Review Article

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The effect of *Chlorella vulgaris* on obesity related metabolic disorders: a systematic review of randomized controlled trials

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Abstract

Objectives: *Chlorella vulgaris* (CV) as a unicellular algae is a dietary supplement with beneficial nutritious content, used for decades in some countries. Positive effects for CV supplementation on metabolic parameters has been established in animal and human studies. However there is a gap for this results summary for a definite conclusion announce. This systematic review aimed to summarize the effects of CV on body weight, lipid profile, and blood glucose.

Content: PRISMA guidelines were charted in this review. Subject search was performed in MEDLINE, ProQuest, PubMed, ISI web of sciences, Google scholar, Cochrane and Scopus databases for randomized clinical trials published in English languages, until December 2020, which assessed the effects of CV on metabolic syndrome related symptoms in clinical trials.

Summary: Out of 4,821 records screened, after duplicate and irrelevant exclusion by title and abstract, 20 articles remained for full text screening. Finally a total of 12 articles met the study inclusion criteria and were assessed for study method and results.

Outlook: The findings showed controversies in anthropometric, glycemic and lipid profile effects. CV may have beneficial effects on obesity-related metabolic disorders; however, collected studies lacked statistical power to reach a definite conclusion. More well-designed studies are required.

Keywords: *Chlorella vulgaris*; metabolic syndrome; obesity.

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Introduction

The global prevalence of obesity continues to increase dramatically, such that if this trend continues, the obesity prevalence will reach 18% in men and exceed more than 21% in women by 2025. Obesity, in particular, central obesity has been shown to increase the risk of cardiovascular disease and type 2 diabetes [1]. This excessive fat accumulation is assessed by body mass index (BMI), a BMI of 25 to <30 kg/m^2 is defined as overweight and BMI ≥ 30 kg/m^2 is classified as obese. Furthermore, metabolic syndrome features including visceral obesity, dyslipidemia, hyperglycemia, and hypertension, have become one of the most public health challenges worldwide [2].

Dietary interventions and lifestyle modifications are integral part of any weight control program [3, 4]. Recently, several dietary supplements and alternative medicine are used as adjunctive therapy to improve metabolic syndrome features [5, 6]. *Chlorella vulgaris* (CV), a green microalgae is identified as a functional food and adjunctive supplement worldwide, mostly in Asia [7]. Since the 1950s, CV, and some other algal species were produced in large quantities to meet the increasing demands [8]. *C. vulgaris* contains a wide range of nutrients including fiber, carotenoids, chlorophyll, minerals, vitamins, and long-chain polyunsaturated fatty acids, and has hepatoprotective, immunomodulatory, anti-hypertensive, anti-diabetic, anti-hyperlipidemic, anti-inflammatory, and antioxidant effects [9–12]. *C. vulgaris* as a dietary supplement is safe and claimed to be effective in

prevention and treatment of dyslipidemia, hyperglycemia, high blood pressure, and overweight/obesity [13], while the studies showed controversial effects on weight control or mentioned biomarkers [14, 15]. Like the other microalgae, Chlorella may also reduce macrophage infiltration into visceral fat, prevent hepatic fat accumulation, decrease oxidative stress, improve insulin sensitivity and satiety, all of which are effective in weight loss [16]. Different doses have been used in previous investigations due to various nutritional habits and contradictory results have been reported. Despite several clinical trials performed on the effects of CV on obesity and relevant metabolic disorders, there is no comprehensive review to illustrate the current progress in this field. Therefore, the present systematic review designed to evaluate outcomes of clinical trials evaluating the effects of CV on obesity-related metabolic syndrome features and weight control.

Materials and methods

Data sources and search strategy

The present systematic review was accompanied built on PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for systematic reviews [17]. The MEDLINE (PubMed), ISI web of sciences, Google scholar, Cochrane, ProQuest and Scopus databases were systematically searched for the eligible articles published from inception until September 2020. Keywords relating to the intervention ('*C. vulgaris*', 'Chlorella', '*C. vulgaris*', 'C.V' and 'algomed'), as MeSH (Medical Subject Heading) terms and text words were searched in combination with the keywords regarding metabolic syndrome features ('lipid profile', 'Dyslipidemia', 'Dislipidemia', 'Triglyceride', 'TG', 'TAG', 'Hypertriglyceridemia', 'cholesterol', 'Total cholesterol', 'Hypercholesterolemia', 'LDL-c', 'HDL-c', 'HDL cholesterol', 'Hypertension', 'HTN', 'Elevated blood pressure', 'BP', 'Blood pressure', 'Glucose', 'Fasting Blood Sugar', 'Fasting Blood Glucose', 'FBS', 'FSG', 'Fasting serum glucose', 'Glucose intolerance', 'HOMA', 'Homa IR', 'Insulin resistance', 'Anthropometry', 'weight', 'BMI', 'body mass index', 'waist circumference', 'WC', 'abdominal obesity', 'visceral obesity', 'obesity'). Ref of ref was checked in order not to miss additional references. The review protocol was registered at PROSPERO database of Systematic Reviews (registration number: CRD42019123683).

Eligibility criteria

Peer-reviewed original articles just in the English language were included; book chapters, hypothesis and conference publications, letters, oral presentation and review articles were excluded. The study population aimed in this review, were healthy or unhealthy (any kind of related or unrelated disease) adult humans. All randomized controlled trials (RCT) which assessed the effects of CV on obesity-related metabolic syndrome features (as the primary or secondary outcome) in comparison with placebo and those investigated the *C. vulgaris* effects as adjunctive therapy were eligible in this review while the animal, *in vitro*, industrial, before-after and epidemiologic (including cohort, case-control, and cross-sectional) studies were excluded. Also, there was no study on pregnant or lactating women and patients with chronic diseases among collected data. Studies with deficient data on patients, control group, intervention, and outcomes were not included in this review.

Data extraction

In the primary screening of the articles, titles and abstracts were evaluated by two independent reviewers according to inclusion and exclusion criteria; if an article was considered as eligible, its full text was obtained and read completely. Some articles which were unclear to be decided were discussed by all co-authors, and the absolute decision was made finally. To avoid bias, and allow for objective assessment, the existing review only included first-hand studies. To preventing any omitting of relevant articles, the reference list was rechecked in included articles. Data extracted from the eligible studies are summarized in Table 1, apart from the results in every aspect of metabolic syndrome features.

Outcomes and quality assessment

The primary outcome in this systematic review was obesity-related status, assessed by validated tools and indexes (*e.g.* BMI more than 30, waist circumference, hip circumference, waist to hip circumference ration, fat percent). Secondary outcomes of concentration were metabolic syndrome features that are related to obesity such as dyslipidemia, glucose intolerance, and glycemic status, impaired blood pressure. The Cochrane Collaboration tool was used to assess the probable risk of bias for the eligible RCT articles [26].

Results

Study and participant characteristics

Figure 1 presents the diagram of the search and selection process in the present systematic review. A total of 4,821 citations were identified across MEDLINE, Scopus, ProQuest, Embase, and Google scholar. Among these articles, 3,884 were duplicate, irrelevant or did not meet inclusion criteria, 58 animal studies, 95 other species of Chlorella, 64 industrial investigations, and three review. Twenty articles were relevant by title and after full text assessment, one was seminar, two article supplemented another species of Chlorella, two articles presented data just in baseline and three in Chinese language, finally 12 articles investigating the effects of obesity-related metabolic syndrome features compared to a control group were included in this

Table 1: Characteristics of trials on the effect of *Chlorella vulgaris* on obesity related metabolic syndrome features.

Study population (age-gender)	No. of participants (analyzed no.)	Study design	Intervention	Comparator	Duration	Outcomes	Reference
Healthy Japanese men; >20 years, M	34 (33)	Randomized clinical trial	40 tablets/day	No control	12 weeks	Body fat percentage and total cholesterol reduction HDL and LDL and blood glucose reduction	Toru Mizoguchi et al. [18]
Non-alcoholic fatty liver patients; 35–70 years, F/M	80 (76)	Randomized open-label clinical trial	1,200 mg/day Chlorella	Metformin + Vit E Metformin Vitamin E	2 month (8 weeks)	Weight reduction BMI reduction ALT and AST reduction Triglyceride decrease No significant change in blood pressure	Yunes Panahi et al. [9, 19]
Healthy volunteers; >20 years, M/F	34 (29)	Double-blinded, randomized, placebo-controlled study	5 g/day	Placebo	4 weeks	Total cholesterol and LDL-C decrease and HDL-C increase in Chlorella group	Sangmi Kim et al. [20]
Major depressive disorder patients	125 (92)	Randomized open-label controlled clinical trial	1800 mg/day	Placebo	6 weeks	Weight change in the Chlorella group is more than placebo	Yunes Panahi et al. [21]
Healthy volunteer	60 (51)	Randomized double-blind placebo-controlled trial	5 g/day	Placebo	8 weeks	No significant change in weight, BMI, blood pressure and lipid profile	Jung Hyun Kwak et al. [15]
Primary dysmenorrhea; 18–35 years, F	46 (44)	Randomized double-blind controlled clinical trial	1,500 mg/day	Placebo	8 weeks	There was no significant change in weight, waist circumference, hip circumference, waist to hip circumference and BMI	Fatemeh Haidari et al. [14]
Hypercholesterolemic adults, M/F	68 (63)	Double-blind trial	5 g/day	Placebo	6 weeks	Significant change in TG and TC in mildly hypercholesterolemic subjects	Na Hee Ryu et al. [22]
Obese adult with NAFLD; 20–50 years, F/M	66 (61)	Randomized controlled trial	1 g/day	Spirulina No intervention	8 weeks	BMI, weight and waist circumference decreased significantly in Chlorella and Spirulina groups	Maryam Chitsaz et al. [23]
NAFLD patients	60 (55)	Randomized double-blind controlled clinical trial	1,200 mg/day	Placebo	8 weeks	BMI and weight reduction was significant in the Chlorella group FBS was decreased in the Chlorella group significantly	Mehrangiz Ebrahimi-Mameghani et al. [24]
Korean smokers, 20–65 years, M	53 (52)	Double-blinded placebo-controlled trial	6.3 g/day	Placebo	1-week run-in 6-week intervention	Blood pressure didn't change significantly	Sun Hee Lee et al. [25]
NAFLD patients	70 (55)	Randomized double-blind controlled clinical trial	1,200 mg/day	Placebo	8 weeks	FBS, Insulin, and HOMA-IR decreased in the intervention group significantly and FBS changes were significant between-group too	Mehrangiz Ebrahimi-Mameghani et al. [13]
Dyslipidemic subjects	100 (63)		500 mg/day	Atorvastatin	8 weeks		

Table 1: (continued)

Study population (age-gender)	No. of participants (analyzed no.)	Study design	Intervention	Comparator	Duration	Outcomes	Reference
		Randomized open-label controlled clinical trial				Weight and BMI reduction were significant in Atorvastatin group Total cholesterol, triglyceride, and LDL-C decreased in both groups No significant change in FBS	Yunes Panahi et al. [9, 19]

ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; BMI, Body mass index; FBS, Fasting blood sugar; HDL, High-density lipoproteins; HOMA-IR, Homeostatic model assessment for insulin; LDL-C, Low-density lipoprotein cholesterol; MDD, Major depressive disorder; NAFLD, Non-alcoholic fatty liver disease; TG, Triglyceride; WC, Waist circumference; WHR, Waist to hip circumference.

systematic review. Seven studies were done in Iran, four in Korea and one in Japan. Majority of subjects were healthy volunteers, dyslipidemic patients, Non-alcoholic Fatty Liver Disease (NAFLD) patients and in one study Major Depressive Disorder (MDD) and patients with primary dysmenorrhea were included. All of interventions duration were 8 weeks or less, except Panahi et al. [19] investigation which was 3 month in length, and CV in tablet form or powder were administered. All clinical trials were parallel in two groups except one study which had no placebo control and one which had three groups. Details are presented in Table 1.

Methodological quality and risk bias

Among the identified studies, one study included three groups and the others followed a two-group clinical trial algorithm (Table 1). Table 2 demonstrates the risk of bias according to Cochrane Collaboration's Criteria, for mentioned articles.

In three studies, there was no comprehensive information on the approved techniques for random sequence generation. Only one study had a low risk of bias for random sequence generation. Except for one study which notified the lack of allocation concealment as well as three studies which did not clearly notify concealment of allocation in their design, remaining studies were apparently far from this risk of bias. Three studies with open-label design and one study with insufficient explanation had high risk of bias for performance, and detection bias, whereas remaining studies minimized the risks of performance, and detection bias through double-blinding method. Eight studies analyzed obesity-related metabolic syndrome features data based on per-protocol approach, one study with the intention to treat approach, while four studies did not provide sufficient details regarding the number of patients included in the final analyses.

Effect of *C. vulgaris* on anthropometric parameters

Of nine trials investigating the effects of CV supplementation on anthropometric parameters such as body weight, BMI, WC, and body fat percentage, five reported significant improving effect on at least one of the anthropometric parameters. Overall, of these five studies, lowering effect of CV on body weight was seen in three investigations [13, 21, 23]. Furthermore, BMI, hip circumference, waist circumference, and fat percentage decreased in some studies [13, 18, 19], while BMI in three

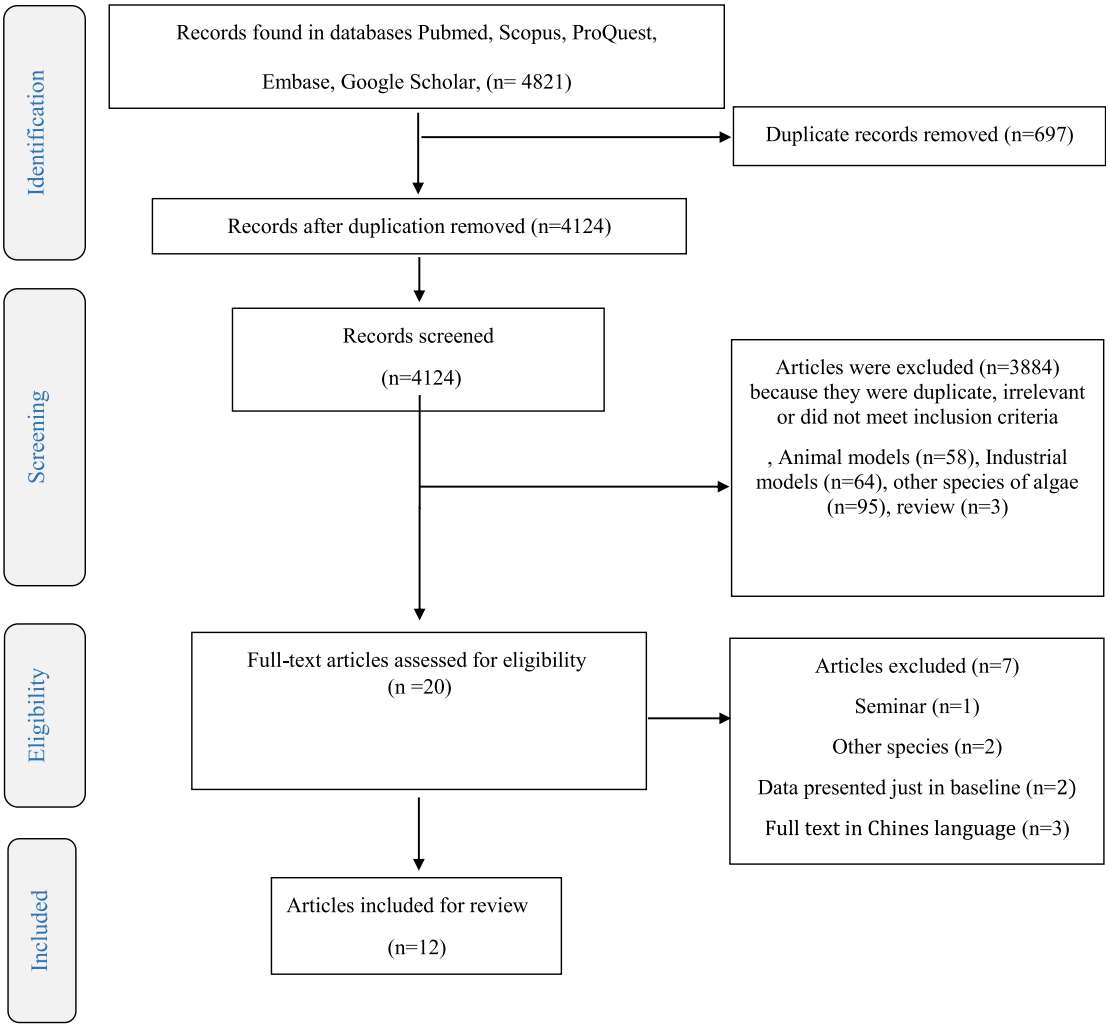

Figure 1: Flow diagram of the literature search and study selection process.

[9, 15, 23], waist circumference in four [13, 14, 19, 23], hip circumference in one [14] and fat percentage in one [27] study, didn't change significantly. Ebrahimi-Mameghani et al. reported significant weight-reducing effects of 2 months of supplementation with CV among patients with NAFLD, while the changes observed in WC and HC were not statistically significant. Panahi et al. showed significant reductions in body weight and BMI in NAFLD patients following 3 months of supplementation with CV, however, WC and WHR remained unchanged [9, 19]. The same author in another study on the patients with major depressive disorder, reported a significantly greater weight reduction in the CV group consuming 1800 mg/d CV for 6 weeks than controls, [21]. However, receiving 500 mg/d for 8 weeks in another study by Panahi et al. didn't cause significant changes in weight and BMI in the patients with dyslipidemia.

Chitsaz et al. compared the effect of CV in comparison with Spirulina among NAFLD patients and observed that the body weight, BMI, and waist circumference remained unchanged following the intake of 1 g/day CV for 8 weeks between groups. But weight significantly decreased in the intervention groups (CV and Spirulina) within group. In a study by Haidari et al. on women with primary dysmenorrhea, no significant changes were observed in body weight, BMI, WC, HC and WHR following 8 weeks of supplementation with CV. In the study of Jung Hyun Kwak et al. in which the effects of *C. vulgaris* supplement on immune response were assessed, no significant changes in anthropometric characteristics of participant's within-group nor intergroup comparison were found [15]. The impact of CV supplementation on body fat percentage was assessed only in one study by Toru Mizoguchi et al. which showed a significant decrease in body fat percent [18].

Table 2: Risk of bias assessment using Cochrane risk of bias assessment tool.

Study	Selection bias		Performance and detection bias	Attrition bias	Reporting bias	Other bias
	Random sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective reporting	
Toru Mizoguchi et al. [18]	Unclear	Unclear	Unclear	Low	Low	Low
Yunes Panahi et al. [9, 19]	Unclear	Unclear	Low	Low	Low	Low
Sangmi Kim et al. [20]	Low	Low	Low	Low	Low	Low
Yunes Panahi et al. [21]	Low	Low	High	Low	Low	Low
Jung Hyun Kwak et al. [15]	Low	Low	Low	Low	Low	Low
Fatemeh Haidari et al. [14]	Low	Low	Low	Low	Low	Low
Na Hee Ryu et al. [22]	Low	Low	Low	Low	Low	Low
Maryam Chitsaz et al. [23]	Low	Low	High	Low	Low	Low
Mehrangiz Ebrahimi-Mameghani et al. [24]	Low	Low	Low	Low	Low	Low
Sun Hee Lee et al. [25]	Unclear	Unclear	Low	Low	Low	Low
Mehrangiz Ebrahimi-Mameghani et al. [13]	Low	Low	Low	Low	Low	Low
Yunes Panahi et al. [9, 19]	Low	Low	High	High	Low	Low

Effect of *C. vulgaris* on lipid profile

In summary, lipid profile was assessed in more than half of the included studies in which supplementation of CV was more effective in lowering triglyceride [9, 19, 22, 23], while some did not report this effect [15, 18]. For total cholesterol, the number of studies with non-significant results was higher [15, 19, 23, 24], than significant ones [9, 22]. HDL-C was affected by CV only in Mizoguchi et al. [18] study. Regarding LDL-C measures, Panahi et al. [9] and Mizoguchi at al [18]. saw decreasing effect for CV, while others did not [9, 15, 19, 22–24]. Finally, only one study [22] investigated some uncommon parameters and revealed effects for non-HDL, HDL/TG, VLDL, and Apo-B but without significant changes in Apo-A and Apo-E. In a study by Panahi et al. [9] supplementation with 600 mg of CV for 8 weeks in the patients with dyslipidemia showed an increase in HDL-C levels and reduction in serum TG, TC and LDL. Another study by the same author [19] on NAFLD patients showed a significant reduction in TG following consumption of 1200 mg/day CV for the same duration. Chitsaz et al. [23], compared the effect of CV and Spirulina and reported a significant reduction in serum TG levels after supplementation with 1 g/d CV for 8 weeks, however, no significant changes in TC, LDL-c, and HDL-C, were observed. In another study by Ebrahimi-mameghani et al. [24], compared with baseline levels, serum TC, LDL-c and TG levels significantly decreased and HDL-C level increased in both groups after 1,200 mg/d CV consumption, while,between-group differences were not significant. Consuming higher dosage of CV (5 g/day) by healthy volunteers in Jung et al. study did not lead to significant between-group differences in lipid profile after 8 weeks. In another study by Mizoguchi et al. [18] in which subjects with high-risk factors received 40 g/d of CV for 12 weeks, a significant reduction was detected in serum LDL-C and HDL-C. Kwak et al. [15] evaluated the effect of supplementation with 5 g/d of CV for 8 weeks and observed that CV could prevent the increase in TC and LDL-c levels, while increase the levels of HDL-C. In Na Hee et al. study [22], compared with controls, significant beneficial effects were observed in TC, TG, VLDL-C, non-HDL-C, and HDL-C/TG levels following CV supplementation. Although these changes were not significant in LDL-C and HDL-C levels within and between groups. In addition, Apo B concentration significantly decreased in the CV group compared with controls. However, Apo A1 and Apo E levels did not show significant changes.

Effect of *C. vulgaris* on glycemic status and insulin resistance

Of four studies investigating the effects of CV on glycemic status, only one found an improvement in FBS [24], one reported a marginally significant effects [19]. CV supplementation did not affect insulin levels in two studies [9, 18], while a reducing effect was observed for one study conducted by Panahi et al. in NAFLD patients [19]. Mizoguchi et al. [18] reported a decreasing effect of 20 tablets (undefined dosage) of CV in 6 weeks on FBS, but not on insulin levels, although Panahi et al. [9] found that 600 mg/d of CV for 8 weeks did not affect FBS or insulin resistance in

patients with dyslipidemia. Panahi et al. in another study among NAFLD patients reported a significant reduction in HbA1c and HOMA-IR and a marginally significant changes in FBS and insulin levels after consuming 1,200 mg/d CV for 8 weeks. Similarly, Ebrahimi-Mameghani et al. [24] reported a significant reduction in FBS following supplementation of the same dosage of CV in NAFLD patients. HOMA-IR was calculated in three studies of which Panahi et al. and Ebrahimi et al. [13, 19] reported beneficial effects, while in another study by Panahi et al. CV did not alter the HOMA-IR values [9].

Effect of *C. vulgaris* on blood pressure

The effect of CV supplementation on blood pressure was assessed in three studies. In Sun Hee et al. [25] study, supplementation of healthy Korean smokers with 6.3 g/d CV for 6 weeks did not affect blood pressure. Jung et al. also found no significant effect of supplementation with 5 g/d CV for 8 weeks on blood pressure. Besides, Panahi et al. revealed no significant effect for CV on systolic and diastolic blood pressure.

Discussion

To our knowledge, this is the first systematic review to comprehensively address the effects of CV on the features of metabolic syndrome. *C. vulgaris*, as a microalgae, was described in 1890 by Dr Martinus Willem Beijerinck for the first time and contains proteins, lipids, carbohydrates, pigments, vitamins and minerals which has made it as a super food with beneficial health promotions [28]. Previously, one meta-analysis had investigated the effect of CV on some cardiovascular risk factors, while that study combined various species of CV such as pyrenoidosa, sorokiniana and vulgaris [29]. Therefore this systematic review collected data from RCTs which had exclusively used CV and assessed any of metabolic disturbances parameters in diseases and health condition.

The findings of present review support the beneficial effects of CV in some anthropometric parameters such as WC. As the obesity is considered a low-grade inflammation situation in the body, anti-inflammatory nutritional materials can ameliorate this inflammation and help weight reduction [30]. Although requiring confirmation, CV has chlorophyll content, a ubiquitous natural pigment in vegetables and algae, which appears to be effective in improving anthropometric indices [31]. In some *in vitro* investigations, chlorophyll showed anti-obesity effects via CD95 (APO-1/CD95) activation system and adenosine monophosphate AMP- activated protein kinase (AMPK) [32]. When AMPK activates, results in beneficial effects for metabolic disturbances treatment [33], beside its key role in energy homeostasis [34].

It is mentioned that CV's effect on weight reduction may also relate to its possible effect on liver function via insulin resistance improvement [19]. In this regard, a RCT by Mizoguchi et al. [18] found beneficial effects in body fat reduction accompanied by one of two key genes in insulin signaling, namely protein tyrosine phosphatase 1B *(PTP-1B)*. Indeed, *PTP-1B* is a negative regulator of insulin pathway and leptin which caused obesity [35]. The important role of PTP-1B in obesity and diabetes were confirmed after this gene deletion in mice, which caused protection against them [36]. The other gene is *growth factor receptor-bound protein 2 (GRB 2),* which its deficiency or suppression *in vitro* condition can lead to fat accumulation and oxidative stress [37]. Both of them are responsible in insulin signaling pathway and finally increase glucose transporter (GLUT4) [18] and Cheng et al. reported PTP-1B activation was inhibited by CV [38]. In some human studies, anti-obesogenic effect of CV was attributed to the polyphenolic compounds such as catechins, epigallocatechin gallate, flavonols, and flavones with antiadipogenic properties [8, 18, 39]. Polyphenols might contribute to antioxidant and anti-inflammatory effects, and other biological activities including inhibition of angiogenesis as well as preadipocyte differentiation [40]. Although investigations which support the CV effect on WC are rare, any mechanism which leads to body fat loss can result in WC reduction.

As mentioned, CV contains some bioactive substances such as carotenoid with high bioavailability which can optimize lipid metabolism [20]. Carotenoids have antioxidant and anti-inflammatory effects which prevent lipid oxidation and decreasing cardiometabloic disease [41]. Exclusively, beta-carotene had shown significant anti-hyperlipidemic effects in rats with a dose-response pattern [42]. Among CV's carotenoids content, beta-carotene and lutein are the most. Increased serum levels of lutein/zeaxanthin and alpha-carotene following CV supplementation may effectively decrease TG and total cholesterol levels [22]. As Han et al. demonstrated lutein use can result in expression of the genes which are responsible in lipid metabolism and their reduction. This is suggested that TC and LDL-C modulation is via LDL-C receptor modification while reducing effect of lutein for TG is related to peroxisome proliferator-activated-receptor (PPAR) α which enhance β-oxidation of fatty acids [10].

Lipid-lowering effects of CV are in part attributable to the high fiber content of this alga which results in increasing the fecal steroid exertion and reducing the intestinal absorption. In this regard, Shibata et al. showed that CV administration in rats can increase fecal neutral steroid excretion which results in liver cholesterol content lowering by intestinal cholesterol absorption [43]. On the other side, CV can enhance the hepatic degradation of cholesterol with Cholesterol 7-alpha hydroxylase enzyme down-regulation. Also, CV can increase the storing of NEFA in the liver and subsequently reduce plasma levels of NEFA leading to a reduction in TG level [11, 44, 45]. Also, CV contains niacin and omega 3, which are both used in TG-lowering treatments and considered key nutrients of microalgae in decreasing TG level [46]. Beneficial impacts of CV on lipid profile may be also explained by its lowering effects on weight [19].

Human studies that evaluate the hypoglycemic effects of CV are rare, though according to animal ones, it seems that CV improves glucose uptake and decreases NEFA level resulting in a potential reduction in blood glucose level. The reduction in plasma NEFA concentration can stimulate glucose uptake and utilization and simultaneously suppress hepatic glucose production [12, 47]. Also, CV can activate the insulin signaling pathways which affect gene expression of PTP-1B and GRB-2 in peripheral blood cells [18, 44]. Moreover, CV supplementation down regulates p53 protein and thereby can reduce apoptosis and improve cell survival in beta cells [48]. Another possible mechanism of CV to reduce insulin resistance could be mediated through its weight-reducing effects [49]. In comparison, more animal studies have studied the glycemic effects of CV, Yuh et al. found improvement and persistent hypoglycemic effect for CV in streptozocin (STZ) -induced diabetic rats [8]. In another study, in spite of no effect of CV on insulin secretion after glucose stimulation, a significant improvement in insulin sensitivity was detected in both diabetic and normal rats [50]. Moreover, in diabetic mice, glucose uptake increase and NEFA decrease occurred after CV consumption [44].

In three included articles, no effect was seen from CV on blood pressure. In one animal study, in which a peptide existing in marine foods like CV was extracted and administered in hypertensive rats, a angiotensin I-converting enzyme (ACE) inhibitory activity was reported for marine peptides [51]. This peptide with Valine and Glutamine sequence in CV has shown effects on ACE which is responsible for regulating blood pressure [52]. This outcome is for CV extract and for lower doses of pure algae supplementation in tablet or capsule form is not valid. Of course human investigations for this peptide administrations and definite conclusion is needed.

In summary, observed controversies can be related to the subject's condition. For example in some studies which included healthy participants, no effect for lipid profile were seen while in the condition of lipid disarray CV supplementation can show its effect. Also, glycemic effects of CV were evaluated while no investigation included patients with impaired glucose status. In addition, short duration is a common character of included studies, this can effects on the outcomes.

Conclusions

CV, a well-known algae, is used for decades, specifically in eastern countries as a functional food. A rare number of investigations have studied its effects on animal and human populations with a wide range of doses and usage duration. Thus, the effective dose is not determined yet, additionally, the higher doses may not be tolerated because of high fiber content which can lead to digestive discomfort. Because of this heterogeneity between studies and their outcomes, it is difficult to reach a definite conclusion. It should be noted that some countries use this kind of algae routinely in their diet -which can increase acceptability, while for the others it can be used in supplemental forms and make it difficult. In this review, these cultural differences were not considered, and maybe a big gap which highlights more attention in future studies. Dose-response studies with a larger sample size and longer durations are warranted to achieve optimal predicted effects.

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Competing interests: The authors declare that they have no competing interests.

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Data availability: Data and material are available.

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