Section A-Research paper

Possible Hypolipidemic actions of Spirulina

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Abstract

Alkaline water bodies are ideal environments for spirulina, which are filamentous microalgae that float freely. Because of its high nutritional content, Spirulina has been a staple diet in Central Africa for many years. On a global scale, it has recently become a popular nutraceutical food supplement. In recent times, a lot of focus and research has gone into determining its therapeutic efficacy for a variety of diseases and disorders, such as high cholesterol, high glucose, heart disease, inflammation, cancer, and viral infections. The anti-inflammatory, hypolipidemic, and antioxidant effects of spirulina are the main reasons for its beneficial effects on health. The hypolipidemic action of Spirulina has been proven time and time again in preclinical investigations using a variety of animal models. Consistent with the hypolipidemic effects of Spirulina found in preclinical investigations, the results of human clinical trials on Spirulina supplementation show some variation due to variations in study design, sample size, and patient characteristics. Poor experimental design and small sample sizes plague the majority of human clinical trials. Specifically, the hypolipidemic impact of spirulina remains largely unknown, as does the exact mechanism by which it exerts its effects. After a lengthy history of use as a food source and a positive safety profile in animal research, spirulina is typically thought to be safe for human ingestion. Though extremely infrequent reports of adverse effects in humans have been documented. For spirulina products to be safe, quality monitoring during cultivation and processing is essential to prevent contamination.

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Skeletal muscle is a highly dynamic tissue that constitutes approximately 30–50% of the total body weight, contains 50–75% of all body proteins, and accounts for 30–50 % of whole-body protein turnover. Skeletal muscle is composed mainly of water (75%), protein (20%), and other substances as inorganic salts, minerals, fat, and carbohydrates (5 %) **(1).**

Muscular tissue is mandatory for maintenance of body posture, locomotion, breathing and metabolism. It acts as a reservoir of amino acids that can support protein synthesis or energy production in vital body tissues during starvation or extreme energy consumption. Skeletal muscle has also a secretory function as it produces and releases several growth factors, cytokines and peptides, referred to as myokines. Thus, skeletal muscle function is critical for human health **(2).**

Many pathophsyological changes of skeletal muscle such as loss of motor units, changes in fiber type, muscle fiber atrophy and reduced neuromuscular activation lead to reduced physical performance that may result in functional disability and affect quality of life, also any dysregulation in the skeletal muscle niche is prone to derail persons' well-being and overall physical state **(3).**

Histological structure

The skeletal muscle consists of striated muscle fibers that are held together by connective tissue or extracellular matrix (ECM) that is essential for force transduction and also blood vessels and nerves pass through it to the muscle**.** Extracellular matrix is arranged in the muscle in three levels according to its relation with the muscle fibers, the endomysium, perimysium and epimysium **(4).**

Each skeletal muscle is wrapped by a layer of dense connective tissue called the epimysium. Septae of connective tissue radiate from the epimysium into the muscle dividing it into bundles of muscle fibres known as the fascicles. Each fascicle is wrapped in connective tissue called the perimysium. Muscle bundles can vary in size from 50 to up to 300 muscle fibers per bundle. The endomysium is the connective tissue layer that separates individual muscle fibers from each other **(4)**.

Endomysium is a thin delicate membrane that is located directly in contact with the sarcolemma of the myofiber **(5)**. It transmits tension between overlapping muscle fibers. It also carries small diameter blood vessels and fine branches of nerve fibers, running parallel to the muscle fibers **(6).**

Perimysium is a thicker connective tissue layer which carries larger blood vessels and nerves to the muscle. While epimysium is the thickest and strongest sheath through it the major vasculature and nerve supply pass to the muscle **(4).** The epimysium is composed mainly of collagen type I and minor amounts of collagen type III **(7)**.

Skeletal muscles cells are called muscle fibers. Each fiber is composed of the plasma membrane or sarcolemma, the cytoplasm or sarcoplasm and elongated nuclei are found peripherally just under the sarcolemma result in a characteristic nuclear location unique to skeletal muscle fibers **(7)**.

The myofibers represent the basic units of skeletal muscle structure**.** In most animals, the typical cross-sectional diameter of the myofiber is 30-70 μm and the length varies from 1 mm up to several centimeters, depending on the muscle type and location **(8)**.

Most of the sarcoplasm (80 %) is occupied by cylindrical myofibrils each of which is 1-2 μm in diameter, that are arranged longitudinally. They extend through the entire length of the myofiber and are aligned precisely with their neighbors. This parallel arrangement of the myofibrils is responsible for the cross striations of light and dark bands characteristic of longitudinal section of skeletal muscle **(9).**

Pawlina, (10) stated that the alternating dark and light bands are called the A bands and the I bands. Using the polarized microscope, the dark bands are birefringent (i.e., they alter the polarized light in two planes). Therefore, they are anisotropic and are given the name A band. The light bands are monorefringent (i.e., they do not alter the plane of polarized light). Therefore, they are isotropic and are given the name I band. The I band is bisected by a dense line called the Z line or Z disc**.** The A band is bisected by a less dense region called the H band. Furthermore, bisecting the light H band is a dense line called the M line, which is best demonstrated in electron micrographs. although in ideal H&E preparations, it can be detected using the light microscope.

As shown in figure I, each muscle fiber is made of thousands of myofibrils and contains billions of myofilaments. When assembled together, in a very orderly and characteristic pattern, the myofilaments form sarcomeres, which are the basic contractile units of skeletal muscle and also the functional unit of the myofibril, the segment of the myofibril between two successive Z lines. It measures 2 to 3 μm in relaxed skeletal muscle with the A band being about 1.6 μm and the I band on each side of the Z band about 1 μm long. It may be stretched to more than 4 μm and during extreme contraction may be reduced to as little as 1 μm. The whole muscle cell exhibits cross-striations because the sarcomeres in adjacent myofibrils are in register **(1).**

Spirulina is referred to free-floating filamentous microalgae with spiral characteristics of its filaments. It is formally called *Arthrospira*, belonging to the class of cyanobacteria with characteristic photosynthetic capability **(11,12).** *Spirulina* was initially classified in the plant kingdom because of its richness in plant pigments as well as its ability of photosynthesis. It was later placed in the bacteria kingdom based on new understanding on its genetics, physiology and biochemical properties **(13).** *Spirulina* naturally grows in high-salt alkaline water reservoirs in subtropical and tropical areas including America, Mexico, Asian and Central Africa **(13,14).** Among large number of *Spirulina* species, three species of *Spirulina*, including *Spirulina*

platensis (*Arthrospira platensis*), *Spirulina maxima* (*Arthrospira maxima*) and *Spirulina fusiformis (Arthrospira fusiformis)* are most intensively investigated as those *Spirulina* species are edible with high nutritional as well as potential therapeutic values **(13–16).**

Early studies were mainly focused on the nutritional value of *Spirulina* as a food source. As early as over 400 years ago, *Spirulina* was eaten as food by the Mayas, Toltecs and Kanembu in Mexico during the Aztec civilization **(17).** *Spirulina* growing in the Lake Texcoco were harvested, dried and used to make *Spirulina* cake as food. It has also been over centuries for the Chadian to consume *Spirulina* in Central Africa. *Spirulina* harvested from the Lake Kossorom (Chat) is used to make cake or broths as meals and also sold on the market **(18).** The nutritional value of *Spirulina* is well recognized with its unusual high protein content (60–70% by dry weight) and its richness in vitamins, minerals, essential fatty acids and other nutrients **(13,14).** Because of its unusual high nutritional values, the Intergovernmental Institution for the use of Micro-algae *Spirulina* Against Malnutrition (IIMSAM) was launched in the middle 70's to promote *Spirulina* as high nutritional food to fight against starvation and malnutrition in the world **(19).** In addition, due to its concentrated nutrition, *Spirulina* was recommended by both National Aeronautics and Space Administration (NASA) and the European Space Agency (ESA) as one of the primary foods during long-term space missions. Starting at middle 1980's, great efforts and extensive investigations have been turned to the development of nutraceuticals or functional food for preventing or managing various diseases. *Spirulina* has become one of such nutraceutical food with diverse beneficial effects on an array of disease conditions. It has been reported that consumption of *Spirulina* as diet supplement has health benefits in preventing or managing hypercholesterolemia, hyperglycerolemia, certain inflammatory diseases, allergies, cancer, environmental toxicant- and drug-induced toxicities, viral infections, cardiovascular diseases, diabetes and other metabolic disease among others **(15,16,20).** In this review, emphasis is given to the potential beneficial effects of *Spirulina* on cardiovascular diseases with highlights on *Spirulina*'s hypolipidemic, antioxidant and antiinflamatory activities in preclinical and clinical studies. In addition, our current understanding on the mechanisms of action and the potential side-effects of *Spirulina* consumption are summarized.

HYPOLIPIDEMIC EFFECTS

Cholesterol is the building block for cell membrane and a precursor of steroid hormones. It forms several distinct particles with lipoproteins, mainly high density lipoproteins (HDL), low density lipoproteins (LDL) and very low density lipoproteins (VLDL). It is well established that LDL and VLDL cholesterol levels are atherogenic whereas HDL-cholesterol has protective effects on the development of atherosclerosis **(21,22).** Increased LDL and VLDL levels are the major independent risk factor for cardiovascular events whereas low level of HDL and elevated triglycerides (TG) are also recognized as residual risk for cardiovascular diseases **(23).** Agents with the ability to decrease LDL/VLDL or total cholesterol levels, increase HDL cholesterol or lower TG have beneficial effects on preventing cardiovascular diseases.

reclinical Studies

The hypolipidemic effect of *Spirulina* or its extracts have been demonstrated in various animal models including mouse, rat, hamster and rabbit. The cholesterol lowering activity of *Spirulina* was first reported in albino rats **(24),** followed by in mice **(25).** In the mouse study, supplementation of 16% *Spirulina* in a high fat and cholesterol diet resulted in a significant reduction in total serum cholesterol, LDL, VLDL cholesterol and phospholipids whereas serum HDL cholesterol was concurrently increased. In addition, high hepatic lipids induced by the high fat and cholesterol diet were markedly reduced by *Spirulina* consumption **(25).**

Since the initial report of hypolipidemic effects of *Spirulina*, several *in vivo* studies were carried out in rats and mice under various experimentally induced conditions. In one study **(26),** hyperlipidemia was induced in Wistar rats by a high fructose (68%) diet. Inclusion of increasing percentages of *Spirulina* (5, 10, and 15%) in the diet significantly improved the hyperlipidemic profiles. Correlating with such improvement in lipid profiles, *Spirulina* feeding resulted in a significant increase in lipoprotein lipase and hepatic triglyceride lipase activity. Such increased lipase activity by *Spirulina* was suggested as a mechanism for improving the hyperlipidemia induced by high fructose diet. In another study with rats **(27),** fatty liver was induced by intraperitoneal injection of carbon tetrachloride (CCl_4), resulting in an increase in liver total cholesterol and

triacylglycerols. However, such increases were significantly reduced by feeding oil extracts of *Spirulina* or defatted fraction of *Spirulina*. In addition, CCl_4-induced increase in total cholesterol level was completely prevented by feeding a diet containing whole *Spirulina*. A similar study was performed in CD-1 mice **(28).** Fatty liver was induced by a daily dose of simmvastatin (75 mg/kg body weight) for five days with a high cholesterol diet and 20 percent ethanol in the drinking water. Serum and hepatic triacylglycerols, total lipids and cholesterol were all significantly increased. However, *Spirulina* feeding for two weeks prior to the onset of fatty liver induction decreased hepatic total lipids by 40%, triacylglycerols by 50% and serum triacylglycerols by 45%, accompanied by a 45% increase in serum HDL cholesterol. The hypolipidemic activity of *Spirulina* was also confirmed in a diabetic mouse model **(29).** Diabetic condition was induced by administration of alloxan (250mg/kg body weight), resulting in evident fatty liver accompanied by altered serum and hepatic triacylglycerols and cholesterol levels. However, mice receiving a diet containing 5% *Spirulina* one week after the administration of alloxan for four weeks totally prevented fatty liver production, decreased serum and hepatic triacylglycerols, and fully or partially normalized HDL, LDL and VLDL cholesterol levels. The study also showed that female mice were more resistant to diabetes induction by alloxan whereas more responsive to *Spirulina* treatment than male mice.

The hypolipidemic effects of *Spirulina* observed in mice and rats were verified in two recent studies with hamsters **(30)** and rabbits **(31).** A group of hamsters fed an atherogenic diet supplemented with *Spirulina* or its ingredient phycocyanin exhibited lower total cholesterol, LDL and VLDL cholesterol whereas HDL cholesterol was not affected. Furthermore, aortic fatty streak area was significantly reduced in hamsters receiving *Spirulina* supplement, indicating the antiatherogenic activity of *Spirulina* **(30).** In the study with rabbits, hypercholesterolemia was induced by a high cholesterol diet and the effects of feeding *Spirulina* (0.5 g daily) for 30 and 60 days on the induced hypercholesterolemia was evaluated **(31).** At the end of the study, serum total cholesterol was decreased by 49% while HDL cholesterol was increased by 25%. No significant changes in serum triacylglycerols were observed.

Taken together, the results from studies with various animal models consistently demonstrate the hypolipidemic activity of *Spirulina*, lowering serum total cholesterol, LDL and VLDL fractions. In addition, other improvements in lipid profile were also observed in certain studies, including an increase in HDL cholesterol levels, decrease in atherogenic indices and triacylglycerol levels.

The first human study was carried out in 1988 with 30 healthy male volunteers with mild hyperlipidemia or hypertention **(32).** The 30 subjects were divided into two groups; one group received 4.2g of *Spirulina* daily for 8 weeks whereas the other group was given *Spirulina* for 4 weeks, followed by on regular food for another 4 weeks. Intake of *Spirulina* for 4 or 8 weeks significantly decreased total serum cholesterol and the decrease was more marked in mild hypercholesterolemic than in normocholesterolemic subjects. Discontinuation of *Spirulina* supplement for 4 weeks resulted in returning of the cholesterol level to the baseline (prior to *Spirulina* supplementation) and HDL levels were slightly increased but not statistically significant. There were no changes in serum triglycerides and body weight. In addition, no subjects reported adverse effects during the study. In a recent before-and-after clinical trial with 36 healthy volunteers (16 male and 20 female) between ages 18 to 65 **(33),** ingestion of *Spirulina* at a dose of 4.5g daily for 6 weeks decreased total plasma cholesterol and triacylglycerols by 10% and 28 %, respectively. Lipoprotein analysis showed that HDL cholesterol was increased by 15% whereas LDL cholesterol was significantly decreased. In addition, both systolic and diastolic blood pressures were significantly reduced in both men and women.

The hypolipidemic effect of Spirulina was also demonstrated in ischaemic heart disease patients with hypercholesterolemic condition (serum total cholesterol levels above 250mg/dL) **(34),** a total of 30 patients were divided into three groups. Two treatment groups received 2 or 4g of *Spirulina* daily for three months whereas control group was not supplemented with *Spirulina*. At the end of the supplementation, plasma total cholesterol was significantly decreased by 22.4% and 33.5% in groups receiving 2g and 4g *Spirulina*, respectively, whereas no significant change was detected in the control group. Lipoprotein fraction analysis showed that LDL and VLDL cholesterol levels were significantly reduced by 31% and 45%, and 22% and 23% in the two treatment groups, respectively. On the other hand, HDL was significantly increased by 11.5% and 12.8%. Furthermore, the concentration of triglycerides was significantly reduced by 22% and 23%.

Finally, a significant loss in body weight was observed in both treated groups whereas no change was detected in the control group. Thus, it was concluded that supplementation of *Spirulina* at a daily dose of 2 or 4 g for three months significantly improved the lipid profile of the patients with ischaemic heart disease.

Non-insulin-dependent diabetes mellitus (NIDDM) or type 2 diabetes mellitus is a recognized independent risk factor for cardiovascular diseases, such as coronary artery disease. The distinction between type 2 diabetes mellitus and cardiovascular disease has been blurred and prevention of cardiovascular diseases is becoming an integrated part of diabetes management. Patients with type 2 diabetes are frequently affected by atherosclerotic vascular disease. The abnormalities of both quantity and quality of lipoproteins in type 2 diabetes patients contribute to an increase in atherosclerotic vascular disease. So far, four human clinical studies have been performed to investigate the hypolipidemic and hyperglycerolemic effects of *Spirulina* in type 2 diabetic patients **(35–38).** The two early studies were carried out by Dr. Iyer's group in India **(35,36).** In a before-and-after study with 15 type 2 diabetes patients **(35),** supplementation of *Spirulina* at a dose of 2g daily for 2 months resulted in a significant decrease in total serum cholesterol, triglycerides and free fatty acid levels. Analysis of lipoprotein fractions revealed that LDL and VLDL cholesterol levels were appreciably reduced. Blood sugar and glycated serum protein levels were also significantly decreased. In a second randomized and controlled study **(36)**, twenty-five patients with type 2 diabetes mellitus were randomly assigned to a study or control group. Subjects in the study group received *Spirulina* at a dose of 2g/day for 2 months. At the end of the study, total serum cholesterol and LDL fraction were reduced whereas HDL was slightly increased in the study group. As a result, a significant decrease in atherogenic indices and the ratios of total cholesterol/HDL and LDL/HDL was achieved. Triglycerides and fasting and post prandial blood glucose levels were significantly reduced. Finally, the level of apolipoprotein B showed a significant fall with a concurrent significant increase in the level of apolipoprotein A1. Thus, the hypolipidemic and hypoglycerolemic effects of *Spirulina* were consistently detected in both clinical studies with type 2 diabetic patients.

The findings from the early studies were confirmed in the two recent human clinical trials with type 2 diabetic patients **(37,38).** Both trials were randomized, controlled studies with a relatively large sample size. One study enrolled 37 patients being randomly divided into a treatment or control group **(37).** Intake of *Spirulina* at a dose of 8g daily for 12 weeks significantly reduced total serum cholesterol, LDL fraction and triglyceride levels. Subjects with higher initial total cholesterol, LDL-cholesterol and triglyceride levels showed higher reduction. In addition, blood pressures were also decreased. The second trial included 60 male patients aging from 40 to 60 years **(38)**. The subjects were randomly assigned into two treatment groups or a control group. The two treatment groups received 1 or 2g *Spirulina* daily for two months. A significant decrease was observed in serum total cholesterol, triglycerides, LDL and VLDL cholesterol in the two treatment groups. Both fasting and post prandial blood glucose levels were also decreased by 16.3% and 12.5% in 1g-treated group and by 21.8% and 18.9% in 2g-treated group whereas no significant changes were detected in the control group. It was also found that mean carbohydrate and protein intake was significantly decreased in both treatment groups. Taken together, the data are consistent with the notion that *Spirulina* is a promising agent as a functional food supplement for controlling hyperglycerolemia and hypercholesterolemia and thus reducing cardiovascular risk in the management of type 2 diabetes.

The hypolipidemic benefit of Spirulina was also reported in patients with nephrotic syndrome and hyperlipidemia **(39)**. One group of patients received medication alone whereas the other group received medication and *Spirulina* capsules. Supplementation of *Spirulina* at a dose of 1g daily for 2 months resulted in a reduction in total serum cholesterol, LDL fraction and triglycerides by 46mg/dL, 33mg/dL and 45mg/dL, respectively. The ratios of LDL/HDL and total cholesterol/HDL were also decreased significantly. It was thus concluded that *Spirulina* supplementation was an effective approach to reduce the increased levels of lipids in patients with hyperlipidemic nephrotic syndrome.

Total and LDL cholesterol levels increase with aging **(40,41)** as does the incidence of cardiovascular disease **(42)**. Three human clinical studies have been carried out to investigate the therapeutic effects of *Spirulina* in elderly population **(43–45).** In one study with 12 subjects (6 male and 6 female) between the ages 60 and 75 **(43)**, subjects received a supplement of *Spirulina* at a dose of 7.5g/day for 24 weeks. Plasma concentrations

of triglycerides, total cholesterol and LDL fraction were decreased after 4 weeks of the supplementation while no changes were observed in dietary intake and anthropometric parameters. It was also noticed that no differences in the hypolipidemic effects of *Spirulina* were observed between mild hypercholesterolemic (cholesterol at or above 200mg/dL) and normocholesterolemic subjects (cholesterol below 200mg/dL). The second before-and-after trial included 26 elderly women aged over 60 with hypercholesterolaemic condition (serum total cholesterol above 200mg/dL) **(43).** Intake of *Spirulina* at a dose of 7.5mg/day for 8 weeks resulted in a significant reduction in serum levels of total cholesterol, LDL cholesterol and oxidized LDL. In addition, apolipoprotein B levels were also decreased. The most recent clinical trial was a randomized, double-blinded, and placebo-controlled study **(45).** Seventy eight subjects between the ages 60 and 87 were randomly assigned into a study or placebo group. After consumption of *Spirulina* at a dose of 8g/day for 16 weeks, total plasma cholesterol and LDL fraction were significantly reduced in female subjects whereas the lowering effect on plasma total cholesterol and LDL fraction was not statistically significant in male subjects. The levels of HDL fraction and triglycerides did not change after the intervention in both men and women. The data from those clinical trials largely support the notion that *Spirulina* supplement is beneficial for managing aging-induced alterations in lipid profile in the elderly population.

Taken together, although differences in study design, sample size and patient conditions resulting in minor inconsistency in response to *Spirulina* supplementation, the cumulative data from those studies clearly demonstrate the hypolipidemic activity of *Spirulina* in human. However, the majority of those human clinical trials are suffered with limited sample size and poor experimental design. Additional clinical trials with large sample size and high quality experimental design are warranted to confirm the hypolipidemic and hypoglycerolemic benefits of *Spirulina* in various target populations.

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