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Meta-analyses

A systematic review and meta-analysis of the impact of Spirulina supplementation on plasma lipid concentrations

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SUMMARY

Background & aims: The impact of Spirulina supplementation on plasma lipid concentrations has not been conclusively studied. Therefore the aim of the meta-analysis was to assess the effect of Spirulina supplementation on plasma lipid concentrations.
Methods: We searched PubMed and Scopus (up to July 03, 2015) to identify randomized controlled trials (RCTs) that investigate the effect Spirulina supplementation on plasma lipid concentrations. Meta-analysis and meta-regression were performed using random-effects models.
Results: Random-effect meta-analysis of data from 7 RCTs showed a significant effect of supplementation with spirulina in reducing plasma concentrations of total cholesterol (WMD: −46.76 mg/dL, 95% CI: −67.31 to −26.22, $p < 0.001$), LDL-C (WMD: −41.32 mg/dL, 95% CI: −60.62 to −22.03, $p < 0.001$) and triglycerides (WMD: −44.23 mg/dL, 95% CI: −50.22 to −38.24, $p < 0.001$), and elevating those of HDL-C (WMD: 6.06 mg/dL, 95% CI: 2.37−9.76, $p = 0.001$).
The impact of spirulina on plasma concentrations of total cholesterol (slope: −1.32; 95% CI: −8.58 to 5.93; $p = 0.720$), LDL-C (slope: −1.01; 95% CI: −8.03 to 6.02; $p = 0.778$), triglycerides (slope: −1.39; 95% CI: −4.26 to 1.48; $p = 0.342$) and HDL-C (slope: 1.79, 95% CI: −0.48 to 4.05; $p = 0.122$) was independent of administered dose. Regarding duration of supplementation with Spirulina, significant associations were found with changes in plasma concentrations of total cholesterol (slope: −1.77; 95% CI: −3.48 to −0.07; $p = 0.042$), LDL-C (slope: −1.73; 95% CI: −3.40 to −0.06; $p = 0.042$) HDL-C (slope: 0.91; 95% CI: 0.68 −1.14; $p < 0.001$) and triglycerides (slope: −1.39; 95% CI: −2.28 to −0.50; $p = 0.002$).
Conclusions: This meta-analysis showed a significant effect of supplementation with Spirulina in reducing plasma concentrations of total cholesterol, LDL-C, triglycerides and elevating those of HDL-C.

1. Introduction

Spirulina is a filamentous, spiral-shaped, water blue-green microalga (Cyanobacterium). The most well-known species of spirulina researched in the scientific literature and safe for consumption are *Spirulina platensis*, *Spirulina maxima* and *Spirulina fusiformis* [1]. Spirulina is considered to be one of the most healing and prophylactic ingredients of nutrition in the 21st century [2,3] due to its nutrient profile, lack of toxicity and therapeutic effects [4]. Spirulina has been consumed as a food by North Africans and

Abbreviations: ACE, angiotensin I-converting enzyme; BMI, body mass index; CI, confidence interval; CHD, coronary heart disease; CMA, comprehensive meta-analysis; HMOX-1, heme oxygenase-1; GK, glucokinase; GSP, glycosylated serum protein; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, assessment-estimated insulin resistance; LDL-C, low-density lipoprotein cholesterol; NF-kB, nuclear factor KB; TC, total cholesterol; WMD, weighed mean difference; TG, triglycerides.

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Mexicans because it contains high amounts of antioxidants such as β-carotene, phycocyanin, microelements (K, Na, Ca, Mg, Fe, Zn), vitamins (tocopherols), eight necessary aminoacids, poly-unsaturated fatty acids, especially γ-linolenic acid and phenolic compounds [5]. Like other nutraceuticals [6–8], Spirulina is recommended in arterial hypertension [9,10], insulin-resistance [2], diabetes mellitus [5,11], non-alcoholic fatty liver disease [12], malnutrition [13], anemia [14], allergic rhinitis [15], cancer [16] and in reduction of drug toxicity [17].

C-phycocyanin, a particular essential pigment of Spirulina, is used as a natural dye in food, cosmetics and pharmaceutical industry [18]. Phycocyanin contains an open-chain tetrapyrrole chromophore known as phycocyanobilin, which can activate atheroprotective heme oxygenase-1 (HMOX-1), a key enzyme in the heme catabolic pathway, in endothelial cells improving atherosclerosis in mice [19]. Moreover, phycocyanin has proven antioxidant, anti inflammatory and radical scavenging properties. Also, phycocyanin showed to decrease fasting blood glucose and glycosylated serum protein (GSP), being useful for diabetic patients [5]. According to experimental studies in alloxan-injured mice, phycocyanin decrease total cholesterol (TC) and triglycerides (TG) levels in serum, increase the hepatic glycogen level and maintain glucokinase (GK) expression in the liver [20]. Also, the angiotensin I-converting enzyme (ACE) inhibitor peptide Ile-Gln-Pro purified from Spirulina proved to be useful in the prevention and treatment of hypertension in rats [2,21]. Furthermore, clinical evidence showed that spirulina has a blood lipid lowering effect in healthy subjects, patients with heart disease, and in diabetic patients [22].

However, the evidence of the effects of Spirulina on plasma lipid parameters has not been conclusive. Therefore the aim of this study was to estimate the effect size of Spirulina supplementation on plasma lipid concentrations by pooling the reported results in randomized controlled trials (RCTs).

2. Methods

2.1. Search strategy

This study was designed according to the guidelines of the 2009 preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement [23]. A systematic literature search was performed in SCOPUS and Medline databases. The search terms (in titles and abstracts) were: (randomized controlled trials OR RCT OR randomized OR lipid OR total cholesterol OR LDL-cholesterol OR HDL-cholesterol OR triglycerides) and (Spirulina). To increase the accuracy of search, the wild-card term "*" was used. The search was limited to studies in human. The literature search in the above-mentioned databases was performed from inception to July 03, 2015. Hand-searching of the retrieved articles was performed to identify further relevant studies that were missed in the database search.

2.2. Study selection

The following criteria was used to identify eligible studies: (i) Randomized controlled trials with either case-control or case-cross-over design, (ii) investigation of the effects of spirulina or standardized spirulina-enriched extracts on plasma/serum lipid concentrations, (iii) providing sufficient information on baseline and end-trial plasma/serum lipid concentrations in both spirulina and control groups. Exclusion criteria were (i) experimental studies, (ii) uncontrolled studies, (iii) administration of non-standardized extracts or extracts containing negligible amounts of spirulina resulting in a daily intake of <5 mg, and (iv) lack of sufficient information on baseline or end-trial lipid concentrations. In case of the latter item, authors of the article(s) were contacted and requested to provide numerical data.

2.3. Data extraction

The following items were extracted from the eligible studies: 1) first author's name; 2) publication year; 3) study location; 4) number of subjects receiving spirulina and control intervention; 5) age, gender and body mass index (BMI) of subjects in the spirulina and control groups; and 6) serum/plasma concentrations of lipid parameters including total cholesterol, LDL-C, HDL-C and triglycerides.

2.4. Quality assessment

Quality assessment of included studies was performed using Jadad scale. According to this scale the following parameters are appraised: randomization (0–2 points), blinding (0–2 points), and dropouts and withdrawals (0–1 point). The total quality score ranges between 0 and 5, representing the lowest and highest quality of study [24]. Jadad scores of ≤ 2 and ≥ 3 were reflected low- and high-quality studies, respectively [25].

2.5. Quantitative data synthesis

Comprehensive meta-analysis (CMA) V2 software (Biostat, NJ) was used for meta-analysis [26]. The units of all lipid factors including total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides were collated in mg/dL. A multiplication by 38.6 and 88.5 was used to convert cholesterol (total cholesterol, HDL-C or LDL-C) and triglyceride units from mmol/L to mg/dL, respectively. Standard deviations (SDs) of the mean difference between pre-treatment and post-treatment values in each group were calculated using the following formula: $SD = \text{square root}\,[(SD_{\text{pre-treatment}})^2 + (SD_{\text{post-treatment}})^2 - (2R \times SD_{\text{pre-treatment}} \times SD_{\text{post-treatment}})]$, assuming a correlation coefficient $(R) = 0.5$. In case of reporting SEM, SD was estimated using the following formula: $SD = SEM \times \text{sqrt}\,(n)$, where n is the number of subjects.

The net between-group change in serum/plasma lipid concentrations in each study was calculated as follows: (value at end of follow-up in the treatment group − value at baseline in the treatment group) − (value at end of follow-up in the control group − value at baseline in the control group). Meta-analysis was performed using a random-effects model and the generic inverse variance weighting method. The choice of random-effects (instead of fixed-effects) model was the heterogeneity of studies in terms of type of spirulina supplement used, spirulina dose, duration of spirulina supplementation, and demographic characteristics of individual trials (underlying disease, age, gender, etc). Effect size was expressed as weighed mean difference (WMD) and 95% confidence interval (CI). In order to evaluate the influence of each study on the overall estimated effect size, a leave-one-out sensitivity analysis was conducted by iteratively removing each study and repeating the analysis.

2.6. Meta-regression

Random-effects meta-regression was performed under an unrestricted maximum likelihood model to explore the association between changes in plasma lipid (total cholesterol, HDL-C, LDL-C and triglycerides) concentrations with dose and duration of supplementation with spirulina.

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