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The effect of Spirulina supplementation on lipid profile: GRADE-assessed systematic review and dose-response meta-analysis of data from randomized controlled trials

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ABSTRACT

Background: Cardiovascular diseases (CVD) are one of the most important causes of death worldwide. Dyslipidemia is one of the main causal risk factors for CVD that can be controlled by modifying lifestyle, which entails the use of healthy diets containing functional foods. The present study was conducted to summarize the effects of Spirulina on the lipid profile in previous randomized controlled trials.
Methods: MEDLINE, Scopus, Clarivate Analytics Web of Science, and the Cochrane Library databases were searched systematically until January 2023, for clinical interventions that investigated the effect of Spirulina supplementation on plasma lipid profile concentrations.
Results: ooled results of 20 studies (with 23 arms and 1076 participants) indicated that Spirulina intervention significantly reduced LDL-C (SMD: −0.6, 95% CI: −0.9, −0.2, P<0.05), TC (SMD: −0.6, 95% CI: −0.9, −0.2, P<0.05) and TG (SMD: −0.6, 95% CI: −0.9, −0.2, P<0.05) levels while HDL-C levels were significantly increased (SMD: 0.3, 95% CI: 0.0, 0.6, P<0.05).
Conclusions: The findings of the present meta-analysis and review show the usefulness of supplementing with Spirulina in improving serum levels of TC, TG, LDL-C, and HDL-C.

1. Introduction

All around the world, cardiovascular disease (CVD) accounts for the largest percentage of deaths [1]. According to several studies reported by the World Health Organization (WHO), 17.9 million people die from CVD every year, which is almost equal to 31.9% of the total number of deaths throughout the world [2]. High blood pressure, insulin resistance, type 2 diabetes (T2DM), dyslipidemia, smoking, overweight, and obesity are among the possible causes of CVD [2].

Dyslipidemia is one of the main causes of CVD, which is defined as an increase in serum levels of triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and a decrease in high-density lipoprotein cholesterol (HDL-C) levels [3]. Dyslipidemia is directly associated with arterial damage, atherosclerosis, and decreased quality of life [3]. Therefore, finding effective lipid-lowering agents is among the primary aims of most research efforts in the world to help reduce the risk of atherosclerotic CVD [4]. In this regard, many studies and reviews have been conducted in the past years, including the investigation of the

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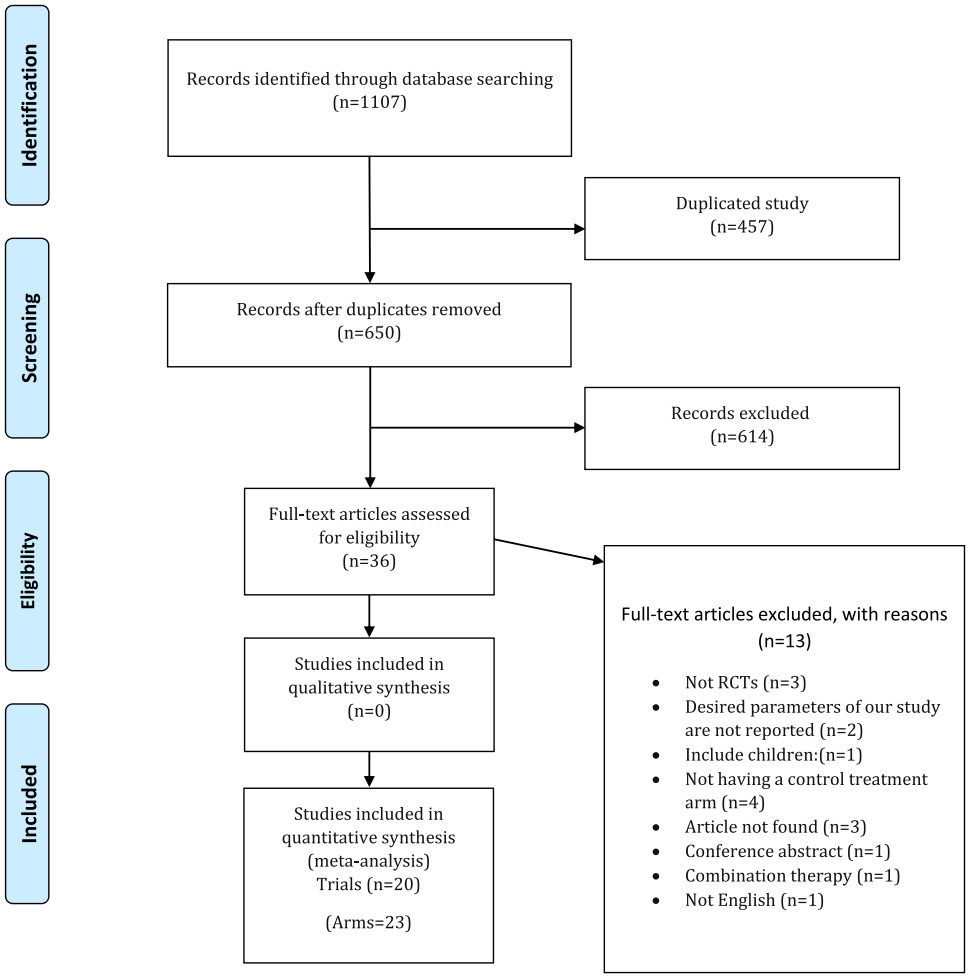

Fig. 1. PRISMA flow diagram.

effect of functional foods and nutraceuticals on modifying the lipid profile [5,6].

Spirulina is a blue-green multicellular microalga, and a member of the Cyanobacteria family, which grows in hot weather and alkaline conditions [7]. Since more than half of its dry weight is protein, it contains all essential amino acids, vitamins, and minerals [8]. One of the light-absorbing structures in Spirulina is the C-phycocyanin pigment, which - according to animal studies - reduces the serum levels of TC and TG [9]. Furthermore, following the identification, of hypoglycemic, anti-inflammatory, antioxidant, neuroprotective, immune-modulating, and anti-cancer actions of Spirulina [10], numerous international health organizations have designated it as one of the superfoods [11].

2. Method

PRISMA statement for systematic reviews and meta-analyses (PRISMA) was followed for this systematic review and meta-analysis [12]. The protocol of the current systematic review was registered at PROSPERO (CRD42023391743).

2.1. Search strategy

The following databases were searched systematically from inception until January 2023: MEDLINE, Scopus, Clarivate Analytics Web of Science, and the Cochrane Library databases. No language or publication year restrictions were imposed. Our search criteria included the following keywords and Medical Subject Headings (MeSH): [1] Spirulina; [2] Lipid profile and [3] Randomized controlled trial. For studies that were missed by our electronic search, we searched relevant reviews and reference lists of the included trials (details were provided in Supplementary Table 1).

2.2. Study selection

Studies were included based on our eligibility criteria: A) studies that include adult participants ($\geq$ 18 years old) who have been treated with Spirulina for any reason. B) Parallel or crossover RCTs that measure the lipid profile factors. C) a comparison between a control group and an intervention should be reported in studies, and D) English articles.

Studies were excluded as follows: A) Preclinical study, B) combination therapy with Spirulina. C) non-trial, animal studies, review articles, conference abstracts, and letters to editor articles, and D) studies did not measure the lipid profile.

2.3. Data extraction

Each eligible RCT was extracted independently by two investigators (M. Ch and I.R). We extracted the following information: name of the first author, publication year, individuals' characteristics (mean age and sex), study design, sample size (control and intervention groups), the dosage of Spirulina, duration of intervention, mean changes, and their SDs of lipid profile throughout the trial for the intervention and control groups, and the confounding variables adjusted in the analyses.

Table 1
Characteristic of included studies.

First author, year, country	Design	Participants (n) Int/con	Health condition	Age means (year) Int/con	Intervention		Dose (gr/day)	Duration of intervention (weeks)	Outcomes (Changes, mg/dl, Pg/ml)	
					Treatment group	Control group			Treatment group	Control group
Karizi/2023/ Iran	RCT-DB	30/30	T2DM	49.63/ 48.76	Spirulina Platensis	Placebo	2	12	TC -41.36 ± 183.83 TG -70.37 ± 170.92 HDL-C 3.1 ± 31.99 LDL-C -38.53 ± 167.54	TC 1.6 ± 204.25 TG -0.7 ± 300.4 HDL-C -1.5 ± 28.82 LDL-C 0.97 ± 224.4
Mazloomi/ 2022/Iran	RCT/DB	23/23	NAFLD	38.87/ 35.78	Spirulina	Placebo	2	8	TC -13.7 ± 39.75 TG -30.35 ± 59.48 HDL-C 4.45 ± 7.81 LDL-C -8.1 ± 22.2	5.31 ± 29.6 12.42 ± 25.88 0.36 ± 9.1 2.52 ± 29.46
Koite/2022/ USA	RCT/DB/ Parallel	20/20	MetS	51.8/ 48.1	Spirulina	Placebo	0.02	12	TC -3 ± 22.21 TG -12 ± 34.2 HDL-C 1 ± 8.68 LDL-C -3 ± 20.87	-5 ± 28.28 14 ± 51.26 1 ± 10.89 -10 ± 23.47
Golestani/ 2021/Iran	RCT/SB	10/10	Obese	21.55	Spirulina+HIIT	Placebo+HIIT	1	4	TC -4.11 ± 24.77 TG -0.27 ± 37.37 HDL-C 3.39 ± 4.2 LDL-C -7.11 ± 18.93	-11.68 ± 16.17 -11.81 ± 21.57 0.88 ± 3.26 -7.89 ± 10.73
Ghaem Far/ 2021/Iran	RCT/TB	22/19	HTN	51.27/ 50.21	Spirulina	Placebo	2	8	TC -3.32 ± 4.61 TG -20.64 ± 10.5 HDL-C 1.22 ± 1.14 LDL-C -2.09 ± 3.56	4.31 ± 4.73 -5.79 ± 10.11 -0.74 ± 1.36 5.06 ± 3.5
Van Den Driessche/ 2020/ Netherlands	RCT/DB	35/35	Healthy	40.2/ 40.2	Spirulina	Placebo	4.8	2.4	TC -0.15 ± 0.67 TG -0.01 ± 0.39 HDL-C -0.18 ± 0.3 LDL-C 0.05 ± 0.62	-0.09 ± 0.69 -0.04 ± 0.38 -0.14 ± 0.31 0.07 ± 0.65
Hernández-Lepe/2019/ Mexico	RCT/DB/ Crossover	12/12	Obese Male	26	Spirulina	Placebo	4.5	12	TC -18 ± 24.1 TG -14 ± 22.63 HDL-C 5 ± 6.7 LDL-C	-4 ± 19.6 -6 ± 19.94 2 ± 7.37 -4 ± 19.69

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Table 1 (*continued*)

First author, year, country	Design	Participants (n) Int/con	Health condition	Age means (year) Int/con	Intervention		Dose (gr/day)	Duration of intervention (weeks)	Outcomes (Changes, mg/dl, Pg/ml)	
					Treatment group	Control group			Treatment group	Control group
									-21 ± 23.73	
Hernández-Lepe/2019/ Mexico	RCT/DB	12/12	Obese Male	26	Spirulina	Placebo	4.5	12	TC -18.2 ± 24.1 TG -14.1 ± 22.63 HDL-C 5.4 ± 6.7 LDL-C -20.8 ± 23.73	-4.5 ± 19.6 -6.1 ± 19.94 1.4 ± 7.37 -3.9 ± 19.69
Yousefi/ 2018/Iran	RCT/DB/ Parallel	19/19	Obese	40.16/ 39.79	Spirulina	Placebo	2	12	TC -7.37 ± 21.42 TG -18 ± 83.39 HDL-C -0.95 ± 7.08 LDL-C -0.15 ± 0.29	2.31 ± 22.95 6 ± 27.79 -0.68 ± 6.08 -0.03 ± 0.18
Zeinalian/ 2017/Iran	RCT/DB	29/27	Obese	34.75/ 33.92	Spirulina	Placebo	1	12	TC -10.38 ± 21.35 TG -7.48 ± 37.55 HDL-C 2.2 ± 6.16 LDL-C -0.85 ± 20.88	-4.22 ± 17.47 -15.26 ± 48.35 3.49 ± 6.93 -3.22 ± 13.6
Szulinska/ 2017/ Poland	RCT/DB	25/25	Obese	49.3/ 50.2	Spirulina	Placebo	2	12	TC -0.3 ± 0.66 TG -0.1 ± 0.6 HDL-C 0 ± 0.18 LDL-C -0.5 ± 0.55	0.2 ± 0.54 0.1 ± 0.73 -0.1 ± 0.25 0 ± 0.56
Park/2016/ Korea	RCT/DB	16/17	Obese	65.3/ 65.3	Spirulina	Placebo	8	12	TC -6.2 ± 24.73 TG -1.8 ± 61.47 HDL-C -4.3 ± 11.69 LDL-C -1.7 ± 25.95	-1.3 ± 26.69 10.5 ± 51.08 4.1 ± 10.26 -7.6 ± 27.58
		25/20	Healthy	66.2/ 66.6	Spirulina	Placebo	8	12	TC -11.9 ± 23.16 TG -3.2 ± 41.29 HDL-C -0.7 ± 9.36 LDL-C -10.6 ± 22.45	2.5 ± 25.45 -5.9 ± 24.69 -0.8 ± 11.31 4.5 ± 27.17
Chitsaz/ 2016/Iran	RCT/DB	20/20	NAFLD	42.8/ 42	Spirulina	Placebo	1	8	TC -2.9 ± 6.57 TG -1.2 ± 22.7 HDL-C	-0.56 ± 13.55 -3.45 ± 59.8 -1.3

(*continued on next page*)

Table 1 (*continued*)

First author, year, country	Design	Participants (n) Int/con	Health condition	Age means (year) Int/con	Intervention		Dose (gr/day)	Duration of intervention (weeks)	Outcomes (Changes, mg/dl, Pg/ml)	
					Treatment group	Control group			Treatment group	Control group
									-1.9 ± 4.92 LDL-C 56.25 ± 248.1	± 6.28 2.6 ± 13.97
Ngo-Matip/ 2014/ Cameroon	RCT/SB	80/79	HIV	36.01/ 35.43	Spirulina	Nothing	10	24	TC -85.4 ± 66.33 TG -67.1 ± 81.07 HDL-C 35.2 ± 26.09 LDL-C -82.5 ± 68.71	22 ± 66.05 32.8 ± 58.51 -3.7 ± 13 18.18 ± 64.09
Anitha/2010/ India	Parallel	40/40	T2DM	45–60	Spirulina	Placebo	1	12	TC -38 ± 9.04 TG -42 ± 10.94 HDL-C 7 ± 7.5 LDL-C -39 ± 10.82	0 ± 9.67 1 ± 8.91 0 ± 4.19 0 ± 10.79
Park/2008/ Korea	RCT/DB/ Parallel	24/19	Healthy Male	66.1/ 66.6	Spirulina	Placebo	8	16	TC -5.6 ± 20.83 TG -2 ± 34.43 HDL-C -3.7 ± 10.41 LDL-C 0.5 ± 23.32	5.4 ± 24.69 3.6 ± 37.61 1.6 ± 10.33 3 ± 24.43
		17/18	Healthy Female	65.6/ 65.4	Spirulina	Placebo	8	16	TC -15.7 ± 25.06 TG -7.3 ± 74.54 HDL-C 0.3 ± 7.91 LDL-C -14.6 ± 21.71	-3.3 ± 23.78 0.5 ± 43.38 1 ± 10.39 -4.5 ± 29.24
Lee/2008/ Korea	RCT/ Parallel	19/18	T2DM	52.1/ 54.5	Spirulina	Placebo	8	12	TC 0.7 ± 21.28 TG -27.3 ± 36.9 HDL-C 1.3 ± 7.89 LDL-C 2.6 ± 19.73	10.3 ± 28.73 17.5 ± 46.1 0.5 ± 9.26 5.9 ± 17.57
Kaur/2008/ India	RCT	20/20	T2DM	46.3/ 47.6	Spirulina	Placebo	1	8	TC -22 ± 19.02 TG -21 ± 19.43 HDL-C 3.6 ± 6.47 LDL-C -21.5 ± 21.06	-0.7 ± 22.38 3.1 ± 20.73 1.2 ± 4.1 -2.6 ± 22.25
		20/20	T2DM	45.95/ 47.6	Spirulina	Placebo	2	8	TC -17.1 ± 17.25 TG	-0.7 ± 22.38 3.1 ± 20.73

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Table 1 (*continued*)

First author, year, country	Design	Participants (n) Int/con	Health condition	Age means (year) Int/con	Intervention		Dose (gr/day)	Duration of intervention (weeks)	Outcomes (Changes, mg/dl, Pg/ml)	
					Treatment group	Control group			Treatment group	Control group
									-18.1 ± 14.6 HDL-C 2.9 ± 3.71 LDL-C -16.4 ± 15.31	1.2 ± 4.1 -2.6 ± 22.25
Parikh/2001/ India	RCT/ Parallel	15/10	T2DM	53.8/ 54.6	Spirulina	Placebo	2	8	TC -6.4 ± 16.47 TG -21.3 ± 35.1 HDL-C 1.4 ± 5.47 LDL-C -7.1 ± 14.03	13.2 ± 19.65 17.5 ± 36.73 -1.7 ± 3.73 9.4 ± 16.81
Serban/1982/ Romania	RCT/SB	15/15	T2DM	61.7/ 61.6	Spirulina+Metformin	Placebo+Metformin	0.8	8	TC -34.8 ± 40.76 TG -36.7 ± 49.62 HDL-C 1.6 ± 7.94 LDL-C -22.6 ± 37.87	-66.67 ± 42.43 -58.8 ± 55.98 2.7 ± 10.07 -11.2 ± 28.22

Abbreviations: RCT, randomized clinical trial; F, Female; M, Male; Int, Intervention; Con, Control; SB, Single-Blind; DB, Double-Blind; TB, Triple-Blind; NR, Not Reported; T2DM, Type 2 diabetes mellitus; NAFLD, Non-alcoholic fatty liver disease; MetS, Metabolic syndrome; HTN, Hypertension; HLP, Hyperlipidemic Nephrotic Syndrome; IHD, Ischemic heart disease HIV; human immunodeficiency virus; HIIT; High-intensity interval training.

2.4. Quality assessment

To evaluate the risk of bias for each of the included studies, the Cochrane Quality Assessment Tool 1 (ROB 1) was used, which consists of seven domains: random sequence generation, allocation concealment, reporting bias, performance bias, detection bias, attrition bias, and other sources of bias. We classified each field of testing as low risk, unclear, or high risk. The overall risk of bias for an RCT was considered: [1] poor; if less than two domains had "high risk", [2] fair; if two domains had "high risk", and [3] good; if more than two domains had "high risk". The potential for bias was assessed independently by two evaluators.

2.5. Statistical analysis

STATA 17 software (StataCorp, College Station, Texas, USA) was used for statistical analysis. The differences were reported as standardized mean differences (SMD) with a 95% confidence interval (CI). We used mean change scores and their standard deviations (SD) to calculate SMDs [13]. The heterogeneities of the studies were calculated using the I^2 statistic ($I^2 > 50\%$ demonstrated significant heterogeneity) [13]. To identify the potential source of heterogeneity, meta-regression was performed based on Spirulina dosage and duration of intervention. Moreover, subgroup analysis was conducted in accordance with the following indicators: baseline means, age, baseline BMI, study design, Spirulina dosage, duration of intervention, participants' health condition, trial location, and overall quality. Furthermore, the effects of Spirulina on the non-linear dose-response relationship and lipid profile were examined. The impact of a single study was verified through an analysis of the impact of exclusion. Publication bias was measured statistically using the Egger regression test. $P < 0.05$ was assessed as statistically significant.

3. Results

3.1. Included studies

After searching PubMed, Scopus, Web of Science and the Cochrane Library databases, 1107 records were identified, and 457 records were removed due to duplication. We reviewed the titles and abstracts and screened 36 records through the full text. In the final step, we included 20 studies qualitatively and quantitatively. A flow diagram for the selection of included studies is presented in Fig. 1.

3.2. Study characteristics

The characteristics of the included studies are outlined in Table 1. The main characteristics are as follows: **A.** Dose: the intervention dose ranged between 0.02 and 10 gr/day. **B.** Duration: 16 RCTs have a treatment duration of 12 weeks or shorter [14–29], and the 4 remained RCTs have a treatment duration of more than 12 weeks [30–33]. **C.** Age: the mean age of patients varies from 21.55 to 66.5. **D.** Number of patients: a total of 1067 subjects were included in these studies. **E.** Study design: most of the included studies adopted parallel study designs and 3 of them used crossover designs [15, 17–19, 27–29].

3.3. Risk of bias assessment

Details of the bias assessment analysis can be found in Supplementary Table 2. Overall, all studies satisfied random sequence generation and incomplete outcome data, and selective reporting. Moreover, 13 studies had a high source of bias in allocation concealment and Blinding [14, 17, 18, 21, 23–25, 27, 30–33]. Finally, 4 studies had good quality [15,19,28,29].

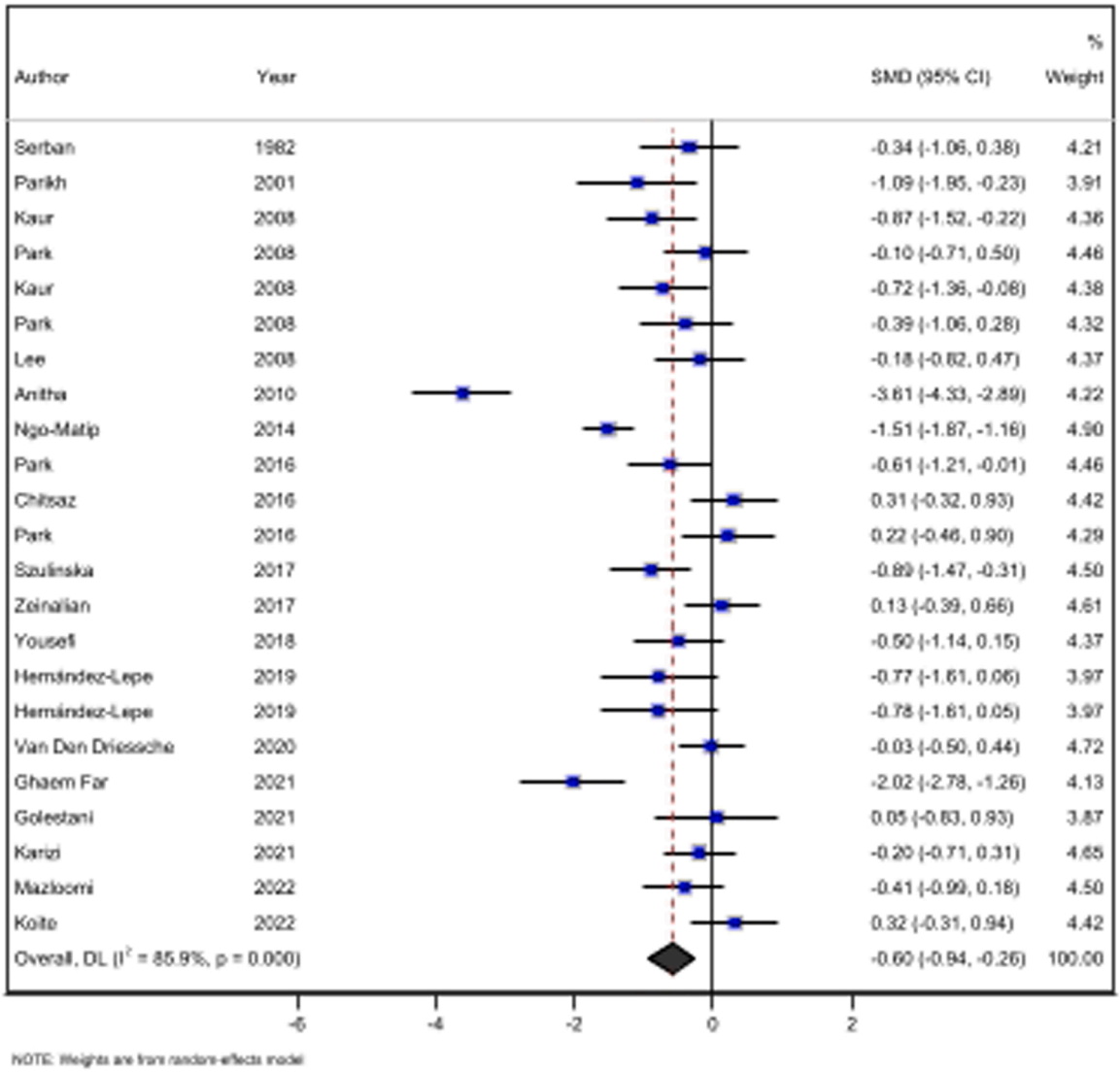

Fig. 2. Forest plot displaying standardized weighted mean difference and 95% confidence intervals for the effect of Spirulina supplementation on LDL-C in trials.

3.4. Effects of Spirulina on LDL-C levels

Pooled results of 23 studies with 1076 participants indicated that Spirulina consumption significantly reduced LDL-C levels (SMD: −0.6, 95% CI: −0.9, −0.2, P<0.05). Heterogeneity was high between studies (I^2 = 97.1%, P<0.00 ((Fig. 2). The baseline BMI, study design, health status, and country can be defined as a source of heterogeneity. The reduction effect of Spirulina was significant in studies with parallel design. Moreover, Spirulina cannot decrease LDL-C levels in healthy, obese, NAFLD, and MetS participants, in a cross-over design, and trials were conducted in Iran, USA, Netherlands, Korea, and Romania countries (details were provided in Supplementary Table 3). The meta-regression analysis showed that Spirulina dosage (ES: 0.01, 95% CI: −0.1, 0.1, P = 0.8) and duration of supplementation (ES: −0.03,95% CI: −0.1, 0.1, P = 0.3), were not sources of heterogeneity (Supplementary Figure 1–2).

3.5. Effects of Spirulina on HDL-C levels

Combining data from 23 studies with 1076 participants showed that Spirulina can increase HDL-C levels significantly (SMD: 0.3, 95% CI: 0.0008, 0.6, P<0.05) and there was significant heterogeneity between studies (I^2 = 82.2%, P<0.00) (Fig. 3). Baseline BMI, study design, health status, and trial location are sources of heterogeneity. The significant effect of Spirulina was observed in studies with Spirulina dosage < 4 gr/day, duration of < 10 weeks, T2DM, HIV, and HTN patients. In addition, studies that were carried out in India and Cameroon showed the significant effect of Spirulina on HDL-C concentrations (details were provided in Supplementary Table 3). The meta-regression analysis demonstrated that Spirulina dosage (ES: −0.006, 95% CI: −01, 0.08, P = 0.8) and duration of supplementation (ES: 0.03, 95% CI: −0.02, 0.09, P = 0.2), were not sources of heterogeneity (Supplementary Figure 3–4).

3.6. Effects of Spirulina on TC levels

Meta-analysis of 23 articles with 1076 participants showed that Spirulina can significantly decrease TC levels (SMD: −0.6, 95% CI: −0.9, −0.2, P<0.05) (Fig. 4). Heterogeneity was high between studies (I^2 = 86.7%, P<0001). The study design, health status, and trial location are sources of heterogeneity. Spirulina had not a significant reduction effect in studies with poor quality, cross-over design, duration of < 10 weeks, T2DM, NAFLD, MetS patients, and participants with BMI> 30 kg/m^2 (details were provided in Supplementary Table 3). The meta-regression analysis indicated that Spirulina dosage (ES: −0.009, 95% CI: −01, 0.1, P = 0.8) and duration of supplementation (ES: −0.05, 95% CI: −0.1,

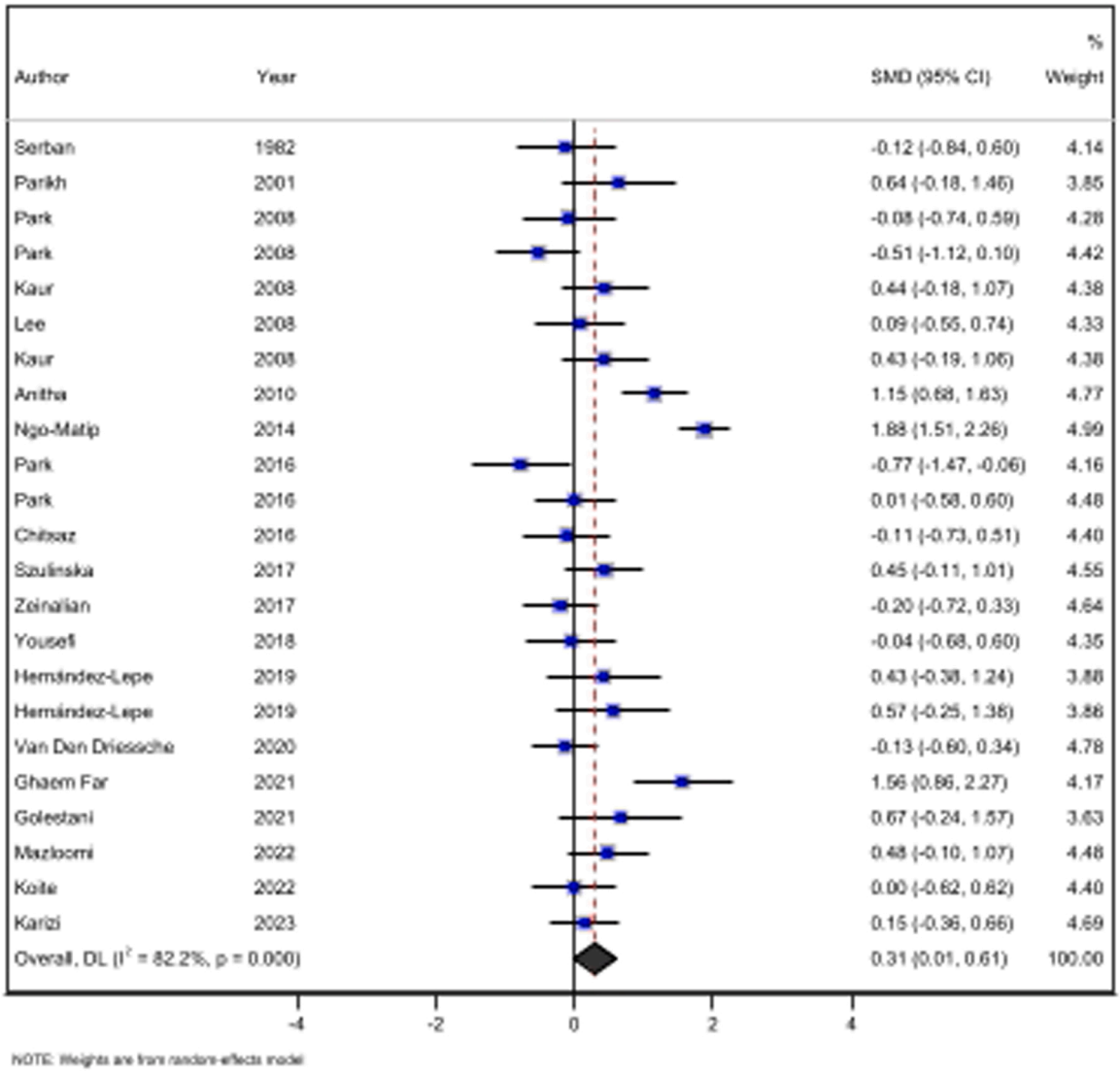

Fig. 3. Forest plot displaying standardized weighted mean difference and 95% confidence intervals for the effect of Spirulina supplementation on HDL-C in trials.

0.02, P = 0.1), were not sources of heterogeneity (Supplementary Figure 5–6).

3.7. Effects of Spirulina on TG levels

Pooled results of 23 studies with 1076 participants indicated that Spirulina administration significantly reduced TG levels (SMD: −0.6, 95% CI: −0.96, −0.25, P<0.05). Heterogeneity was high between studies (I^2 = 86.7%, P<0.00) (Fig. 5). Baseline BMI, design of studies, health status, and trial location are sources of heterogeneity. Studies with fair quality, parallel design, and studies with intervention doses of < 4 gr/day indicated a significant reduction effect of Spirulina on TG. Moreover, Spirulina intervention can decrease TG levels significantly in T2DM, HIV, HTN patients, and subjects with baseline BMI< 30 kg/m^2 (details were provided in Supplementary Table 3). The meta-regression analysis revealed that Spirulina dosage (ES: 0.02, 95% CI: −01, 0.1, P = 0.6) and duration of supplementation (ES: 0.03, 95% CI: −0.1, 0.05, P = 0.4), were not sources of heterogeneity (Supplementary Figure 7–8). Fig. 6.

3.8. Dose-response analysis

A non-linear dose-response meta-analysis was carried out based on a restricted cubic spline. Results revealed Spirulina supplementation has a linear improvement in HDL-C, with the greatest improvement at 4 g/d (SMD: 2.86, 95% CI: 1.5, 4.1, $p < 0.001$; Fig. S9). Moreover, the greatest reduction in TC levels was observed after Spirulina administration at 9 g/d (SMD: −13.1, 95% CI: −21.8, −4.4; Fig. S10), and TG levels after Spirulina administration at 6 g/d (SMD: −18.5, 95% CI: −33.6, −3.4; Fig. S11). Although, a non-linear dose-response association between Spirulina dosage and LDL-C levels was not detected (Fig. S12).

3.9. Influence analysis and publication bias

In influence analyses, the pooled effects of Spirulina supplementation on lipid profile did not change after systematically dropping each trial. Furthermore, we also omitted the studies with a high risk of bias. The aggregated results were similar when compared with the overall analysis. All results of the influence analysis suggest that the data in this meta-analysis are relatively stable and credible. The Egger regression test demonstrated no significant publication bias in LDL-C, TC, and TG parameters. Although, a significant publication bias was detected for HDL-C (intercept =1.8; 95% CI: 0.3–3.2; p = 0.01).

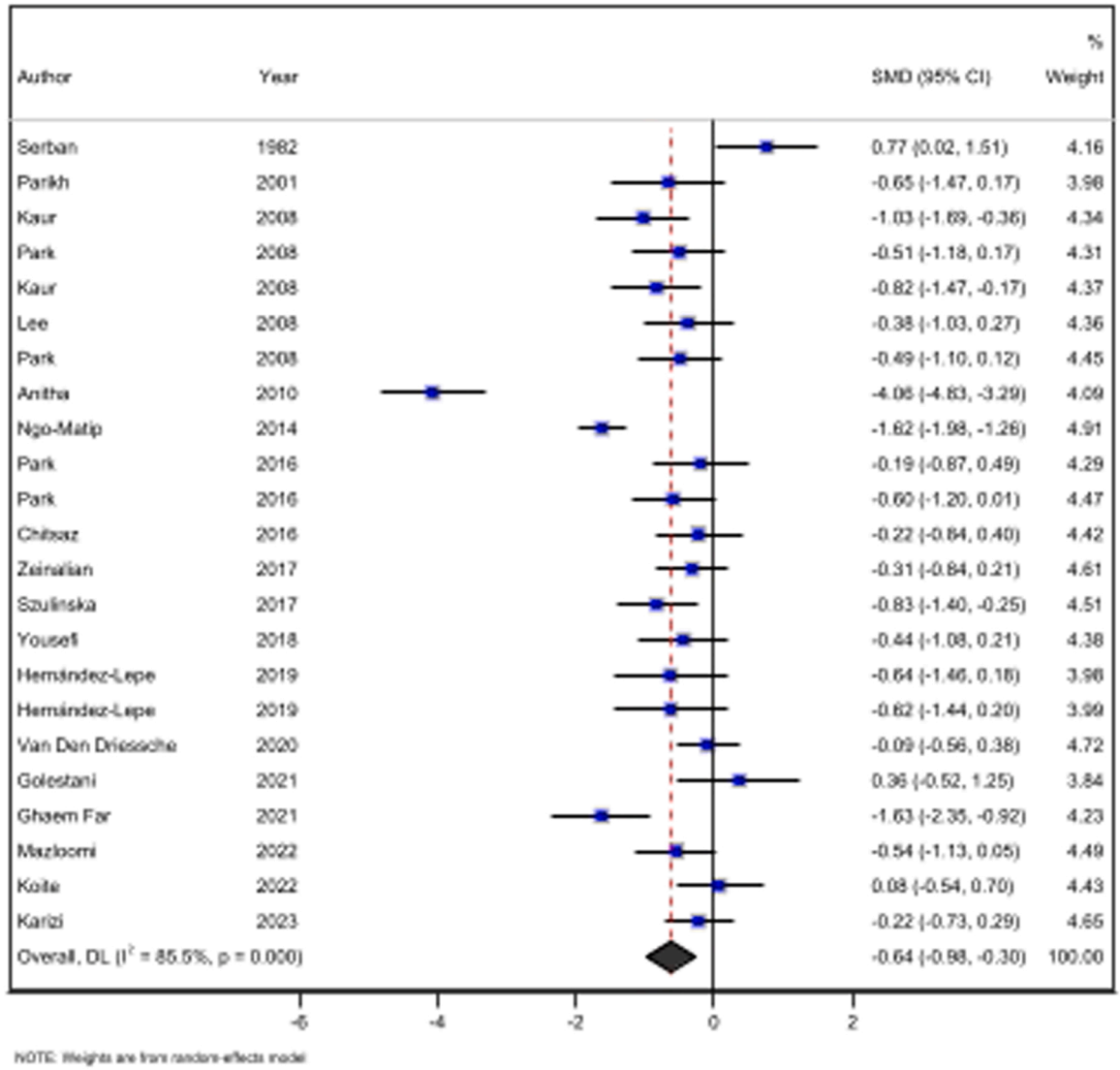

Fig. 4. Forest plot displaying standardized weighted mean difference and 95% confidence intervals for the effect of Spirulina supplementation on TC in trials.

3.10. Grading the evidence

Based on the grading analysis, the certainty of evidence from the included studies was determined high because the inconsistency, indirectness, imprecision, and publication bias were highly graded and just in TG variable inconsistency was low grade (details were provided in Supplementary Table 4).

4. Discussion

The current study is an updated meta-analysis to evaluate the effect of Spirulina supplementation on serum lipid profile indices [9]. Our findings of available RCTs demonstrated that Spirulina consumption had a reducing effect on TC, LDL-C, and TG concentrations, and an increasing effect on HDL-C levels. Moreover, we detected a significant dose-response association for the impact of Spirulina supplementation on plasma lipid profile concentrations. Moderate Spirulina dosage, about 4 gr/day, had the largest effect on HDL-C levels, and doses of 5 gr/day had the largest effect on TG concentrations. However, high doses of Spirulina at around 10 gr/day demonstrated the greatest effect on TC. Moreover, we concluded that the favorable effect of Spirulina supplementation in improving lipid profile parameters was greater than the minimal clinically important difference (MCID), which is important in clinical judgment for clinicians [45]. Regarding the GRADE assessment of these results, the certainty of the evidence was high concerning TC, LDL-C, HDL-C, and TG alterations.

The mechanism underlying the hypolipidemic effect of Spirulina is not clearly understood to date. The C-phycocyanin protein is the main component of Spirulina proposed to increase the activity of GSH peroxidase and superoxide dismutase, scavenge free radicals, and inhibit lipid peroxidation. Moreover, C-phycocyanin can reduce nicotinamide adenine dinucleotide phosphate (NADPH) and NADH formation, and inhibit NADPH oxidase expression that might account for the hypolipemic effects of Spirulina [34,35]. The glycolipid H-b2 is another ingredient isolated from Spirulina, which reduces pancreatic lipase activity, leading to a decrease in digestion and subsequent absorption of fat in the intestinal environment [36]. Furthermore, Gamma-linolenic acid derived from Spirulina can be effective in regulating cholesterol levels through esterification [37]. Since Spirulina is a low-fat and low-calorie protein source, its intake may lead to a decrease in the formation of hepatic TG, and an increase in the hepatic activity of TG lipase and lipoprotein lipase, which will contribute to the improvement of the lipid profile [37,38]. Studies have shown that algae supplementation can be effective in reducing the intestinal absorption of cholesterol and reabsorption of bile in the intestinal ileum. Spirulina is a blue-green alga that can exert hypolipidemic effects from this route [39,40]. According to the

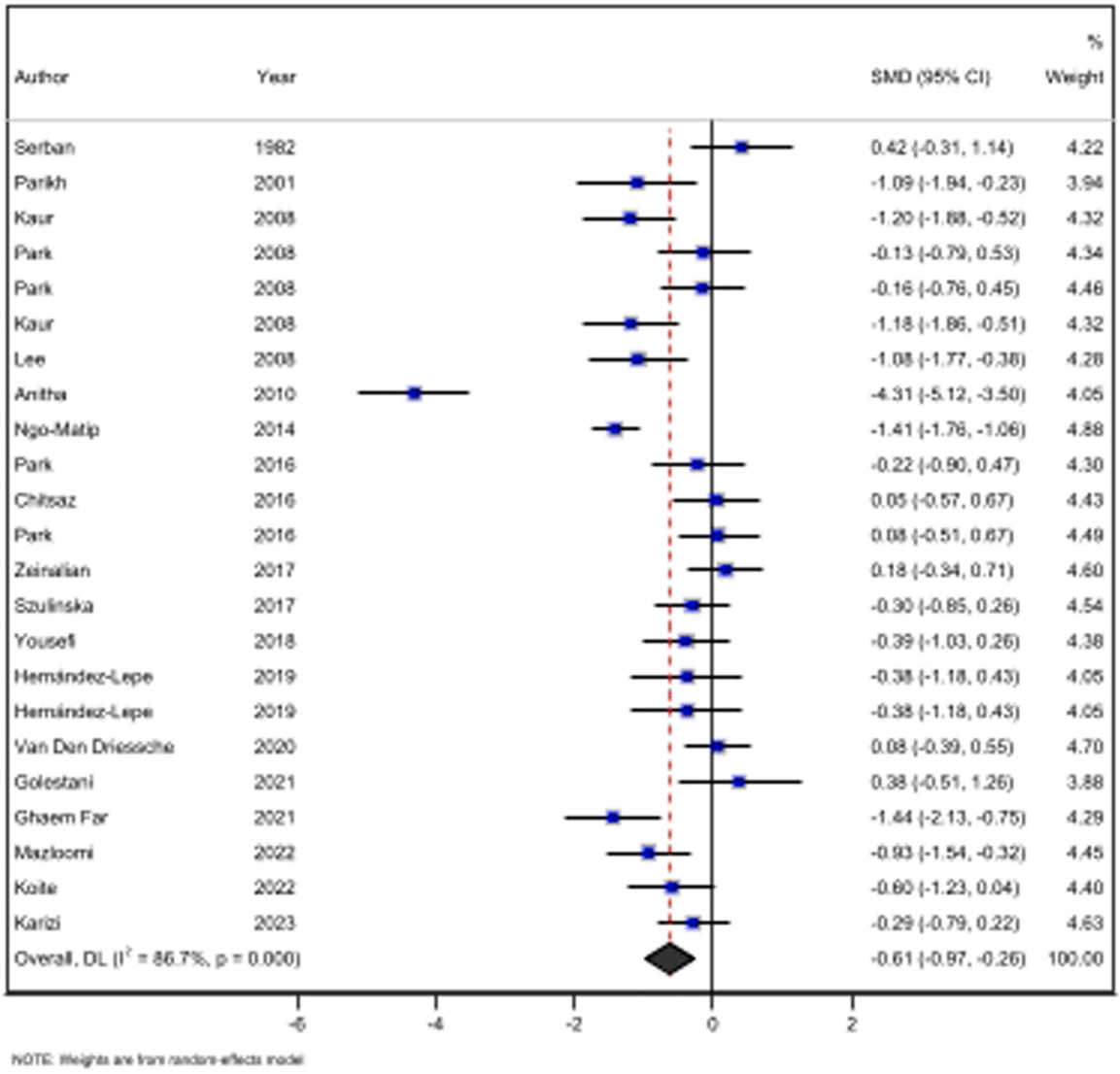

Fig. 5. Forest plot displaying standardized weighted mean difference and 95% confidence intervals for the effect of Spirulina supplementation on TG in trials.

literature, the hypolipidemic effects of Spirulina might be explained by all these biological processes (Fig. 2).

The safety of Spirulina has been described in several toxicology studies. Short-term or long-term Spirulina consumption has not been shown to cause serious toxicity or significant complications [41]. However, due to the presence of considerable protein and amino acid amounts, Spirulina should be used with caution in patients with protein or amino acid limitations such as phenylketonuria or maple syrup urine disease [42]. Moreover, in people who have a history of allergy to algae, Spirulina should be used with caution [43]. In one study, anaphylaxis was reported following the use of Spirulina supplementation [43]. In addition, it has been reported in a few documents that the use of Spirulina with immunosuppressive drugs is not recommended due to its immunomodulatory effects [42]. The purity of Spirulina preparations is also another factor that should be considered [44]. The concentrations of heavy metals/minerals are one of the concerns of using Spirulina supplements, which is related to the algae growth environment [44]. Nevertheless, according to the study by Al-Dhabi, the concentration of heavy metals/minerals in commercial supplements was not detected to exceed the present threshold levels regulated [44,45].

The most important limitation of the present study was the heterogeneity of the obtained results. Subgroup analysis revealed that the health status of the participants, their baseline BMI, trial design, and the location of the trials can be among the causes of these heterogeneities. In addition, due to the significance of the publication bias results for HDL-C, the respective results should be interpreted with caution. Conducting advanced dose-response analyses along with GRADE assessment of the evidence and the clinical significance of the results are among the most important strength points of this study.

5. Conclusion

In conclusion, the present meta-analysis revealed a significant effect of Spirulina intervention in reducing TC, LDL-C, and TG levels, while improving HDL-C concentrations. Furthermore, well-designed studies are needed to clarify the impact of Spirulina administration on cardiovascular outcomes in the future.

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CRediT authorship contribution statement

SH, AS, IR and MR contributed to the study conception, literature search, data extraction, data analysis, and manuscript drafting. IR, LSB,

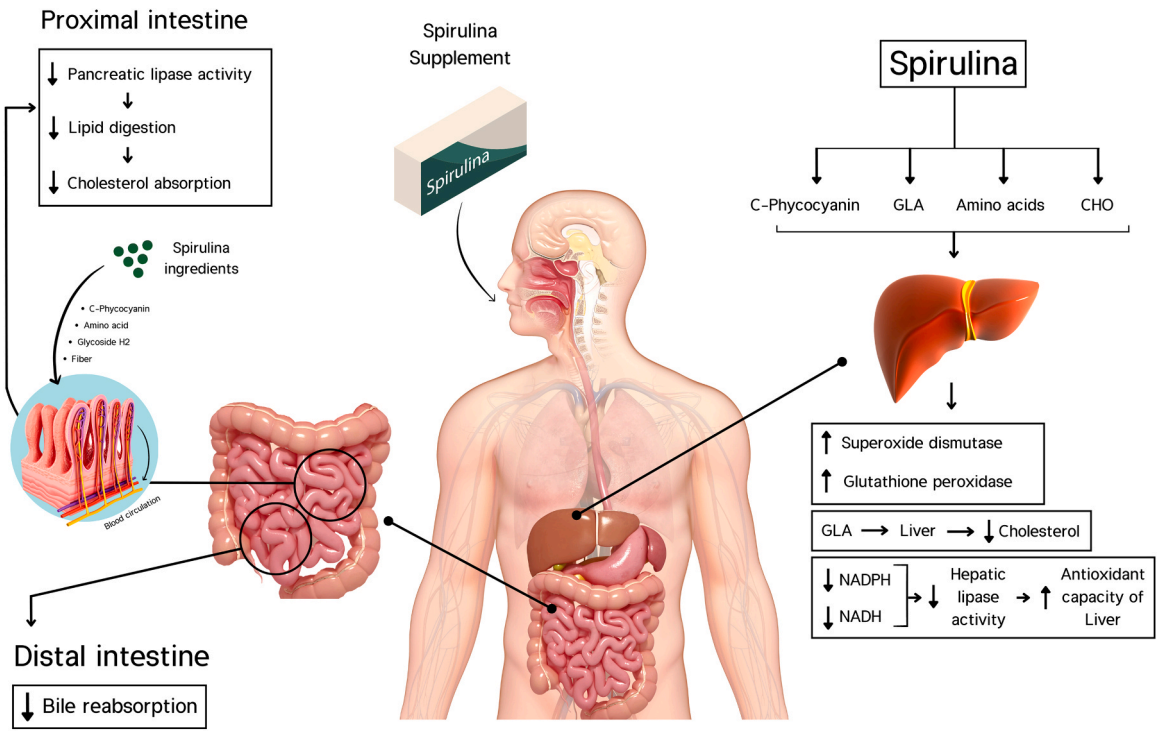

Fig. 6. Possible hypolipidemic mechanisms of Spirulina supplementation.

MC and SM. Contributed to the literature search, data extraction, and manuscript drafting. AS, VH, and SMM contributed to the manuscript drafting. AS, MR and SH critically revised the manuscript. All authors take full responsibility for the analyses and interpretation of the report. All authors read and approved the final manuscript.

Declaration of Competing Interest

All authors declare that they have no conflicts of interest.

Data availability

No data was used for the research described in the article.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.phrs.2023.106802.

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