

## Spirulina : Potential clinical therapeutic application

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### ABSTRACT

Spirulina or Arthrospira is a blue-green alga that became famous after it was successfully used by NASA as a dietary supplement for astronauts on space missions. It has the ability to modulate immune functions and exhibits anti-inflammatory properties by inhibiting the release of histamine by mast cells. Multiple studies investigating the efficacy and the potential clinical applications of Spirulina in treating several diseases have been performed and a few randomized controlled trials and systematic reviews suggest that this alga may improve several symptoms and may even have an anticancer, antiviral and antiallergic effects.

**Key words:** Spirulina, antiviral activity, antibacterial activity, C-Phycocyanin, Zeaxanthin, Cholesterol Reduction effect, Gamma linolenic acid and Prostaglandin Stimulation.

### INTRODUCTION

**Scientific Name(s):** *Arthrospira platensis* and *Arthrospira maxima* . Family: *Phormidiaceae* **Common Name(s):** Spirulina , dihe , tecuitlatl

*Spirulina* is a microscopic and filamentous cyanobacterium that derives its name from the spiral or helical nature of its filaments. It has a long history of use as food and it has been reported that it has been used during the Aztec civilization. *Spirulina* refers to the dried biomass of *Arthrospira platensis*, an oxygenic photosynthetic bacterium found worldwide in fresh and marine waters. This alga represents an important staple diet in humans and has been used as a source of protein and vitamin supplement in humans without any significant side-effects. Apart from the high (up to 70%) content of protein, it also contains vitamins, especially B<sub>12</sub> and provitamin A (β-carotenes), and minerals, especially iron. It is also rich in phenolic acids, tocopherols and γlinolenic acid. *Spirulina* lacks cellulose cell walls and therefore it can be easily digested<sup>1</sup>. Many toxicological studies have proven *Spirulina*'s safety. *Spirulina* is relatively easy to cultivate but flourishes only in alkaline lakes with an extremely high pH and in large outdoor ponds under controlled conditions. There are only a few areas worldwide that have the ideal sunny climate for production of this alga, including Greece (Nigrita, Serres), Japan, India, United States and Spain. Currently, *Spirulina* can be found in health food stores and is sold mainly as a dietary supplement in the form of health drinks or tablets. Microalgae have been used for more than 10 years as dietary supplements without significant side-effects<sup>2</sup> .

### 2. Taxonomy

The name *Spirulina* comes from a Latin word meaning tiny spiral. *Spirulina* is microscopic, spiral-shaped, vegetable bacteria. *Spirulina* is a genus of the phylum Cyanobacteria which are classified as bacteria. Even though it is single-celled attaining sizes of 0.5 millimeters in length, which makes some individual *Spirulina* cells visible to the naked eye. There are several species of *Spirulina*. The ones most commonly used in nutritional supplements are *Spirulina platensis* and *Spirulina maxima*<sup>3</sup>. They are a significant component of the marine nitrogen cycle and an important primary producer in many areas of the ocean, but are also found in habitats other than the marine environment; in particular cyanobacteria are known to occur in both freshwater,<sup>4</sup> hypersaline inland lakes<sup>5</sup> and in arid areas where they are a major component of biological soil crusts.

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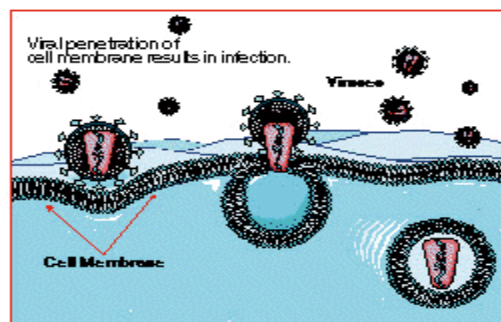
### 3. Research reveals health benefits

An international detective hunt has been underway for 20 years. Researchers in Japan, China, India, Europe and the USA are discovering how and why this microalgae is so effective for human and animal health.

#### Potent Anti-Viral Activity [Fig. I] :

There are several new peer reviewed scientific studies about *Spirulina*'s ability to inhibit viral replication, strengthen both the cellular and humoral arms of the immune system and cause regression and inhibition of cancers. When attacking a cell, a virus first attaches itself to the cell membrane. However, because of *Spirulina* extract, the virus cannot penetrate the cell membrane to infect the cell. The virus is stuck, unable to replicate. It is eventually eliminated by the body by natural defenses. *Spirulina* extracts may become useful therapeutics that could help AIDS patients lead longer more normal lives<sup>6,7,8</sup>. One in vitro study found that calcium *Spirulina* extract interfered with replication of several enveloped viruses, including herpes simplex, cytomegalovirus, mumps and measles viruses, influenza A virus, and HIV-1<sup>7</sup>. Other researchers have discovered a water-soluble extract of *Spirulina* that was shown to inhibit viral cell-penetration and replication of the Herpes Simplex Virus Type 1 (HSV-1) in cultured HeLa cells in a dose-dependent manner<sup>8</sup>. HIV-1 adsorption and penetration were inhibited by an aqueous extract of *Spirulina*, while a crude hot water extract reduced HIV-1 replication.<sup>2</sup> This type of in vitro activity is common to acidic polysaccharides from a variety of sources. Enterovirus is also susceptible to *Spirulina*<sup>9</sup>. *Spirulina* demonstrated some in vitro activity against common human bacterial pathogens, but less than the standard comparator<sup>10</sup>. Another more recent study showed *in vitro* that an aqueous extract of *S. platensis* inhibited HIV-1 replication in human T-cells, peripheral blood mononuclear cells and Langerhan cells<sup>11</sup>.

**Anti AIDS activity :** In 1986, the NCI began studying thousands of types of blue-green algae for effects against the AIDS virus and 100 types of cancer. In



[Fig. I]

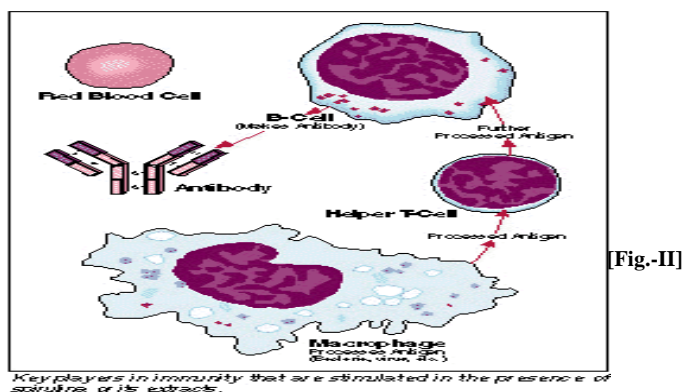
Spirulina prevents viral penetration of cell membrane

1989, the NCI announced that chemicals from blue-green algae were found to be "remarkably active" against the AIDS virus<sup>12</sup>. These are the naturally occurring sulfolipid portions of the glycolipids. Sulfolipids can prevent viruses from either attaching to or penetrating into cells, thus preventing viral infection. These scientists further speculated that if sulfolipids proved effective, used in combination with drugs like AZT, they would be safer and more effective. Scientists used extracts of the blue-green algae *Lyngbya*, *Phormidium*, *Oscillatoria* (a member of the *Spirulina* family) and *Anabaena*. *Spirulina* is known to contain glycolipids and sulfolipids<sup>13</sup>. It contains 5-8% lipids, and of that, about 40% are glycolipids, and 2-5% are sulfolipids<sup>14</sup>. In 1996, NCI scientists announced another extract from the blue-green algae *Nostoc*, *Cyanovirin-n*, could be a broad spectrum virucidal agent against HIV. This unique antiviral protein was selected for further high-priority preclinical development<sup>15</sup>. This has implications for AIDS. Some researchers believe the inability to absorb nutrients in the intestines can cause serious immune deficiency. One strategy for halting the progression of AIDS is based on supplementation (to correct malabsorption) and *Lactobacillus* (to maintain proper intestinal flora and prevent infection)<sup>16</sup>.

**Anti-bacterial Activity :**

This heightened bacterial clearance indicates that *Spirulina* supplementation improves the activity of phagocytic cells, namely monocytes, macrophages, heterophils and thrombocytes in chickens. This bacterial clearance is entailed by entrapment of bacteria by cells of the mononuclear phagocytic system residing in the liver. Apparently, the bacterial clearing within the microenvironment of these organs is increased by the immunopotentiating effect of *Spirulina* due to elevated mononuclear phagocytosis. Therefore, it can be implied that dietary *Spirulina* improves both cell-mediated (T-cell) and mononuclear phagocytic system potential in chickens, allowing them to better resist disease encounters<sup>17</sup>.

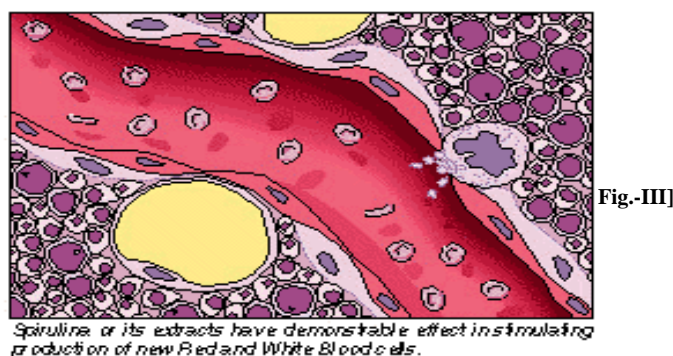
**Immunomodulator & Anticancer Activity [Fig.-II] :**



Part of the global effort to identify natural substances with an immune system boosting or anti-cancer effect focuses on blue-green algae. One unusual phytonutrient in blue-green algae is the natural blue protein pigment, phycocyanin. *Spirulina* is a powerful tonic for the immune system. Medical scientists find it not only stimulates the immune system, it actually enhances the body's ability to generate new blood cells. Feeding studies show even small amounts build up both humoral and cellular arms of the immune system<sup>18</sup>. *Spirulina* accelerates production of the humoral system (antibodies and cytokines), allowing it to better protect against invading germs. *Spirulina* up-regulates the key cells and organs, improving their ability to function in spite of stresses from environmental toxins and infectious agents<sup>19,20,21,17,22,18</sup>. In 1979, Russian scientists published initial research on the immune stimulating effects on rabbits from lipopolysaccharides in *Spirulina*<sup>23</sup>. More recent studies in China and Japan have shown polysaccharide extracts increased macrophage function, antibody production and infection fighting T-cells. In 1991-94 in China, polysaccharides and phycocyanin from *Spirulina* increased immunity in mice by enhancing bone marrow reproduction, growth of thymus and spleen and biosynthesis of serum protein.<sup>19,24,25,21</sup>. In 1993 in Japan, hamsters treated with a polysaccharide extract had better recovery rates when infected with a herpes virus<sup>8</sup>. In 1996, a

water extract unique to *Spirulina*, Calcium *Spirulina*, inhibited replication of HIV-1, Herpes Simplex and other viruses, yet was very safe for human cells. In further 1993-96 studies, chickens fed a diet with less than 1% *Spirulina* showed improved immune performance without any adverse side effects. The whole immune system array of killer cells, helper cells and antibody production was supercharged<sup>17,22</sup>. Similar benefits were found for cats<sup>18</sup>. Researchers are testing the theory that *Spirulina* and its extracts act much like a broad spectrum vaccine against bacteria<sup>26</sup>. In vitro and animal experiments suggest that *Spirulina* and its extracts might be immunostimulatory. Activation of monocytes and macrophages, as well as<sup>27,28</sup>, augmentation of interleukin and interferon production, have also been demonstrated<sup>29</sup>. A clinical study in healthy men found that oral administration of *Spirulina* for 3 months resulted in enhanced interferon production and natural killer cell capacity<sup>30</sup>. C-phycocyanin inhibited platelet aggregation in in vitro experiments<sup>31</sup>. *Spirulina* also has been reported to reduce gastric secretory activity<sup>32</sup>. In research in Japan, phycocyanin was taken orally by mice with liver cancer. This suggests eating phycocyanin may increase survival of cancer stricken organisms, and raises lymphocyte activity<sup>33</sup>. These results suggest phycocyanin acts not by a limited attack on local cancer, but by strengthening the body's resistance through the lymph system. Phycocyanin may be active in preventing a host of degenerative organ diseases by increasing immunity. A Japanese patent states a small dosage of phycocyanin daily maintains or accelerates normal control cell functions that prevents generation of malignancy such as cancer or inhibits its growth or recurrence<sup>34</sup>. Chinese scientists documented phycocyanin stimulates hematopoiesis (creation of blood), emulating the hormone erythropoietin (EPO). EPO is produced by healthy kidneys and regulates bone marrow stem cell production of red blood cells. They claim phycocyanin regulated white blood cell production, even when bone marrow stem cells are damaged by toxic chemicals or radiation<sup>24</sup>. [Fig.-III].

Beta carotene is one of the most well known natural anti-cancer substances, source of Vitamin A for humans. *Spirulina* having over ten times more beta carotene than any other food, including carrots and is one of the most effective substances for deactivating free radicals. Beta carotene prevents free radicals from reacting, and decreases incidence of lung cancer, prevents chemically induced tumors in animals, prevents precancerous prechromosome dam-



age and enhances immunological resistance. The Harvard University School of Dental Medicine reduced oral cancer cells with *Spirulina* extracts. A beta carotene solution applied to cancerous tumors in mouths of hamsters reduced the number and size of tumors or caused them to disappear<sup>35</sup>. When a beta carotene extract was fed to 20 hamsters pretreated to develop mouth cancer, none developed the disease. Tissue samples contained an immune stimulating substance believed to have destroyed cancer cells before they could multiply<sup>36</sup>. In 1995, *Spirulina* reversed oral cancer in pan tobacco chewers in Kerala, India. Complete regression of oral leukoplakia was found in 45% of those using one gram a day for one year, compared to only 7% with a placebo. Within one year of discontinuing *Spirulina*, 45% of the lesions returned. This was the first human study of its chemopreventive potential<sup>37</sup>. CV has definite chemopreventive effect by inducing apoptosis via decreasing the expression of Bcl-2 and increasing the expression of caspase 8 in hepatocarcinogenesis-induced rats<sup>38</sup>. C-phycocyanin showed a dose-dependent inhibition of HeLa and human chronic myeloid leukemia cell growth and proliferation in vitro experiments<sup>39,40</sup>. Induction of apoptosis was considered to be one of the mechanisms involved. Survival rates increased in mice with liver cancer treated with C-phycocyanin<sup>41</sup>, and tumor regression has been reported in animals with oral cancer<sup>42,36,43</sup>. *Spirulina*

induced lesion regression in tobacco chewers with oral leukoplakia in a study conducted in India<sup>44</sup>. They reported that 45% of their study cohort showed complete regression of leukoplakia after taking *Spirulina* supplements for 1 year. The authors also reported that there was no rise in the serum concentration of retinal  $\beta$ -carotene despite supplementation and concluded that other constituents within *Spirulina* may have been responsible for the anticancer effects. It has been argued that the combined antioxidant and immunomodulation characteristics of *Spirulina* may have a possible mechanism of tumor destruction and hence play a role in cancer prevention.

#### **Anti Allergic & antiasthmatic Activity :**

Despite experimental data suggesting that C-phycoyanin can selectively inhibit release of histamine from mast cells and prevent increases in immunoglobulin E, studies demonstrating clinical efficacy are inadequate. A small study in patients with mild to moderate asthma suggested that *Spirulina* supplementation (1 g/day) produced improvement in lung function parameters<sup>45</sup>, while a study evaluating *Spirulina* in allergic rhinitis suggested a positive effect on laboratory values but no clinical outcomes were reported<sup>46</sup>. It has been well documented that *Spirulina* exhibits anti-inflammatory properties by inhibiting the release of histamine from mast cells<sup>47,48</sup>. In a recent randomized, double-blind placebo-controlled trial<sup>49</sup>, individuals with allergic rhinitis were fed daily, either with placebo or *Spirulina* for 12 weeks. Peripheral blood mononuclear cells were isolated before and after the *Spirulina* feeding and levels of cytokines [IL-4, IFN- $\gamma$  and IL-2], which are important in regulating IgE-mediated allergy, were measured. The study showed that high dose of *Spirulina* significantly reduced IL-4 levels by 32%, demonstrating the protective effects of this microalga toward allergic rhinitis. Ishii et.al. studied the influence of *Spirulina* on IgA levels in human saliva and demonstrated that it enhances IgA production, suggesting a pivotal role of microalga in mucosal immunity<sup>50</sup>. A Japanese team identified the molecular mechanism of the human immune capacity of *Spirulina* by analysing blood cells of volunteers with pre- and post-oral administration of hot water extract of *Spirulina platensis*. IFN- $\gamma$  production and NK cell damage were increased after administration of the microalga extracts to male volunteers<sup>51</sup>. In a recent double-blind, placebo-controlled study from Turkey evaluating the effectiveness and tolerability of *Spirulina* for treating patients with allergic rhinitis, *Spirulina* consumption significantly improved the symptoms and physical findings compared with placebo ( $P < 0.001$ ), including nasal discharge, sneezing, nasal congestion and itching<sup>52</sup>. It is well understood that deficiency of nutrients is responsible for changes in immunity, which manifests as changes in production of T-cells, secretory IgA antibody response, cytokines and NK-cell activity. The above studies suggest that *Spirulina* may modulate the immune system by its role in covering nutritional deficiencies.

#### **Cholesterol Lowering effect and Weight Loss Activity :**

Experiments in rats suggest that C-phycoyanin exhibits hypercholesterolemic action<sup>53</sup>. Two small clinical studies have examined the role of *Spirulina* in hyperlipidemia secondary to nephritic syndrome. Both populations showed an improved lipid profile with *Spirulina* supplementation; however, the control group in 1 experiment also showed improvement. The gamma linolenic acid content of *Spirulina* may have played a role in the mechanism of action<sup>54,55</sup>. *Spirulina* is one of cholesterol reducing foods. In Japan, study conducted by the Department of Internal Medicine of Tokai University concluded *Spirulina* did lower serum cholesterol and was likely to have a favorable effect on alleviating heart disease since the arteriosclerosis index improved. No adverse effects were noted<sup>56</sup>. Researchers in West Germany had previously discovered cholesterol reduction during a weight loss study with *Spirulina*. In this double blind crossover study against a placebo, about 6 tablets three times a day over four weeks showed a small but statistically significant reduction of body weight. There was also a significant drop in serum cholesterol levels<sup>57</sup>. Japanese research showed lower cholesterol without weight loss, suggesting that cholesterol reduction was not related to weight loss. *Spirulina* was chosen because it previously lowered serum cholesterol in rats<sup>58,59</sup>. A recent study with rats attempted to find the compound in *Spirulina* that lowered serum cholesterol. Researchers

discovered that the benefit may be through its effect on metabolism of lipoproteins. The oil soluble portion was found to suppress cholesterol levels in the serum and liver of rats<sup>60</sup>. In the first human study, gave 4.2 g day<sup>-1</sup> of *Spirulina* to 15 male volunteers and, although there was no significant increase in HDL levels, they observed a significant reduction of LDL cholesterol after 8 weeks of treatment. The atherogenic effect also declined significantly in the above group<sup>61,62</sup>. In a more recent study administered *Spirulina* supplements in ischemic heart disease patients and found a significant reduction in blood cholesterol, triglycerides and LDL cholesterol and an increase in HDL cholesterol. More research is needed before *Spirulina* can be recommended to lower cholesterol levels but its role as a natural food supplement in combating hyperlipidaemia, in combination with other therapeutic options, should not be overlooked. Finally, <sup>63</sup> in a clinical study, found a significant reduction in LDL:HDL ratio in 15 diabetic patients who were given *Spirulina*. However, this study was small and better studies are needed before *Spirulina* can be recommended in diabetes. It may also reduce blood pressure. In a recent study with rats, it was found to reduce high blood pressure<sup>60</sup>. A 5% *Spirulina*-supplemented diet prevented fatty liver in rats<sup>64</sup>.

#### **Antidiabetic activity :**

*Spirulina* may have a positive effect against diabetes. A water soluble fraction was found to be effective in lowering the serum glucose level at fasting while the water-insoluble fraction suppressed glucose level at glucose loading<sup>65</sup>. Two small studies have investigated the effects of *Spirulina* supplementation in type 2 diabetes, with improvement noted in fasting blood sugar and lipid profiles. Suggested mechanisms of action include hypoglycemia caused by fiber content or possible insulin-stimulating action of peptides and polypeptides of *Spirulina* proteins. The actions on lipids have been attributed to gamma linolenic acid content.<sup>63,66</sup>

#### **Nephroprotective Activity :**

Kidneys play an essential role in cleansing the body of toxins. Heavy metals and many drugs are known to be toxic to the kidneys. Scientists are interested in substances that can help cleanse the kidneys of toxic side effects from heavy metal poisoning or from high intake of medicines or pharmaceutical drugs. The following study suggest *Spirulina* may have a beneficial effect for humans suffering from heavy metal poisoning. They also suggest kidney side effects from pharmaceutical drugs may decrease when it is eaten along with the administration of drugs. In Japan, *Spirulina* reduced kidney nephrotoxicity from mercury and three pharmaceutical drugs in laboratory rats, suggest that the *Spirulina* diet greatly decreased BUN and serum Creatinine levels, and in two cases, brought serum Creatinine down to original levels<sup>67</sup>. In a follow-up study, urinary excretion of two enzymes were measured as further indicators of renal function. The activities of both were significantly reduced in the group fed 30% *Spirulina*. The effective compound responsible for the suppression of renal toxicity was the water soluble extract, phycocyanin<sup>68</sup>. A 1997 study found liver detoxification of chemical dioxins (polychlorinated dibenzo-p-dioxins). The fecal excretion of dioxin was 7 to 11 times higher for rats on a treatment diet of chlorophyll rich foods (20% chlorella, 20% *Spirulina* or 2% chlorophyllin). These findings suggest chlorella, *Spirulina* and chlorophyllin are useful as a new approach in the treatments of patients exposed to lipophilic xenobiotics<sup>69</sup>. *Spirulina* decreased cisplatin-induced nephrotoxicity in rats, an effect attributed to an antioxidant action<sup>70</sup>. Millions of people in Bangladesh, India, Taiwan and Chile are consuming high concentration of arsenic through drinking water and are at risk of chronic arsenic poisoning for which there is no specific treatment. A placebo-controlled, double-blind study was conducted to evaluate the effectiveness of *Spirulina* extract plus zinc in the treatment of chronic arsenic poisoning<sup>71</sup>. Results showed that *Spirulina* extract plus zinc twice daily for 16 weeks may be useful for the treatment of chronic arsenic poisoning with melanosis and keratosis. More randomized trials are required but the results are promising.

#### **Lactobacillus Increasing Activity :**

Healthy lactobacillus in the intestines provides humans with three major benefits: better digestion and absorption, protection from infection, and stimulation of the immune system. For these reasons, many people take lacto-

bacillus supplements. Research in Japan showed Spirulina increased lactobacillus in rats 3 times over a control group<sup>68</sup>. Since Spirulina did not supply this additional B1, it improved B1 absorption. The study suggests Spirulina should increase lactobacillus in humans and increase absorption of B1 and other dietary vitamins. It was previously reported that Spirulina contains growth promoters, in the form of unique polysaccharides, that enhances the growth of lactic acid bacteria<sup>72</sup>.

#### **Wound Healing and Antibiotic Effects :**

People have used Spirulina in face creams and body wraps, and there are reports of people taking it in baths to promote skin health. Pharmaceutical compounds in France containing Spirulina accelerated wound healing. Patients used whole Spirulina, raw juice and extracts in creams, ointments, solutions and suspensions<sup>73</sup>. A study in Japan showed cosmetic packs containing Spirulina and its enzymatic hydrolyzates promoted skin metabolism and reduced scars<sup>74</sup>. Additional research showed extracts of Spirulina inhibited the growth of bacteria, yeast and fungi<sup>75,76</sup>. The antibiotic substances in these extracts may have medical applications.

#### **Nutritional Effect :**

As little as ten grams a day brings rapid recovery from malnutrition, especially for infants. Spirulina was given to undernourished children in Mexico,<sup>77</sup> and adults<sup>78</sup> with beneficial results. In Togo, rapid recovery of malnourished infants was reported in a village clinic. Children given 10 to 15 grams per day mixed with millet, water and spices, recovered in several weeks<sup>79</sup>. In India, large scale studies with preschool children showed carotenes in Spirulina helped children recover from symptoms of Vitamin A deficiency<sup>80,81</sup>. In Romania, tablets were given to patients with nutritional deficiencies in a Bucharest municipal clinic. Patients had suffered weight loss in conjunction with chronic pancreatitis, rheumatoid arthritis, anemia, diabetes and other symptoms. The patients gained weight and their health improved<sup>82</sup>. In China, Spirulina was prescribed at Nanjing Children's Hospital as a 'baby nourishing formula' with baked barley sprouts. 27 of 30 children aged two to six recovered in a short period from bad appetite, night sweat, diarrhea and constipation<sup>83</sup>. In another study, children deficient in the essential mineral zinc, made more rapid recovery with high zinc Spirulina than a standard zinc supplement<sup>84</sup>. Spirulina consumption was purported to aid in weight loss because of its high phenylalanine content, but a Food and Drug Administration review found no evidence to support this claim.<sup>85,86</sup> A study of Spirulina supplementation for 8 weeks demonstrated clinical improvement in weight gain and increased hemoglobin levels in malnourished children in the West African nation of Burkina Faso<sup>87</sup>. Similar results have been demonstrated among children who are HIV-positive<sup>88</sup>. Blueberry- and Spirulina-enriched diets enhance striatal dopamine recovery and induce a rapid, transient microglia activation after injury of the rat nigrostriatal dopamine system<sup>89</sup>. Clinical effect of cidofovir and a diet supplemented with *Spirulina platensis* in white spot syndrome virus (WSSV) infected specific pathogen-free *Litopenaeus vannamei* juveniles<sup>90</sup>. *Chlorella* sp. microalgae supplemented enteral diet has significant protective effects on intestinal mucosa barrier in obstructive jaundice, and reduces intestinal translocation of bacteria and endotoxin<sup>91</sup>. Iron is the most common mineral deficiency worldwide. Iron anemia is prevalent in women, children, older people, and especially women on weight loss diets. Iron is essential for healthy red blood cells and a strong immune system, but typical iron supplements are not well absorbed by the human body. Because Spirulina is known to have a very high iron content, it was tested against a typical iron supplement. Spirulina fed rats absorbed 60% more iron than rats fed the iron supplement, suggesting there is a highly available form of iron in Spirulina.<sup>92</sup> An earlier study showed it corrected anemia in rats<sup>93</sup>. In Japan, study shows that Spirulina is useful in hypochromic anemia<sup>94</sup>. Diet with Spirulina can eliminate iron deficit symptoms and optimize athletic health and physical capacity<sup>95</sup>.

#### **Anti-inflammatory effect :**

Gamma linolenic acid (GLA), an essential fatty acid, is a precursor for the body's prostaglandins, master hormones that control many body functions. The prostaglandin PGE1 is involved in many tasks including regulation of blood pressure, cholesterol synthesis, inflammation and cell proliferation. PGE1 is usually formed from dietary linolenic acid, and the GLA progresses to PGE1

<sup>96</sup>. Dietary saturated fats and alcohol and other factors may inhibit this process, resulting in GLA deficiency and suppressed PGE1 formation<sup>97</sup>. Numerous studies have shown GLA deficiency may figure in degenerative diseases and other health problems. Clinical studies show dietary intake of GLA can help arthritis,<sup>98</sup> heart disease,<sup>99</sup> obesity<sup>100</sup> and zinc deficiency<sup>101</sup>. Alcoholism, manic-depression, aging symptoms and schizophrenia also have been ascribed partially to GLA deficiency<sup>102</sup>. A source of dietary GLA may help conditions of heart disease, premenstrual stress, obesity, arthritis and alcoholism<sup>103</sup>. In Spain, the GLA in Spirulina and evening primrose oil is prescribed for treatment of various chronic health problems<sup>104</sup>. The few known sources of GLA include two foods, human milk and Spirulina, and oil of the evening primrose plant, black currant and borage seeds. Ten grams of Spirulina has over 100 mg of GLA. This high amount of GLA is well documented<sup>105,106,107</sup>. It is about 5% essential fatty acids and 20% of this is GLA. Inhibition of NO and prostaglandin E(2) over-production through suppressing iNOS and COX-2 induction and attenuation of TNF-alpha formation and neutrophil infiltration into inflammatory sites by C-PC may contribute, at least in part, to its antihyperalgesic activity<sup>108</sup>. In mice with chemically-induced arthritis, phycocyanin exerted a scavenging action against reactive oxygen species and anti-inflammatory activity<sup>109</sup>.

#### **Radiation effect- reducing Activity :**

Years after the Chernobyl disaster, four million people in Ukraine and Belarus live in dangerously radioactive areas. The water, soil and food over an 11,000 square mile area is contaminated. Over 160,000 children are victims of radiation poisoning, with birth defects, leukemia, cancer, thyroid disease, anemia, loss of vision and appetite and depressed immune system, now called "Chernobyl AIDS." Spirulina reduced urine radioactivity levels by 50% in only 20 days. This result was achieved by giving 5 grams a day to children at the Minsk, Belarus Institute of Radiation Medicine. The Institute program treated 100 children every 20 days. An unpublished 1993 report confirmed 1990-91 research, concluding "Spirulina decreases radiation dose load received from food contaminated with radionuclide, Cesium-137 and Strontium-90. It is favorable for normalizing the adaptive potential of children's bodies in conditions of long-lived low dose radiation"<sup>110</sup>. Based on testing in 1990, the Belarus Ministry of Health considered this food was advisable for the treatment of people subject to radiation effects, and requested additional donations from the Earthrise Company of California and Dainippon Ink & Chemicals of Japan<sup>111</sup>. Previous research in China in 1989 demonstrated a natural polysaccharide extract of Spirulina had a protective effect against gamma radiation in mice<sup>112</sup>. Subsequent research showed phycocyanin and polysaccharides enhanced the reproduction of bone marrow and cellular immunity<sup>113</sup>. In a 1991 study of 49 kindergarten children aged 3 to 7 years old in Beryozova, Spirulina was given to 49 children for 45 days. Doctors found T-cell suppressors and beneficial hormones rose, and in 83% of the children, radioactivity of the urine decreased<sup>112</sup>. A Russian patent was awarded in 1994 for the use of Spirulina as a medical food to reduce allergic reactions from radiation sickness. The patent was based on a, Consumption of Spirulina food lowered the levels of IgE in the blood, which in turn, normalized allergic sensitivities in the body<sup>114</sup>. Research continuing through 1999 in Belarus showed immune building, normalization of peroxide lipid oxidation and detoxifying effects of Spirulina supplements in children and teenagers. Scientists theorized Spirulina may form non-absorbable complexes of radionuclide through analogues such as calcium or potassium and promotes their excretion<sup>115</sup>. Spirulina protect mouse and human bone marrow cells against gamma radiation<sup>45,70,116,117,118,119</sup>.

#### **Antifatigue Activity:**

*Spirulina* has been promoted as 'the food of the future' with 'exceptional constituents' that contribute to high energy levels. A few of these constituents such as polysaccharides (Rhamnose and Glycogen) and essential fat (GLA) are absorbed easily by human cells and help in energy release. *Spirulina* increases healthy lactobacillus in the intestine, enabling the production of Vitamin B6 that also helps in energy release<sup>120</sup>.

#### **Antioxidant activity:**

Spirulina is nature's richest whole-food source of antioxidants. It contains a spectrum of practically every natural antioxidant known, including: the antioxidant vitamins B-1, B-5, and B-6, B-12 the minerals zinc, manganese,

and copper, the amino acid methionine and the antioxidants beta-carotene, vitamin E and the trace element selenium. *Spirulina* contains phenolic acids, tocopherols and β-carotene which are known to exhibit antioxidant properties. The amounts of phenolic acids, α-tocopherol and β-carotene were determined in *Spirulina* extracts. The results obtained indicate that *Spirulina* provides some antioxidant protection for both *in vitro* and *in vivo* systems. Among several alga genera, *Spirulina* and *Chlorella* deserve special attention due to their importance as human food and their *in vitro* and/or *in vivo* antioxidant potential<sup>121</sup>. There is a current worldwide interest in finding new and safe antioxidants from natural sources such as plant material to prevent oxidative deterioration of food and to minimize oxidative damage to living cells<sup>122</sup>. The use of synthetic antioxidants has decreased due to their suspected activity as promoters of carcinogenesis as well as a general consumer rejection of synthetic food additives<sup>123</sup>. The role of dietary antioxidants and their potential benefits in health and disease have attracted great attention<sup>124</sup>. Components with antioxidant activities can be found in only a few species of algae<sup>125</sup>. Although the occurrence of phenolic compounds in plants is well known and these groups of compounds possess antioxidant activity in biological systems<sup>126</sup>, the antioxidant characteristics of algae are poorly known. Some studies reported that cancer was prevented by alga extracts<sup>127,42</sup>, because of their antioxidant properties of β-carotene<sup>127</sup>. However, the possibility exists that there are other unknown constituents in algae with antioxidative activity that might enhance the antioxidant synergism<sup>125</sup>. Tutour<sup>128</sup> proposed that some compounds such as vitamin C, phenols, amines and phospholipids from algae could regenerate vitamin E.

#### Zeaxanthin :

The most prevalent carotenoid in *Spirulina* is zeaxanthin [zeaxanthin is a xanthophyll]. Zeaxanthin is a very important antioxidant for two reasons: 1) It is one of the few antioxidants that can cross the blood brain barrier and bring antioxidant protection to the eyes, brain and central nervous system and 2) it is also one of the few antioxidants that never becomes a pro-oxidant. Zeaxanthin and astaxanthin are two carotenoids that never become pro-oxidants in any situation. These two facts about zeaxanthin are leading researchers to study zeaxanthin more and more, and as they do, they're finding out that it is a powerful antioxidant with many benefits. It beat Vitamin E by over 400 times! An article summarized some of the benefits of zeaxanthin and its closely related xanthophylls carotenoid lutein: "Lutein and zeaxanthin are the only carotenoids found in both the macula and lens of the human eye and play a protective role in the eye, and are important nutrients for the prevention of cardiovascular disease, stroke and lung, breast cancer. They may also be protective in skin conditions attributed to excessive ultraviolet (UV) light exposure."<sup>129</sup>. A study done in the Netherlands examined the role that zeaxanthin and beta-carotene had on inflammation-caused atherosclerosis. They found that the inverse relationship between these carotenoids and leukocytes may explain the possible protective effect of carotenoids on atherosclerosis through their work as anti-inflammatories<sup>130</sup>.

#### CONCLUSION

The aims of this review are to summarize the mechanisms of action, highlight the potential effects of this alga in humans and address current clinical applications, based mainly on *in vivo* studies and a few well-designed *in vitro* studies and the highest levels of evidence available in the literature.

#### ABBREVIATION:

HSV-1	:Harpies simplex virus-1
HIV	:Human immunodeficiency virus
AIDS	:Acquired immunodeficiency syndrome
NCI	:National cancer institute
EPO	:Erythropoietin
CV	:Chlorella vulgaris
IL-4	:Interleukin -4
IL-2	:Interleukin-2
IFN-α	:Interferon
IgE	:Immunoglobulin E
NK	:Natural killer
HDL	:High density lipoprotein
LDL	:Low density lipoprotein
WSSV	:White spot syndrome virus
GLA	:Gamma linolenic acid
PGE1	:Prostaglandin
COX-2	:Cyclooxygenase

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