The effect of spirulina on type 2 diabetes: a systematic review and meta-analysis

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Abstract:

Background and aims: The aim of the present study was to investigate the effect of spirulina on lipid profiles and glycemic related markers in type 2 diabetes patients.

Methods: PubMed, Scopus, Cochrane Library, ISI Web of Science, and Google Scholar was searched from inception to August 2019. All clinical trials which investigated the effect of spirulina supplementation on glycemic related markers and lipid profile among type 2 diabetes patients were included. Random effects modelling was utilized for pooling analysis to compensate for the between study heterogeneity

Results: We found a significant reduction in fasting blood glucose (-17.88 mg/dl; 95% CI: -26.99, -8.78; I^2: 25%), triglyceride (-30.99 mg/dl; 95% CI: -45.20, -16.77; I^2: 50%), total-cholesterol (-18.47 mg/dl; 95% CI: -33.54, -3.39; I^2: 73%), LDL-C (-20.04 mg/dl; 95% CI: -34.06, -6.02; I^2: 75%), VLDL (-6.96 mg/dl; 95% CI: -9.71, -4.22; I^2: 33%), in addition to a significant increase in HDL-C (-6.96 mg/dl; 95% CI: -9.71, -4.22; I^2: 33%), after spirulina administration. No significant effect was observed on HbA1C or post prandial blood sugar following spirulina consumption.

Conclusion: The present study suggests that spirulina supplementation can elicit beneficial effects on fasting blood glucose and blood lipid profiles.

Keywords: Spirulina, Arthrospira platensis, Diabetes Mellitus, meta-analysis.

Introduction:

Type 2 diabetes is a non-communicable disease, manifest via impairment in glucose metabolism, affecting both developed and developing countries (Association, 2017). Although many strategies have been suggested for ameliorating or treating diabetes, the incidence of this disease is growing rapidly (Roglic, 2016). Such high incidence imposes a critical burden on health care system utilization, which consequently confers a large economic cost annually, (Thornton, Seabury, Lopez, McKenzie, & Goldman, 2016). Thus, any viable alternative, complementary, or adjunct therapy that may alleviate some economical and/or health care burden represents an issue of high importance.

In contemporary practice, lifestyle modification, including change in diet and physical activity, is a first step to treatment of type 2 diabetes (Karimian, Hadi, Pourmasoumi, Najafgholizadeh, & Ghavami, 2019; Rockette-Wagner et al., 2015). However, many patients find it difficult to adhere with dietary restrictions (A. Hadi, Pourmasoumi, Najafgholizadeh, Kafeshani, & Sahebkar, 2019). On the other hand, many pharmacological agents cause adverse side-effects which limits their palatability and success (S. E. Kahn et al., 2006; Shah & Mudaliar, 2010). In this case, the efficacy of functional food and natural medicines as adjuvant therapies, concomitant with pharmacological agents, has become an interesting area for many researchers (Amir Hadi, Pourmasoumi, Mohammadi, Symonds, & Miraghajani, 2018; Pourmasoumi, Hadi, Najafgholizadeh, Joukar, & Mansour-Ghanaei, 2019).

Spirulina (Arthrospira maxima) is a microalga, belonging to the family of cyanobacteria with the most curative and prophylactic components of nutrition (van den Driessche, Plat, Konings, & Mensink, 2019); possessing cardio-protective and antioxidant activity due to high amount of phycocyanins, polyphenols, carotenoids, vitamins, essential fatty acids and protein (Soni, Sudhakar, & Rana, 2017). The beneficial effect of spirulina in many non-communicable diseases has been shown previously (Ali, Barakat, & Hassan, 2015; Ramamoorthy & Premakumari, 1996; Wells et al., 2017). Furthermore, animal studies indicated that spirulina can improve metabolic parameters related with glycemic status and lipid profile in diabetic mice (Andrica et al., 2016; Ma, Fang, Zheng, Ren, & Lu, 2016). However, there is lack of consensual evidence from clinical trials. Therefore, the present systematic review and

meta-analysis was performed to summarize the current evidence and investigate the effect of spirulina supplementation on glycemic related markers and blood lipid profiles in type 2 diabetes patients.

Methods:

The present systematic review and meta-analysis was conducted in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) as a standard guideline (Moher, Liberati, Tetzlaff, & Altman, 2009).

Search strategy

A systematic literature search was carried out in electronic databases including Medline (http://www.ncbi.nlm.nih.gov/pubmed), Scopus (http://www.scopus.com), and ISI Web of Science (http://www.webofscience.com), Cochrane Library (http://www.cochranelibrary.com) and Google Scholar (http://scholar.google.com) from inception to August 2019. The comprehensive electronic search was performed by using following keywords in combination with wildcard '*' and medical subject headings (MeSH): ("Spirulina" OR "Arthrospira") AND ("diabetes" OR "diabetic" OR "diabetes mellitus" "blood glucose" OR "glucose metabolism disorders" OR "hyperglycemia" OR "Hemoglobin A, Glycosylated"). The references of related clinical trials and pertinent review articles were also hand-searched to identify any additional studies of interest, which might have been missed during the electronic search.

Study selection

To identify eligible studies, two authors independently screened the studies which was included by primary search. After excluding duplicates, studies were reviewed first by title/abstract, and was articles obviously irrelevant were excluded. Subsequently, the full-texts of remaining studies were scanned. All clinical trials which investigated the effect of spirulina supplementation on glycemic related markers and lipid profile among type 2 diabetes patients were included. Studies were excluded if the duration of studies was <1 weeks, spirulina was administrated as part of a complex substance, spirulina was

compared with an active agent/component, and the outcome of interest was not reported in the studies. Any discrepancy was settled by the third author.

Data abstraction and assessment of quality

Eligible clinical trials were separately reviewed by two authors (A.H and M.P) and following information was recorded from each study: the first author's last name, years of publication, country of origin, total number of participants in each arms as well as their characteristics (mean age, gender), study design, duration of intervention, details of intervention and control groups, dose of spirulina supplementation and outcomes of interest which reported.

Cochrane Risk of Bias Tool for Randomized Controlled Trials were used to detect potential risk of bias in included studies (20). This scale included several criteria to evaluate adequacy of random sequence generation, allocation concealment, blinding as well as detection of incomplete outcome data, reporting selective outcome, and other potential sources of bias. Based on recommendations of the Cochrane Handbook, judgment of each item appears by "Low", "High" and "Unclear" risk of bias. Any disagreement in data extraction and quality assessment judgment was resolved by discussion with a third investigator.

Statistical analysis

The whole process of statistical analyses was conducted by using the Cochrane Program Review Manager Version 5.3 and STATA software (version 11.0; Stata Corporation). To estimate pooled effect size, data from all variables, including fasting blood glucose (FBS), post prandial blood sugar (PPBS), glycated hemoglobin A1C (HbA1C), triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and very-low density lipoprotein cholesterol (VLDL), which were reported in three or more studies, were extracted as mean difference and standard deviation (SD). In any instance where mean change and SD of change were not reported directly for intervention and control groups, it was calculated following a suggested formula (J. P. Higgins & Green, 2011). A random effects test was applied for pooling analysis to compensate the between study heterogeneity (Dersimonian & Laird; J. P. T. Higgins et al., 2011). Sensitivity analysis

was conducted by eliminating each study, one at a time, to determine the influence of each study on the overall result. Egger's regression asymmetry test and Begg's rank-correlation methods was also performed to explore potential publication bias (Egger, Smith, Schneider, & Minder, 1997; Sterne & Bradburn, 2001). To evaluate the potential influence of putative moderators such as baseline measures and duration of administration on changing variable in response to spirulina supplementation, the meta-regression was applied. Results were assumed statistically significant when $P<0.05$.

Results:

The study selection process and the reason for study exclusion at each step is illustrated in **Figure 1**. The electronic selection process yielded 907 unduplicated trials, in which 896 of them were excluded by title/abstract screening, and 11 studies remained for full-text assessment. Three studies were omitted due to not being conducted on diabetes patients (n=2) or not reporting outcomes of interest (n=1). One study administrated 2 different doses of spirulina and was considered as 2 separate arms. Therefore, 8 studies comprising 9 arms met eligibility criteria and were included in the present meta-analysis.

Studies' characteristics

Characteristics of included studies are detailed in **Table 1**. In brief, 8 clinical trials (9 arms) (Alam et al., 2016; Anitha & Chandralekha, 2010; Beihaghi & Taherzadeh, 2017; Kaur, Sachdeva, & Grover, 2008; Lee, Park, Choi, Huh, & Kim, 2008; Mani, Desai, & Iyer, 2000; Parikh, Mani, & Iyer, 2001; SERBAN et al., 1982) comprising 334 diabetes patients, with a mean age of 51 years old, were included to meta-analysis. The studies were conducted in various countries including India (Alam et al., 2016; Anitha & Chandralekha, 2010; Kaur et al., 2008; Mani et al., 2000; Parikh et al., 2001), Iran (Beihaghi & Taherzadeh, 2017), Romania (SERBAN et al., 1982) and South Korea (Lee et al., 2008), and published between 2001 and 2017. The baseline BMI of participants was only reported in 4 trials (Lee et al., 2008; Mani et al., 2000; Parikh et al., 2001; SERBAN et al., 1982). Duration of intervention ranged from 45 to 90 days, and the dose of spirulina administration varied between 0.8 and 8 g/day. Only one trial (SERBAN et al., 1982) reported that participants received placebo as a control group.

Two trials recruited only male participants (Anitha & Chandralekha, 2010; Kaur et al., 2008), whilst of the remaining studies enrolled patients of both gender.

Risk of bias assessment

Five trials were randomized (Alam et al., 2016; Beihaghi & Taherzadeh, 2017; Lee et al., 2008; Parikh et al., 2001; SERBAN et al., 1982), however, only one study (Alam et al., 2016) sufficiently addressed information around allocation concealment. Only 2 studies (Alam et al., 2016; SERBAN et al., 1982) were blinded. The data regarding attrition and reporting biases were well-addressed in all trials. **Table 2** presents the risk in each item of bias among included studies in detail.

Meta-analysis

The effect of spirulina supplementation on glycemic related markers

The result of our meta-analysis suggested a significant effect of spirulina supplementation on FBS levels (-17.88 mg/dl; 95% CI: -26.99, -8.78; I^2: 25%). However, no notable influence was detected for HbA1C (-0.12 %, 95% CI: -0.70, 0.46; I^2=84%) or PPBS (-15.03 %, 95% CI: -44.99, 14.92; I^2=0%) after spirulina intervention **(Figure 2)**.

The effect of spirulina on blood lipid profiles

Pooled effect sizes revealed a significant reduction in TG (-30.99 mg/dl, 95% CI: -45.20, -16.77; I^2=50%), TC (-18.47 mg/dl, 95% CI: -33.54, -3.39; I^2=73%), LDL-C (-20.04 mg/dl, 95% CI: -34.06, -6.02; I^2=75%) and VLDL (-6.96 mg/dl, 95% CI: -9.71, -4.22; I^2=45%) following spirulina supplementation. In addition, the result indicated that spirulina supplementation yielded a significantl increase in HDL-C serum concentration (4.18 mg/dl, 95% CI: 1.67, 6.69; I^2=33%) **(Figure 3)**.

Meta-repression

The meta-regression revealed that the effect of spirulina supplementation on TC and LDL-C was inversely associated with baseline values (TC: coefficient= -0.89, P=0.01; LDL-C: coefficient= -1.13, P=0.005). In addition, the change in TG blood concentrations in response to spirulina intervention was related to the duration of intervention (TG: coefficient= -0.87, P=0.03). However, the change in of the

remaining variables were independent from the dose of spirulina supplementation, duration of intervention, and baseline measures, respectively.

Sensitivity analysis and publication bias

Sensitivity analysis, by removing each RCT one by one, indicated that the pooled effect size of TG was non-significant after excluding Mani et al. (-16.77 mg/dl; 95% CI: -33.97, 0.43; I^2: 77%). In addition, by removing Anitha et al. from TG overall effect size, the heterogeneity was altered from 50% to 7%, while the results remained significant (-24.51 mg/dl; 95% CI: -38.62, -10.39). The overall results of remaining variables were not influenced by individual studies.

No evidence of publication bias was detected according to Egger's regression asymmetry test and Begg's rank-correlation methods in FBS (Begg's test P=0.67; Egger's test P=0.86), HbA1C (Begg's test P=0.85; Egger's test P=0.77), BSPP (Begg's test P=1.0; Egger's test P=0.99), TG (Begg's test P=0.65; Egger's test P=0.10), HDL-C (Begg's test P=0.54; Egger's test P=0.12), VDLD (Begg's test P=0.99; Egger's test P=0.12). Although Egger's regression asymmetry test indicated significant evidence of publication bias in TC (Egger's test: P=0.005) and LDL-C (Egger's test: P=0.01), however these results were not confirmed by Begg's rank-correlation methods (TC: P=0.45; LDL-C: P=0.65).

Discussion:

The present systematic review and meta-analysis suggests that spirulina supplementation can elicit a beneficial impact on metabolic parameters including FBS, TG, TC, LDL-C, HDL-C and VLDL. However, no favorable effect was observed in HbA1C and PPBS; which might be due to low number of included studies that reported on these parameters. In addition, as HbA1C levels change over longer periods of time, it might that the duration of the included studies was not sufficient to truly reflect the efficacy of spirulina on decreasing in HbA1C. The meta-regression indicated that the change in blood TC and LDL-C concentrations was associated with baseline values, so that higher baseline measures of TC or LDL-C led to greater reductions in blood concentration of these parameters. In addition a greater reduction in TG was observed when the duration of spirulina supplementation was longer.

Patients with type 2 diabetes suffer from innumerable complications, and are at risk of several additional diseases, such as non-alcoholic fatty liver (Gupte et al., 2004) and cardio-vascular disease (Appleton et al., 2013). The current study revealed a significant reduction in FBS and lipid profile following spirulina consumption. Although the mechanisms underlying the beneficial activity of spirulina are not well-understood, although several putative pathways are attributed to spirulina's hypoglycemic and hypolipidemic activity. One of the bioactive components of spirulina is C-phycocyanin, a protein which can inhibit lipid peroxidation, scavenge free radicals, as well as enhance GSH peroxidase and superoxide dismutase activity (Sharma, Tiwari, Tripathi, & Rai, 2011; Upasani & Balaraman, 2003). Spirulina can inhibit pancreatic lipase activity via glycolipid H-b2 (Han et al., 2006), and regulate cholesterol and prostaglandin synthesis via its gamma-linolenic acid components (Karkos, Leong, Karkos, Sivaji, & Assimakopoulos, 2011; Serban et al., 2016). Spirulina also possesses hypoglycemic properties via stimulation of insulin secretion from β-cell, or elevation of blood glucose transport to peripheral tissues by its protein and amino acid constituents (Layam & Reddy, 2006).

The beneficial effect of spirulina on type 2 diabetes is not only related with aforementioned parameters, but also associated with body weight and inflammatory factors, where both are involved with this disease (Gutiérrez-Rebolledo et al., 2015; Miczke et al., 2016; Park & Lee, 2016). Increases in body weight, especially abdominal obesity and inflammation, are associated with insulin resistance (B. B. Kahn & Flier, 2000; Shoelson, Lee, & Goldfine, 2006), such that spirulina can also improve diabetes by weight loss activity and alleviation of inflammation through suppressing the NF-KB activity and reducing pro-inflammatory cytokines production (Chen et al., 2012; Khan, Bhadouria, & Bisen, 2005).

Spirulina is regarded to be generally safe in commonly-used doses and only rare cases of unwanted effect have been reported (Belay, 2002; Deng & Chow, 2010). Except one study (Beihaghi & Taherzadeh, 2017), none of the included studies reported evidence of adverse effects attributed to spirulina consumption. Beihaghi et al.(Beihaghi & Taherzadeh, 2017) reported that participants experienced side-effects such as abdominal discomfort and diarrhea after 8 g/d spirulina consumption, which was alleviated in many of them after a few days. In addition, it has been shown that feeding mice for 7 days with 10g/kg and 30 g/kg of body weight of dried and fresh spirulina, respectively, did not

cause any form of toxicity (Hutadilok-Towatana, Reanmongkol, Satitit, Panichayupakaranant, & Ritthisunthorn, 2008). However, there is a concern about contamination with low levels of mercury and other heavy metals from open water sources (Johnson & Shubert, 1986), which should be avoided by controlling the growth and processing of spirulina.

There are several limitations which should be acknowledged in the present study. First, the number of included studies were somewhat low, and the duration of studies was relatively short. Second, there are several factors related with type 2 diabetes, such as insulin levels, insulin resistance, and homeostatic model assessment of insulin resistance (HOMA-IR), which are essential in the etiology of this disease. However, none of included studies reported on these factors, and future studies should be conducted to investigate the effect of spirulina on these parameters. Finally, the quality of methodology of the included studies was low, and they had a significant risk of bias in several items. In this case, although the overall results indicated promising effect on metabolic parameters in diabetic patients, these findings are not conclusive enough to utilize in clinical practice, and more clinical trials, with high quality methodology are needed to affirm the efficacy of spirulina in diabetic treatment.

Conclusion:

The present meta-analysis highlights that spirulina supplementation can yield improvements in FBS as well as lipid profiles. This study summarizes the currently available information from clinical trials and provides better insight to the effect of spirulina supplementation on type 2 diabetes. Spirulina is a natural functional agent, and generally safe supplement with a low cost, along with a beneficial impact on improving metabolic abnormalities manifest in type 2 diabetes. The favorable effects of spirulina suggest it may be a beneficial adjuvant therapy in conjunction with conventional medicine. However, the results of present study should be considered as primary findings and further studies are needed to confirm the veracity of the results.

Conflict of Interest

There are no conflicts to declare.

Funding

None.

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Figures

Figure 1: Flow chart of the process of the study selection.

Figure 2. Forest plot detailing mean difference and 95% confidence intervals (CI) for the effect of spirulina consumption on fasting blood sugar, hemoglobin A1C, blood sugar post-prandial.

Figure 3. Forest plot detailing mean difference and 95% confidence intervals (CI) for the effect of spirulina consumption on lipid profiles.

Tables

Table 1. The main characteristics of included studies.

Table 2. The summary of review authors' judgments about each risk of bias item for included studies.

Table 1. The main characteristics of included studies.

First author (publication year)	Country	Number and gender (M/F)	Mean age	BMI	Clinical Trial design/ randomized/ Blinding	Duration (Days)	Comparison group	Amount Of Spirulina intake	Notes about participants	Outcomes of interest
Alam et al. (2016)	India	Intervention: 30 Control: 10 (Both gender)	Range: 41-60 years Intervention: 45.07 ± 7.67 Control: 44.00 ± 9.39	NR	Parallel/ Yes/ NR	45 days	Metformin 500 mg/day	Spirulina powder 7g/day	Type 2 Diabetes	FBS, HbA1C, BSPP
Lee et al. (2008)	Korea	Intervention: 19 Control: 18 (Both gender)	Range: years Intervention: 52.1 ± 10.02 Control: 54.5 ± 6.36	Intervention: 23.8±2.17 Control: 23.4±2.12	Parallel/ Yes/ NR	84 day	-	Spirulina tablet 8.0 g/day	Type 2 Diabetes	FBS, HbA1C, TC, TG, HDL-C, LDL-C
Kaur et al. (2008)	India	Intervention: (1) 20 (2) 20 Control: 20 (Male)	Range: 40-60 years Intervention: (1) 46.3±7.60 (2) 45.95±7.15 Control: 47.6±6.70	NR	Parallel/ NR/ NR	60 day	-	Spirulina tablet (1) 1 g/day (2) 2 g/day	Non-insulin dependent diabetes mellitus	FBS, HbA1C, BSPP, TC, TG, HDL-C, LDL-C, VLDL
Anitha et al. (2010)	India	Intervention: 40 Control: 40 (Male)	Range: 45 – 60 years Intervention: NR Control: NR	NR	Parallel/ NR/ NR	84 day	-	Spirulina tablet 1g/day	Non-insulin dependent diabetes mellitus	FBS, HbA1C, TC, TG, HDL-C, LDL-C, VLDL
Parikh et al. (2001)	India	Intervention: 15 Control: 10 (Both gender)	Intervention: 53.8 ± 7.2 Control: 54.6 ± 5.4	Intervention: 25.22±5.4 Control: 25.1±2.7	Parallel/ Yes/ NR	60 day	-	Spirulina tablet 2 g/day	Type 2 Diabetic	FBS, HbA1C, BSPP, TC, TG, HDL-C, LDL-C, VLDL

Mani et al. (2015)	India	Intervention: 15 Control: 7 (Both gender)	Intervention: 47.80±9.10 Control: 53.40±6.13	Intervention: 29.24±0.30 Control: 25.75±0.13	Parallel/ NR/ NR	60 day	-	Spirulina tablet 2 g/day	Non-insulin dependent diabetes mellitus	FBS, TC, TG, HDL-C, LDL-C, VLDL
Serban et al. (2015)	Romania	Intervention: 15 Control: 15 (NR)	Range years: 30-70 Intervention: 61.7 ±6.85 Control: 61.6±8.90	Intervention: 36.6±6.05 Control: 36.2±6.93	Parallel/ Yes/ Yes	60 day	Metformin + Placebo	Metformin + Spirulina tablet 0.8 g/day	Type 2 Diabetes	FBS, HbA1C, TC, TG, HDL-C, LDL-C
Beihaghi et al. (2017)	Iran	Intervention: 20 Control: 20 (Both gender)	Range years: 30-60 Intervention: NR Control: NR	NR	Parallel/ Yes/ NR	90 day	-	Spirulina tablet 8 g/day	Type 2 Diabetes	FBS, HbA1C

Abbreviations: FBS: Fasting Blood Sugar; HbA1C: glycated hemoglobin; BSPP: Blood Sugar post prandial; TG: Triglyceride; TC: Total-Cholesterol; LDL-C: Low-Density Lipoprotein; HDL-C: High-Density Lipoprotein; NR: Not Reported.

Table 2. The summary of review authors' judgments about each risk of bias item for included studies.

Study	Random sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective reporting	Other bias
Alam et al. (2016)	L	L	L	L	L	L
Lee et al. (2008)	L	U	H	L	L	L
Kaur et al. (2008)	U	U	H	L	L	L
Anitha et al. (2010)	U	U	H	L	L	U
Parikh et al. (2001)	L	U	H	L	L	L
Mani et al. (2015)	U	U	H	L	L	U
Serban et l. (2015)	L	U	L	L	L	U
Beihaghi et al. (2017)	L	U	H	L	L	U

H: high risk of bias; L: low risk of bias; U: unclear or unrevealed risk of bias. Criteria defined for risk of bias assessment are according to the Cochrane guidelines.

According to Cochrane criteria, study consider as a poor quality if it had high risk of bias in ≥2 items or unclear risk of bias in ≥3 criteria.