovery was observed in oral cancer patients [38]. *Spirulina* is the richest natural source of beta-carotene and phycocyanin [20]. Both -carotene and phycocyanin contain anti-cancer activity [48]. Administration of phycocyanin to mice with liver cancer significantly increased their survival rate. Phycocyanin appears to possess hematopoietic function enhancing the thymocyte population, which in turn enhances natural resistance against cancer, ulcer, bleeding piles and other diseases (Fig. 1) [17, 54, 55, 69]. Phycocyanin may also prevent cancer by scavenging DNA damaging agents such as peroxynitrite [4]. Recently, it is reported that c-phycocyanin induced apoptosis of human chronic myeloid leukemia cell line-K562 [64]. The c-phycocyanin treatment to K-562 cells resulted in typical apoptotic characteristics including cytochrome-c release in to cytosol, cleavage of PARP, cell shrinkage, membrane blabbing and DNA fragmentation. The c-phycocyanin treatment suppresses expression of bcl-2 with out affecting Bax (pro-apoptotic gene) expression. Thus, the *Spirulina* seems to induce mitochondrial apoptotic pathway in tumor cells by tilting the bcl-2/Bax ratio towards apoptosis [64]. In an *in vitro* study, sulphated polysaccharides (Ca-Sp) appear to inhibit tumor invasion and metastasis of B16-BL-6 melanoma. This anti-metastasis activity is attributed to blocking the adhesion and

migration of tumor cells to laminin substrate and of the heparanase activity [40]. The Ca-Sp have shown to inhibit proliferation of cancer cells including ascitic heptoma cells and sarcoma cells by interfering in the synthesis of DNA and RNA [34, 53]. The *Spirulina* is shown to possess a modulatory effect on hepatic carcinogen metabolizing enzymes that may involve in anti-tumor [41].

METABOLIC EFFECTS OF SPIRULINA

Spirulina exhibits regulatory effects on lipid and carbohydrate metabolisms [42]. In addition to hypocholesterolemic effect, *Spirulina* also shows hypoglycemic effect [31]. Ninety per cent of diabetics are non-insulin dependent and this syndrome can be effectively controlled with prudent diet therapy. Diet with *Spirulina* supplementation significantly reduces blood sugar levels and glycated serum protein levels confirming the hypoglycemic effect of *Spirulina* [37]. In patients with type-2 diabetes mellitus, *Spirulina* diet lowered fasting blood glucose, postprandial glucose and reduction in the glycosylated hemoglobin (HbA-1c) [47]. Recent studies revealed that *Spirulina* diet enriched with zinc had beneficial effect on basal and postprandial glycaemia, content of cholesterol and triglycerides in type-2 diabetic patients [71].

In humans, *Spirulina* have shown to reduce the level of cholesterol, triacylglycerol and LDL [31, 42]. The solvent fraction of *Spirulina* suppressed cholesterol levels in the serum and liver of rats [5, 24]. *Spirulina* diet in patients with diabetes mellitus resulted in the reduction of atherogenic indices [47]. These findings indicate the beneficial effect of *Spirulina* supplementation in preventing secondary complications in type II diabetics. *Spirulina* is also known to have hypocholesterolemic effect in patients with hyperlipidemic nephritic syndrome [58]. The lipid lowering function may be attributed to its ability to increase the activity of lipoprotein lipase [24]. Another important positive role of *Spirulina* in alleviating heart diseases is its significant potential to lower blood pressure [24].

OTHER EFFECTS OF SPIRULINA

The dietary intake of GLA can help in arthritis, heart diseases, obesity, aging symptoms, manic depression, alcoholism and schizophrenia [21]. *Spirulina* is a good source of GLA and exhibits good anti-oxidant properties [39, 50]. It reduces kidney and testicular toxicity by heavy metals such as mercury, lead and pharmaceutical drugs [59, 61, 62, 69]. *Spirulina fugiformis* significantly inhibits genotoxicity with concomitant increase in the liver enzymatic and non-enzymatic anti-oxidants and detoxification system [39, 50, 51, 62]. The inflammatory responses may partly be due to accumulation of proinflammatory cytokines such as TNF- α and TNF- β and decrease of α -adrenergic receptor function and these functions are shown to be reversed by *Spirulina* [12]. Thus, *Spirulina* possess anti-inflammatory, anti-oxidant, membrane stabilizing functions in various tissues [15, 65, 66]. *Spirulina* preparations are widely used in cosmetics and pharmaceutical compounds due to its antibacterial, anti-fungal, anti-parasite and anti-oxidant activity. *Spirulina* and its enzymatic hydrolyzates appear to promote skin metabolism and reduce scars [26]. Sodium-Spirulin (Na-Sp) and Ca-Sp shows inhibitory effect on the progression of arteriosclerosis by inhibiting vascular smooth muscle cell proliferation [27-28]. Studies also indicate that *Spirulina* might help in weight loss and wound healing [3].

CONCLUSION

Several scientific findings suggested that *Spirulina* proved to be a potential and ideal candidate for conjugative therapy due to the possible synergetic effect of many phytochemicals in whole cell. It has been demonstrated that the use of *Spirulina* and its extracts may reduce cancer and viral diseases. More research is needed to determine its usefulness against AIDS and other killer diseases. *Spirulina* species also have antibacterial and antiparasitic activity. Scientists in India, China, Japan, USA and other countries are studying this remarkable food to unlock its potential. However, it is already clear that this safe and natural food provides concentrated nutritional support for optimum health and wellness. The multifunctional role of *Spirulina* species makes it an ideal natural drug with immense prophylactic and therapeutic properties

REFERENCES

- [1] Al-Batsham, H.A.; Al-Mufarrej, S.I.; Al-Homaidan, A.A. and Qureshi, M.A. (2001) *Immunopharmacol. Immunotoxicol.*, **23**(2), 281-289.
- [2] Balloni, W.; Tomaselli, L.; Giovannetti, L. and Margheri M.C. (1980) Consiglio Nazionale delle Ricerche. Firenze-Academia dei Georgofili, CNR, Tipografia Coppini; pp.49-82.
- [3] Becher, E.W.; Jakober, B. and Luft, D. (1986) *Nutr. Rep Int.*, **33**, 565-574.
- [4] Bhat, V.B. and Madyastha, K.M. (2001) *Biochem. Biophys. Res. Commun.*, **275**(1), 20-25.
- [5] Ble-Castillo, J.L.; Rodriguez-Hernandez, A.; Miranda-Zamora, R.; Juarez-Oropeza, M.A. and Diaz-Zagoya, J.C. (2001) *Life Sci.*, **70**(22), 2665-2673.
- [6] Blinkova, L.P.; Gorobets, O.B. and Batur, A.P. (2001) *Zh. Mikro. Biol. Immunobiol.*, **2**, 114-118.
- [7] Campanella, L.; Russo, M.V. and Avino, P. (2002) *Ann. Chim.*, **92**(4), 343-352.
- [8] Ciferri, O. and Tiboni, O. (1985) *Ann. Rev. Microbiology*, **89**, 503-526.
- [9] Colla, L.M.; Bertolin, T.E. and Costa, J.A. (2004) *Z. Naturforsch.*, **59**, 55-59.
- [10] Dagnelie, P.; Van Staveren, W.A. and Van den Berg, H. (1991) *Am. J. Clin. Nutr.*, **53**, 695-697.
- [11] Dillon, J.C.; Phuc, A.P. and Dubacq, J.P. (1995) *World Rev. Nutr. Diet.*, **77**, 32-46.
- [12] Gemma, C.; Mesches, M.H.; Spesi, B.; Choo, K.; Holmes, D.B. and Bickford, P.C. (2002), *J Neurosci.*, **22**(14), 6114-6120.
- [13] Gireesh, T.; Nair, P.P. and Sudhakaran, P.R. (2004) *Br. Nutr.*, **92**(2), 241-245.
- [14] Gomez-Coronado, D.J.; Ibanez, E.; Ruperez, F.J. and Barbas, C. (2004) *J. Chromatogr. A.*, **1054**, 227-233.
- [15] Gorban, E.M.; Orynychak, M.A.; Virstiuk, N.G.; Kuprash, L.P.; Panteleimonova, T.M. and Sharabura, L.B. (2000) *Lik. Sprava.*, **6**, 89-93.
- [16] Hayashi, O.; Hirahashi, T.; Katoh, T.; Miyajima, H.; Hirano, T. and Okuwaki, Y. (1998) *J. Nutr. Sci. Vitaminol.*, **44**(6), 841-851.
- [17] Hayashi, O.; Katoh, T. and Okuwaki, Y. (1994) *J. Nutr. Sci. Vitaminol.*, **40**, 431-441.
- [18] Hernandez-Corona, A.; Nieves, I.; Meckes, M.; Chamorro, G. and Barron, B.L. (2002) *Anti-viral Res.*, **56**(3), 279-285.
- [19] Hirahashi, T.; Matsumoto, M.; Hazeki, K.; Saeki, Y.; Ui, M. and Seya, T. (2002) *Int. Immunopharmacol.*, **2**(4), 423-434.
- [20] Hu, Z.H. and Liu, Z.L. (2001) *Se. Pu.*, **19**(1), 85-87.
- [21] Huang, Y.S.; Cunnane, S.C.; Horrobin, D.F. and Davignon, J. (1982) *Atherosclerosis*, **41**, 193-208.
- [22] Hyashi, K.; Hyashi, T. and Kojima, J. (1996) *AIDS Res. Hum. Retrovir.*, **12**(15), 1463-1471.
- [23] Hyashi, T. and Hayashi, K. (1996) *J. of Natural Products.*, **59**, 83-87.
- [24] Itawa, K.; Inayama, T. and Kato, T. (1999) *J. Nutr. Sci. Vitaminol.*, **36**, 165-171.
- [25] Johnson, P. and Shubert, E. (1986) *Nutritional Res.*, **6**, 85-94.
- [26] Jorjani, G. and Amirani, P. (1978) *Maj. Iimy Puz. Danisk. Jundi Shap.*, **1**, 14-18.
- [27] Kaji, T.; Fujiwara, Y.; Hamada, C.; Yamamoto, C.; Shimada, S.; Lee, J.B. and Hayashi, T. (2002) *Planta. Med.*, **68**(6), 505-509.
- [28] Kaji, T.; Okabe, M.; Shimada, S.; Yamamoto, C.; Fujiwara, Y.; Lee, J.B. and Hayashi, T. (2004) *Life Sci.*, **74**(19), 243-249.
- [29] Kapoor, R. and Mehta, U. (1998) *Plant Food Hum. Nutr.*, **52**(4), 315-324.
- [30] Kataoka, N. and Misaki, A. (1983) *Agric. Biol. Chem.*, **47**(10), 2349-2355.
- [31] Kato, T. and Takemoto, K. (1984) *Japan Nutr. Assoc. Jour.*, **37**, 321.
- [32] Kim, H.M.; Lee, K.H.; Cho, H.H. and Moon, Y.H. (1998), *Biochem. Pharmacol.*, **55**, 71071-71076.
- [33] Lee, A.N. and Werth, V.P. (2004) *Arch. Dermatol.*, **140**(6), 723-727.
- [34] Lisheng, L. (1991) *Marine Sciences Qindao Chiana.*, **5**, 33-38.
- [35] Liu, X.M. and Zhang, H.Q. (2002) *Yao Xue Xue Bao.*, **37**(8), 616-620.
- [36] Luescher-mattli, M. (2003), *Current Medical Chemistry-Anti-Inflammatory Agents.*, **2**, 219-225.
- [37] Mani, U.V.; Iyer, U.M. and Nayak, U.S. (2002) *J. Medicinal Food.*, **5**(2), 91-96.
- [38] Mathew, B.; Sankaranarayanan, R.; Nair, P.P.; Varghese, C.; Somanathan, T.; Amma, B.P.; Amma, N.S. and Nair, M.K. (1995) *Nutr. and Cancer*, **24**(2), 197-202.

- [39] Miranda, M.S.; Cintra, R.G.; Barros, S.B. and Mancini Filho, J. (1998) *Braz. J. Med. Biol. Res.*, **31**(8), 1075-1079.
- [40] Mishima, T.; Murata, J.; Toyashima, M.; Fujii, H.; Nakajima, M.; Hayashi, T.; Kato, T. and Saiki, I. (1998), *Clin. Exp. Metastasis.*, **16**(6), 541-550.
- [41] Mittal, A.; Kumar, P.V.; Banerjee, S.; Rao, A.R. and Kumar, A. (1999) *Phytother. Res.*, **13**(2), 111-114.
- [42] Nayaka, N.; Homma, Y. and Goto, Y. (1988) *Nutrition Reports Intl.*, **37**(6), 1329-1337.
- [43] Nemoto-Kawamura, C.; Hirahashi, T.; Nagai, T.; Yamada, H.; Katoh, T. and Hayashi, O. (2004) *J. Nutr. Sci. Vitamol.*, **50**(2), 129-136.
- [44] Nichols, B. and Wood, B. (1986) *Lipids*, **3**(1), 46-50.
- [45] Otlés, S. and Pire, R. (2001) *J. AOAC Int.*, **84**(6), 1708-1714.
- [46] Parada, I.L. and Zulpa de Caire, G. (1998) *Int. J. Food Microbiol.*, **45**(31), 225-228.
- [47] Parikh, P.; Mani U.V. and Iyer, U.M. (2001) *J. Med. Food.*, **4**(4), 193-199.
- [48] Peto, R. (1981) *Nature*, **290**, 201-208.
- [49] Pinero Estrada, J.E.; Bermejo Bescos, P. and Villar del Fresno, A.M.:(2001) *Farmacol.*, **56**(5-7), 497-500.
- [50] Premkumar, K.; Abraham, S.K.; Santhiya, S.T. and Ramesh, A. (2004) *Fitoterapia*, **75**(1), 24-31.
- [51] Premkumar, K.; Pachiappan, A.; Abraham, S.K.; Santhiya, S.T.; Gopinath, P.M. and Ramesh, A. (2000) *Fitoterapia*, **72**(8), 906-911.
- [52] Pugh, N.; Ross, S.A.; ElSohly, H.N.; ElSohly, M.A. and Pasco, D.S. (2001) *Planta Med.*, **67**(8), 737-742.
- [53] Qishen, P. (1988) *Chinese J. of Genetics*, **15**(5), 374-381.
- [54] Qureshi, M.A. and Ali, R. (1996) *Immununopharmacol. immunotoxicol.*, **18**(3), 457-463.
- [55] Qureshi, M.A.; Garlich, J.D. and Kidd, M.T. (1996) *Immununopharmacol. immunotoxicol.*, **18**(3), 465-476.
- [56] Qureshi, M.A.; Kidd, M.T. and Ali, A.R. (1995) *J. Nutr. Immun.*, **3**(4), 35-45..
- [57] Roughan, P. G. (1989) *J. Sci. Food Agric.*, **47**, 85-93.
- [58] Samuels, R. (2002) *J. Med. Food.*, **5**(2), 91-96.
- [59] Saxena, P.S. and Kumar, M. (2004) *Indian J. Exp. Biol.*, **42**(10), 998-1002.
- [60] Schwartz, J. and Shklar, G. (1987) *J. Oral Maxillofac. Surg.*, **45**, 510-515.
- [61] Seshadri, C.V. (1993) All India Project, MCRC, Madras.
- [62] Shastri, D.; Kumar, M. and Kumar, A. (1999) *Phytother. Res.*, **13**(3), 258-260.
- [63] Shih, S.R.; Tsai, K.N.; Li, Y.S.; Chueh, C.C. and Chan, E.C. (2003) *J. Med. Viro.*, **70**(1), 119-125.
- [64] Subhashini, J.; Mahipal, S.V.; Reddy, M.C.; Mallikarjuna Reddy, M.; Rachamulla, A. and Reddanna, P. (2004) *Biochem. Pharmacol.*, **68**(3), 453-462.
- [65] Torres-Duran, P.V.; Miranda-Zamora, R.; Paredes-Carbajal, M.C.; Mascher, D.; Ble-Castillo, J.; Diaz-Zagoya, J.C. and Juarez-Oropeza, M.A. (1999) *J. Ethnopharmacol.*, **64**(2), 141-147.
- [66] Upasani, C.D. and Balaraman, R. (2003) *Phytother. Res.*, **17**(4), 330-334.
- [67] Watanabe, F.; Takenaka, S.; Kittaka-Katsura, H.; Ebara, S. and Miyamao, E. (2002) *J. Nutr. Sci. Vitamol.*, **48**(5), 325-331.
- [68] Yang, H.; Lee, E.H. and Kim, H.M. (1997) *Life Sci.*, **61**(13), 1237-1244.
- [69] Zang, H. Q.; Lin, A. P.; Sun, Y. and Deng, Y. M. (2001) *Acta. Pharmacol. Sin.*, **22**(12), 1121-1124.
- [70] Zaretskaia, E.S.; Gmshinskii, I.V.; Mazo, V.K.; Zorin, S.N. and Aleshko-Ozhevskii Iu, P. (2004) *Vopr. Pitan.*, **73**(2): 28-31.
- [71] Zaretskaia, E.S.; Gmshinskii, I.V.; Mazo, V.K.; Zorin, S.N. and Aleshko-Ozhevskii Iu, P. (2004) *Vopr. Pitan.*, **73**(4): 17-20.