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Review article

# Response of Spirulina Supplementation in Lipid profiles against hypercholesterolemia and Associated Complications

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**ABSTRACT:**
Hyperlipidemia is a health state characterized by an increase in one or additional of the plasma lipids, phospholipids, triglycerides, cholesterol, and cholesterol esters along with the plasma lipoproteins likewise VLDL and LDL. Elevation of plasma lipids is the foremost risk issue connected with cardiovascular diseases. In the meantime, statins and fibrates stay the chief anti-hyperlipidemic means in favor of elevated triglycerides and plasma cholesterol cure with the severe side effects on the vital organs and muscles. Many targeting approaches of *Spirulina* utilization as an entire nutrient supplement express the prospect to normalize the lipid profiles owing to potential constituents in hyperlipidemia treatment during clinical trials. Multiple studies investigating the effectiveness and the potential clinical relevance of Spirulina in treating several illnesses have been performed and a few randomized controlled trials and efficient assessments put forward that this alga might improve numerous indications and may even have hyperlipidemia. The present review focuses mostly on hyperlipidemia types, lipid metabolism, actions and new drug targets for the elevated lipid profile treatment.

**Keywords**: Hyperlipidemia, Lipid metabolism, lipid profile, *Spirulina*, Clinical trials.

## 1. INTRODUCTION

Hyperlipidemia is considered one of the major risk factors causing cardiovascular diseases (CVDs).CVDs accounts for one-third of total deaths around the world, it is believed that CVDs will turn out to be the main cause of death and disability worldwide by the year 2020 [1, 2]. Hyperlipidemia is an increase in one or more of the plasma lipids, including triglycerides, cholesterol, cholesterol esters, and phospholipids and or plasma lipoproteins including very-low-density lipoprotein and low-density lipoprotein, and reduced high-density lipoprotein levels [3]. Hypercholesterolemia and hypertriglyceridemia are the main cause of atherosclerosis which is strongly related to ischemic heart disease (IHD) [4]. There is a strong relation between IHD and the high mortality rate. Furthermore, elevated plasma cholesterol levels cause more than four million deaths in a year [5].

Atherosclerosis is a process of arteries hardening due to the deposition of cholesterol in the arterial wall which causes narrowing of the arteries. Atherosclerosis and atherosclerosis-associated disorders like coronary, cerebrovascular, and peripheral vascular diseases are accelerated by the presence of hyperlipidemia [6]. Hyperlipidemia relates to increased oxidative stress causing significant production of oxygen free radicals, which may lead to oxidative modifications in low-density lipoproteins, which present a significant function in the initiation and progression of atherosclerosis and associated cardiovascular diseases [7].

### 1.1 Plasma lipoproteins composition and structure

Lipoproteins are macromolecules aggregate composed of lipids and proteins; this structure facilitates lipids compatibility with the aqueous body fluids. Lipoproteins are composed of non-polar lipids (triglycerides and cholesteryl esters), polar lipids (phospholipids and unsterilized cholesterol), and specific proteins known as apolipoproteins. Apolipoproteins are amphiphilic proteins that bind to both lipids and the plasma [8].

### 1.2 Lipoprotein classification

Chylomicrons (CM), very low-density lipoproteins (VLDL), low-density lipoproteins (LDL), intermediate-density lipoproteins (IDL), and high-density lipoproteins (HDL) are the five classes of lipoproteins present in plasma. These

classes are heterogeneous; they have different compositions, sizes, and densities [8]. As the triglyceride and cholesteryl ester contents of the core increase the lipoprotein size increases, and the density of lipoproteins increase also proportionally to their protein contents, and contrariwise to their lipid contents [9, 10].

**1.3 Lipid and lipoprotein metabolism**

Almost all the dietary fats are absorbed from the intestinal lumen into the intestinal lymph and packed into chylomicrons. These lipoproteins move into the bloodstream where they got hydrolyzed by endothelial lipoprotein lipase which hydrolyzes the triglyceride into glycerol and non-esterified fatty acids. After which the chylomicron remnants are absorbed in the liver and packaged with cholesterol, cholesteryl esters and ApoB100 to form VLDL. After the release of VLDL into the bloodstream, it will be converted into IDL by the action of lipoprotein lipase and hepatic lipase, where phospholipids and apolipoproteins are transferred back to HDL. Furthermore, after the hydrolysis by hepatic lipase, IDL will be converted to LDL and loss more apolipoproteins [11].

Peripheral cholesterol is returned to the liver by a reverse cholesterol transport pathway using HDLs which are originally synthesized by the liver and released into the blood. In the blood, HDL cholesterol is esterified by LCAT to cholesteryl ester and transferred to VLDL and chylomicrons to return to the liver through LDL receptor. Cholesteryl esters are transferred to LDL particles by CETP and then subjected to LDL-receptors mediated endocytosis. Finally, cholesteryl esters are hydrolyzed to cholesterol and extracted from the body as bile acid [12].

**1.4 Primary and secondary hyperlipidemia**

The main cause of hyperlipidemia includes changes in lifestyle habits in which the risk factor is a mainly poor diet in which fat intake from saturated fat and cholesterol exceeds 40 percent of the total calories uptake. Hyperlipidemia, in general, can be classified as primary and secondary hyperlipidemia in it is also called familial due to a genetic defect, it may be monogenic: a single gene defect or polygenic: multiple gene defects. Primary hyperlipidemia can usually be resolved into one of the abnormal lipoprotein patterns [13]. Secondary hyperlipidemia is acquired because it is caused by other disorders like diabetes, nephritic syndrome, chronic alcoholism, hypothyroidism, and with the use of drugs like corticosteroids, beta-blockers, and oral contraceptives. Secondary hyperlipidemia together with significantly per triglyceridemia can cause pancreatitis [14].

**1.5 Symptoms of hyperlipidemia**

Generally, hyperlipidemia does not have any obvious symptoms but they are usually discovered during a routine examination or until it reaches the danger stage of a stroke or heart attack. Patients with high blood cholesterol levels or patients with familial forms of the disorder can develop xanthomas which are deposits of cholesterol that may form under the skin, especially under the eyes. At the same time, patients with elevated levels of triglycerides may develop numerous pimple-like lesions at different sites in their body [15].

## 2. COMPLICATIONS ASSOCIATED WITH HYPERLIPIDEMIA

**2.1 ATHEROSCLEROSIS**

Hyperlipidemia is the most important risk factor for atherosclerosis, which is the major cause of cardiovascular disease. Atherosclerosis is a pathologic process characterized by the accumulation of lipids, cholesterol, and calcium and the development of fibrous plaques within the walls of large and medium arteries [16].

**2.2 Coronary artery disease (CAD)**

Atherosclerosis, the major cause of coronary artery disease, is characterized by the accumulation of lipids and the formation of fibrous plaques within the wall of the arteries resulting in the narrowing of the arteries that supply blood to the myocardium and results in limiting blood flow and insufficient amounts of oxygen to meet the needs of the heart. An elevated lipid profile has been connected to the development of coronary atherosclerosis [17].

**2.3 Myocardial infarction (MI)**

MI is a condition that occurs when blood and oxygen supplies are partially or completely blocked from flowing in one or more cardiac arteries, resulting in damage or death of heart cells. The occlusion may be due to ruptured atherosclerotic plaque. The studies show that about one-fourth of survivors of myocardial infarction were hyperlipidemic [18].

**2.4 Ischemic stroke**

Stroke is the fourth leading cause of death. Usually, strokes occur due to blockage of an artery by a blood clot or a piece of atherosclerotic plaque that breaks loose in a small vessel within the brain. Many clinical trials revealed that lowering low-density lipoprotein and total cholesterol by 15% significantly reduced the risk of the first stroke [19].

**2.5 Drugs classes for hyperlipidemia**

Since LDL is the major atherogenic lipoprotein, reduction of this lipoprotein would be expected to reduce atherosclerosis and therefore reduce cardiovascular adverse effects. In addition to high LDL, the presence of risk factors and CHD should qualify to initiate drug therapy along with lifestyle changing. Monotherapy has been shown to be effective in treating hyperlipidemia, but combination therapy may be required for a comprehensive approach. Currently, antihyperlipidemic drugs contain five major classes that include statins, fabric acid derivatives, bile acid-binding resins, nicotinic acid derivatives, and drugs that inhibit cholesterol absorption [20].

## 3. *SPIRULINA*

*Spirulina* is an oxygenic photosynthetic blue-green alga or cynobacterium grown worldwide in fresh and marine waters. *Spirulina* is well known complete dietary supplement for mankind. Currently, *Spirulina* corresponds to a significant

staple diet in humans and has been applicable as a foundation of protein and vitamin supplements in humans with no significant side effects. *Spirulina* now belongs to the substances that are listed by the US Food and Drug Administration under the safe category. Due to the high content of highly valuable proteins, indispensable amino acids, vitamins, beta carotene, other pigments, mineral substances, essential fatty acids, and polysaccharides, *Spirulina* has been created as appropriate for bioactive additives [4]. It contains several functional complexes that supply its antioxidant, anti-inflammatory, and immunostimulant potential, such as flavonoids, phenols, and polysaccharides. The essential active ingredients are phycocyanin, phycocyanobilin, and beta carotene. Phycocyanin belongs to a group called phycobiliproteins, which are proteins present in cyanobacteria and capture light to be passed onto chlorophylls during photosynthesis. The structure is similar to bilirubin, given its antioxidant properties. Bilirubin is a pigment found in bile from the breakdown of hemoglobin that gives bile its orange-yellow hue [4]. Bilirubin has been found to have effective antioxidant activity by inhibiting oxidation and radical byproducts in plasma proteins and aromatic amino acid residues.

Supplementations of *Spirulina* reduce the blood cholesterol, Low-Density Lipoprotein, triglyceride, and High-Density lipoprotein cholesterol induction which are fairly functional in heart disease patients [7]. Chemical analyses of *Spirulina* indicate that it is an excellent source of macro and micronutrients their constituents are-

Protein: *Spirulina* contains a high amount of protein between 55-70% by the dry weight. Protein contains all the essential amino acids which are very useful for the better yield of the biomass from *Spirulina*.

**Essential fatty acids:** *Spirulina* has a high amount of polyunsaturated fatty acids 1.5-2.0% of 5-6% total lipid. *Spirulina* is rich in linolenic acid, stearidonic acid, eicosapentaenoic acid and arachidonic acid.

**Phytopigments:** *Spirulina* contains many pigments including chlorophyll-a, xanthophylls, echinenone, myxoxanthophyll, beta carotene, chlorophyll, etc [21]. Pigment phycocyanin has been reported to have significant antioxidant, anti-inflammatory, hepatoprotective, and broad-spectrum radical scavenging properties. Spirulina plays a role as lipophilic antioxidants and they are thought to be responsible for the therapeutic property of carotene as a hypolipidemic agent [22].

**Minerals**: *Spirulina* is a rich source of potassium, calcium, chromium, copper, iron, magnesium, manganese, phosphorus, sodium and zinc.

**Vitamins**: *Spirulina* contains vitamin B1, B2, B3, B6, B12, Vitamin C, Vitamin D and Vitamin E.

**Antioxidants:** *Spirulina* enclose antioxidant organic complex and enzymes that inhibit the oxidative damage, which results mainly from decreased oxygen states. This escorts to the creation of ROS similar to hydroxyl free radical, singlet oxygen and anion of superoxide radical, hydrogen peroxide [23]. Superoxide and catalase are the foremost enzymes that restrict oxidative damage which are constituent of *Spirulina* along with polyphenols which proceed as antioxidants action [24]. Water soluble Ascorbate (vitamin C) and the lipid-soluble α- tocopherol (vitamin E) and carotenoids also show their potential antioxidants action.

## 4. *SPIRULINA* CLINICAL TRIAL FINDINGS AGAINST HYPERLIPIDEMIA

In a study, rabbits have induced hypercholesterolemia by feeding a high cholesterol diet (350 mg/d) and the outcomes of supplementing this diet with 0.5g/d *Spirulina* were calculated by measuring the points of serum total cholesterol, triacylglycerol, and high-density lipoprotein after 30 and 60 days of experimentation. Finding directed that levels of serum cholesterol decreased from 1,054±101 $mgdL^{-1}$ in the rabbits fed a cholesterol diet without *Spirulina* to 516±163 $mgdL^{-1}$ to those given to eat with a high cholesterol diet supplemented with *Spirulina* ($p<0.0001$). The addition of *Spirulina* to the cholesterolemic diet did not cause significantly diminish the triacylglycerols levels. *Spirulina* deliberates phycocyanin, a protein pigment extracted from *Spirulina*, caused hypocholesterolemic action in rats [25]. The occurrence of antioxidant composites like phycocyanin, phenolic compounds, and poly-unsaturated fatty acids in the microalgae *Spirulina* can be the cause of the *Spirulina* assets on the decrease of serum lipids points. In vivo, the antioxidant ability of *Spirulina* extracts was assessed through the plasma of male rats getting 2 and 7 weeks daily 5 mg of the extract [26].

Plasma antioxidant capability was determined in homogenated brain incubated at 37°C for 1 h. During treatment, the antioxidant ability of plasma was 71% for the experimental faction and 54% for the untreated group [27]. The finding considered that the sum of b-carotene, a-tocopherol, and phenolic acids present in *Spirulina* extracts was accountable via the antioxidant action. The *Spirulina* poly-unsaturated fatty acids also displayed noteworthy action having the therapeutic properties to reduce blood cholesterol levels [28, 29]. Therefore, it could be finished off that supplementing $0.5g.d^{-1}$ of *Spirulina* reduces the induced hypercholesterolemia in rabbits. The serum cholesterol stages were reduced in the rabbits fed a hypercholesterolemic diet exclusive of *Spirulina* in contrast to those fed a hypercholesterolemic diet complemented with *Spirulina*. In contrast, the serum levels of HDL were higher in the groups fed with *Spirulina* [30, 31]. These results showed the potential of biomass *Spirulina* to decline the total cholesterol and to enlarge the serum HDL-cholesterol, reflecting a defensive aspect next to the atherosclerosis development.

Cell membrane and steroid hormones are based on cholesterol that constructs the cell. Cholesterol shapes

numerous separate elements with lipoproteins, mainly high-density lipoproteins, low-density lipoproteins, and very-low-density lipoproteins. HDL-cholesterol has defensive impacts on the expansion of atherosclerosis, whereas LDL and VLDL cholesterol points are atherogenic [32, 33]. Elevated LDL and VLDL stages are the chief independent risk feature intended for cardiovascular incidents while low downstage of HDL and raised triglycerides are also familiar as remaining risks for cardiovascular diseases [34].

*Spirulina* discontinuation supplementation for 4 weeks resulted in the cholesterol stage the prior to *Spirulina* supplementation (baseline). The ability to decrease low-density lipoproteins, very-low-density lipoproteins or total cholesterol levels, increase HDL cholesterol or inferior triglyceride have valuable achieve in preventing cardiovascular diseases and HDL levels were slightly increased but not statistically significant. There were no alters in body weight and serum triglycerides. In addition, no subjects accounted for unfavorable consequences during the study [35].

The *Spirulina* hypolipidemic result was also displayed in ischaemic heart disease patients through a hypercholesterolemic state in which cholesterol levels rise above 250mg/dL. Total of 30 patients were separated into three groups. Two treatment groups be given 4g of *Spirulina* daily intended for three months but the control group was not complemented with *Spirulina* [36]. At the supplementation end, total cholesterol was considerably diminished through 22.4% and 33.5% in groups receiving 2g and 4g *Spirulina*, whereas no significant transform was perceived in the untreated group. Analyses of lipoprotein fractions demonstrated a significant reduction of LDL and VLDL cholesterol stage in the two separate treatment clusters. Conversely, HDL was noteworthy increased by 13%. In addition, the triglycerides concentration was considerable decrease by 23%. In conclusion, a major loss in body weight was examined in both treated groups while in the control group no modification was perceived. Consequently, it was concluded that *Spirulina* supplementation (4g) significantly recover the patient's lipid profile level having ischaemic heart disease within three months at a daily.

Two months continued with two treatment groups with 1 or 2g *Spirulina* supplementation exhibited beneficial action. Declinment was detected in serum lipid profiles in the different groups of treatment. Blood glucose levels (fasting and postprandial) were also diminished in 1g treated group and by 21.8% and 18.9% in the 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. Relative consequences of exogenous fatty acid supplementations on the lipids as of the *Spirulina* documented [37]. Opposite outcomes on cholesterol metabolism and their mechanisms are encouraged as an outcome of dietary palmitic and oleic acid in hamsters rats [38].

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 also decreased significantly. It was thus concluded that *Spirulina* supplementation was an effective approach to reducing 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 [32]. Three human clinical studies have been carried out to investigate the therapeutic effects of *Spirulina* in the elderly population [42-44]. In one study with 12 subjects (6 male and 6 female) between the ages 60 and 75, 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 dissimilarities in the hypolipidemic effects of *Spirulina* were monitored between mild hypercholesterolemia (cholesterol at or above 200mg/dL) and normocholesterolemic (cholesterol below 200mg/dL). The subsequent before and after trial included 26 elderly women aged over 60 with the hypercholesterolaemic condition [45]. Intake of *Spirulina* at a dose of 7.5mg/day for 8 weeks outcome in a noteworthy drop in serum levels of total cholesterol, LDL cholesterol, and oxidized LDL, in addition, apolipoprotein B levels were also diminished. *Spirulina* supplementation on obesity shared disorder recently documented, finding observed as *Spirulina* had shown hypolipidemic impact in obese subjects distress from lipid disorders owing to *Spirulina* action. Spirulina (till 14g) is secure and intended for the recovery of dyslipidemia supported on LDL-C receptors [46]. Adequate studies have not been executed in order to make a strong statement that *Spirulina* has minimal to no toxic consequences. *Spirulina* is currently marketed as a supplement for its high antioxidant, anti-inflammatory, immunomodulatory, and hyperlipidemia activities. Investigation shows *Spirulina's* diverse activities have established favorable in the prevention and treatment of CVD [47]. A clinical study found a significant decline in LDL: HDL ratio in the case of diabetes who has agreed on *Spirulina* [48, 49].

Although the hypolipidemic consequence of *Spirulina* has been revealed in preclinical and clinical studies, our consideration of its mechanism of action is approximately lacking. The active components in Spirulina accountable in favor of the hypolipidemic movement remain to be identified. In a study with *Spirulina* concentrate, it was found that phycocyanin could connect cholesterol metabolites to bile acids and diminish cholesterol solubility [50]. Feeding rats with phycocyanin noteworthy augmented fecal excretion of bile acid cholesterol. It was thus proposed that declines in intestinal cholesterol and bile acid assimilation by phycocyanin feeding may correspond to a mechanism with regard to *Spirulina*-based hypocholesterolemic action. Water-soluble protein phycocyanin enriched in *Spirulina* their intake significantly decreases in serum total cholesterol and atherogenic index whereas serum HDL-C was concurrently increased. It was thus put forward that phycocyanin might be the active ingredient in *Spirulina* responsible for the hypolipidemic action [51-53]. Conversely, additional studies with elevated purified or expressed phycocyanin are necessitated to prove the results.

## 5. CONCLUSION

Recently, great attention and extensive studies have been devoted to evaluating the therapeutic benefits of *Spirulina* on various diseased conditions including hypercholesterolemia, hyperglycerolemia, cardiovascular diseases, inflammatory diseases, cancer, and viral infections. The cardiovascular benefits of Spirulina primarily result from its hypolipidemic, antioxidant, and anti-inflammatory activities. Data from preclinical studies with various animal models consistently demonstrate the hypolipidemic activity of *Spirulina*. In addition, efforts should be taken to standardize the dose of *Spirulina* in future human clinical studies. *Spirulina* is generally considered safe for human consumption supported by its long history of use as a food source and its favorable safety profile in animal studies.

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