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Special Article

Effect of brown seaweed on plasma glucose in healthy, at-risk, and type 2 diabetic individuals: systematic review and meta-analysis

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Context: *Sustained hyperglycemia triggers chronic disease, including type 2 diabetes. A considerable volume of research has explored the effects of brown seaweed on plasma glucose control, but equivocal findings have been reported.* ***Objective:*** *A systematic review and meta-analysis was conducted to assess the evidence from human randomized controlled trials (RCTs) on the effects of brown seaweed on plasma glucose in healthy, at-risk, and individuals with type 2 diabetes.* ***Data Sources:*** *MEDLINE/PubMed, EMBASE, and the Cochrane Library were searched for reports published between 2000 and 2020.* ***Data Extraction:*** *Population, intervention, comparator, outcome, and study design data were extracted.* ***Data Analysis:*** *Eighteen RCTs met our inclusion criteria. The reported results varied across and between populations. Meta-analyses showed a significant effect, favoring the intervention group for both fasting (mean difference −4.6 [95% CI −7.88, −1.33]) and postprandial (mean difference −7.1 [95% CI −7.4, −6.9]) plasma glucose.* ***Conclusion:*** *Brown seaweed and its extracts show potential for preventing and managing hyperglycemia. Our meta-analysis confirms that brown seaweed positively affects plasma glucose homeostasis, with particularly promising postprandial plasma glucose effects. However, further research is needed because no high-quality RCT was identified. Species-specific and dose–response research is also required.*
Systematic Review Registration: *PROSPERO registration no. CRD42020187849.*

INTRODUCTION

Glucose homeostasis is essential for health, as sustained hyperglycemia leads to negative consequences such as islet cell stress, impaired glucose tolerance, and type 2 diabetes (T2DM).[1] The global prevalence of diabetes among adults rose from 108 million in 1980 to 422 million in 2014, and the prevalence is predicted to reach 700 million by 2045.[2] T2DM accounts for approximately 90% of these cases.[3]

Hyperglycemia and T2DM can be treated with a combination of dietary modification and exercise.[4,5] Treatment at early or pre-diabetic stages (ie, of individuals with elevated plasma glucose levels but who do not

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meet the criteria for diabetes) could reduce the incidence of T2DM.[6,7] Dietary approaches are a cornerstone strategy for controlling plasma glucose.[8]

A large volume of research has looked at the potential of marine algae for preventing and managing metabolic conditions.[9] Among these algae are marine seaweeds, a group of macroscopic multicellular species of 4 major classes of algae taxonomically classified by color depending on the pigment they contain. The 4 major classes are Chlorophyceae (green algae), Cyanophycea (blue-green algae), Rhodophyceae (red algae) and Phaeophycea (brown algae).[10]

Marine algae and seaweeds have long been popular as food ingredients and medicine, mainly in Asian countries. Their health benefits have been well documented as they are a traditional part of the diet. Edible seaweeds are considered highly nutritious natural foods that provide few calories while being rich in nonstarch polysaccharides, proteins, minerals, and vitamins.[11] Some of the health benefits attributed to seaweeds include antidiabetic, antihypertensive, antioxidant and anti-inflammatory effects.[12]

Brown seaweed accounts for 7 million of the 10 million tonnes of seaweed produced each year globally and comprises over 1800 species.[13] Most edible brown seaweeds come from the genera *Laminaria*, *Undaria*, and *Hizikia*.[14] Brown seaweeds derive their color from the carotenoid fucoxanthin in chloroplasts, and these 3 genera are found primarily in colder waters in the northern hemisphere. In the initial scoping of the current literature, it was that evident brown seaweed is the most recurrent seaweed type used in studies of seaweed in the human diet. Brown seaweeds have been gaining attention due to their biological compounds, including polysaccharides (eg, alginate, fucoidan), proteins (eg, phycobiliproteins), polyphenols (eg, phlorotannins), carotenoids (eg, fucoxanthin), and n-3 long-chain polyunsaturated fatty acids (eg, eicosapentaenoic acid).[15–19] It has been suggested that these biological compounds show promising antidiabetic effects.[15,16] Bioactivities reported in the literature pertain to peptides extracted from brown seaweeds such as *Undaria pinnatifida* (Wakame) and are reported to exhibit antidiabetic activity via inhibition of dipeptidyl-peptidase 4.[17–19]

These suggested antidiabetic properties of brown seaweeds have been studied in vitro after observational studies showed a relationship between seaweed consumption and reduced risk of T2DM.[20] While in vitro studies provide indicative data, they do not predict in vivo effects, and evidence from randomized controlled trials (RCTs) in humans is essential for this. The current evidence for the antidiabetic effects of brown seaweed is equivocal. The results of human intervention studies have reported varied findings, so there is a need to synthesize the evidence. This work aims to systematically review the evidence from human RCTs on the effects of brown seaweed on plasma glucose in healthy, at-risk, and T2DM individuals.

METHODS

This systematic review protocol was registered in the International Prospective Register Of Systematic Reviews (PROSPERO registration number CRD42020187849). The study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[21] Moreover, the Population, Intervention, Comparison, Outcome, Study (PICOS) framework was used to develop the research question and inclusion criteria and to guide the search strategy (Table 1).

Eligibility criteria

Population: Studies including adults (≥18 years) reported as (i) healthy with a Body Mass Index (BMI) of 18.5 and 24.9 kg/m^2, (ii) at risk of T2DM (ie, with hyperglycemia or prediabetes, overweight or obesity [BMI ≥ 25 kg/m^2]), or (iii) with T2DM (ie, impaired glucose tolerance, impaired fasting glucose, insulin resistance, or impaired insulin sensitivity diagnosed according to standard criteria) were eligible.

Interventions: Experimental studies investigating the effect of brown seaweed species and/or their extracts were included.

Comparator: Placebo.

Outcomes: Fasting or postprandial plasma glucose levels.

Study design: Parallel and crossover RCTs were eligible.

Data sources and search strategy

Following an initial scoping review, a sensitive search strategy was created using a combination of medical

Table 1 **PICOS criteria for inclusion of studies**

Parameter	Criterion
Population	Healthy, or at-risk of type 2 diabetes mellitus (ie, with hyperglycemia/prediabetes or overweight/obesity), or adults (≥18 years) with type 2 diabetes mellitus
Intervention	Brown seaweed and/or brown seaweed species extracts
Comparison	Placebo
Outcome	Plasma glucose
Study design	Randomized controlled trials

subject heading (MeSH) search terms and Boolean Connectors. The search included brown seaweed, its most used variants/extracts, and words relevant to the outcomes and participants (see Appendix 1 in the Supporting Information online). The literature search was carried out in May 2020 in the following databases: MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials. Also, Google Scholar was searched for additional relevant material. Searches were restricted to those published in the English language published between 2000 and 2020.

Study selection and data extraction

Titles, abstracts, and full-text reviews of search results were screened independently by one reviewer (K.V.), with a 20% check by a second reviewer (M.A.-M.) to establish consistency. A standardized electronic data collection form was designed based on the PICOS framework, and relevant data were extracted from each included study. One reviewer (K.V.) completed this process with a 100% check by a second reviewer (M.A.-M.). Data extracted included study identifiers and study design. In the case of any disagreement in this process, a third author was contacted (V.R.).

Quality assessment and risk of bias

The risk of bias was assessed using the Cochrane Collaboration's tool for RCTs, which considers 6 domains (ie, selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias).[22] Overall risk of bias of each publication was categorized as "low risk", "high risk", or "unclear risk", following the Cochrane Collaboration tool suggested scores. Quality was assessed independently by the first author (K.V.) and a second author (M.A.-M.). In the case of any disagreement, a third reviewer was consulted (V.R.).

Synthesis and analysis

A narrative summary of studies that satisfied the inclusion criteria is included in this review, and the main characteristics were tabulated. Studies that reported sufficient data on plasma glucose outcomes were included in a meta-analysis. Separate meta-analyses were run for postprandial plasma glucose (PPG) and fasting plasma glucose (FPG). Quality assessment and risk of bias were considered when synthesizing narrative and quantitative results.

The meta-analysis was based on the mean difference (MD) and standard deviation (SD) of changes from baseline to follow-up when PPG or FPG was reported.[23,24] Only data for the higher doses were used whenever more than one dose was given in a study. When provided, intention-to-treat data were used in the analyses. Outcomes were included only if quantitative data were reported or derived from graphs using WebplotDigitizer software.[25]

Meta-analyses were calculated following the methods suggested by the Cochrane Review.[22] Combined-design meta-analytic formulae, using the method in Curtin et al 2002,[26] were used to combine parallel and crossover trial results. Such meta-analyses were undertaken to determine the treatment effect and statistical heterogeneity (I^2) for the primary outcome measure, PPG or FPG, each being analyzed separately. A random-effects model was used because I^2 yielded a percentage greater than 85% (implying significant heterogeneity).[23] The analysis was performed using R statistical software, using the library "metafor". The main results are presented in forest plots and described in the results.

RESULTS

An initial scoping review identified 376 articles, which helped identify relevant references for refining our search strategy. Subsequent database searches then identified 41 articles, and further searches using Google Scholar identified an additional 3 articles. After removing duplicates and then title and abstract screening the search results, 21 full papers were retrieved and assessed for inclusion. During the assessment, 3 more articles were excluded (Fig. 1). This review included 18 RCTs, from which 12 had a crossover design[27–38] and 6 had a parallel design.[39–42]

Of the 18 studies, 10[28,29,32–35] involved an acute intervention as an oral glucose tolerance test (OGTT), measuring the intervention's effect on PPG over 2 to 3 h. Five studies[27,30,40–42] conducted only long-term interventions analyzing the effect on FPG. The remaining 3[39–41] reported on both FPG and PPG. In all the included studies, a placebo was used as a control comparator (Table 2).[27–42]

The study populations ranged from 12 to 97 participants. Ten studies[29–38] were conducted on healthy participants (n = 256) with a normal FPG (<100 mg/dL) and BMI (18.5 and 24.9 kg/m^2). A further 6 were carried out on individuals at risk of developing T2DM (n = 357).[28,40–44] Yoshinaga and Mitamura (2019)[28] and Lee and Jeon (2015)[40] investigated effects on prediabetic individuals (FPG > 125 mg/dL), while Wright et al (2019),[42] Hernández-Corona et al (2014),[41] Jensen et al (2012b),[43] and Shin et al (2012)[44] investigated effects on individuals with overweight or obesity (BMI > 25 kg/m^2). Only 2 studies, Sakai et al (2019)[27] and Kim

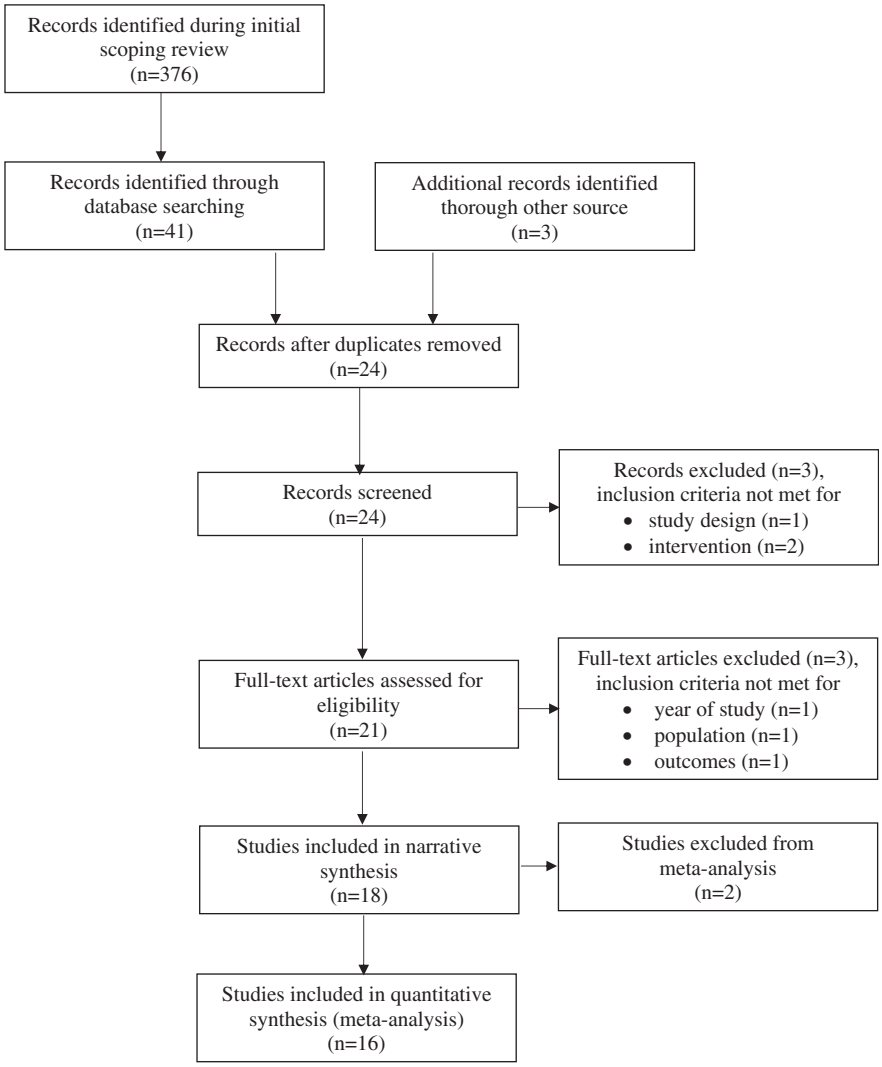

Figure 1 **PRISMA flow diagram.**

et al (2008),[39] were conducted on participants with T2DM (n = 48) (Table 2).[27–42]

Twelve studies[27,30–32,34,37,38,40–42,44] investigated seaweed extracts over whole seaweed, with the most common extract being sodium alginate (n = 6). The dosage varied between studies (ranging from 0.072 g to 70 g), mainly depending on the intervention provided (eg, seaweed extract vs whole seaweed). The characteristics of the included studies are described in Table 2.

Evidence for individuals with T2DM

Sakai et al (2019)[27] and Kim et al (2008)[39] used subjects with T2DM (FPG 150 to 300 mg/dL), but who were otherwise in good health. Kim et al (2008)[39] reported that the daily ingestion of 48 g brown seaweed significantly lowered FPG and PGB ($P < 0.05$). In contrast, Sakai et al (2019)[27] investigated the effect of high-molecular-weight fucoidan and reported no significant effect on FPG.

Evidence for individuals at risk of T2DM

Lee and Jeon (2015)[40] and Yoshinga and Mitamura (2019)[28] reported results from prediabetic individuals, indicating significant ($P < 0.05$) lowering of PPG.[28,40] Lee and Jeon (2015)[40] also investigated effects on FPG but reported no significant *Ecklonia cava* dieckol-rich extract effect. Wright et al (2019),[42] Hernández-Corona et al (2014),[41] Jensen et al (2012b),[43] and Shin et al (2012),[44] conducted interventions that analyzed the effect of various brown seaweed extracts on plasma glucose in individuals with overweight or obesity. Moreover, they used a number of different doses (ranging from 0.072 g to 22 g) and extract types, including fucoidan, sodium alginate, and polyphenols. Despite

Table 2 **Characteristics of studies included**

Study Country	Study design	Population Characteristic	Type of brown seaweed	Control	Outcome (plasma glucose) measured
Sakai et al. 2019[27] Japan	Randomized, double-blind, placebo-controlled, cross-over design study	n = 28 Participants with T2DM	Type: Mozuku Fucoidan extract Dose: 1.620 g Duration: 3 months	Placebo beverage	Fasting
Kim et al. 2008[39] Korea	Randomized, double-blind, placebo-controlled, parallel design study	n = 20 Participants with T2DM	Type: *Laminaria japonica* (Sea Tangle) and *Ulva lactuca* (Sea Mustard) Dose: 48 g Duration: 4 wk and 2 h	Placebo	Fasting and post-prandial
Yoshinaga and Mitamura, 2019[28] Japan	Randomized, open-label, 2-period, crossover design	n = 26 Pre-diabetic participants	Type: *Undaria pinnatifida* (Wakame) Dose: 4.0 g Duration: 2 h	Placebo	Postprandial
Lee and Jeon, 2015[40] Korea	Randomized, double-blind, placebo-controlled, parallel design study	n = 63 Pre-diabetic participants	Type: *Ecklonia cava* Dieckol-rich extract Dose: 1.5 g Duration: 3 months and 2 h	Placebo	Fasting and postprandial
Shin et al. 2012[44] Korea + the USA	Randomized, double-blind, placebo-controlled, parallel design study	n = 97 Participants with overweight	Type: *Ecklonia cava* Dieckol-rich extract Dose: 0.072 g and 0.144 g Duration: 3 months	Placebo	Fasting
Hernández-Corona et al. 2014[41] Mexico	Randomized, double-blind, placebo-controlled, parallel design study	n = 25 Participants with overweight/obesity	Type: (no name given) Fucoidan extract Dose: 0.5 g Duration: 3 months and 2 h	Placebo	Fasting and postprandial
Wright et al. 2019[42] Australia	Randomized, double-blind, placebo (microcrystalline cellulose) controlled, parallel design study	n = 72 Participants with obesity	Type: *Fucus vesiculosus* Fucoidan extract Dose: 1.0 g Duration: 3 months	Microcrystalline cellulose Dose: 1.0 g	Fasting
Jensen et al. 2012b[43] Denmark	Randomized, double-blind, placebo-controlled, parallel design study	n = 96 Participants with obesity	Type: *Laminaria hyperborea* and *Laminaria digitate* (Oarweed) Sodium alginate extract Dose: 22.0 g Duration: 3 months	Placebo	Fasting
van den Driessche et al. 2020[30] Netherlands	Randomized, double-blind, placebo (microcrystalline cellulose) controlled, cross-over design study	n = 35 Healthy participants	Type: *Undaria pinnatifida* (Wakame) Dose: 4.8 g Duration: 3 months	Microcrystalline cellulose Dose: 0.4 g	Fasting
Murray et al. 2018[31] Australia + Ireland	Randomized, double-blind, placebo controlled, cross-over design study	n = 38 Healthy participants	Type: *Fucus vesiculosus* (Bladder Wrack) Dose: 0.5 g and 2.0 g Duration: 2 h	Cellulose Dose: 0.5 g and 2.0 g	Postprandial

(continued)

Table 2 **Continued**

Study Country	Study design	Population Characteristic	Type of brown seaweed	Control	Outcome (plasma glucose) measured
Paradis et al. 2011[36] Canada	Randomized, double-blind, placebo-controlled, cross-over design study	n = 23 Healthy participants	Type: *Ascophyllum nodosum* (Rockweed) and *Fucus vesiculosus* (Bladder Wrack) Dose: 0.5 g Duration: 3 h	Placebo	Postprandial
Tanemura et al. 2014[33] Japan	Randomized, placebo (as test meal) controlled, crossover design study	n = 12 Healthy participants	Type: *Undaria pinnatifida* (Wakame) *Undaria pinnatifida* sporophylls (Mekabu) Dose: 70.0 g Duration: 3 h	Control meal with neither Wakame/Mekabu	Postprandial
El Khoury et al. 2014[34] Canada	Randomized, placebo-controlled, crossover design study	n = 24 Healthy participants	Type: *Laminaria hyperborea* Sodium alginate extract Dose: 4.06 g, 8.13 g and 8.13 g Duration: 2 h	Placebo beverage	Postprandial
Williams et al. 2004[37] USA	Randomized, double-blind, placebo-controlled, cross-over design study	n = 48 Healthy participants	Type: (no name given) *Sodium alginate* extract Dose: 1.6 g Duration: 2 h	Placebo bar	Postprandial
Jensen et al. 2012a[35] Denmark	Randomized, double-blind, placebo-controlled, 4-way, crossover design study	n = 19 Healthy participants	Type: *Laminaria hyperborea* and *Lessonia trabeculata* Sodium alginate extract Dose: 9.9 g and 15.0 g Duration: 3.5 h	Control preload beverage without sodium alginate	Postprandial
Huang et al. 2019[29] USA	Randomized, double-blind, placebo-controlled, cross-over design study	n = 12 Healthy participants	Type: (no name given) Sodium alginate extract Dose: 0.625 g Duration: 2 h	Placebo beverage	Postprandial
Wolf et al. 2002[38] USA	Randomized, double-blind, placebo-controlled, cross-over design study	n = 30 Healthy participants	Type: (No name given) *Sodium Alginate* extract Dose: 3.75 g Duration: 2 h	Placebo beverage	Postprandial
Kato et al. 2018[32] Japan	Randomized, double-blind, placebo-controlled, cross-over design study	n = 15 Healthy participants	Type: (no name given) Calcium alginate extract Dose: 3.2 g and 5.0 g Duration: 2 h	Control meal without calcium alginate	Postprandial

their differences, none of these studies reported any significant effect on plasma glucose levels.

Evidence for healthy individuals

Most studies (n = 10) were carried out on healthy adults with a normal FPG and BMI. These RCTs were crossover designs. The study of van den Driessche et al (2019)[30] was the only long-term intervention (17 days) measuring the effects on FPG. Their results showed that *Undaria pinnatifida* (Wakame) had no significant effect.[30] The other 9 studies monitored the effect of brown seaweeds on PPG in short-term interventions (2 to 3.5 h).[29,31–38] Similar to van den Driessche et al (2019),[30] Tanemura et al (2014)[33] used the brown seaweed *Undaria pinnatifida* (Wakame) and its sporophylls (Mekabu). The Wakame meal had no significant effect when compared against a control, whereas the Mekabu meal significantly lowered PPG ($P < 0.05$).[33]

Huang et al (2019),[29] El Khoury et al (2014),[34] Jensen et al (2012a),[35] Williams et al (2004),[37] and Wolf et al (2002)[38] investigated the effect of the brown seaweed extract sodium alginate on PPG in healthy adults. Williams et al 2004 analyzed sodium alginate's effect in a bar and reported a significant reduction ($P < 0.05$) in PPG in healthy adults.[37] The other 4 studies used test beverages as their intervention. Kato et al (2018)[32] also used alginate extract from brown seaweed. However, since high sodium levels are a risk factor for hypertension, the calcium salt of alginic acid (calcium alginate) was used. Results testing both 5% calcium alginate and 8% calcium alginate reported significant ($P < 0.05$) reduction in PPG. Murray et al (2018)[31] studied the effect of brown seaweed (containing 28% polyphenols and 67% fucoidan extract) on healthy adults. Neither low nor high doses (0.5 g and 2 g) produced a significant effect on PPG. Like Murray et al (2018)[26], Paradis et al (2011)[36] used a blend of brown seaweeds (10% polyphenols, 90% algal polysaccharides). Their results showed that the 500 mg dose had no significant effect in terms of lowering PPG.

Meta-analysis

Three studies adopted both parallel and crossover designs and provided both FPG and PPG data. Three other studies used only a parallel design, and a further 7 studies used only a crossover design. The meta-analysis of the effects of brown seaweed on FPG and PPG is presented in Figures 2[28–31,33,35–41,43,44] and 3.[27,39–42]

There was a greater reduction in PPG (MD −7.1 [95% CI −7.4, −6.9]) favoring the intervention group, and this difference was statistically significant ($P < 0.001$). This suggests that brown seaweed significantly reduces PPG in patients with T2DM, those at risk of T2DM, and healthy individuals. The overall quality of these studies was also

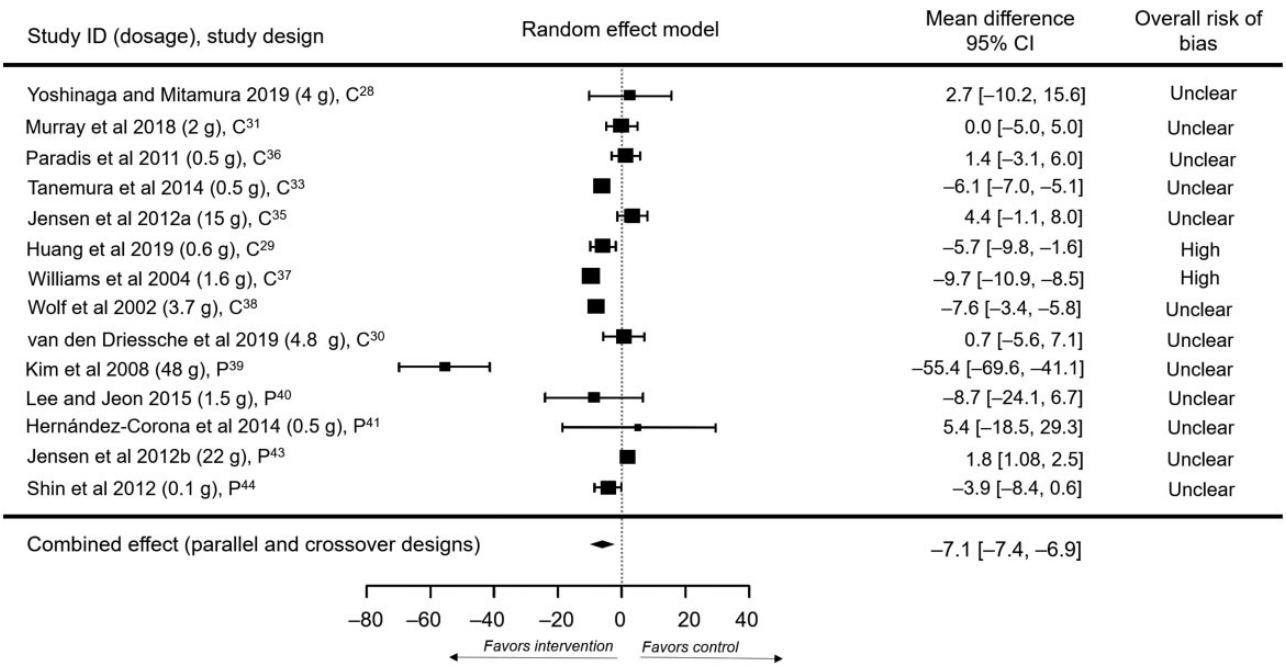

Figure 2 **Postprandial plasma glucose outcomes meta-analysis.**
Results present the mean difference changes from baseline to follow-up among groups. Overall risk of bias analyzed with the Cochrane Collaboration's tool for randomized controlled trials. *Abbreviations:* 95% CI, 95% confidence interval; C, crossover study design; P, parallel study design.

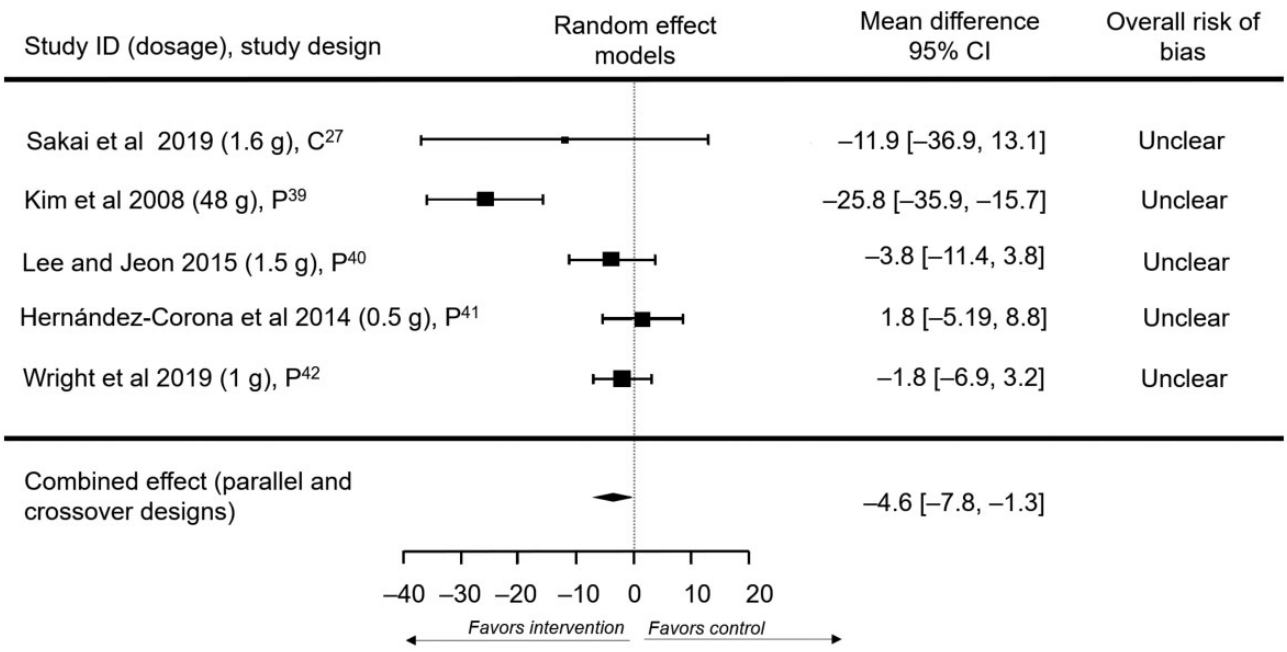

Figure 3 **Fasting plasma glucose outcomes meta-analysis.**
Results present the mean difference changes from baseline to follow-up among groups. Overall risk of bias analyzed with the Cochrane Collaboration's tool for randomized controlled trials. *Abbreviations:* 95% CI, 95% confidence interval; C, crossover study design; P, parallel study design.

rated as unclear for all outcomes evaluated. Heterogeneity for this pooled estimate was high ($I^2 = 99\%$), likely because of the variability between interventions (Fig. 2).

There was an overall reduction in FPG (MD –4.6 [95% CI –7.9, –1.3]) favoring the intervention group, and this difference was statistically significant ($P = 0.006$), suggesting an effective reduction in the intervention groups compared with the control groups (Fig. 3). Heterogeneity for this pooled estimate was high ($I^2 = 99\%$), likely because of the large variability in dosages and intervention characteristics. However, the overall quality of these studies was rated as unclear for most outcomes evaluated.

Table 3[27–42] presents the details of the meta-analyses for crossover, parallel, and combined study designs. For FPG, both crossover and parallel trials showed an effect size favoring the intervention. The combined effect was weighted towards the parallel trials and was significant. For PPG, the combined effect was weighted towards the crossover trials and thus showed an effect size favoring the intervention, with a tight confidence interval.

Risk of bias across studies

The risk of bias across all the included studies was variable. However, most of the studies had an unclear risk of bias (15/18), and 3[29,32,37] had a high risk of bias. Half of the studies described the methods used to generate the allocation sequence in sufficient detail for assessing whether it should produce comparable groups. Less than half (7/18) described the methods used to conceal the allocation sequence in sufficient detail for determining whether intervention allocations could have been foreseen before or during enrolment. Few (4/18) described all measures used to blind the trial participants and researchers from knowing which intervention a participant received. Blinding methods were insufficiently described in most studies, and 2 (crossover studies) used open-label designs. Only Murray et al (2018)[31] detailed measures taken to achieve blind outcome assessment. Most of the studies (13/18) described the completeness of the outcome data for each main outcome, including attrition and exclusions from the analysis, or reported attrition and exclusions.

Most of the studies were assessed as unclear or high (14/18) in another type of bias, since these were either financed by food or pharmaceutical industries or received food supplements from companies. In none of these studies, the role of the funding or supplement providers was disclosed or clarified (Table 4).[27–42]

DISCUSSION

This systematic review of 18 RCTs with a total of 646 participants found mixed reported effectiveness of brown seaweed on plasma glucose in healthy individuals, those at risk of T2DM, and individuals with

Table 3 **Details of random effects meta-analyses of crossover, parallel, and combined study designs**

Outcome	Design	Pooled effect size	Weight	Standard error	95% confidence interval	
FPG	Parallel	−4.07	0.33	1.73	−7.46	−0.67
	Crossover	−11.90	0.02	6.39	−24.42	0.62
	Combined	−4.60	0.36	1.67	−7.88	−1.33
PPG	Parallel	1.50	7.64	0.36	0.79	2.21
	Crossover	−8.40	52.80	0.14	−8.67	−8.13
	Combined	−7.15	60.44	0.13	−7.40	−6.90

FPG, fasting plasma glucose; PPG, post-prandial plasma glucose.

diagnosed T2DM. Our meta-analysis showed promising effects of brown seaweed over glucose control. However, the results should be interpreted cautiously, considering that most evidence had an unclear or high risk of bias. Furthermore, across the included studies, the wide range of variables (eg, study design and duration, type of brown seaweed used, dosage, and other study-specific variables) might have affected the results.

Studies conducted in vitro[45–47] and in diabetic mice[48,49] show that *Ascophyllum nodosum* (Rockweed) and *Undaria pinnatifida* (Wakame) regulate plasma glucose. However, only 2 of the identified studies have been conducted in humans with T2DM,[27,39] and they have limited evidence. Our meta-analysis suggests that brown seaweed has a significant effect on glucose control. While both studies showed significant effects, they were not directly comparable, as their only similarity was their study population.[27,39] The latter study (Kim et al 2008)[39] showed the most remarkable success in improving plasma glucose response, with results suggesting that significance may be dose-dependent, as Kim et al 2008 administered a considerably larger dose (48 g) in comparison with Sakai et al 2019 (1.62 g).[27] Another important difference between these two studies was the type of intervention used. Kim et al 2008[39] opted for whole brown seaweed rather than a seaweed extract, supporting in vitro research showing that *Laminaria japonica* (Kombu) may have potential in managing T2DM.[50] Further investigations in diabetic individuals are required in order to clarify the potential of brown seaweeds for regulating plasma glucose in T2DM.

People with T2DM or those at risk of getting T2DM often present more than one comorbidity (eg, obesity).[51] In the studies retrieved in our review, not all of those that evaluated participants with overweight or obesity showed impaired plasma glucose control. However, in addition to looking at changes in plasma glucose, a small amount of weight loss was also reported in 2 studies,[41,44] which might be a confounding factor, because weight loss is associated with a positive effect on glycemic control.[52] Furthermore, both interventions included dietary modifications, and that may have affected the overall outcome and could also be a source of bias.

All studies retrieved were placebo controlled. However, only one study conducted on participants with overweight or obesity described in its methods the type of control measure used. Wright et al (2019)[42] used a placebo filled with microcrystalline cellulose, a common bulking agent in food production. While there are contradictory reports on whether microcrystalline cellulose has hypoglycemic effects,[53] it serves as insoluble fiber and may influence satiety and energy intake, influencing weight. In addition, the use of a fiber control would have helped determine whether any plasma glucose changes were due to the seaweed polysaccharides specifically or to other biological compounds it contains.

Murray et al (2018)[31] and van den Driessche et al (2019)[30] also used cellulose as their placebo and, similar to Wright et al (2019),[42] reported no significant difference between the intervention and the placebo. However, it is important to note that fiber has a lowering effect on postprandial glycemia[54] and could be a potential reason for the lack of difference between the intervention and the placebo regarding glycemic response.

Studies investigating the effect of brown seaweed on plasma glucose in individuals with prediabetes reported a significant lowering of PPG,[28,40] with the suggested mechanism being inhibition of the carbohydrate hydrolyzing enzymes α-amylase and α-glucosidase. The studies differed in seaweed species, dosage, and method of administration. This supports data from animal research in which *Ecklonia cava* and *Undaria pinnatifida* (Wakame) reportedly decreased PPG levels, with the same suggested mechanism.[55,56]

The largest number of studies was carried out on healthy adults, and these studies provided a robust volume of data. However, the results were not consistent throughout the studies because of their considerable heterogeneity. Very few of these studies, which were conducted on healthy participants with an average FPG level and presumably optimal glucose tolerance, showed a significant effect from the brown seaweed intervention. There remains an unanswered question on weather the effectiveness of seaweed might vary according to a established glucose tolerance or other metabolic factors, such as weight.

Table 4 **Risk assessment bias of studies included**

Study ID	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias	Overall assessment
	Random sequence generation	*Allocation concealment*	*Blinding of participants and personnel*	*Blinding of outcome assessment*	*Incomplete outcome data*	*Selective reporting*	*Anything else, ideally prespecified*	
Murray et al. 2018[31]	Low	Low	Low	Low	Low	Unclear	Unclear	**Unclear**
Lee and Jeon 2015[40]	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low	**Unclear**
Tanemura et al. 2014[33]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	**Unclear**
Jensen et al. 2012a[35]	Low	Low	Unclear	Unclear	Low	Unclear	Unclear	**Unclear**
Wright et al. 2019[42]	Low	Unclear	Low	Unclear	Low	Low	Unclear	**Unclear**
Sakai et al. 2019[27]	Low	Unclear	Unclear	Unclear	Low	Unclear	Unclear	**Unclear**
Huang et al. 2019[29]	Low	Low	Unclear	Unclear	Unclear	Unclear	Unclear	**High**
El Khoury et al. 2014[34]	Low	Low	High	High	Low	Low	Unclear	**Unclear**
Hernandez-Corona et al. 2014[41]	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	**Unclear**
Williams et al. 2004[37]	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	**High**
Yoshinaga and Mitamura 2019[28]	Low	High	High	High	Low	Low	Unclear	**Unclear**
Kato et al. 2018[32]	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear	**High**
Shin et al. 2012[44]	Unclear	Low	Unclear	Unclear	High	Unclear	Unclear	**Unclear**
Wolf et al. 2002[38]	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear	**Unclear**
Kim et al. 2008[39]	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	**Unclear**
Jensen, et al. 2012b[43]	Low	Low	Low	Unclear	Low	Low	Unclear	**Unclear**
Paradis et al. 2011[36]	Low	Low	Unclear	Unclear	Low	Low	Unclear	**Unclear**
van den Driessche et al. 2019[30]	Unclear	Unclear	Low	Unclear	Low	Unclear	Low	**Unclear**

This systematic review had some limitations. The first and most important was the heterogeneity among studies in terms of study design, type of brown seaweed, doses, and population characteristics. Also, the small number of studies made it difficult to determine whether weight loss significantly affected plasma glucose outcomes. Furthermore, the available RCTs included parallel and crossover trials. In most of those with a crossover design, it was not clear whether the crossover design was appropriately used, or whether the order of receiving supplements or foods was correctly assigned or may have created a potential bias from carry-over effects. Thus, most of the evidence retrieved had an unclear or high risk of bias. In addition, the studies were mainly financed by food or pharmaceutical industries. Thus, the varied evidence for a beneficial effect of brown seaweed/brown seaweed extracts could be due to several limitations across and within this review's studies. The limitations identified here should provide guidance in designing further studies to improve the quality of the evidence.

The review included studies that used brown seaweed or extracts of it as their main intervention. The species of brown seaweed used, the form, and the administration method varied across studies, which may have influenced its effectiveness due to variations in composition and structure. Five of the studies that used brown seaweed species extract failed to report the source of their extract. Further limitations included the varying glucose tolerance and insulin resistance between study populations. The participants in each study population were, therefore, likely to respond differently depending on the dosage.

To our knowledge, this is the first systematic review and meta-analysis of RCTs measuring the effect of brown seaweed on plasma glucose, focusing on human participants. Seven of the 18 studies included in this review were published in the past 3 years, indicating the topic's current relevance. Only RCTs with a placebo as a comparator were included, which should reduce the effects due to differences in population characteristics. Also, synthesizing the available evidence by conducting a combined meta-analysis that merged parallel and crossover design studies, following previously defined statistical methods,[26] added strength to our study, helping establish the statistical significance of differences in results; otherwise, the results of individual studies may have appeared to conflict with one another. Statistical significance increases the validity of any observed results, increasing the reliability of this review.

Current research focuses more on seaweed supplementation than whole seaweed consumption. The findings to date provide varied results; therefore, further high-quality RCTs are required to determine an effective intervention and dosage method. Future work should explore the preventative potential of brown seaweed intake, in view of the time it takes for T2DM to develop. Further research is also needed on T2DM participants, and on comparing the outcomes for intervention with seaweed with those for current pharmacological treatments such as Acarbose.

CONCLUSION

This systematic review and meta-analysis found that brown seaweed and its extracts possess the potential to prevent and manage T2DM, either through dietary intake or supplementation. In addition, the meta-analysis confirms that brown seaweed positively affects plasma glucose homeostasis, with the most promising PPG effects. However, due to the limited number of studies and the lack of high-quality studies, there is inadequate evidence as yet to confirm the seaweed species and dosage of most benefit.

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Supporting information

The following Supporting Information is available through the online version of this article at the publisher's website.

Appendix S1. **Search strategy**

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