

A Potent Mixture Of Antioxidants In *Spirulina* Have Numerous Advantages For Human Health

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Abstract

Spirulina is a free-floating filamentous microalga that grows in alkaline water. Spirulina was consumed as food by the Mayas, Toltecs, and Kanembu in Mexico during the Aztec civilization approximately 400 years ago. Spirulina is a well-known source of essential nutrients such as proteins, vitamins, amino acids, minerals, fatty acids, and so on. It's popular in human and animal nutrition, as well as the cosmetics business. In vivo and in vitro experiments have yielded promising results in the treatment of certain malignancies and allergies, anaemia, hepatotoxicity, viral infection, vascular disorders, radiation protection, and obesity. Spirulina's antioxidant effects have been proven in numerous preclinical research. Antioxidants aid in the prevention of many human diseases.

Keywords: *Spirulina*, *Microalgae*, Antioxidant, Anticancer

Introduction

Cancer is becoming a leading cause of death worldwide [1]. It is often exceeded only by cardiovascular illness in the industrialized world, while developing countries are responsible for the globally expanding trend. In the year 2000, there were over 10 million new cancer cases and over 7 million deaths from cancer globally. Developing countries contributed 53% of the incidence and 56% of the deaths. Between 1990 and 2000, the incidence and mortality grew by 2.4% each year; by 2020, these diseases are expected to account for seven out of every ten deaths in developing nations (Fig. 1) [2-5].

Cancer Worldwide	Males	Females	Persons	Year ²
Number of new per year	7,427,148	6,663,001	14,090,149	
Incidence rate per 100,000 population ¹	205.4	165.3	182.3	2012
Number of deaths per year	4,653,132	3,547,898	8,201,030	
Mortality rate per 100,000 population ¹	126.3	82.9	102.4	2012
1. World age-standardized 2. Latest estimates available				

Figure 1. Static of cancer incidence and deaths in 2012.

Based on the high expense of cancer treatment options (Fig. 2) [6] antioxidants therapy has been developed in recent years to prevent cancer. According to research, free radicals can cause degenerative diseases such as cancer, ageing, and age-related macular degeneration [7].

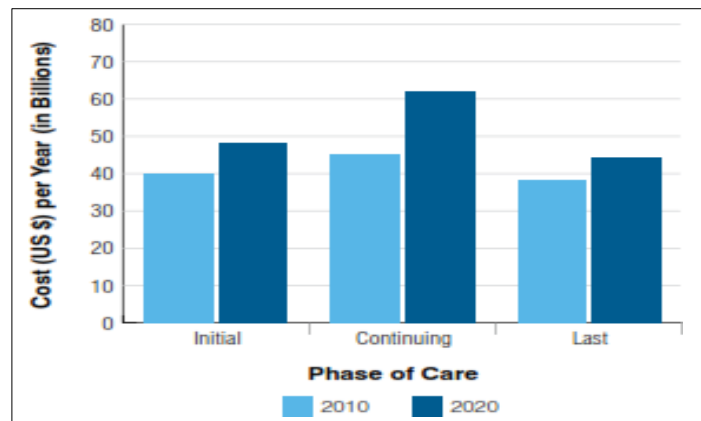


Figure 2. Cost of cancer care by phase of care, in 2010.

Antioxidants are chemicals that neutralize free radicals or their activity and hence help to protect the body from them. Carotenoids, flavonoids and related polyphenols, -lipoic acid, glutathione, and other antioxidants are examples. Vegetables and fruits are the body's primary source of antioxidants. Due to the scarcity of fruits and vegetables in many parts of the world, scientists devised new ways to supply antioxidants [8, 9]. Since the mid-1980s, tremendous efforts and extensive research have been directed towards the creation of nutraceuticals or functional foods for the prevention or treatment of numerous diseases [10-13]. The first findings on antioxidants used to preserve food lipids came from natural sources; in 1852, Wright claimed that elm bark was excellent in keeping butterfat and lard [8, 9, 13].

Spirulina was first categorised as a plant because of its high concentration of plant pigments and ability to photosynthesis. It was later classified as a bacteria based on fresh knowledge of its genetics, physiology, and metabolic features [14]. *Spirulina* grows naturally in high-salt alkaline water reservoirs in subtropical and tropical regions such as America, Mexico, Asia, and Central Africa [14, 15]. *Spirulina*'s nutritional value is well recognised due to its unusually high protein content (60-70% by dry weight) and abundance of vitamins, minerals, vital fatty acids, and other elements [15-17]. Recent research indicates that *Spirulina*, a



Figure 3. Microscopic view of *Spirulina*.

Unicellular blue-green algae (Fig. 3), may offer a number of health advantages and therapeutic capabilities, as well as the ability to operate as an antioxidant and anti-inflammatory agent [18]. Since the 1980s, *spirulina* has also been employed in health foods, feed, and biochemical goods. *Spirulina* is, in fact, the most concentrated and nutritious entire food known to science. Furthermore, *Spirulina* has no adverse effects and is non-toxic in nature [9, 14, 16].

Spirulina has been shown to be effective in preventing viral and bacterial infections, cancer, allergies, diabetes, inflammation, and hyperlipidemia. Furthermore, due to its concentrated nutrition, *Spirulina* has been recommended as one of the principal diets during long-term space missions by both the National Aeronautics and Space Administration (NASA) and the European Space Agency (ESA). Although the molecular mechanism by which *Spirulina* affects on the immune system remains largely unknown, it has been orally delivered to patients as an anti-cancer and anti-viral drug. A recent study found that when *Spirulina* was supplemented with Selenium and paired with anticancer medications, there was a significant decrease in proliferation and an increase in apoptosis [9, 13, 17, 19, 20].

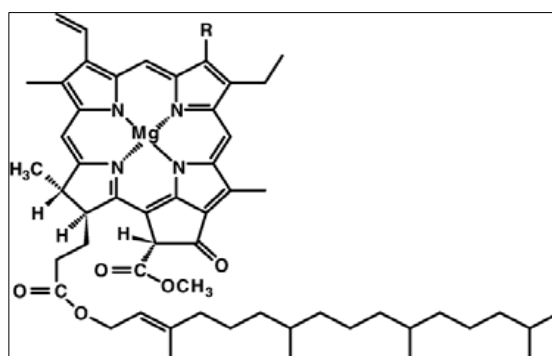
Spirulina is an excellent source of Chlorophyll, Phycocyanin, and Carotenoids. It is also used as a natural colour in the culinary, cosmetic, and pharmaceutical industries [21].

Phytonutrients	
Beta-Carotene	6.8 mg
Zeaxanthin	9 mg
Chlorophyll	30 mg
Total Carotenoids	15 mg
C-Phycocyanin	240 mg
Total Phycocyanins	519 mg
Superoxide Dismutase	1080 units

Figure 4. Amount of pigment in one gram *Spirulina* powder.

Chlorophyll

Chlorophyll is a necessary component of many common items. It is utilized as a natural food



Figurer 5. Structure of chlorophyll.

colouring agent as well as an addition in pharmaceutical and cosmetic applications. It also possesses antimutagenic and antioxidant effects (Fig. 5) [22, 23].

In certain trials, chlorophyll was found to enhance wound healing by more than 25%. Because chlorophyll promotes tissue growth, it inhibits bacterial growth and accelerates wound healing. Because chlorophyll has a similar chemical structure to haemoglobin, it is expected to stimulate tissue growth in a similar way by facilitating quick carbon dioxide and oxygen exchange. Because of this feature, chlorophyll is employed in proctology as well as the treatment of ulcers and oral infections [23-25].

Chlorophyll derivatives, such as pheophorbide b and pheophytin b, have long been recognised as powerful antioxidants. These compounds, however, are present in extremely low concentrations in fruits and vegetables. The most important function of chlorophyll derivatives in cancer prevention is

mutagen trapping in the gastrointestinal tract. Furthermore, the capacity of both natural and commercial chlorophyll derivatives to operate as photosensitizers has allowed them to be used as effective agents in cancer photodynamic treatment. In cancer cell lines, antioxidant activity, anti-mutagenic activity, regulation of xenobiotic metabolising enzymes, and induction of apoptotic events have been demonstrated in vitro and in vivo [23, 25].

Carotenoids

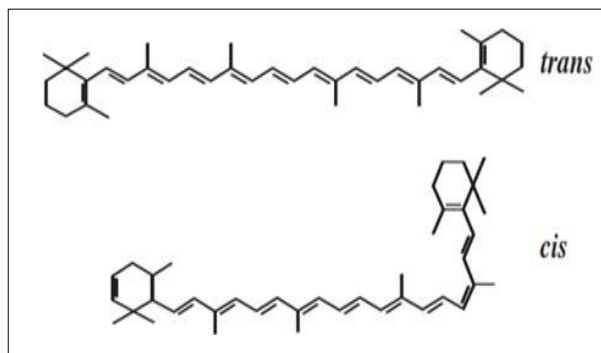


Figure 6. Molecular structure of nature's two forms of beta- carotene.

Spirulina extracts containing carotenes and other carotenoids (Fig. 6) are commonly utilised as natural colouring ingredients [19]. Carotenoids are essential antioxidants. Numerous studies have found that persons who eat a lot of carotenoids-rich foods had a lower chance of getting various types of cancer [10].

They have antioxidant properties, especially when exposed to light. Carotenoids also have essential metabolic activities in animals and humans, such as vitamin A conversion, immunological response augmentation, and protection against diseases such as cancer by scavenging free radicals, with β -carotene being a key carotenoid. *Spirulina* is a possible antioxidant with anti-carcinogenic and radio protective properties. *Spirulina* contains up to 2,000 IU/g of β -carotene per gramme of dry weight [26-28]. Consuming antioxidant-rich foods such as carotenoids, phycoerythrin, superoxide dismutase, and vitamins C and E is another excellent strategy to help prevent cancer. [7, 29]. Numerous studies have shown that people with diets high in carotenoids have a lower risk of developing various types of cancer [30], but most people only get 25-30% of the daily dietary carotenoid intake recommended in a cancer-preventive diet; and many people are unwilling to make radical dietary changes[19]. *Spirulina* is a complete food with beta-carotene that is naturally chelated. *Spirulina* contains not just beta-carotene but also other significant carotenoids including zeaxanthin and beta-cryptoxanthin, as well as lesser known carotenoids like myxoxanthophyll and echinenone. *Spirulina* extracts have the ability to prevent carcinogenesis [31]. *Spirulina* was proven to stabilize liver disease and prevent it from developing to cirrhosis in one research. Another mouse study found that *Spirulina* greatly reduced skin and gastrointestinal tumours. *Spirulina* has been demonstrated to lower the size of tumours as well as their incidence. They came to the conclusion that diets high in carotenoid-rich fruits and vegetables may protect against prostate cancer [19]. Many previous investigations have identified similar associations between carotenoid intake and different types of cancer. Beta-carotene may also protect the skin from the damaging effects of sunshine and aid in the prevention of skin cancer [26]. The trial's findings were startling in that, contrary to expectations, the beta-carotene supplemented group experienced a tiny (statistically insignificant) increase in lung cancer incidence. Surprisingly, the group in the research with the highest dietary beta carotene levels had the lowest incidence of lung cancer [26]. *Spirulina* contains more beta carotene than any other food, including carrots, and is the highest source of beta carotene. One of the most powerful compounds for deactivating free radicals, which harm cells and cause cancer, is beta carotene. Free radicals are molecular fragments of pollutants, harmful substances, medicines, and physical and emotional stress [32]. Beta carotene reduces the incidence of lung

cancer, prevents chemically generated tumours in animals, prevents precancerous pre-chromosome damage, and improves immunological resistance. The evidence relating to natural beta carotene and cancer prevention is compelling [7, 26]. *Spirulina* will provide natural carotene insurance to those who do not consume 4-9 servings of fruits and vegetables each day [19]. According to the National Cancer Institute of the United States of America, a daily consumption of 6.0 mg β -carotene may be effective in lowering the risk of cancer. Anyone who consumes 4.0 g of *Spirulina* daily will acquire 6 mg of β -carotene [28].

In an experiment with 40 hamsters, beta carotene was found to strongly suppress the formation of squamous cell carcinoma of the hamster buccal pouch when a solution was administered topically three times weekly for 22 weeks. Beta carotene was reported to suppress oral carcinogenesis in an initiation-promotion hamster buccal pouch system in a second experiment with 80 hamsters. Both initiation and promotion were inhibited by beta carotene [33]. *Spirulina* fusiform has been shown in studies with preschool children in India to be an efficient source of dietary vitamin A. *Spirulina* supplementation did not enhance serum concentrations of retinal or beta carotene, and it was not associated with toxicity [32, 34].

Another study found that beta-carotene lowers the size of existing tumors in hamsters and slows future tumors formation, lengthening the hamsters' survival time [10, 33]. Numerous studies have found that those with rich beta-carotene diets had a lower risk of developing various malignancies. Smokers, in particular, should keep their beta-carotene levels high. Low beta-carotene levels in smokers' blood have been linked to the development of lung cancer later in life. Researchers at Albert Einstein College of Medicine discovered that beta-carotene can help prevent the formation and progression of cervical cancer. Beta-carotene may also protect the skin from the damaging effects of sunshine and aid in the prevention of skin cancer. Diet, Nutrition, and Cancer, a seminal research conducted by the US National Science Foundation in the early 1980s, showed that diets high in beta carotene were associated with a lower risk of cancer based on epidemiological evidence. In fact, over 200 studies of beta-carotene consumption in the diet found a reduction in a variety of malignancies [19, 26].

Phycocyanin

Spirulina contains phycocyanin, which is one of the essential components that distinguishes it from other green foods such as chlorella, wheat grass, and barley [35]. The Japanese discovered that phycocyanin protects the liver and kidneys while detoxifying and activates the immune system. "*Spirulina* is thought to potentiate the immune system, leading to suppression of cancer development and viral infection [36], according to researchers at the Osaka Medical Centre for Cancer and Cardiovascular Diseases." *Spirulina* selectively reduced tumour cell line development, demonstrating anticancer action against human stomach cancer cells (AGS), human liver cancer cells (Hep3B), human lung cancer cells (A549), and breast cancer cells (MCF-7) [16]. Phycocyanin is a highly effective water-soluble antioxidant [27, 37]. In Japan, phycocyanin has been the subject of extensive investigation. The Japanese discovered that phycocyanin protects the liver and kidneys while detoxifying and activates the immune system. "*Spirulina* is thought to potentiate the immune system, leading to suppression of cancer development and viral infection [19]," according to researchers from the Osaka Medical Centre for Cancer and Cardiovascular Diseases. C-phycocyanin (C-PC) is a primary *Spirulina Bili* protein with antioxidant and radical scavenging capabilities (Fig. 7) [38].

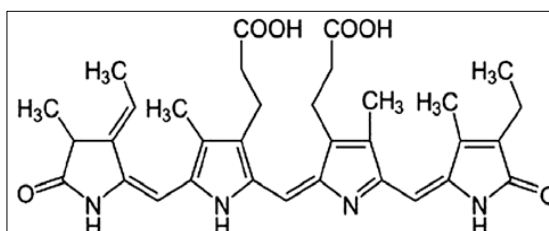


Figure 7. Chemical structure of C-phycocyanin.

C-PC, a selective cyclooxygenase-2 inhibitor, promotes apoptosis in RAW 264.7 macrophages activated with lipopolysaccharide. It is also believed to have anti-inflammatory and anticancer effects. Phycocyanin can scavenge free radicals such as alkoxyl, hydroxyl, and peroxy radicals. It also reduces nitrite production, lowers the expression of inducible nitric oxide synthase (iNOS), and inhibits liver microsomal lipid peroxidation. *Spirulina* phycocyanin inhibits the growth of human leukaemia K562 cells [35].

Serum glutamate oxaloacetate and glutamate pyruvate transaminase activity increased, as did liver GSH levels. *Spirulina* supplementation to mercuric chloride-intoxicated rats restored the activity of antioxidant enzymes superoxide dismutase, catalase, and glutathione-S-transferase to near normal levels. The findings clearly show that *Spirulina* treatment improves the antioxidant defence mechanism in mercuric chloride-induced toxicity and suggests that it may have a therapeutic effect in free radical-mediated disorders [39, 40]. With an IC(50) of 5.0 μ M, phycocyanin is a robust peroxy radical scavenger, and the rate constant ratios obtained for phycocyanin and uric acid (a recognised peroxy radical scavenger) were 1.54 and 3.5, respectively. These findings strongly suggest that the covalently linked chromophore, phycocyanobilin, is involved in phycocyanin's antioxidant and radical scavenging activities [7, 41].

Other studies of *Spirulina* application in cancers

Liver fibrosis is a chronic liver disease that can progress to cirrhosis if significant damage is not repaired. Inhibiting activated hepatic stellate cell (HSC) proliferation and, as a result, inducing HSC apoptosis is one therapeutic treatment for liver fibrosis. It has been reported that antioxidants can limit HSC growth. The aqueous extract of *Spirulina* was chosen as the antioxidant source in this investigation to explore the inhibitory effect on the proliferation of HSC [42].

The effects of aqueous *Spirulina* and chlorella extract on the proliferation of human liver cancer cells, HepG2, were also tested and compared in pairs. The total phenol concentration of *Spirulina* was nearly five times that of chlorella (6.86 \pm 0.58 vs 1.44 \pm 0.04 mg tannic acid equivalent/g algae powder, respectively). Both algae's aqueous extracts inhibited HSC and HepG2 proliferation, however *Spirulina* was a stronger inhibitor than chlorella [42].

Spirulina's water-soluble polysaccharides appear to have antioxidant, anticancer, and antiviral properties [36]. Furthermore, *Spirulina* has no secondary negative effects, with no reported cases of human or animal death, as with other microalgae, owing to the presence of hepato and neurotoxins in those microalgae. *Spirulina* extracts were examined for immunomodulatory properties in tandem with initial antiviral and anti-cancer research. *Spirulina*'s immune system improvement has thus become an important study avenue for potential uses of this organism. *Spirulina* has just been added to the list of Generally Recognised as Safe (GRAS) goods by the United States Food and Drug Administration [16, 20].

Exercise is widely known to increase the formation of reactive oxygen and nitrogen species, which contribute to skeletal muscle fatigue and injury. *Spirulina* was studied in two clinical studies for its antioxidant properties in reducing exercise-induced skeletal muscle exhaustion and injury. In one study with 16 student volunteers, eating 5% *Spirulina* for three weeks resulted in a significant decrease in plasma oxidative marker malondialdehyde (MDA) and an increase in blood superoxide dismutase (SOD) activity [11, 29, 43].

Spirulina extract was discovered to stimulate antitumor natural killer cell response in a study conducted by the Department of Microbiology and Immunology at Hokkaido University in Japan. The researchers transplanted tumours into a specific species of mouse for their investigation. After giving the mice hot water extracts of *Spirulina*, they looked for molecular signals in the mice cells' major histocompatibility complex. Initially, a sub cell line showed minor NT response expressions, but as the study progressed, they discovered natural killer cell activation signals going off via expressions of Rae-1, a ligand for NK activation. The implanted melanoma gradually retreated when natural killer cells arrived on the scene of the tumor-ridden cells, until the natural killer cell defense effectively eradicated the entire tumour [36, 37].

Endonuclease assays and radio autography were used in China to evaluate the effect of a water soluble polysaccharide from *Spirulina platensis* on DNA excision repair. The presence of the polysaccharide greatly increased both the repair activity of radiation damaged DNA excision and the unscheduled DNA synthesis (UDS). During an examination of the time course of the excision process, it was discovered that the presence of *Spirulina* polysaccharide not only increased the initial rates of damaged DNA excision and the UDS, but also delayed the saturations of both important excision and repair DNA synthesis reactions [44, 45].

Spirulina polysaccharides have been studied by researchers in both Japan and China for their possible use in cancer therapy. In a study titled "Inhibition of tumour invasion and metastasis by Calcium Spirulan," researchers from Japan's Toyama Medical and Pharmaceutical University discovered that Calcium Spirulan greatly reduced lung metastasis by preventing tumour penetration of cell membranes [46].

The current study's findings definitely suggest to *Spirulina's* therapeutic potential in Cadmium-induced teratogenesis, most likely through its antioxidant action. Cadmium levels in organic foods are often high. The USDA organic programme does not control, measure, or limit the content of heavy metals in "certified organic" foods, which is a little-known fact. According to Natural News, many "organic" foods contain dangerous quantities of heavy metals like cadmium, lead, mercury, arsenic, and even lighter metals like aluminium [47, 48].

Spirulina's iron chelating characteristics were discovered when human neuroblastoma cells were exposed in vitro to hazardous quantities of iron and then to *Spirulina*, revealing that the iron-induced oxidative stress was reduced. Geriatric patients given *Spirulina* for 16 weeks demonstrated a significant improvement in antioxidant potential, as evaluated by increasing levels of antioxidant status in their plasma. A double-blind, placebo-controlled trial on individuals following exercise found that *Spirulina* supplementation reduced the quantity of creatine kinase (an indication of muscle breakdown). Furthermore, their time to exhaustion on the treadmill increased by 52 seconds. This could be explained by *Spirulina's* antioxidant capacity [32].

Spirulina was studied for its effect on IgA levels in human saliva and found that it increases IgA synthesis, implying that microalga plays an important role in mucosal immunity. A Japanese team discovered the molecular mechanism of *Spirulina's* human immunological potential by analysing blood cells from volunteers who received pre- and post-oral administration of *Spirulina platensis* hot water extract. The administration of micro alga extracts to male volunteers boosted IFN- γ production and Natural Killer (NK) cell destruction. A recent double-blind, placebo-controlled study [49].

In a Turkish study evaluating the efficacy and tolerability of *Spirulina* for the treatment of allergic rhinitis, *Spirulina* consumption significantly improved symptoms and physical findings compared to placebo ($P < .001$), including nasal discharge, sneezing, nasal congestion, and itching [49].

Spirulina can also be used to produce numerous enzymes, including antioxidant enzymes. It has a high concentration of the superoxide dismutase enzyme, which is a key free radical scavenging enzyme. This enzyme can be utilized therapeutically to treat oxidative stress-related disorders or as a component in anti-wrinkle skin creams and face masks, as ageing is thought to be a result of oxidative stress [9, 50].

Irradiation, for example, can produce reactive oxygen species (ROS) in a biological system. These have an impact on a variety of systems, including the digestive, hematopoietic, and immunological systems. Antioxidant enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase, as well as non-enzymatic antioxidants such as beta-carotene, glutathione, vitamin E, and others, are used in defence mechanisms. *Spirulina's* radiation protection may be related to phytopigments (carotenoids, chlorophyll, phycocyanin) as well as polysaccharides [51].

Another mouse study found that *Spirulina* greatly reduced skin and gastrointestinal tumours. *Spirulina* has been demonstrated to diminish both the size and the frequency of tumours [39]. The researchers investigated the histopathologic and hematologic effects of *Spirulina platensis* and *Moringa oleifera* Lam., as well as their synergism, in tumor-induced Sprague-Dawley rats. For four

weeks, 1,2-dimethylhydrazine and 7,12-dimethylbenzanthracene were administered intraperitoneally to induce tumours. To reach the requisite 50% and 75% concentrations, readily available capsules and tablets of *Spirulina* and malunggay combined with water were employed. For two weeks after tumour induction, the extracts were administered intraperitoneally, while 5-fluorouracil was administered intravenously as a positive control therapy. Following therapy, blood was collected from each treatment group and dissected for hematologic and histopathologic examinations, respectively. The results demonstrate that all extracts have anti-tumor efficacy in the liver but not in the lungs. Furthermore, all save the 75% *Spirulina* extract were effective against the formation of gastric tumours, whereas both concentrations of *Spirulina* and its 75% concentration successfully inhibited the development of small and large intestine tumours, respectively. All of the extracts had a negative effect on the total blood count. Finally, *S. platensis* was found to be more effective against tumour formation [52].

As a result, using Selenium-enriched *Spirulina* as a vector for anti-cancer therapy delivery allows any anticancer treatment to be associated with Se. The fictionalization of selenium nanoparticles (SeNPs) with *Spirulina* polysaccharides (SPS) reported in a study allows for high drug delivery and a considerable anti-proliferative effect. The findings show that using SPS as a surface decorator could be an efficient technique to improve nanomaterial cellular absorption and anticancer efficacy. SPS- SeNPs could be a promising choice for further research as a chemopreventive and chemotherapeutic drug for human tumours [53].

Also study of antimicrobial activities of *Spirulina* extract against *Staphylococcus aureus* (Gram positive bacterium), *Escherichia coli* (Gram negative bacterium), *Candida albicans* (yeast) and *Aspergillus niger* (fungus) showed that *C. albicans* is the most sensitive microorganism to all *Spirulina* fractions, which were obtained by the supercritical fluid extraction. This antimicrobial activity could be related to a synergic effect of fatty acids.

Conclusion

Spirulina is a powerful antioxidant combination, and the majority of its health advantages are connected with its antioxidant pigments. Carotenoids (a blend of carotenes and xanthophylls), chlorophyll, and the distinctive blue pigment phycocyanin are among them. Numerous research have established some of its medical applications, but many of its hidden qualities have yet to be discovered. It has anti-oxidant, anti-inflammatory, anti-cancer, anti-aging (prevents cell death), drug delivery system, and other qualities. This Review has also briefly explained these behaviours in humans. I hope that this review will be useful in future research to uncover the other components found in *Spirulina*.

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