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Effects of Spirulina supplementation on obesity: A systematic review and meta-analysis of randomized clinical trials

Sajjad Moradi[a,b], Rahele Ziaei[c], Sahar Foshati[d], Hamed Mohammadi[e], Seyed Mostafa Nachvak[b], Mohammad Hossein Rouhani[c,*]

[a] Halal Research Center of IRI, FDA, Tehran, Iran
[b] Nutritional Sciences Department, School of Nutritional Sciences and Food Technology, Kermanshah University of Medical Sciences, Kermanshah, Iran
[c] Department of Community Nutrition, School of Nutrition and Food Science, Food Security Research Center, Isfahan University of Medical Sciences, Isfahan, Iran
[d] Department of Clinical Nutrition, School of Nutrition and Food Science, Food Security Research Center, Isfahan University of Medical Sciences, Isfahan, Iran
[e] Students' Research Committee, Department of Clinical Nutrition, School of Nutrition and Food Science, Isfahan University of Medical Sciences, Isfahan, Iran

A R T I C L E I N F O

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A B S T R A C T

Objective: Evidence has suggested that Spirulina supplementation may affect anthropometric indices. Therefore, a systematic review and meta-analysis was performed to summarize published randomized clinical trials which assess the effect of Spirulina supplementation on obesity.
Setting: Pertinent studies were identified using Embase, Scopus, ISI Web of Science, PubMed and Cochrane library databases up to May 2019. Mean Differences (MD) were pooled using a random-effects model. Heterogeneity, sensitivity analysis and publication bias were reported using standard methods.
Results: Results of 5 studies (7 treatment arms) showed a significant reduction in weight (MD: -1.56 Kg, 95% CI: -1.98 to -1.14) after Spirulina supplementation. Subgroup analysis based on health status revealed that weight change in obese subjects (MD: -2.06 Kg, 95% CI: -2.45 to -1.68) was greater than overweight participants (MD: -1.28 Kg, 95% CI: -1.62 to -0.93) following Spirulina supplementation. Also, pooled analysis showed that Spirulina supplementation led to a significant reduction in body fat percent (MD: -1.02, 95% CI: -1.49 to -0.54) and waist circumference (MD: -1.40, 95% CI: -1.40 to -1.39), but not in body mass index and waist to hip ratio.
Conclusion: Spirulina supplementation significantly reduces body weight, especially in obese individuals.

1. Introduction

Despite many proposed prevention and treatment strategies, overweight and obesity are dramatically on the rise. According to the latest reports from the World Health Organization, global prevalence of obesity has been tripled since 1975. Currently, about 2.5 billion people are suffering from overweight or obesity worldwide.[1] As a widely accepted fact, overweight and obesity are the risk factors for debilitating chronic diseases such as cardiovascular diseases, cancer and cerebrovascular diseases.[2,3] Based on recent evidence, not only general obesity but also central obesity and normal-weight obesity can impose major risks to health. Therefore, it seems that all of the anthropometric indices including body weight, body mass index (BMI), waist circumference, waist-to-hip ratio and body fat percentage may be important.[4–6]

Although lifestyle modification is the main treatment of obesity, poor compliance with lifestyle changes leads to fail optimum long-term weight loss.[7] Pharmacological treatments may be used when lifestyle modification has not been effective alone.[8] However, anti-obesity drugs have side effects and they cannot be used for long-term.[9] Thus, patients prefer to use dietary supplements for management of obesity and its complications.[10] In recent decade, several studies focused on nutritional supplements and herbs to manage obesity and its complications.[11,12]

Spirulina, name derives from the spiral or helical nature of its filaments, is a spiral blue-green microalgae and filamentous

Abbreviations: BMI, body mass index; COX-2, cyclooxygenase-2; DSI-EC, Dietary Supplements Information Expert Committee; ERK1/2, extracellular signal-regulated kinase; FDA, Food and Drug Administration; IKK-β, inhibitor of nuclear factor kappa-B kinase subunit beta; JNK, c-Jun N-terminal kinase; MD, mean differences; RCTs, randomized controlled trials; ROS, reactive oxygen species

* Corresponding author at: Department of Community Nutrition, School of Nutrition and Food Science, Isfahan University of Medical Sciences, P.O. Box 81745, Isfahan, Iran.
E-mail address: sm_rouhani@nutr.mui.ac.ir (M.H. Rouhani).

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cyanobacterium that belongs to family Oscillatoriaceae and has a long history of use as food or food supplement.[13,14] It is an edible cyanobacteria or a microscopic blue-green algae rich in many nutrients, such as phytochemicals, vitamins, minerals, essential and non-essential amino acids, essential fatty acids and fiber. Spirulina supplementation can be considered as an adjuvant therapy for the treatment of a wide range of illnesses due to its antioxidant, anti-inflammatory, antitumor, immunomodulatory, antiviral and antibacterial properties.[15] Several studies suggested that Spirulina may be useful in management of obesity because it has favorable effect on appetite, food absorption, gut microbiota, insulin resistance, oxidative stress, and inflammation.[15–19]

Although supplementation with Spirulina seems to be an appropriate choice for obese subjects, the scientific evidence in this field is relatively limited and heterogeneous.[19–26] Some studies reported that Spirulina supplementation had a favorable effect on weight loss.[19,20,24–26] In contrast, Szulinska et al and Hernández-Lepe et al indicated that Spirulina could not improve other anthropometry measurements.[25,26]

Based on our searches in scientific databases, no article has been published to summarize the effects of Spirulina on weight management. Moreover, clinical trial studies have shown contradictory effects of Spirulina on obesity. Therefore, we aimed to conduct a systematic review and meta-analysis of published randomized controlled trials (RCTs) to assess the effect of Spirulina supplementation on obesity.

2. Methods

A systematic and comprehensive search of the Embase, Scopus, ISI Web of Science, PubMed and the Cochrane library was conducted using the following search terms: ((“Arthrospira” OR “Spirulina”) AND (“Intervention” OR “Intervention Study” OR “Intervention Studies” OR “Controlled” trial OR “Randomised” OR “Random” OR “Randomly” OR “Placebo” OR “Assignment” OR “Randomized controlled trial” OR “Randomized clinical trial” OR “Randomized clinical trial” OR “RCT” OR “Blinded” OR “Double blind” OR” Double blinded” OR “Open-label” OR “Trial” OR “Clinical trial” OR "Non-Randomized Controlled Trials" OR "Non-Randomized Trials" OR "Non-Randomized " OR "Clinical Trials" OR "Clinical Trial" OR "Trial" OR "Trials" OR "Pragmatic Clinical Trial" OR "Clinical Trial" OR "Trial" OR "Controlled Clinical Trial" OR "Controlled Trial" OR "Clinical Trial, Phase IVOR "Clinical Trial, Phase III" OR "Clinical Trial, Phase II" OR "Clinical Trial, Phase I" OR "Adaptive Clinical Trial" OR "Adaptive Clinical Trial" OR "Cross-Over Studies” OR "Cross-Over trial" OR "Equivalence Trial" OR "Equivalence Trial" OR "Non-Randomized Controlled Trials " OR "Pilot Projects" OR "Pilot trial" OR "Pilot study" OR "Cross-Over study" OR "Cross-Over trial " OR "Cross Over trial " OR "Cross Over study " OR "Double-Blind Method" OR "Double-Blind Method" OR "Double-Blind " OR "Double-Blind trial " OR "Double-Blind study")). Whenever possible, Medical Subject Headings (MESH) terms were used. The search was restricted to studies published in English language from inception to May 2019. Electronic database searches were completed along with reference list and citation hand searching. Initial research was independently performed by two authors (HM and SM). Any disagreement in this regard were resolved by face to face discussion.

2.1. Study selection

First, results of electronic and manual searches were exported to EndNote software, version X7 (Thomson Reuters) and duplicate publications were removed. Then, two investigators (SM and HM) selected eligible articles separately by reading title, abstract and full text version of remaining publications. Finally, all human randomized clinical trials (RCTs) which examined the effects of Spirulina supplementation on anthropometric measurements (i.e., body weight, body mass index, waist circumference, body fat, waist to hip ratio) were included. Studies were excluded if they were: (1) RCTs with treatment duration less than 2 weeks, (2) studies without appropriate control group and (3) conducted on < 18-year old subjects. Disagreements regarding the study selection process were resolved by discussion with the third researcher (MHR).

2.2. Data extraction

Following data were extracted from included studies using a predesigned abstraction form: first author's specification, publication year, location of the study, study design and blinding, total sample size, type and dose of supplementation and placebo, study duration, characteristics of subjects (age, gender and health status) and the final result. The process of data extraction was undertaken independently by two investigators (SM and HM) to minimize potential errors.

2.3. Quality assessment of studies

Two reviewers (HM and SM) independently evaluated the methodological quality of the eligible studies through Cochrane Collaboration’s tool including six domains: 1) random sequence generation; 2) allocation concealment; 3) blinding of participants and personnel; 4) blinding of outcome assessment; 5) incomplete outcome data; and 6) selective reporting. Each domain was classified to three categories: low risk of bias, high risk of bias and unclear risk of bias. According to guideline, overall quality of individual study was considered as good (low risk for more than 2 item), fair (low risk for 2 item) or weak (low risk for less than 2 item).[27]

2.4. Statistical analysis

All analyses were performed using STATA software version 12 (STATA corp, College Station, TX, USA). Mean difference (MD) and the standard deviation (SD) of the anthropometric measurements in intervention and control groups were applied to calculate overall effect size. The heterogeneity between studies was examined by I-squared (I^2). The level of heterogeneity across studies was rated as low, moderate or high corresponding to I^2 value of 0–30%, more than 30%–60% and more than 60%, respectively. Due to the fact that included RCTs were carried out in different settings, a random-effects model was used to conduct meta-analyses. To find the potential sources of between-study heterogeneity, we carried out a pre-planned subgroup analysis based on dose of intervention (“≤ 2 g/d” or “ > 2 g/d”) and baseline body mass index (BMI) (“obese” or “overweight and obese”). Sensitivity analysis was performed to explore the inference of each study on overall effect. We also assessed publication bias by the Begg-adjusted rank correlation test and the Egger's regression asymmetry test.[28,29] P value < 0.05 was accepted as statistically significant.

3. Results

3.1. Selection and identification of studies

From a total of 926 publications obtained by initial electronic and hand search (328 duplicates), 541 articles were excluded because they were unrelated to the topic. After reading the full text of the remaining eight papers,[19,30–36] three studies were further excluded for the following reasons: lack of an appropriate control group,[30] subjects were infant [31] or children.[32] Finally, five eligible RCTs [19,33–36] were included in the systematic review and meta-analysis. A flow chart the systematic search and study selection process is presented in Fig. 1.

3.2. Characteristics of studies

Table 1 describes the main characteristics of included studies. Overall, 7 effect sizes were extracted from 5 RCTs including 145 subjects in Spirulina group and 133 subjects in control group. Mean age of

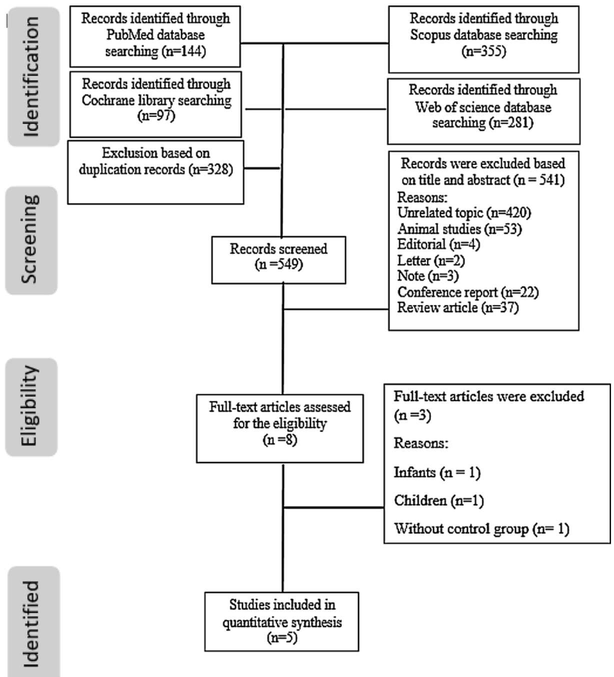

Fig. 1. PRISMA flowchart describing the study's systematic literature search and study selection.

participants ranged from 26 to 49 years old. Most RCTs (4 of 5) adopted a parallel design [19,33,34,36] except for one study which used a crossover design.[30] Studies were published between 1996 and 2018 and were conducted in Iran,[19,36] India,[33] Mexico[35] and Poland.[34] Dose of Spirulina ranged from 1 to 4.5 g/day. The duration of intervention was varied from 6 to 12 weeks. One study enrolled participants with hypercholesterolemia [33] and other studies recruited overweight and obese subjects.[19,34–36]

Risk of bias assessed by Cochrane collaboration tool is presented in Table 2. After evaluating the quality of included studies, the quality score of four studies were higher than 2 and classified as good quality. However one study classified as fair quality.

3.3. Effect of Spirulina supplementation on weight

Pooled analysis of 5 RCTs (7 treatment arms) showed that Spirulina supplementation significantly reduced weight (MD: -1.76 Kg, 95% CI: -2.65 to -0.88, I^2 = 48.7%) in comparison with control (Fig. 2). Subgroup analysis was conducted based on dose of Spirulina and health status. As illustrated in Fig. 3, subgroup analysis based on dose of supplementation indicated that there was no difference between low-dose (MD: -1.55 Kg, 95% CI: -2.11 to -0.98) or high-dose (MD: -1.55 Kg, 95% CI: -2.23 to -0.86) supplementation. Furthermore, subgroup analysis based on "obese" or "overweight" status showed that Spirulina supplementation resulted in greater weight reduction in "obese" subgroup (MD: -2.06 Kg, 95% CI: -2.45 to -1.68) compared with "overweight" subgroup (MD: -1.28 Kg, 95% CI: -1.62 to -0.93) (Fig. 4).

3.4. Effect of Spirulina supplementation on other anthropometric measurements

The effect of the Spirulina supplementation on other anthropometric measurements was shown in Table 3. Pooled analysis revealed that Spirulina supplementation led to a significant reduction in body fat percentage (MD: -1.02, 95% CI: -1.49 to -0.54) and waist circumference (MD: -1.40, 95% CI: -1.40 to -1.39). In contrast, Spirulina had no effect on BMI (MD: -0.98, 95% CI: -2.06 to 0.18) and waist to hip ratio (MD: -0.01, 95% CI: -0.02, 0.00).

3.5. Sensitivity analysis

Effect sizes for the impact of Spirulina supplementation on body weight were robust in the sensitivity analysis, suggesting that omission of each RCT did not have a significant effect on the results. Also, sensitivity analysis for other anthropometric parameters showed same results.

3.6. Publication bias

The funnel plot for effect of Spirulina supplementation on body weight is slightly skewed to the right (Fig. 5). However, filled funnel plot showed there was no any filled studies (Fig. 6). In addition, Begg's rank correlation and Egger's weighted regression tests were performed to explore the publication bias. The results of Begg's test indicated no publication bias for body weight (P = 0.41) and body fat percent (P = 0.60) and waist circumference (P = 0.31), BMI (P = 0.43) and waist to hip ratio (P = 0.57). Moreover, the results of Egger's test showed no publication bias for body weight (P = 0.81) and body fat percent (P = 0.98) and waist circumference (P = 0.50), BMI (P = 0.60) and waist to hip ratio (P = 0.14).

4. Discussion

To the best of our knowledge, meta-analysis ahead is the first one to evaluate the effects of Spirulina supplementation on obesity. The findings of the present study support the beneficial effect of Spirulina on body weight, body fat percentage and waist circumference. The effects of Spirulina supplementation on BMI and waist-to-hip ratio were

Table 1
Main characteristics of included studies.

First author (publication year)	Country	Sample size (Male/ Female)	Target Population	Mean Age (years)	RCT design (Blinding)	Duration (weeks)	Dose of Spirulina	Comparison	Results
Ramamoorthy et al (1996)	India	30 (NR)	Overweight hypercholesterolemia patient	50	Parallel (No)	12	(2-4 g/d)	Placebo (NR)	Significant reduction in BW
Szulinska et al (2017)	Poland	50 (25/25)	Obese subjects	49.3	Parallel (Double)	12	2g/d	Placebo (NR)	Significant reduction in body mass, BMI, and WC
Zeinalian et al (2017)	Iran	56 (9/47)	Obese subjects	34.75	Parallel (Double)	12	1 g/d	Placebo (NR)	Significant reduction in BW and BMI
Yousefi et al (2018)	Iran	52 (7/31)	Obese or overweight subjects	40.16	Parallel (Double)	12	2g/d	Placebo (NR)	Significant reduction BW, WC, BF and BMI
Hernandez-Lepe et al (2018)	Mexico	57 (NR)	Obese or overweight subjects	26	Crossover (Double)	6	4.5 g/d	Placebo (NR)	Significant reduction BW and BF

NR: not reported, BMI: body mass index, WC: waist circumference, BW: body weight, BF: body fat.

Table 2
Risk of bias assessment for included randomized controlled clinical trails.

Domain	Ramamoorthy et al. (1996)	Szulinska et al. (2017)	Zeinalian et al. (2017)	Yousefi et al. (2018)	Hernandez-Lepe et al. (2018)
Random sequence generation (selection bias)	+	+	+	+	+
Allocation concealment (selection bias)	?	?	+	?	+
Blinding of participants and personnel (Performance bias)	?	+	+	+	+
Blinding of outcome assessment (Detection bias)	–	+	+	+	–
Incomplete outcome data (Attrition bias)	+	+	+	+	+
Selective reporting (Reporting bias)	?	–	?	+	?
Score	2	4	5	5	4
Overall quality	Fair	Good	Good	Good	Good

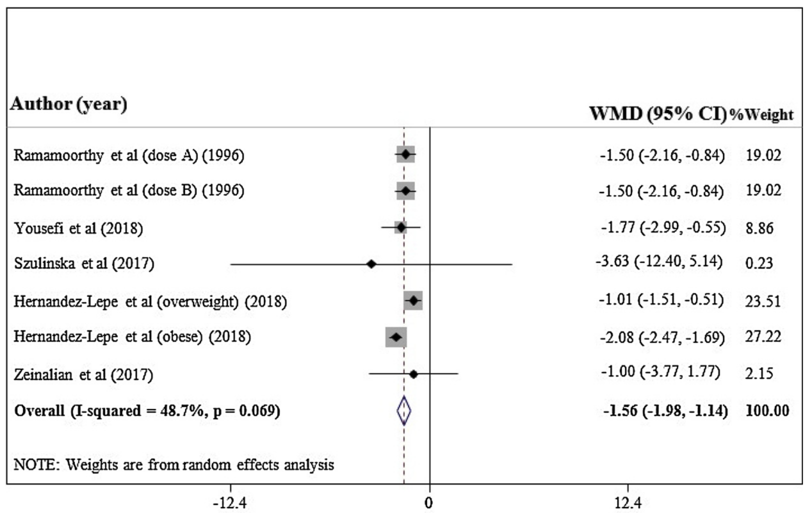

Fig. 2. Effect of Spirulina supplementation on body weight compared with placebo.

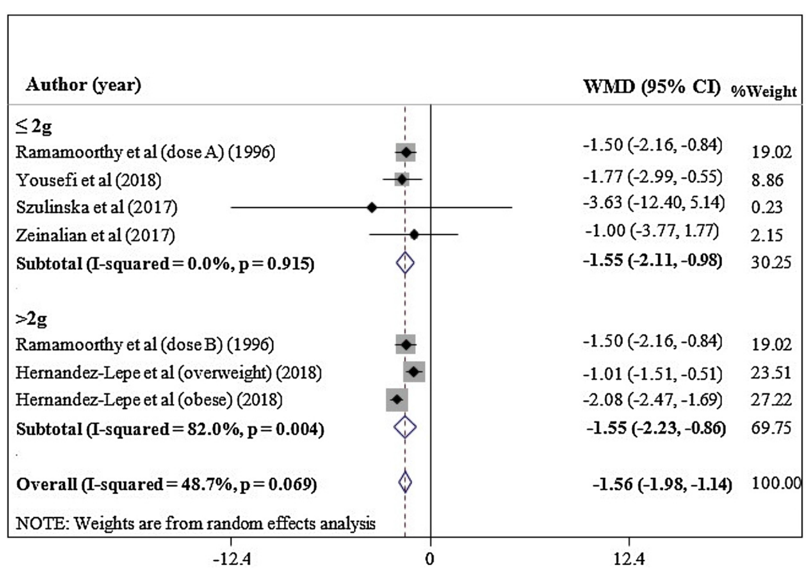

Fig. 3. Effect of Spirulina supplementation on body weight compared with placebo stratified by Spirulina dosage.

not statistically significant.

As illustrated in Fig. 7, the underlying mechanisms of anti-obesity effects of Spirulina has been ill-defined. Some of the proposed mechanisms are reduction of macrophage infiltrations into visceral fat, prevention of liver-lipid accumulation,[37] amelioration of oxidative stress [38] and appetite decline.[39] Obesity is considered as a low-grade inflammation state associated with immune impairment and change in gut microbiota.[17] Spirulina contains many functional bioactive ingredients with antioxidant and anti-inflammatory activities, including phenolic phytochemicals, phycobiliprotein, C-phycocyanin and β-carotene. Therefore, it can inhibit inflammatory responses via anti-oxidative and anti-inflammatory mechanisms.[40] Phycocyanin scavenges free

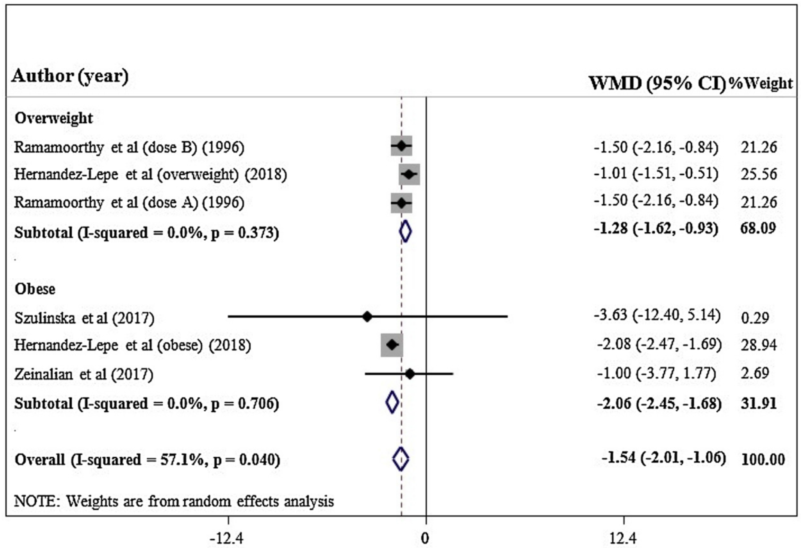

Fig. 4. Effect of Spirulina supplementation on body weight compared with placebo stratified by baseline body weight status.

Table 3
Effect of Spirulina supplementation on other anthropometric parameters.

Anthropometric parameters	No. of studies	Effect size[1]	95% CI	I^2 (%)	P for heterogeneity
Body mass index	3	−0.94	−2.06, 0.18	99.9%	0.0001 >
Body fat percent	3	−1.02	−1.49, -0.54	72.4%,	0.027
Waist circumference	2	−1.40	−1.40, -1.39	100.0%	0.0001 >
Waist to hip ratio	2	−0.01	−0.02, 0.00	0.0%,	0.550

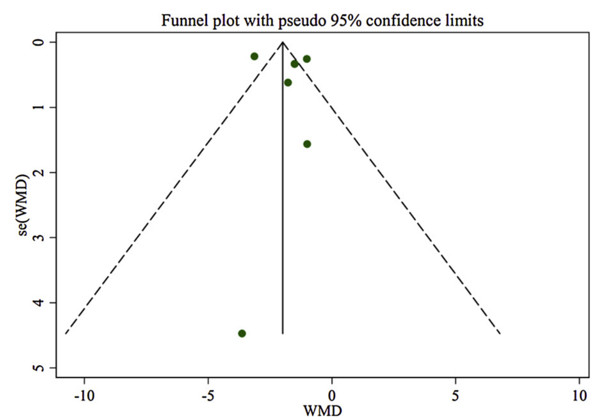

Fig. 5. Funnel plot for evaluation publication bias.

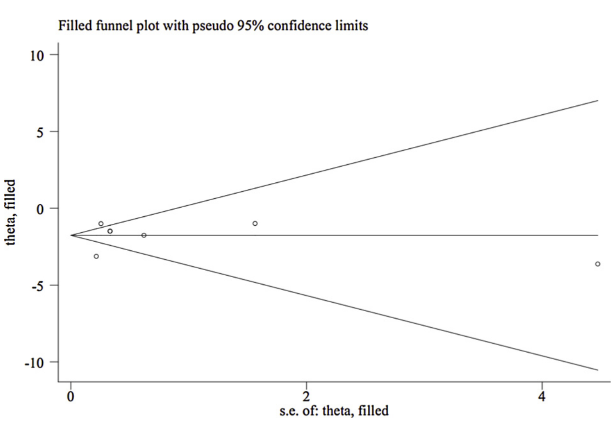

Fig. 6. Filled funnel plot showing filled studies.

radicals, suppresses nitric oxide synthase expression and nitrite production, and inhibits lipid peroxidation. Also Phycocyanin is a selective cyclooxygenase-2(COX-2) inhibitor.[41,42] β-Carotene protects against singlet oxygen-mediated lipid peroxidation, interacts with the intracellular accumulation of reactive oxygen species (ROS), and inhibits expression of inflammatory genes.[43] Spirulina also regulates some signaling pathways including extracellular signal-regulated kinase (ERK1/2), c-Jun N-terminal kinase (JNK), p38, and inhibitor of nuclear factor kappa-B kinase subunit beta (IKK-β), resulting in antioxidant and anti-inflammatory effects.[38,44] Furthermore, Spirulina has an ameliorating impact on insulin resistance in human and experimental studies[45–47] because of its anti-oxidative and anti-inflammatory effects and its role in stimulating of insulin secretion. Studies showed that experimental blockage of hyperinsulinemia may prevent obesity. Another important finding of the present study revealed that weight change in obese subjects was greater than overweight participants following Spirulina supplementation. Spirulina has noticeable immunomodulatory and anti-inflammatory effects which can attenuated obesity-induced pro-inflammatory cytokines.[18] Therefore, it is reasonable to observe greater impact of Spirulina in obese participants.

Spirulina may have microbial-modulating activity. Therefore, its anti-obesity effects may be achieved by changing the gut microbiota composition and promoting beneficial bacterial growth.[17,48] Moreover, Spirulina may exert an inhibitory impact on jejunal cholesterol absorption and pancreatic lipase. It seems that C-phycocyanin is the major responsible compound for this effect.[49,50]

Also, Spirulina may be effective on lowering weight by affecting appetite and related adipokins. Appetite controlling effect of Spirulina has been indicated in some interventional studies.[51,52] It is suggested that phenylalanine content of Spirulina may be responsible for cholecystokinin release which affects the appetite center in the brain. In addition, Spirulina can improve leptin secretion from visceral fat and improve leptin resistance.[45] Impaired leptin synthesis or sensitivity is involved in disturbances of energy homeostasis and obesity.[53]

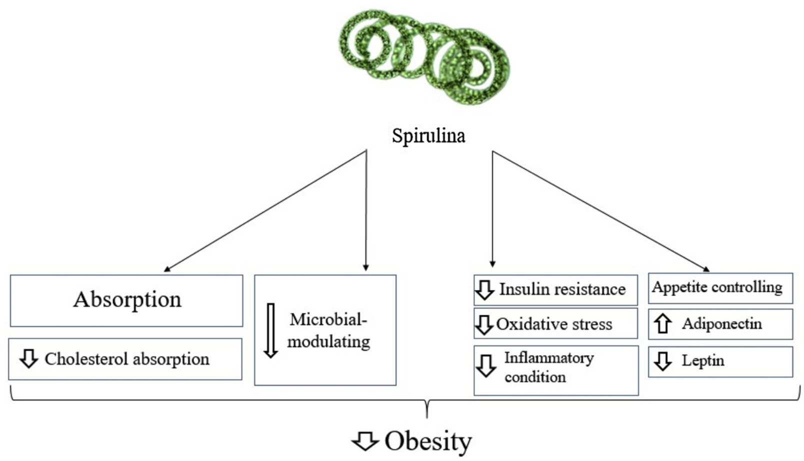

Fig. 7. An overview of various possible mechanisms involved in the effect of Spirulina on obesity.

Adiponectin, which has been considered as a therapeutic target in obesity,[54] is shown to be raised following Spirulina supplementation.[55]

In toxicological studies conducted on animals and humans, no toxic or side effects were reported for Spirulina. So, Spirulina is generally considered safe for human and its side-effects are negligible in routine dosage. The Food and Drug Administration (FDA) has categorized *Arthrospira* products as "generally recognized as safe" for human consumption and the Dietary Supplements Information Expert Committee (DSI-EC) concluded that there is not a serious health risk for Spirulina.[56] However, rare potential adverse effects for Spirulina were reported in some case reports including acute rhabdomyolysis and anaphylaxis.[17] It is better to consider an allergy risk assessment before supplementation.

The present meta-analysis had some limitations that need to be acknowledged. Limited number of studies is the most important limitation of this systematic review and meta-analysis. More studies should be conducted in this field. Also, duration of intervention could confound the results. Because of low number of studies, we could not run subgroup analysis based on duration of study. In addition, there are several clinical research challenges (including complexity of intervention, organization, budget, subject availability and teamwork) that may affect results of a clinical trial.[57] Unfortunately, the contribution of each challenges was not determined in included studies. It is possible that final findings confounded by these factors. Another issue which should be addressed is clinical goal in RCTs. Although some studies reported a statistically significant improvement in obesity measurements, results may be not clinically significant. It means that intervention could not achieve clinical goal. In management of obesity, body fat should be significantly reduced (5% of current body weight) and patient should be able to be normal-weight for long-term.[58] Included studies did not discuss regarding achievement clinical goal. It is suggested that future studies focus on this topic.

The main strength of the current study is that our findings can be used directly in practice. In addition, we showed that weight status of individuals have important role on efficacy of Spirulina supplementation.

5. Conclusion

Findings of the present study suggest that Spirulina supplementation significantly reduces body weight, body fat percentage and waist circumference, but has not effect on BMI and waist to hip ratio. Subgroup analyses indicate that the impact may more pronounced on obese subjects rather than overweight individuals. For future studies conducting more specific interventions according to different age or gender groups is suggested.

Conflicts of interest

No potential competing interests.

Funding

None.

References

1. World Health Organization. *Obesity and overweight.* 2018; 2018 Accessed 2018-12-19 https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight.
2. Ezzati M, Riboli E. Behavioral and dietary risk factors for noncommunicable diseases. *N Engl J Med.* 2013;369:954–964.
3. Moradi S, Mirzaei K, Abdurahman AA, Keshavarz SA, Hossein-nezhad A. Mediatory effect of circulating vaspin on resting metabolic rate in obese individuals. *Eur J Nutr.* 2016;55(3):1297–1305.
4. Lee CMY, Huxley RR, Wildman RP, Woodward M. Indices of abdominal obesity are better discriminators of cardiovascular risk factors than BMI: a meta-analysis. *J Clin Epidemiol.* 2008;61:646–653.
5. Romero-Corral A, Somers VK, Sierra-Johnson J, et al. Normal weight obesity: a risk factor for cardiometabolic dysregulation and cardiovascular mortality. *Eur Heart J.* 2010;31:737–746.
6. Oliveros E, Somers VK, Sochor O, Goel K, Lopez-Jimenez F. The concept of normal weight obesity. *Prog Cardiovasc Dis.* 2014;56:426–433.
7. Rios-Hoyo A, Gutierrez-Salmean G. New dietary supplements for obesity: what we currently know. *Curr Obes Rep.* 2016;5(2):262–270.
8. Vesely JM, DeMattia LG. Obesity: drugs and dietary supplements. *FP Essent.* 2014;425:16–23.
9. Kang JG, Park C-Y. Anti-obesity drugs: a review about their effects and safety. *Diabetes Metab J.* 2012;36(1):13–25.
10. Cicero AFG, Colletti A. Role of phytochemicals in the management of metabolic syndrome. *Phytomedicine.* 2016;23(11):1134–1144.
11. Rivellese AA, Ciciola P, Costabile G, Vetrani C, Vitale M. The possible role of nutraceuticals in the prevention of cardiovascular disease. *High Blood Press Cardiovasc Prev.* 2019;26(2):101–111.
12. Patti AM, Al-Rasadi K, Giglio RV, et al. Natural approaches in metabolic syndrome management. *Arch Med Sci.* 2018;14(2):422–441.
13. Kulshreshtha A, Jarouliya U, Bhadauriya P, Prasad G, Bisen P. Spirulina in health care management. *Curr Pharm Biotechnol.* 2008;9(5):400–405.
14. Yousefi R, Saidpour A, Mottaghi A. The effects of Spirulina supplementation on metabolic syndrome components, its liver manifestation and related inflammatory markers: a systematic review. *Complement Ther Med.* 2018;42:137–144.
15. Wu Q, Liu L, Miron A, Klímová B, Wan D, Kuča K. The antioxidant, immunomodulatory, and anti-inflammatory activities of Spirulina: an overview. *Arch Toxicol.* 2016;90:1817–1840.
16. Abebe W, Agrawal DK. Role of tyrosine kinases in norepinephrine-induced contraction of vascular smooth muscle. *J Cardiovasc Pharmacol.* 1995;26(1):153–159.
17. Finamore A, Palmery M, Bensehaila S, Peluso I. Antioxidant, immunomodulating, and microbial-modulating activities of the sustainable and ecofriendly Spirulina. *Oxid Med Cell Longev.* 2017;2017:3247528.
18. Karczewski J, Sledzinska E, Baturo A, et al. Obesity and inflammation. *Eur Cytokine Netw.* 2018;29(3):83–94.
19. Yousefi R, Mottaghi A, Saidpour A. Spirulina platensis effectively ameliorates anthropometric measurements and obesity-related metabolic disorders in obese or overweight healthy individuals: a randomized controlled trial. *Complement Ther Med.* 2018;40:106–112.
20. Ramamoorthy A, Premakumari S. Effect of supplementation of Spirulina on

hypercholesterolemic patients. *J Food Sci Technol (Mysore).* 1996;33:124–128.
21. Lee EH, Park J-E, Choi Y-J, Huh K-B, Kim W-Y. A randomized study to establish the effects of Spirulina in type 2 diabetes mellitus patients. *Nutr Res Pract.* 2008;2:295–300.
22. Mazokopakis EE, Starakis IK, Papadomanolaki MG, Mavroeidi NG, Ganotakis ES. The hypolipidaemic effects of Spirulina (Arthrospira platensis) supplementation in a Cretan population: a prospective study. *J Sci Food Agric.* 2014;94:432–437.
23. Miczke A, Szulińska M, Hansdorfer-Korzon R, et al. Effects of Spirulina consumption on body weight, blood pressure, and endothelial function in overweight hypertensive Caucasians: a double-blind, placebo-controlled, randomized trial. *Eur Rev Med Pharmacol Sci.* 2016;20:150–156.
24. Zeinalian R, Farhangi MA, Shariat A, Saghafi-Asl M. The effects of Spirulina platensis on anthropometric indices, appetite, lipid profile and serum vascular endothelial growth factor (VEGF) in obese individuals: a randomized double blinded placebo controlled trial. *BMC Complement Altern Med.* 2017;17:225.
25. Szulinska M, Gibas-Dorna M, Miller-Kasprzak E, et al. Spirulina maxima improves insulin sensitivity, lipid profile, and total antioxidant status in obese patients with well-treated hypertension: a randomized double-blind placebo-controlled study. *Eur Rev Med Pharmacol Sci.* 2017;21:2473–2481.
26. Hernández-Lepe M, López-Díaz J, Juárez-Oropeza M, Hernández-Torres R, Wall-Medrano A, Ramos-Jiménez A. Effect of Arthrospira (Spirulina) maxima supplementation and a systematic physical exercise program on the body composition and cardiorespiratory fitness of overweight or obese subjects: a double-blind, randomized, and crossover controlled trial. *Mar Drugs.* 2018;16:E364.
27. Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *Bmj.* 2011;343:d5928.
28. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics.* 1994:1088–1101.
29. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *Bmj.* 1997;315(7109):629–634.
30. Mazokopakis EE, Starakis IK, Papadomanolaki MG, Mavroeidi NG, Ganotakis ES. The hypolipidaemic effects of Spirulina (Arthrospira platensis) supplementation in a Cretan population: a prospective study. *J Sci Food Agric.* 2014;94(3):432–437.
31. Masuda K, Chitundu M. *Multiple micronutrient supplementation using spirulina platensis and infant growth, morbidity and motor development: evidence from a randomized trial in Zambia.* 2018; 2018.
32. Samuels R, Mani U, Iyer U, Nayak U. Hypocholesterolemic effect of Spirulina in patients with hyperlipidemic nephrotic syndrome. *J Med Food.* 2002;5(2):91–96.
33. Ramamoorthy A, Premakumari S. Effect of supplementation of Spirulina on hypercholesterolemic patients. *J Food Sci Technol.* 1996;33(2):124–128.
34. Szulinska M, Gibas-Dorna M, Miller-Kasprzak E, et al. Spirulina maxima improves insulin sensitivity, lipid profile, and total antioxidant status in obese patients with well-treated hypertension: a randomized double-blind placebo-controlled study. *Eur Rev Med Pharmacol Sci.* 2017;21(10):2473–2481.
35. Hernández-Lepe M, López-Díaz J, Juárez-Oropeza M, Hernández-Torres R, Wall-Medrano A, Ramos-Jiménez A. Effect of Arthrospira (Spirulina) maxima supplementation and a systematic physical exercise program on the body composition and cardiorespiratory fitness of overweight or obese subjects: a double-blind, randomized, and crossover controlled trial. *Mar Drugs.* 2018;16(10):364.
36. Zeinalian R, Farhangi MA, Shariat A, Saghafi-Asl M. The effects of Spirulina Platensis on anthropometric indices, appetite, lipid profile and serum vascular endothelial growth factor (VEGF) in obese individuals: a randomized double blinded placebo controlled trial. *BMC Complement Altern Med.* 2017;17(1):225.
37. Fujimoto M, Tsuneyama K, Fujimoto T, Selmi C, Gershwin ME, Shimada Y. Spirulina improves non-alcoholic steatohepatitis, visceral fat macrophage aggregation, and serum leptin in a mouse model of metabolic syndrome. *Dig Liver Dis.* 2012;44(9):767–774.
38. Wu Q, Liu L, Miron A, Klimova B, Wan D, Kuca K. The antioxidant, immunomodulatory, and anti-inflammatory activities of Spirulina: an overview. *Arch Toxicol.* 2016;90(8):1817–1840.
39. Yousefi R, Mottaghi A, Saidpour A. Spirulina platensis effectively ameliorates anthropometric measurements and obesity-related metabolic disorders in obese or overweight healthy individuals: a randomized controlled trial. *Complement Ther Med.* 2018;40:106–112.
40. Nasirian F, Dadkhah M, Moradi-Kor N, Obeidavi Z. Effects of Spirulina platensis microalgae on antioxidant and anti-inflammatory factors in diabetic rats. *Diabetes Metab Syndr Obes.* 2018;11:375–380.
41. Park WS, Kim HJ, Li M, et al. Two classes of pigments, carotenoids and C-phycocyanin, in Spirulina powder and their antioxidant activities. *Molecules (Basel, Switzerland).* 2018;23(8).
42. Liu Q, Huang Y, Zhang R, Cai T, Cai Y. Medical application of Spirulina platensis derived C-phycocyanin. *Evid Based Complement Altern Med.* 2016;2016:7803846.
43. Deng R, Chow TJ. Hypolipidemic, antioxidant, and antiinflammatory activities of microalgae Spirulina. *Cardiovasc Ther.* 2010;28(4):e33–45.
44. Sadek KM, Lebda MA, Nasr SM, Shoukry M. Spirulina platensis prevents hyperglycemia in rats by modulating gluconeogenesis and apoptosis via modification of oxidative stress and MAPK-pathways. *Biomed Pharmacother.* 2017;92:1085–1094.
45. Fujimoto M, Tsuneyama K, Fujimoto T, et al. Spirulina improves non-alcoholic steatohepatitis, visceral fat macrophage aggregation, and serum leptin in a mouse model of metabolic syndrome. *Dig Liver Dis.* 2012;44(9):767–774.
46. Szulinska M, Gibas-Dorna M, Miller-Kasprzak E, et al. Spirulina maxima improves insulin sensitivity, lipid profile, and total antioxidant status in obese patients with well-treated hypertension: a randomized double-blind placebo-controlled study. *Eur Rev Med Pharmacol Sci.* 2017;21(10):2473–2481.
47. Gargouri M, Magné C, El Feki A. Hyperglycemia, oxidative stress, liver damage and dysfunction in alloxan-induced diabetic rat are prevented by Spirulina supplementation. *Nutr Res.* 2016;36(11):1255–1268.
48. Hua P, Yu Z, Xiong Y, Liu B, Zhao L. Regulatory efficacy of Spirulina platensis protease hydrolyzate on lipid metabolism and gut microbiota in high-fat diet-fed rats. *Int J Mol Sci.* 2018;19(12).
49. Iwata K, Inayama T, Kato T. Effects of Spirulina platensis on plasma lipoprotein lipase activity in fructose-induced hyperlipidemic rats. *J Nutr Sci Vitaminol (Tokyo).* 1990;36(2):165–171.
50. Nagaoka S, Shimizu K, Kaneko H, et al. A novel protein C-phycocyanin plays a crucial role in the hypocholesterolemic action of Spirulina platensis concentrate in rats. *J Nutr.* 2005;135(10):2425–2430.
51. Mazokopakis EE, Starakis IK, Papadomanolaki MG, Mavroeidi NG, Ganotakis ES. The hypolipidaemic effects of Spirulina (Arthrospira platensis) supplementation in a Cretan population: a prospective study. *J Sci Food Agric.* 2014;94(3):432–437.
52. Zeinalian R, Farhangi MA, Shariat A, Saghafi-Asl M. The effects of Spirulina Platensis on anthropometric indices, appetite, lipid profile and serum vascular endothelial growth factor (VEGF) in obese individuals: a randomized double blinded placebo controlled trial. *BMC Complement Altern Med.* 2017;17(1):225.
53. Sáinz N, Barrenetxe J, Moreno-Aliaga MJ, Martínez JA. Leptin resistance and diet-induced obesity: central and peripheral actions of leptin. *Metabolism.* 2015;64(1):35–46.
54. Achari AE, Jain SK. Adiponectin, a therapeutic target for obesity, diabetes, and endothelial dysfunction. *Int J Mol Sci.* 2017;18(6).
55. Vazquez-Velasco M, Gonzalez-Torres L, Mendez MT, et al. Glucomannan and Glucomannan plus Spirulina-enriched squid-surimi added to high saturated diet affect glycemia, plasma and adipose Leptin and adiponectin levels in growing FA/FA RATS. *Nutr Hosp.* 2015;32(6):2718–2724.
56. Marles RJ, Barrett ML, Barnes J, et al. United States pharmacopeia safety evaluation of spirulina. *Crit Rev Food Sci Nutr.* 2011;51(7):593–604.
57. Higgins I, Parker V, Keatinge D, et al. Doing clinical research: the challenges and benefits. *Contemp Nurse.* 2010;35(2):171–181.
58. Wadden TA, Bray GA. *Handbook of obesity treatment.* Guilford Publications; 2018.