Effect of Microalgae Arthrospira on Biomarkers of Glycemic Control and Glucose Metabolism: A Systematic Review and Meta-analysis

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Abstract: Diabetes mellitus and insulin resistance are associated with an increased risk of cardiovascular disease (CVD) incidence and a higher rate of CVD-related death. In this study, the effects of Arthrospira (Spirulina) a blue-green algae supplementation on biomarkers of glycemic control and glucose metabolism has been evaluated. PubMed, Scopus, and ISI Web of Science were searched systematically of English human subjects and PubMed for pre-clinical animal studies (rats and mice) from January 2008 until November 2020. The pooled weighted mean difference (MD) and its 95% confidence interval (CI) were calculated and pooled using a random-effect model. Seven clinical and 27 preclinical studies were included. Pooled results of the clinical studies showed that Arthrospira supplementation significantly reduced the fasting blood sugar (FBS): (0.63- 2.90-) 1.77-, total cholesterol (TC): (0.46- ، 4.61-) 2.54-, triglycerides (TG): (0.89- ، 6.54-) 3.71- and increased the high-density

Conflict of interest: All the authors declare that they have no conflict of interest.
Curr Probl Cardiol 2022;47:100942
0146-2806/$ – see front matter
https://doi.org/10.1016/j.cpcardiol.2021.100942

lipoprotein cholesterol (HDL-C): (3.86 ، 0.67) 2.27; however, Arthrospira was not significantly effective in terms of reducing the glycated hemoglobin A1c (HbA1C): (1.04 ، 2.23-) 0.59- and low−density lipoprotein cholesterol (LDL-C). Pooled results of preclinical studies showed that Arthrospira supplementation reduced FBS [-10.31 (-12.49, -8.13)] and HbA1C [-5.12 (-8.06, -2.19)] significantly in diabetic animals. Subgroup analysis of clinical studies showed that intervention duration less than 2 months [-2.52 (-4.37, -0.67)] and the dose less than 2 gram [-3.22 (-5.67, -0.76)] showed significant improvement in terms of reducing the FBS in humans. It can be concluded that Arthrospira can be considered as an effective FBS, TG, TC, and HDL-C adjusting nutraceutical agent for diabetes mellitus. Due to the differences in the results of clinical and animal studies in terms of HbA1c, more studies are needed for a definitive conclusion. (Curr Probl Cardiol 2022;47:100942.)

Introduction

Various studies have shown that type 1 diabetes or type 2 increases the risk of cardiovascular diseases (CVD) such as coronary stroke, heart disease, cardiomyopathy, peripheral arterial disease, and congestive heart failure.[1] Glycemic control (HbA(1c) [A1C]) showed to be a strong independent risk factor of (CVDs) such as carotid intima-media thickness (IMT). CVDs are the most common causes of death globally, and type 2 diabetes doubles the risk of heart disease.[2,3] In diabetes, insufficient insulin secretion (type 1 diabetes), or defect of insulin action (type 2 diabetes) leads to hyperglycemia and disorders of carbohydrates, proteins, and lipids metabolism in the body. There are several antidiabetic drugs approved by ADA which are called Standards of Medical Care in Diabetes.[4] They enhance the insulin secretion or inhibition of endogenous glucose production signaling. However, it is almost difficult for T2DM patients to maintain a delicate balance between insulin injections, exercise, and diet, to keep their blood sugar at a normal level. Recently to prevent the harmful effects of chemical antidiabetic drugs in long-term use and due to the development of high-effectiveness herbal medicines by pharmaceutical companies, the interest in

using plant sources with hypoglycemic effects with weak or no side effects has been increased.[5-10]

Arthrospira *(Spirulina*) is a filamentous blue-green microalga that was first classified under the plant kingdom because of its rich plant pigments; however, it was later reordered under bacterial kingdom (cyanobacteria) based on its physiological, genetic, and biochemical characteristics.[11] The main species of spirulina are Spirulina maxima (Arthrospira maxima); Spirulina platensis (Arthrospira platensis) and Spirulina pacifica.[12,13] Spirulina exhibits hypoglycemic, anti-inflammatory, antioxidative, hypolipidemic, neuroprotective, immunomodulatory, and anticancer activities.[14-18] It has been suggested that the hypoglycemic effect of *Arthrospira* is due to phytochemicals such as flavonoids, phytopigments, and sterols in this microalga.[19] The hypoglycemic effect of Spirulina is proved by many studies;[14] however, results in this regard are not consistent and some reported no positive effect for Spirulina on fasting blood glucose (FBS) level in patients with type 2 diabetes.[20,21] So far a meta-analysis has investigated the impact of Spirulina supplementation on serum lipid profile and another meta-analysis studied the glycemic control in patients with metabolic syndrome.[22] To the best of our knowledge, this is the first meta-analysis and systematic review that evaluate the effect of Spirulina supplementation on biomarkers of glycemic control and glucose metabolism, including FBS, HbA1C, insulin, HOMA-IR, TG, TC, LDL−C, and HDL−C in both human and animal studies. The final result will provide an overview of the current and potential hypoglycemic effect of Spirulina.

Methods

Search strategy

This systematic search was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA).[23] The search was performed covering the PubMed, Scopus, and ISI Web of Science databases for clinical studies and PubMed for pre-clinical animal studies (rats and mice), from January 2008 until November 2020. The search was conducted using related keywords and MeSH terms including ("Spirulina" OR "Spirulina platensis" OR "Spirulina fusiformis" OR "Spirulina maxima" OR "Arthrospira" OR "Arthrospira maxima") AND ("fasting blood glucose" OR "FBS" OR "blood glucose" OR "diabetes" OR "hemoglobin A1c"). Manuel search of journals was performed to obtain relevant missing articles.

Inclusion criteria

The titles, abstracts and if necessary, the full texts of extracted studies were collected, entered in a digital library, and screened to check for their eligibility by two independent reviewers (FG & AA). Inclusion criteria for the present study were: (1) randomized clinical trial (RCT) study design and/or preclinical articles with human and/or animal subjects, (2) the exposure of interests were fasting blood sugar (FBS), glycated hemoglobin A1c (HbA1c), insulin, homeostasis model assessment of insulin resistance (HOMA−IR), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), and total cholesterol (TC) levels, (3) the outcome of interest was at least one of the exposure of interests reported as result, and (4) the relative risk (RR) with corresponding 95% confidence interval (CI, or data to calculate them) were reported. If data were duplicated in more than one study, we included the study with the largest number of cases.

Data extraction

The following data were extracted from the include studies: the first authors' name, year of publication, country of study, age, study design, sample size, the dosage of spirulina, duration of the study, the mean and SD for FBS, insulin, HOMA−IR, and serum lipoproteins in each intervention group.

Statistical method

We extracted the mean and standard deviation (SD) of the outcomes (FBS, HbA1C, TC, TG, LDL-C, and HDL-C in clinical studies, FBS, HOMA−IR, insulin, and body weight in preclinical studies), and calculate mean changes along with SD before and after the intervention in both *Arthrospira* and control groups. The standardized Mean Difference (SMD) and 95% confidence interval (CI) were reported to estimate changes in two groups. The significance of SMD was checked by Z-test, and P values less than 0.05 were statistically considered significant. In case of the high degree of heterogeneity (I^2 statistic values above 50%, and the chi-square test P values < 0.1), a random-effect model was used to camp out pooled effect size. Egger's regression test and the Begg test were used to investigating publication and the trim and fill methods if in case of confirmation of publication bias was significant.

Results

Search result

The primary electronic searches for title and abstract yielded a total of 45 studies. Excluding included duplicates, mixture of Arthrospira *(Spirulina*) with other herbs, not available data or hazard ratio, reviews and conferences, and undesired titles and/or abstracts. Finally, the seven clinical trials[7,18,21,24-27] with 214 participants and 27 preclinical studies[5,6,14,17,28-49] were selected and included in our meta-analysis (Fig 1).

Study characteristics

The basic characteristics of all included studies are summarized in Tables 1 and 2. We included 7 clinical and 27 preclinical (rat and mice)

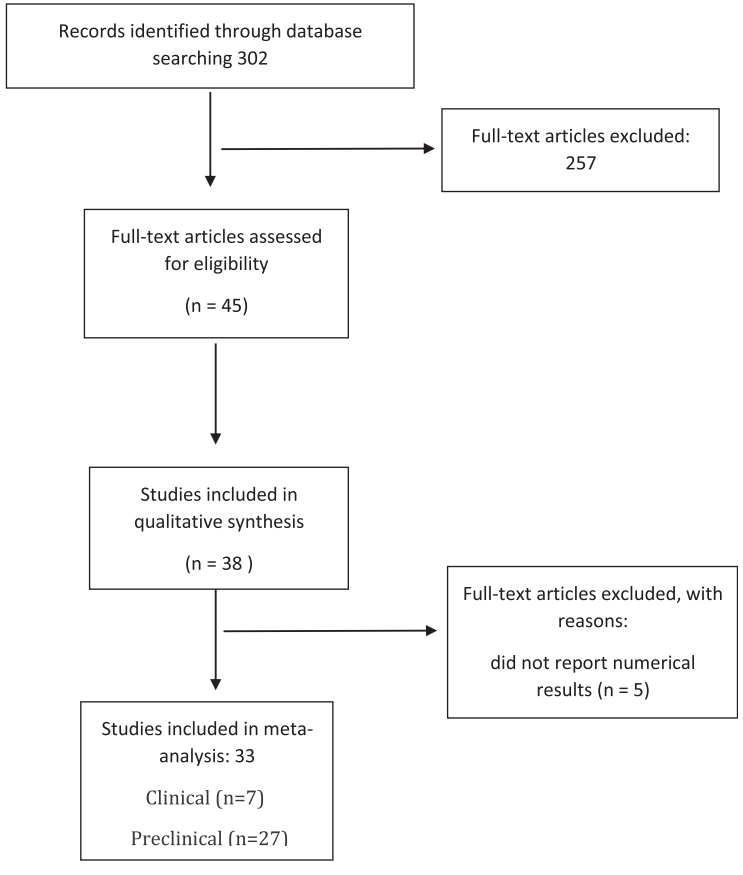

FIG 1. The study selection flowchart

TABLE 1. Characteristics of included clinical studies

Author (Ref)	Publication year	Country	Study design	Sample size (control/ intervention)	Follow up Duration (week)	Dosage (mg/day)	Age (years; control/intervention)
Lee (21)	2008	Korea	Randomized placebo-controlled, parallel-group trial	19/18	12	8000	54.5 ± 6.36, 52.1 ± 10.02
Alam (24)	2016	India	Randomized single blind standard controlled trial	10/10	6	14 000	30-60
Parikh (18)	2001	India	Randomized Placebo controlled, parallel group trial	15/10	8	2 000	54.20
Kaur (25)	2008	India	Randomized controlled trial	20/20	8	2000	40-60
serban (26)	2015	Romania	Randomized, single blinded study	15/15	8	800	30-70
Beihaghi (27)	2017	Iran	Randomized Controlled Trial	20/20	12	8000	30-60
Mani (7)	2016	India	Randomized placebo controlled, parallel group trial	15/7	8	2 000	53.40 ± .32/ 47.80 ± 2.35

TABLE 2. Characteristics of included preclinical studies

Author (Ref)	Publication year	Country	Diabetic model	Sample size (control/ intervention)	Target population	Treatment duration (day)	dosage (mg/kg)	Age (week)	Biological sex (M/F)
Rodríguez-Hernández(28)	2001	México	Alloxan	6/6	Diabetic rats	28	5%	NA	Male
Layam(5)	2007	India	STZ	6/6	Diabetic rats	45	15	7-8	Male
Senthilkumar (29)	2008	India	Alloxan	6/6	Diabetic rats	30	2.5	6- 8	male
Gupta (30)	2010	India	Dexamethasone	6/6	Diabetic rats	21	500	NA	Male
Pandey(31)	2011	India	STZ	5/5	Diabetic rats	40	15	10-12	Male
Moura(32)	2011	Brazil	Alloxan	10/10	Diabetic rats	44	17%	8	NA
Devesh (33)	2012	India	Dexamethasone-induced insulin resistance	6/6	Diabetic rats	21	500	NA	Male
Joventino (34)	2012	Brazil	Alloxan	6/13	Diabetic rats	10	100	NA	Male
Jarouliya (35)	2012	India	Fructose	10/10	Diabetic rats	30	500	10-14	Male
El-Baz(36)	2013	Egypt	STZ	10/10	Diabetic rats	45	15	NA	Male
Senthil (37)	2013	India	STZ	6/6	Diabetic rats	45	200	NA	Male
Kumari (57)	2013	India	Alloxan	NA	Diabetic mice	28	400	NA	NA

(*continued on next page*)

TABLE 2. (*continued*)

Author (Ref)	Publication year	Country	Diabetic model	Sample size (control/ intervention)	Target population	Treatment duration (day)	dosage (mg/kg)	Age (week)	Biological sex (M/F)
AbouZid (38)	2013	Egypt	NA-STZ	6/6	Diabetic mice	7	50	NA	Male
Salem (39)	2014	Egypt	Alloxan	20/20	Diabetic rats	28	15	NA	Male
El-Desouki (40)	2015	Egypt	Alloxan	10/10	Diabetic rats	21	2000	NA	Male
Fadda (41)	2015	Egypt	STZ	5/5	Diabetic rats	35	15	NA	Male
Pankaj (42)	2016	India	Alloxan	6/6	Diabetic rats	21	15	NA	NA
Lee (14)	2017	Korea	STZ	6/6	Diabetic rats	4	200	NA	Male
Gargouri (17)	2018	Tunisia	Alloxan	6/6	Diabetic rats	21	50000	12	Male
Aissaoui (43)	2017	Algeria	Alloxan	8/8	Diabetic rats	50	10%	10-13	Male
Garcia (44)	2018	Brazil	STZ	8/8	Diabetic rats	42	50	NA	Male
Oriquat (6)	2018	Egypt	STZ	10/10	Diabetic rats	30	750	NA	Male
Simon (45)	2018	India	STZ	6/6	Diabetic rats	28	400	NA	Female
Nasirian (46)	2018	Iran	STZ	8/8	Diabetic rats	5	30	10	Male
El-Sayed(47)	2018	Egypt	STZ	6/6	Diabetic rats	30	50	NA	Male
Wan (48)	2019	China	HFHS	8/8	Diabetic rats	56	150	NA	Male
El-Moataaz (49)	2019	Egypt	Alloxan	10/10	Diabetic rats	30	30	NA	Male

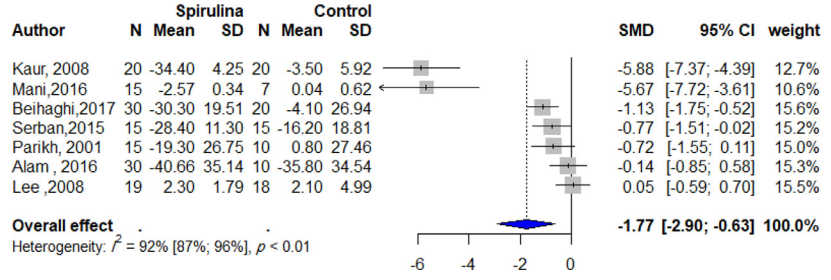

FIG 2. Forest plot of standard mean difference between Spirulina and placebo groups on human for the effect of Spirulina supplementation on FBS.

studies which were published between the years 2008 and 2019. Participants were aged between 30 to 60 years old, and the dosage of spirulina ranged from 0.8 to 14 g/day for humans and 0.0025 to 5 g/day for animal samples. In human studies, the sample size in the intervention group was 114 cases and in the control group was 100. In preclinical studies for sample size in the intervention group was 206, and in the control, group was 213. The duration of studies varied from 1 week to 12 weeks.

Clinical outcomes

The pooled mean difference of 7 clinical trials conducted on human samples, showed that 7 studies examined the effect of *Arthrospira* on FBS, 4 studies on HbA1C, 5 studies on TG and TC, and 4 studies on HDL-C and LDL-C. The combination of the results of these studies showed that except for HbA1C and LDL-C, the mean of other variables was significantly different between the two groups of *Arthrospira* and control. As shown in Figures 2-7, the mean of FBS in the *Arthrospira* group was significantly lower than the control group [SMD: -1.77; 95% CI (-0.63, -2.90). Also, the pooled result indicated that *Arthrospira* consumption can significantly reduce TG and TC compared to the control

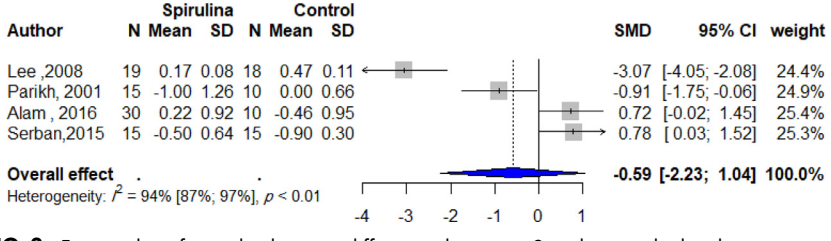

FIG 3. Forest plot of standard mean difference between Spirulina and placebo groups on human for the effect of Spirulina supplementation on HbA1C.

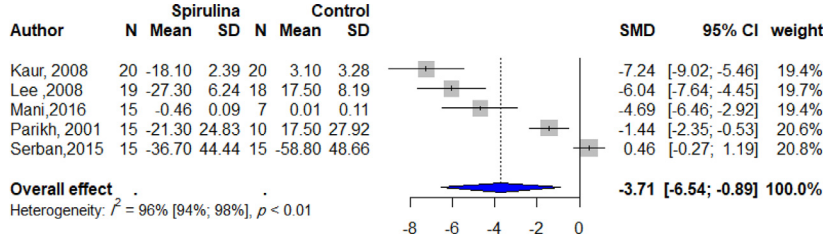

FIG 4. Forest plot of standard mean difference between Spirulina and placebo groups on human for the effect of Spirulina supplementation on TG.

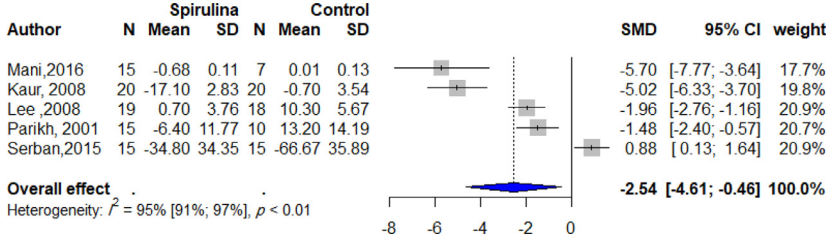

FIG 5. Forest plot of standard mean difference between Spirulina and placebo groups on human for the effect of Spirulina supplementation on TC.

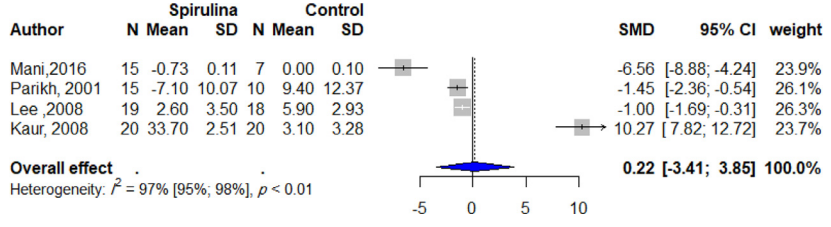

FIG 6. Forest plot of standard mean difference between Spirulina and placebo groups on human for the effect of Spirulina supplementation on LDL-C

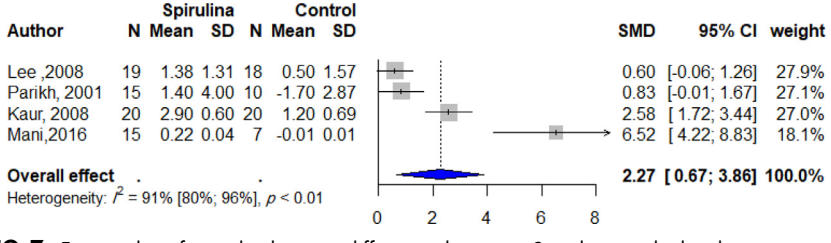

FIG 7. Forest plot of standard mean difference between Spirulina and placebo groups on human for the effect of Spirulina supplementation on HDL-C.

group. The standardized mean difference with a 95% confidence interval was obtained for TG -3.71(-6.54, -0.89) and TC -2.54 (-4.61, -0.46). In the case of HDL-C, *Arthrospira* consumption significantly increases the

HDL-C level 2.27 (0.67, 3.86), however in the case of LDL-C 0.22 (-3.41, 3.85) and HbA1C -0.59 (-2.23, 1.04), no significant difference was observed between the two groups.

Non-clinical outcomes

From 27 studies on preclinical studies, 27 studies examined the effect of *Arthrospira* on FBS, 4 studies on HbA1C, 8 studies on body weight, 9 studies on insulin, and 4 studies on HOMA-IR. The results showed that except for HbA1C and FBS, other variables were not significant. As shown in Figures 8 and 9, the mean of HbA1C and FBS in the *spirulina* group was significantly lower than in the control group. The standardized mean difference with 95% confidence interval was obtained for HbA1C -5.12 (-8.06, -2.19) and for FBS -10.31 (-12.49, -8.13). As shown in Figures 10–12, the pooled result for bodyweight 3.18 (-0.13, 6.48), insulin1.28 (-2.11, 4.66), and HOMA-IR -1.80 (-5.80, 2.21) were not significant.

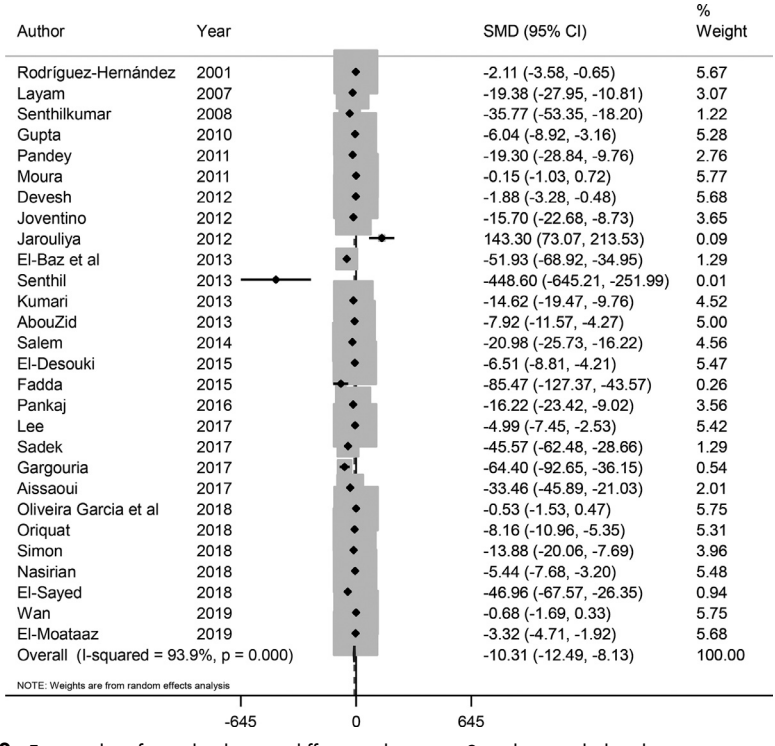

FIG 8. Forest plot of standard mean difference between Spirulina and placebo groups on rat for the effect of Spirulina supplementation on FBS.

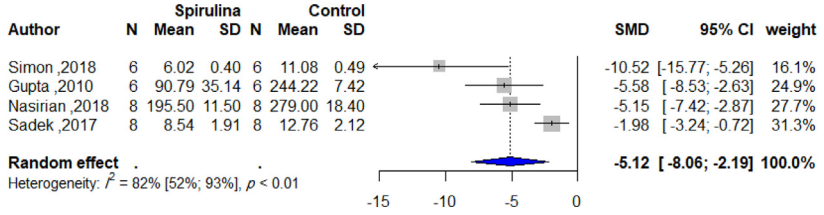

FIG 9. Forest plot of standard mean difference between Spirulina and placebo groups on rat for the effect of Spirulina supplementation on HbA1C.

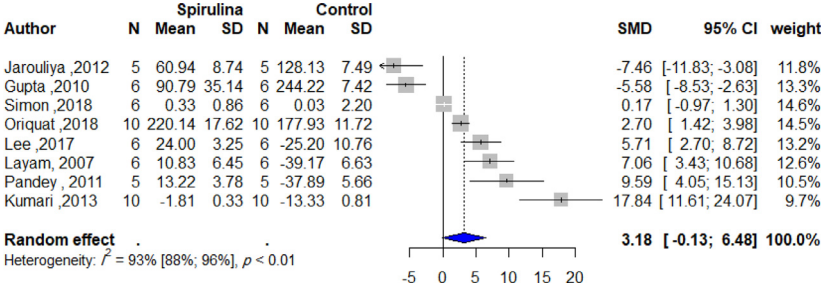

FIG 10. Forest plot of standard mean difference between Spirulina and placebo groups on rat for the effect of Spirulina supplementation on Body weight.

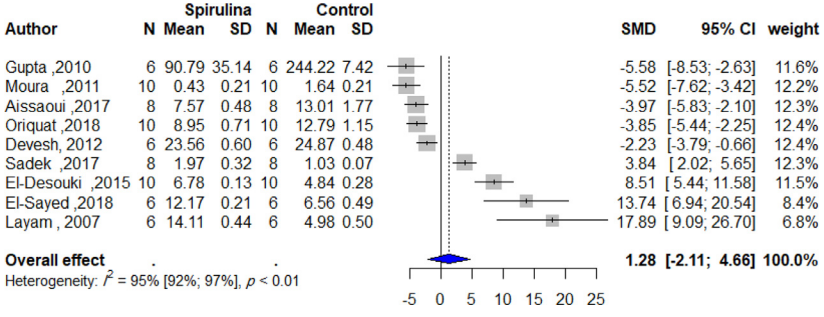

FIG 11. Forest plot of standard mean difference between Spirulina and placebo groups on rat for the effect of Spirulina supplementation on Insulin.

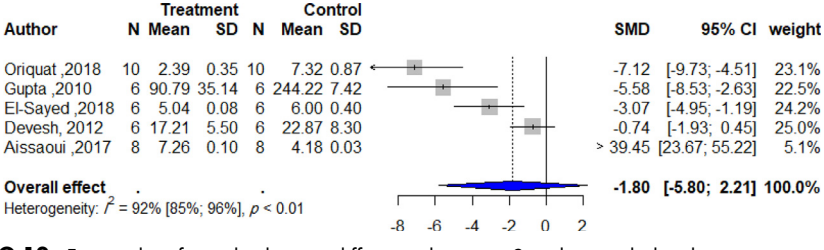

FIG 12. Forest plot of standard mean difference between Spirulina and placebo groups on rat for the effect of Spirulina supplementation on HOMA-IR.

Human sub-group analysis

Subgroup analysis was performed on two variables of drug dose (g2≥ and g <2) and study duration period length (< 2 months and ≥ 2 months). Regarding FBS study duration less than 2 months [-2.52 (-4.37, -0.67)] and the dose less than 2 gram [-3.22 (-5.67, -0.76)] showed significant results. In terms of HbA1C, only one study with a duration of more than 2 months showed a significant effect of spirulina consumption on HbA1C [-3.09 (-4.05, -2.12)]. In terms of triglycerides, cholesterol, and LDL, only one study that had a duration of more than 2 months and a dose of more than 2 grams showed a significant effect of spirulina consumption on reducing triglyceride [-7.37 (-9.22, -5.53)], cholesterol [-2.01. (-2.80, -1.21)] and [LDL -1.02 (-1.71, -0.33)]. In the case of HDL, 3 studies with a duration of fewer than 2 months and a dose of less than 2 g reported a significant effect on the increase in HDL levels.

Human sub-group analysis

Subgroup analysis was performed on two variables of drug dose (<200 mg and <200 mg) and study duration (30> days and <30 days) that in all indicators except for FBS, a significant difference was observed between the subgroups. In terms of weight changes, 3 studies with a duration of more than 30 days [11.93 (5.76, 18.10)] and 2 studies with a dose of less than 200 mg reported a significant effect of spirulina on weight gain [8.55 (5.60, 11.50)]. In terms of insulin, only 2 studies with a dose of less than 200 mg showed a significant effect of [16.56 (11.33, 21.80)]. In the case of the HOMA-IR index, there was no difference between the results of the two subgroups in terms of study duration, but in the case of spirulina dose, only one study with a dose of less than 200 mg showed a significant effect of spirulina on HOMA-IR reduction [3.33 (-5.17, -1.48)].

Discussion

In the current meta-analysis, we reviewed the evidence for the effects of Arthrospira supplementation on the major biomarkers of glycemic control and glucose metabolism in clinical and preclinical studies. Our study showed a significant decrease in FBS levels both in clinical and preclinical studies, and significant improvement of TC, TG, and HDL-C levels in clinical studies compared to the control group. Results of preclinical studies showed a significant decrease in HbA1c levels followed by consumption of spirulina.

Hamedifard et al. in a meta−analysis conducted in 2016,[22] reported that the use of Arthrospira supplementation in patients with MetS and related disorders caused a significant decrease in FBS, TC, and LDL−C and a significant increase in HDL−C level but did not influence the TG. Out of 7 clinical studies we evaluated in terms of FBS only one study reported no significant positive effect on FBS level[21] while two of the studies showed great significant effects.[7,25] Based on the results of the mentioned studies and the pooled results of our clinical and pre-clinical studies, it seems that spirulina supplementation decreases the FBS level efficiently.

Of four clinical studies that have been evaluated the HbA1C, two showed that spirulina decreased the HbA1C[18,21] and on the contrary two studies reported elevated levels of HbA1C[24,26] therefore no significant effect on HbA1C level in clinical studies were found. Pooled results of 4 pre-clinical studies on HbA1C showed a positive effect on HbA1C level, however, due to the small number of articles in both clinical and pre-clinical lines, these results cannot be conclusively accepted and more high-quality studies are needed to comment more conclusively.

Our sub-group analysis of clinical studies of human diabetic subjects showed that a dose less than 2 grams of spirulina can reduce the FBS level more effectively. A study on streptozotocin diabetic rats showed that spirulina dose of 15 mg/kg body weight yielded better results compared to the lower doses of 5 and 10 mg/kg [5]. They reported that spirulina increased the hexokinase activity and decreased the glucose-6-phosphatase (G-6-pase) activity. The role of G-6-pase in glucose homeostasis and T2DM was reported previously and it was mentioned that G-6-pase activity is several folds higher in diabetic animals.[50] Therefore decreasing the G-6-pase followed by spirulina treatment might be one of the possible mechanisms in adjusting FBS levels. Hexokinases is an enzyme responsible for irreversible phosphorylation of glucose to glucose-6-phosphate and it has been reported that its' activity is reduced in non-insulin-dependent DM subjects.[51] Another study claimed that the mechanism of action of spirulina may be through the increase in glucagon-like peptide-1, and glucose-dependent insulinotropic polypeptide.[52] The increased activity of NADPH oxidases in diabetic subjects also is reported and it seems that another possible mechanism for the antidiabetic effect of Arthrospira might be due to the down-regulation of NADPH and NADH cofactor.[47] Hu et al. identified 3 peptides with the anti-diabetic activities in Arthrospira platensis during in-vitro studies that influence α-amylase, α-glucosidase, and DPPIV which are effective components of diabetes relate pathways[8].

A meta-analysis by Serban et al. on the effect of spirulina on serum lipid profile showed that spirulina reduced the TC, TG, and LDL-C and increased the HDL-C level.[20] Hamedifard et al. also reported that spirulina supplementation improved the TC, LDL-C, and HDL-C in patients with MetS but not TG.[22] Our results proved that Arthrospira improved the TC, TG, and HDL-C in diabetic subjects but not LDL-C. A review study on the effect of spirulina on weight loss and lipid profile showed the positive effect of spirulina on weight loss;[11] however, the results of our preclinical studies did not show any positive effect of spirulina supplementation on weight loss. Subgroup analysis in preclinical studies showed that spirulina at doses less than 200 mg cause significant weight gain. Zeinalian et al. in a study on obese people showed that spirulina consumption improved the TC and HDL-C levels and also decreased the BMI with no change in TG and LDL-C.[53] Another study on obese people with BMI $>25-40$ kg/m2 showed a positive effect in reducing waist circumference, weight loss, body fat, and TG.[54] A study on the effect of Spirulina on lipoprotein lipase activity showed increased activity of lipoprotein lipase.[55] It was also found that spirulina intake would normalize the hepatic steatosis and improve the liver function tests.[56] In addition, it is believed that spirulina can increase the gut microbiota which would reduce the lipid levels by improving insulin sensitivity;[56] however, our results showed no positive effect of spirulina consumption on insulin resistance score (HOMA-IR) and insulin in preclinical studies.

Conclusion

According to the results of this study, it can be concluded that Arthrospira (spirulina) supplementation improved the FBS, TC, TG, and HDL-C levels in diabetic patients and the FBS and HbA1C levels in diabetic animals. Our results did not show any significant positive effect on HOMA-IR, weight loss, and insulin followed by consumption of spirulina in animal models.

Ethical Standards

This article does not contain any studies with human participants performed by any of the authors.

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