Complementary Therapies in Medicine 42 (2019) 137–144

Contents lists available at ScienceDirect

Complementary Therapies in Medicine

journal homepage: www.elsevier.com/locate/ctim

The effects of Spirulina supplementation on metabolic syndrome components, its liver manifestation and related inflammatory markers: A systematic review

Reyhaneh Yousefi[a], Atoosa Saidpour[b], Azadeh Mottaghi[c,*]

[a] M.Sc. in Nutrition, Preventive Medicine and Public Health Research Center, Iran University of Medical Sciences, Tehran, Iran
[b] Assistant Professor (PhD) of Nutrition, Department of Clinical Nutrition & Dietetics, Faculty of Nutrition and Food Technology, National Nutrition and Food Technology Research Institute, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[c] Assistant Professor (PhD) of Nutrition, Research Center for Prevention of Cardiovascular Diseases, Institute of Endocrinology and Metabolism, Iran University of Medical Sciences, Tehran, Iran

ARTICLE INFO

Keywords:
Spirulina
Arthrospira
Metabolic syndrome

ABSTRACT

Aims: The aim of this systematic review was to assess the effects of Spirulina supplementation on metabolic syndrome components, its liver manifestation and related inflammatory markers.
Methods: We searched PubMed and Scopus (up to August 2017) to identify relevant studies. English randomized controlled trials (RCTs) investigating the effects of Spirulina supplementation on factors associated with metabolic syndrome in human models, were included in the review.
Results: Among 720 articles related to Spirulina in the primary search, 22 of them were eligible human RCTs and finally 18 of them were included in the review. The systematic review revealed that oral dosage range of 1-19gr/day for 0.5–6 months of Spirulina supplementation have positive effects on metabolic syndrome components.
Conclusion: Spirulina can be possibly administered as a safe and efficient supplementation in the case of metabolic syndrome components, although determining the optimal dosage and period of supplementation still needs further investigations.

1. Introduction

Metabolic syndrome (MetS) is defined as a cluster of interconnected physiological, biochemical, clinical and metabolic abnormalities including; atherogenic dyslipidemia, hypertension, glucose intolerance, abdominal obesity proinflammatory state, and a prothrombotic state.[1,2] MetS is also a worldwide issue of public health as the reports of incidence rate is growing over time, and its worldwide prevalence has been estimated between 10–84%, depending on the region, urban or rural environment, composition (sex, age, race, and ethnicity) of the population, and the definition of the syndrome used.[1] The prevalence of risk factors of MetS, namely obesity, has also experienced an upward trend among children as well as adults.[3,4] Nowadays nutraceuticals are highly regarded as alternative therapies in order to prevent such health problems[5] and in the same way microalgae Spirulina is also discussed as an alternative treatment.[6,7]

Spirulina (Arthrospira) is a spiral blue-green microalgae and a member of cyanobacterium subgroup.[8–11] Spirulina Platensis (SP), Spirulina Maxima (SM) and Spirulina Fusiformis (SF) are the main edible species.[12] Spirulina is rich in protein with high quality and almost all essential amino acids.[9,10] In addition, it is a rich source of minerals, vitamins and antioxidants including phycocyanins, carotenoids, tocopherols and phenolic compounds.[8–16] Spirulina also contains 4–7% lipid that is mostly composed of essential poly unsaturated fatty acids like ϒ-linolenic acid, α-linoleic acid, Eicosapentaenoic acid (EPA), Docosahexaenoic acid (DHA). [10,12] Thanks to its nutrient content Spirulina has been represented as a nutraceutical food,[17] as it has been proposed as an effective supplementation improving antioxidant status and protecting cancer incidence.[18,19] Although Spirulina is found to be effective in improving some components of MetS in animal studies,[20–22] the scientific literature according to human survey is relatively heterogeneous. The current systematic review aims at summarizing published data on the beneficial effects of spirulina supplementation in relation to MetS.

2. Methods

We have done this review to adhere to the Preferred Reporting Items

* Corresponding author.
E-mail addresses: r.yousefi@sbmu.ac.ir (R. Yousefi), a.saidpour@sbmu.ac.ir (A. Saidpour), Mottaghi.a@iums.ac.ir (A. Mottaghi).

https://doi.org/10.1016/j.ctim.2018.11.013
Received 2 September 2018; Received in revised form 6 October 2018; Accepted 9 November 2018
Available online 12 November 2018
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for Systematic Review and Meta-Analyses (PRISMA) guidelines.[23]

2.1. Search strategy and study selection

Two search engines (Pubmed and Scopus) were investigated up to August 2017, in order to find relevant articles surveying the impact of spirulina supplementation on MetS components. The search terms (in title, abstract or keywords) are as follows: (Spirulina OR Arthrospira) AND (obes* OR "body mass index" OR BMI OR "waist circumference" OR "hip circumference" OR "waist to hip ratio" OR WHR OR anthropomet* OR "blood pressure" OR hypertension OR "serum triglyceride" OR "serum low density lipoprotein cholesterol" OR "serum high density lipoprotein cholesterol" OR LDL-C OR HDL-C OR "serum total cholesterol" OR "insulin resistance" OR "fasting blood glucose" OR FBS OR "blood glucose" OR diabet* OR "fatty liver" OR SGOT OR SGPT OR ALT OR AST OR "metabolic syndrome" OR inflammat* OR antioxidant OR "oxidative stress"). Finally in this systematic literature search, randomized control trials on human subjects were included in the review. A literature search was performed on studies and was restricted to articles published in English. Citations were stored and managed with the reference software EndNote X6.

2.2. Eligibility criteria

We considered all clinical trials describing association of Spirulina supplementation with MetS components including human studies and excluded all animal studies, narrative, nonsystematic reviews, and conference abstracts.

3. Results

3.1. Search results

After the initial search, the studies were examined in order to evaluate their relevance to the specific issues and compliance with the inclusion criteria (Fig. 1). In the beginning, 974 articles were obtained. After excluding duplicate articles (n = 227), a number of 720 papers remained for further investigation. Among these number of articles, 497 of them were irrelevant papers that mostly discussed Spirulina's breeding condition, laboratory methods for isolation of different components of Spirulina or Spirulina supplementation effects on non-laboratory animal species. After further assessments, we also eliminated another 201 papers that were animal studies, reviews and studies on mechanisms of action of different components of Spirulina. Among the remaining 22 human randomized clinical trials, three of them were articles without accessible full-text and one of them was a study protocol. Eventually, a series of 18 RCTs met the inclusion criteria and were preferred for the final systematic review (Table1).

3.2. Spirulina supplementation and body weight

Spirulina was recently discussed as an efficient supplementation for weight management. As Zeinalian et al. found a 12 week supplementation of SP (1 g/day) effective for reducing body weight and BMI.[24] Three months of SM supplementation at a dose of (2 g/day) in hypertensive and overweight patients also resulted in significant decrease in weight and body mass index[25] and decrease in BMI and waist circumference referring to another study.[26] In another survey of six months intervention with 6 g/day Spirulina, a significant weight reduction was reported in non-alcoholic fatty liver disease (NAFLD) patients.[27]

According to Fujimoto et al.[28] Spirulina is effective in body weight reduction through reducing the infiltration of macrophages into visceral fat and preventing liver lipid accumulation and oxidative stress. Spirulina is rich in phenylalanine, a potent releaser of cholecystokinin that affects the brain's appetite center, which in turn acts as a body weight suppressant.[27] It has been already proved that antioxidants are effective in obesity treatment through different mechanisms, including lipase inhibitory effect, suppressive effect on food intake, inhibitory effect on adipocyte differentiation, stimulatory effects on energy

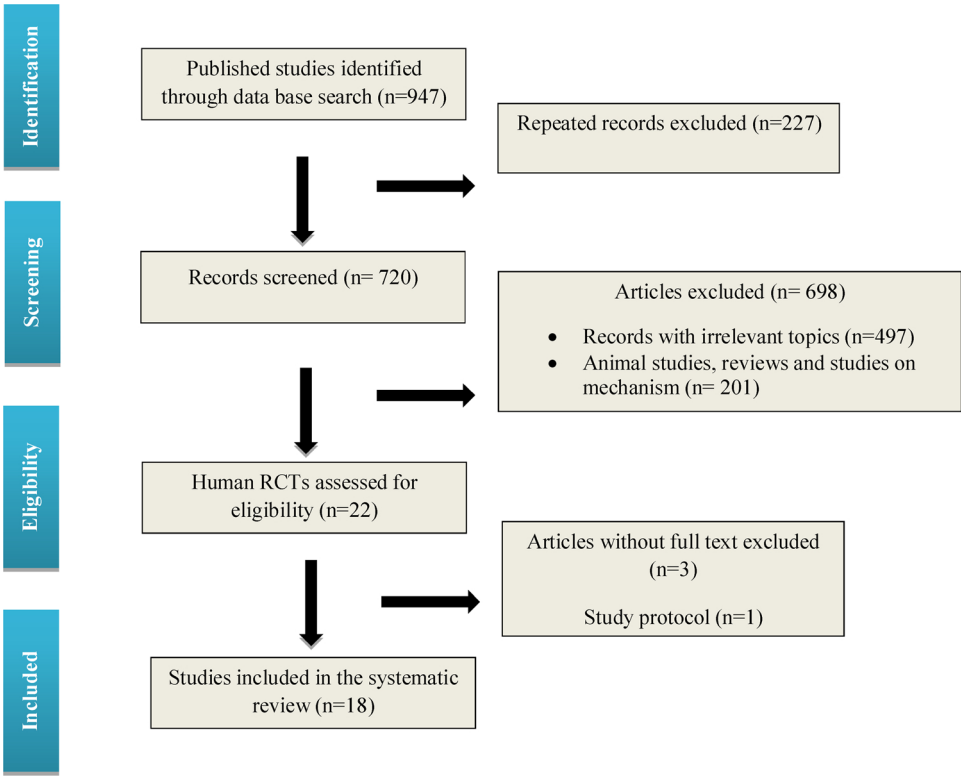

Fig. 1. Flow diagram of the study selection procedure showing the number of eligible RCTs for the systematic review.

Table 1
Selected studies analyzing the impact of Spirulina supplementation on metabolic syndrome components.

Author	Year	Location	Design	Duration of trial	Inclusion criteria	Supplementation form species	Spirulina	Participants	Age(years)	Male %	Results
Szulinska et al.	2017	Poland	Double-blind placebo-controlled trial	3 months	obese patients receiving standard pharmacological antihypertensive treatment	500 mg capsules Spirulina Maxima	2 g/day	Case: n = 25 Control: n = 25	Case: 49.3 ± 8.7 Control: 50.2 ± 7.2	50%	Decrease in body mass, BMI, WC, LDL-C, IL-6 and improved total antioxidant status and insulin sensitivity in supplemented patients compared to placebo group
Zeinalian et al.	2017	Iran	Randomized double-blind placebo-controlled trial	12 weeks	BMI ≥ 30 kg/m2	500 mg pills Spirulina Platensis	1 g/day	Case: n = 29 Control: n= 27	20–50	16	Body weight, BMI, serum TC and appetite were decreased significantly in Spirulina group
Park et al.	2016	Korea	Randomized double-blind placebo-controlled trial	12 weeks	78 elderlies	— —	8 g/day	Case: 41 Control: 37	60-78	55	Lower plasma concentration of TC and LDL-C, increase in IL-2, IL-2/IL-6 ratio and total antioxidant status level, decrease in thiobarbituric acid reactive substances level in the non-obese group receiving Spirulina
Miczke et al.	2016	Poland	Randomized double-blind placebo-controlled trial	3 months	Hypertensive and overweight patients without cardiovascular disease	2 g pills Spirulina maxima	2 g/day	Case: n = 20 Control: n = 20	Case: 53.0 ± 5.8 Control: 53.6 ± 5.5	52.5	Reduced BMI, weight and SBP in Spirulina receiving group
Ismail et al.	2015	Bangladesh	Randomized placebo-controlled, parallel-group trial	2 months	COPD patients controls with no respiratory problems	500 mg capsules —	1 g/day 2 g/day	Case:n_1 = 15, n_2 = 15 Control: n= 20	45- 60	100	Improved antioxidant activity and blood lipid profile
Winter et al.	2014	Cameroon	Randomized, double-blind, placebo-controlled trial	3 months	HIV-infected, adult female receiving pre-highly-active antiretroviral therapy	500 mg tablets Spirulina platensis	5 g/day	Case: n = 28 Control: n= 30	23-35	0	An increase in TAOS for spirulina receiving patients vs. the decrease in the placebo group.
Mazokopakis et al.	2014	Greece	open-label, non-randomized trial	6 months	Adults with NAFLD	3 g sachets Spirulina platensis	6 g/day	Case: n = 15	29-62	86.6	Reduced TG, LDL-C, TC, weight, HOMA-IR, TC/HDL-C and increased HDL-C
Mazokopakis et al.	2013	Greece	open-label, non-randomised trial	3 months	Adults with recently diagnosed dyslipidaemia	0.5 g tablets Spirulina platensis	1 g/day	Case: n = 52	Case: n=47	61.5	Mean level of TG, LDL-C, TC, and TC/ HDL-C decreased significantly
Torres-Duran et al.	2012	Mexico	Quasi-experimental study	15 days	volunteer runners in a nonprofessional level with at least 1 year practice before the study	powder Spirulina maxima	5g in 250 mL water daily	Case: n = 41	10-26	51	Reduced fasting plasma triacylglycerol concentrations
Marcel et al.	2011	Cameroon	Randomized clinical trial	2 months	insulin-resistant HIV-infected patients	powder Spirulina platensis	19 g/day	Spirulina: n = 17 Soybean: n=16	37.5	21.2	larger increase in insulin sensitivity in the Spirulina vs. soybean group
Ngo-Matip et al	2010	Cameroun	Multicentre single-blind, randomized, parallel-group trial	12 months	HIV antiretroviral-naïve patients	package of powder spirulina platensis	10 g/day	Case: 82 Control: 87	Case: 36.01 ± 9.44 Control: 35.43 ± 10.04	25.6	Significant increase in HDL-C and a significant decrease in TC, LDL-C, and TG
Ferreira-Hermosillo et al.	2010	Mexico	Case report	3 months	Non-alcoholic fatty liver diseases patients	0.5 g tablets Spirulina maxima	4.5 g/day	Case: n = 3	A 43-year-old man, a 77-year-old man and a 44-year-old woman	—	improved blood lipids
Kalafati et al.	2009	Greece	A double-blind, placebo-controlled, counterbalanced crossover study	4 weeks	healthy moderately trained men	— Spirulina platensis	6 g/day	Case: n= 9	23.3 ± 1.7	100	Higher GSH levels at rest and 24 h after exercise and lower thiobarbituric acid-reactive substance levels after supplementation
Lee et al.	2008	Korea	Randomized placebo-controlled, parallel-group trial	12 week	Patients with type 2 diabetes	0.2 g pills of freeze-dried Spirulina Spirulina platensis	8 g/day	Case: n = 19 Control: = 18	Case: 52.1 ± 2.3 Control: 54.5 ± 1.5	54	Lower DBP, plasma malondialdehyde and TG level, increased plasma adiponectin level
Park et al.	2008	Korea	Randomized double-blind	16 weeks	Volunteers aged > 60 years		8 g/day	Case: n = 41 Control: n = 37	58.5	58.5	lower plasma cholesterol, higher plasma IL-2 concentration, and a

(*continued on next page*)

Table 1 (*continued*)

Author	Year	Location	Design	Duration of trial	Inclusion criteria	Supplementation form species	Spirulina	Participants	Age(years)	Male %	Results
			placebo-controlled parallel trial			0.2 g pills of freeze-dried Spirulina —					reduction in IL-6 concentration in males An increased superoxide dis-mutase activity In females
Torres-Duran et al	2007	Mexico	Quasi-experimental study	6 weeks	Overweight patients	0.5 g tablets Spirulina Maxima	4.5 g/day	Case: n= 36	18–65	44.4	Decreased TAG and the LDL-C concentrations, indirectly declined TC and increased HDL-C values and also reduced systolic and diastolic blood pressure
Parikh et al.	2001	India	Randomized Placebo controlled, parallel group trial	2 months	Patients with type 2 diabetes	500 mg tablets —	2 g/day	Case: n = 15 Control: n = 10	Case: 53.8 ± 7.2 Control: 54.6 ± 5.4	60	lower fasting blood glucose, postprandial blood glucose levels, HbA1c, TC, LDL-C and increased HDL-C
Mani et al.	2000	India	Randomized placebo-controlled, parallel-group trial	2 months	non-insulin dependent diabetes mellitus patients	1 g tablets —	2 g/day	Case: n = 15 Control: n = 7	Case: 47.80 ± 2.35 Control: 53.40 ± 2.32	50	Decreased blood sugar levels, glycated serum protein levels, TG, TC, free fatty acid levels, LDL-C, VLDL-C and HDL-C/LDL-C ratio

BMI: Body mass index, DBP: diastolic blood pressure, NAFLD: non-alcoholic fatty liver disease, TG: triglycerides, LDL-C: low density lipoprotein cholesterol, HDL-C: high density lipoprotein cholesterol, TC: total cholesterol, HIV: human immunodeficiency virus, COPD: obstructive pulmonary disease, HOMA-IR: Homeostatic model assessment- insulin resistance, IL: interleukin, TAOS: total antioxidant capacity of the serum, WC: waist circumference.

expenditure, and regulatory effect on lipid metabolis.[29] Therefore, regarding the antioxidant content of Spirulina[12] and improvement of the body's total antioxidant capacity after Spirulina supplementation,[11,30] it is expected that this supplementation may play a successful role in weight reduction. On the other hand, some of the human studies reported no improvement in anthropometric indices following Spirulina supplementatio.[8,14] Anyway, further studies are necessary in order to figure out the mechanism by which Spirulina affects human body weight.

3.3. Spirulina supplementation and hypertension

Elevated blood pressure is one of the metabolic abnormalities that affect patients with MetS. The positive effect of 4.5 g/day of Spirulina supplementation for 6 weeks on blood pressure was reported in a sample of overweight patients.[31] A reduction in blood pressure was also indicated in a sample of patients with type-2 diabetes after an intervention consisting of consuming 8 g/day Spirulina for 12 week.[14] In addition, three months of regular consumption of Spirulina at a dose of 2 g/day resulted in improvement in blood pressure in overweight patients with hypertensio.[25]

Phycocyanin (a blue dye antioxidant) is responsible for ameliorating blood pressure by enhancing endothelial nitric oxide synthase (eNOS) expression in the aorta when stimulated by adiponectin. Furthermore, it has been suggested that peptides that inhibit angiotensin I converting enzyme (ACE) and renin-angiotensin system are derived from Spirulina, that may play a critical role in lowering blood pressur.[32] It is also recommended that C-phycocyanin inhibits platelet aggregation through inhibition of calcium mobilization and mediation of free radicals released by platelet.[31]

On the contrary, some of the interventional studies have not verified the hypotensive effect of Spirulina supplementation, since the blood pressure of the studied samples remained unchanged after the intervention.[8,27] In order to ascertain the hypotensive effect of Spirulina, further studies with larger sample sizes and longer durations are required.

3.4. Spirulina supplementation and lipid metabolism

A spectrum of lipid abnormalities occurs in MetS which includes perturbations in the structure, metabolism, and biological activities of both atherogenic and antiatherogenic lipoproteins. Impaired lipid metabolism is mostly caused by high insulin resistance and leads to oxidative stress and an endothelial dysfunction, thereby reinforcing macrovascular atherosclerotic disease.[1] Spirulina has been highly recommended and widely used for lipid abnormalities treatment in recent years and almost all studies reported that 1–10 g/d Spirulina supplementation for 15 days to 6 months led to reduction in at least one or more blood lipid measures including TC, TG, LDL-C, VLDL or increased HDL-C.[8,13,14,24,26,27,31,33,34] In a study on a rat model, it was found that a constituent of SP inhibited jejunal cholesterol absorption and ileal bile acid reabsorption and it was attributed to the C-phycocyanin content of Spirulina.[35] C-phycocyanin also inhibits oxidative changes in plasma proteins and aromatic amino acid residues[36]; therefore increases the activity of lipoprotein lipase enzyme which is a key enzyme in the metabolism of triglycerides and lipoproteins.[37] It is also suggested that phycocyanin can effectively inhibit pancreatic lipase[38] and on the other hand, active compounds of Spirulina can bind cholesterol metabolites bile acids, so cholesterol solubility decreased and fecal excretion of cholesterol and bile acids increased.[39] Furthermore, Spirulina contains 5–6% essential fatty acids, including approximately 30% of γ -linolenic acid (GLA) and linolenic acid (LA), which can prevent the accumulation of fat and cholesterol in the body.[8] In a study on HepG2 cells, a human hepatoma cell line, the following potential mechanisms were suggested for the lipid lowering: Spirulina lipid extract significantly downregulated the expression of 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMGR), the rate-limiting enzyme in cholesterol biosynthesis, and also suppressed the expression of LDL receptor (LDLR) and lipogenic genes, such as fatty acid synthase and stearoyl-CoA desaturase 1. The repression of lipogenic genes was induced concurrently with decreased mature forms of sterol-regulatory element-binding protein-1 (SREBP-1) and SREBP-2, which effectively regulate transcription of the above-mentioned genes.[40] Thus Spirulina consumption is proposed as a beneficial supplementation for improving blood lipids.

3.5. Spirulina supplementation and glucose metabolism

Impaired glucose tolerance is a key MetS phenotypes, defining as a condition in which a normal insulin concentration does not lead to efficient insulin response in the peripheral target tissues.[1] Along with other functional foods applied to improve insulin resistance, Spirulina is also discussed as an alternative nutritional therapy. In an examination on obese patients receiving antihypertensive treatment consumption of 2 g/day of SM resulted in improved insulin sensitivity ratio compared to the placebo group. For patients with type 2 diabetes, Spirulina supplementation(2 g/day) for two months resulted in lower fasting blood glucose, postprandial blood glucose and HbA1c levels.[33] SP supplementation with a dose of 6 g/day for six months was also successful in reducing HOMA-IR in adults with NAFLD.[27] Moreover in a sample of insulin-resistant HIV-infected patients, high-dose (19 g/day) of Spirulina supplementation for two months resulted in a significant rise in insulin sensitivity in comparison with soybean consumption.[41] A study of non-insulin dependent diabetes mellitus patients demonstrated that 2 g/day Spirulina supplementation for two months led to decreased blood sugar levels and glycated serum protein levels.[42] On the contrary, there are studies that observed no glucose metabolism improvement following Spirulina supplementation,[14,31] revealing the need for further and more accurate studies in this field.

The mechanism of improvement in glucose metabolism somewhat refers to Spirulina fiber and protein content, leading to reduced glucose absorption and increased insulin secretion, respectively.[33] To a certain extent, the effect of increased insulin sensitivity following Spirulina consumption has been attributed to lower levels of interleukin-6 (IL-6)[13,14] that inhibits insulin signaling molecules like insulin receptor substrate which can finally result in suppressing translocation of glucose transporter type 4 (GLUT-4) to the cell surface and lower glucose uptake in muscle and adipose tissue.[41]

3.6. Spirulina supplementation, inflammation and oxidative stress

Obesity induced localized and systemic inflammation is responsible for a wide array of comorbidities including oxidative stress,[1] insulin-resistant metabolic dyslipidemia, type 2 diabetes, cardiovascular disease and hypertension.[43] Therefore, inflammation management is a key therapeutic intervention in MetS components. In three interventional studies 8 g/day Spirulina intake for 16-12 weeks led to higher plasma IL-2 concentration, reduced IL-6 concentration, increased in superoxide dismutase (SOD) activity,[13] a reduction of plasma malondialdehyde level and increased plasma adiponectin value[14] and also a significant increase in IL-2/IL-6 ratio and total antioxidant status level and a decrease in thiobarbituric acid reactive substances level in non-obese subjects.[34] Improved total antioxidant status is also reported after 2 g/day and 5 g/day spirulina consumption in separate studies.[26,30] Spirulina supplementation in COPD patients for 2 months resulted in reduction of malondialdehyde (MDA), lipid hydroperoxide and increase in glutathione (GSH), vitamin C, and the activity of SOD and glutathione-s-transferase (GST) following 1 g/day supplementation.[11] Spirulina supplementation also resulted in higher GSH levels at rest and 24 h after exercise and lower thiobarbituric acid-reactive substance levels after exercise.[15]The antioxidant and anti-inflammatory activity of Spirulina is almost attributed to its antioxidant content like

phycocyanin and ß-carotene.[44] Phycocyanin effectively scavenges free radicals and reactive oxygen species (ROS), suppresses inducible nitric oxide synthase (iNOS) expression, reduces nitrite production and inhibits lipid peroxidation in liver microsomes.[12,45] ß-caroten also acts as an antioxidant and anti-inflammatory agent,[12] it is also considered as an efficient membrane antioxidant, through inhibiting oxygen-mediated lipid peroxidation.[46] In addition, ß-caroten blocks intracellular accumulation of ROS, inhibits expression of inflammation associated genes the same as iNOS, COX-2, TNF-α and IL-1ß and also inhibits promoter activity of iNOS and nuclear factor kappaB (NF-$_k$B).[47,48]

3.7. Spirulina supplementation and non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease (NAFLD) encompasses a spectrum of liver manifestations ranging from simple steatosis to nonalcoholic steatohepatitis (NASH), fibrosis and cirrhosis, which may ultimately terminate to hepatocellular carcinoma.[49] There is accumulating evidence demonstrating an association between NAFLD and MetS. Indeed, to some extent NAFLD is recognized as the liver manifestation of MetS or as the underlying cause of metabolic syndrome.[49,50] On the other hand liver abnormalities including Increased serum transaminase, nonalcoholic steatohepatitis (NASH), nonalcoholic fatty liver disease (NAFLD), hepatic fibrosis and cirrhosis are also defined as systemic effects of MetS on hepatic tissue.[1] According to animal and human studies, there are different anti-oxidants, anti-inflammatory, and insulin sensitizer dietary supplements which have shown beneficial effects on NAFLD improvement.[51] Spirulina has been recently considered as a dietary supplement for reducing liver enzymes in patients with NFLD. In an open-label, non-randomized trial, a 6 months SP intervention at a dose of 6 g/day resulted in lower AST, ALT and γ-glutamyltransferase in a sample of adults with NAFLD.[27] Moreover, in a Case report of 3 NAFLD patients, 4.5 g/day SM supplementation resulted in lower liver aminotransfrases.[16] Although, the effect of Spirulina supplementation on predisposing factors of NAFLD such as obesity, insulin resistance, dyslipidemia, inflammation and oxidative stress have been previously discussed in detail.

Currently, first-line therapy for NAFLD is lifestyle modification techniques such as weight loss through diet and exercise. Moreover, a wide range of drugs and supplements, including antioxidants, anti-inflammations, insulin sensitizers, and lipid lowering agents, have been applied in patients and experimental models of NAFLD as alternative therapies.[51] Due to Spirulina's content of nutrients, it is widely reported that this microalgae is effective as an antioxidant, anti-inflammatory, insulin sensitizing, lipid lowering and weight loss agent.[12] Probiotics and prebiotics are also recently recommended for NAFLD treatment.[51] Whereas Spirulina consumption seems to promote the growth of intestinal micro flora as well and has probiotic effect,[52] expecting that Spirulina induces its liver protecting action via this mechanism. In animal studies it has been indicated that ingestion of Spirulina as an anti-inflammatory agent reduced hepatic MDA levels and also elevated GSH, SOD, and nitric oxide levels, whereas vacuolar degeneration, fatty infiltration, and fibrosis were prevented in the liver. Similar antioxidant effects of Spirulina supplementation on the prevention of hepatotoxicity were also described with decreases in the leakage of liver enzymes in plasma, and also lower hepatic lipid peroxidation, hemorrhage, and hepatocyte necrosis in the livers of rats.[40] All in all, it seems that Spirulina is highly effective on preventing fatty liver, although the underlying mechanisms have not been fully understood. Based on the present knowledge, Spirulina inhibits hepatic lipogenesis, prevents progression of fatty liver to NASH by inhibiting lipid peroxidation and scavenging free radicals, or indirectly enhancing the activity of antioxidant enzymes in the liver. Still further studies are necessary to explore the mechanism accurately.

4. Discussion

This review was conducted to evaluate the effects of Spirulina supplementation on distinct metabolic syndrome components. Eighteen interventional studies were meticulously selected in order to be applied in the final systematic review.

As described earlier, Spirulina is a functional food and Considering its nutrient content, a wide array of medical and nutritional effectiveness is expected.[12] Spirulina can be effective as a blood pressure-reducing agent through increasing eNOS synthetize, inhibiting ACE, suppressing renin- angiotensin system, vasoconstricting metabolites and platelet aggregation.[31,32,53] Spirulina may be a suitable supplementation for body weight reduction, due to its impacts on brain's appetite center and also its high antioxidants compounds that effectively trigger mechanisms that lead to body weight loss.[12,27,28] However, the weight reduction effect of Spirulina is still controversial.[8,14] Considering spirulina's fiber, vitamins, phycocynin, γ -linolenic acid, it seems that this nutraceutical acts actively as a lipid-lowering agent through impressing lipid absorption, metabolism and excretion.[10] Spirulina improves glucose metabolism because of its high fiber content, protein and amino-acids that stimulate insulin secretion and also ameliorates insulin signaling via lowering inflammatory mediators.[14,33] Given the powerful antioxidant compounds of spirulina that are phycocyanin and ß-carotene, spirulina is proposed as a successful supplementation for lowering oxidative stress and inflammation.[12] NAFLD is also reported to be ameliorated following Spirulina supplementation.[27] Since mechanisms underlying the protective effect of Spirulina on MetS components have not been fully understood, more studies are needed to identify functional components of Spirulina, responsible for the therapeutic effects and also more accurate mechanisms of its action.

4.1. Strengths and limitations

The present review bears some notable strength indeed. As we realized this is basically the first systematic review which presents the effects of Spirulina supplementation on metabolic syndrome components and the possible mechanisms in details. While researches continue to explore complementary therapies for obesity related metabolic abnormalities, Spirulina supplementation has also been introduced as an effective intervention.

Undoubtedly, this review does have some limitations as the others. In particular we were prevented to conduct a meta-analysis due to the lack of homogeneity between outcome assessment and dosage of treatment. Furthermore, a lack of studies with longer follow-up period limited the generalizability of our findings to the entire metabolic syndrome affected population.

5. Conclusion

Eventually, Spirulina may be suggested to patients with MetS and also NAFLD as a safe and therapeutic supplementation or a food component.

Author contributions

All the authors made a substantial contribution to conception, design and/or analysis and interpretation of data, and/or the drafting or critical revision of the review.

Funding/Support

Authors did not receive any fund or grant.

Financial disclosure

Authors have no relevant or material financial interests that relate

to the research described in this paper.

Declarations of interest

None.

Acknowledgments

The authors would like to thank all the staff at Nutrition, Faculty of Nutrition and Food Technology, Shahid Beheshti University of Medical Sciences.

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