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SEAWEED AS ADJUVANT THERAPY FOR METABOLIC SYNDROME A SYSTEMATIC REVIEW

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INTRODUCTION

The metabolic syndrome is a cluster of metabolic disorders associated with obesity, decreased of high-density lipoproteins cholesterol levels, increased of triglyceride levels, increased blood pressure and hyperglycemia. Metabolic syndrome is becoming one of the main public health problems of the 21st century.

To prevent life-style-related diseases, researchers attention is increasingly focusing on some of the so called “functional foods” which may be useful for their prevention and treatment.

Rich in unique bioactive compounds not present in terrestrial food sources, seaweeds are considered a novel source of this type of food. Seaweeds are rich in vitamins, minerals, dietary fiber, proteins, polysaccharides and various functional polyphenols, compounds with potential to be exploited in human health applications.

The aim of this study was to systematically review the scientific evidence on the effect of seaweed consumption on the different components of the metabolic syndrome, as well as identifying gaps in current knowledge, which will help in the planning and implementation of future studies.

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METHODS

Search strategy

A systematic literature search was performed in Medline, Cochrane, Scielo, DOAJ and IBECS databases. The search terms (in titles and abstracts) were: (metabolic syndrome OR hypertension OR blood pressure OR diabetes OR glucose OR lipids OR cholesterol OR triglycerides OR obesity OR weight) AND (seaweed).

Study selection

The following criteria was used to identify eligible studies: (i) Randomized controlled trials with parallel case design or case-crossover design, systematic reviews or meta-analysis (ii) investigation of the effects of seaweeds or standardized extracts on any of the metabolic syndrome components. Exclusion criteria were (i) animals or in vitro studies, (ii) narratives reviews, (iii) descriptive studies, (iv) uncontrolled studies, (v) studies that do not include the study parameters.

Data extraction

The following items were extracted from the eligible studies: 1) first author's name; 2) publication year; 3) duration; 4) country; 5) number of subjects receiving seaweed and control intervention; 6) study design; 7) size study; 8) characteristic of the subjects (age, gender, inclusion/exclusion criteria); 9) description of the intervention; and 10) results variables that include serum/plasma concentrations of lipid parameters, glucose levels, anthropometrics measures and blood pressure.

Quality assessment

It was performed using Jadad scale. According to this scale the following parameters are appraised: randomization (0-2 points), blinding (0-2 points), and dropouts (0-1 point). Jadad scores of ≤2 and ≥3 were reflected low- and high-quality studies, respectively.

RESULTS

The literature search identified 89 potentially relevant reports from which, only 12 full text articles were targeted for a systematic review, with a number of participants between 55 and 10 per treatment branch, duration between single dose and 16 weeks, and quality criteria ranging from 1 point to 5 points on the Jadad scale. This information is shown in Table 1 and 2.

Table 1. General characteristics

Nº	Authors	Year	Country	Jadad	Number of Subjects	Intervention/Control
1	Allsopp P. et al	2015	Northern Ireland	5	20/20	Palmaria palmata / Placebo
2	Lee SH. et al	2015	Korea	4	40/40	AG-dieckol / Placebo
3	Paradis ME. et al	2011	Canada	5	13/13	Ascophyllum nodosum and Fucus vesiculosus / Placebo
4	Jensen GM. et al	2012	Denmark	5	48/48	Alginato / Placebo
5	Teas J. et al	2009	Ecuador	4	30	Group 1: Placebo / Undaria pinnatifida 4 g/d Group 2: Undaria pinnatifida 4 g/d Undaria pinnatifida 6 g/d
6	Kim MS. et al	2008	Korea	2	10/10	Sea tangle and Sea mustard/ Placebo
7	Tanemura Y. et al	2014	Japan	1	12	Mebaku / Wakame / Placebo
8	Mikami N. et al	2017	Japan	3	20/20/20	Grupo 1: Fucoxanthin 0 mg/d / Placebo Grupo 2: Fucoxanthin 1 mg/d / Placebo Grupo 3: Fucoxanthin 2 mg/d / Placebo
9	Dumelod BD. et al	1999	Philippines	1	10	Carrageenan / Placebo
10	Abidov M. et al	2010	Russia	4	NAFLD 36/36 NLF 19/19	NAFLD: Xanthigen / Placebo NLF: Xanthigen / Placebo
11	Murray M. et al	2018	Australia	5	38	Asian: Fucus vesiculosus 1/ Fucus Vesiculosus 2 / Placebo Non asian: FV1/FV2/Placebo
12	Hitoe S. et al	2017	Japan	4	11/11/11	Fucoxanthin 1mg/d Fucoxanthin 3 mg/d Placebo

Table 2. Chacteristics of the RCT

Nº	Study design	Sample Population	Intervention	Control	Duration	Outcomes	Results
1	Randomized double- blind placebo-controlled trial with parallel-group design.	N=40 **Inclusion criteria:** Healthy participants from across Northern Ireland, aged 18-65 years who expressed an interest completed a screening questionnaire. **Exclusion criteria:** Participants were excluded if they regularly consumed seaweed (>5 g/weeks), used vitamin or mineral supplements, used immune-altering medication or had a history of thyroid problems.	(n=16) Age mean (SD): 30.8 (115.7) Male/ Female 06/09 Baguette with P. palmata (230 g) per día	(n=20) Age mean (SD): 33.50 (14.14) Male/ Female 11/09 Placebo	4 weeks	TG CT LDLc HDLc BMI	**TG:** Significantly increase (from 91 to 120,75 mg/dL; p < 0.001) in intervention group compared to placebo group. **CT:** No significant difference was observed. **LDLc:** No significant difference was observed. **HDLc:** No significant difference was observed. **BMI:** No significant difference was observed.
2	Randomized double- blind placebo-controlled trial with parallel-group design	N=80 **Inclusion criteria:** Subjects aged between 20 and 65 years with fasting plasma glucose (FPG) between 100 and 180 mg/dL. **Exclusion criteria:** Surgery within the past 6 months; any treatment with either insulin or anti-diabetic drugs within the past 3 months; treatment with adrenocorticosteroid hormone within the past 2 months; TSH > 10 µU/mL or <0.1 µU/mL; creatinine >1.5 mg/dL; elevations >2-fold in the normal limit of ALT or AST; alcohol abuse, significant gastrointestinal disorders or unbalanced nutrition. Pregnant and lactating women were excluded, as were those seeking to become pregnant.	(n=36) Age: 53.6 ± 8.5 Male/ Female 25/11 An AG-dieckol (extract of Eckloniа cava) dosage of 500 mg 3 times per day (1500 mg/day)	(n=37) Age: 53.0 ± 6.9 Male/ Female 27/10 Placebo	12 weeks	FPG HbA_{1c}(%) Postprandial glucose	**FPG:** No significant difference was observed. **HbA_1 (%):** No significant difference was observed. **Postprandial glucose:** AG-dieckol group showed a significant decrease (-12,34± 43,5 mg/dL) compared to placebo group (9,55 ± 36,8 mg/dL)
3	Double-blind, randomized, placebo-controlled crossover study.	N=23 **Inclusion criteria:** Subjects aged between 18 and 60 years. Nonsmokers, with a BMI 20-30 kg/m². Female volunteers of childbearing age were eligible if they were using contraceptive methods. **Exclusion criteria:** Volunteers allergic to iodine, using natural health products, suffering from gastrointestinal problems, diabetes, thyroid or liver dysfunctions. Volunteers with untreated hypertension (systolic blood pressure SBP> 140 mm Hg and (or) diastolic blood pressure DBP> 90 mmHg, as well as those with a SBP> 130 mm Hg and (or) DBP> 85 mm Hg along with ≥3 other cardiovascular risk factors. Breastfeeding or pregnant women. Volunteers consuming >2 alcoholic drinks per day or >9 per week.	Characteristics of the subjects (n=13) Age mean (SD): 39.9 (12.7) years Commercially available blend of brown seaweed (Ascophyllum nodosum and Fucus vesiculosus) Two 250 mg seaweed capsules were consumed 30 mn prior to the consumption of 50 g of carbohydrates from bread.	Placebo 2 placebo capsules were consumed 30 mn prior to the consumption of 50 g of carbohydrates from bread.	Single dose	FPG Postprandial glucose	**FPG:** No significant difference was observed between intervention group (100(7.4) mg/dL) and placebo group (100.5 (8.3) mg/dL) (p = 0.45) **Postprandial glucose:** Concentrations did not differ between treatments at each postprandial time points.
4	Randomized double-blind, placebo-controlled with parallel-group design	N=96 **Inclusion criteria:** Subjects aged between 20 and 55 years, with BMI (kg/m²): 30–45. **Exclusion criteria:** Any known chronic illnesses (such as metabolic disease, liver and kidney disease, or CVD), hypertension >160/100 mm Hg, elevated fasting total cholesterol (CT) (>6.5 mmol/L), diabetes or fasting glucose >7.0 mmol/L, a high level of physical activity (>10 h/week), the use of dietary supplements, a regular use of medications (not include contraceptives) and smoking.	(n=38) Male/ Female 15/23 Age (44.6 ± 7.6) Energy-restricted diet (-300 kcal/day) plus an alginate-based preload supplement (15 g fiber) administered 3 times/d before main meals.	(n=42) Male/ Female 11:31 Age (41.2 ±7.4) Energy-restricted diet (-300 kcal/day) plus a placebo preload supplement	12 weeks	TG CT HDLc LDLc Glucose HbA_{1c} (%) BMI Weight Waist SBP DBP	**Lipid metabolism** did (TG, CT, HDLc and LDLc) not differ between treatment groups in the ITT analysis (p> 0.1) **FPG:** No significant difference was observed. **HbA_{1c}(%):** The reduction was greater in the alginate group (-0.10 ± 0.00%) than in the control group (0.01 ±0.03%) (p= 0.024) **BMI:** No significant difference was observed. **Weight:** No difference was observed between treatment groups in the intension-to-treat (ITT) analysis; however, in the completer analysis was shown a greater weight loss in alginate group (-1,7 ±0,5kg) than in the control group (p=0,031) **Waist:** No significant difference was observed. **SBP:** Larger decrease in the placebo group (-5.4 ± 1.6 mm Hg) than in the alginate group (-1.6 ± 1.8 mm Hg) (p = 0.035). **DBP:** Larger decrease in the placebo group (-2.9 ± 1.2) than in the alginate group (-2.5 ±1.7) (p = 0.020)
5	Randomized double-blind placebo-controlled crossover study.	N=30 **Inclusion criteria:** Participants with at least one symptom of MS were invited to participate. **Exclusion criteria:** Participants with high blood glucose> 110 mg/dL)	(n=14) Male/Female 07/06 Age (years) Men: 45.9 ± 10.3 Women: 46.5 ± 14.7 Group 2: 1 month of 4 g/d *Undaria pinnatifida* followed by 1 month of 6 g/d *Undaria pinnatifida*.	(n=13) Male/Female 06/08 Age (years) Men: 47.2 ± 9.4 Women: 45.3 ±11.1 Group 1: 1 month of placebo followed by 1 month of 4 g/d *Undaria pinnatifida*	4 months	Waist Weight BMI SBP	**Waist:** Decrease only on women participants. **-Group 1:** Significant decrease between baseline and placebo after treatment with placebo (-2,3 cm, p<0,01). Changes between baseline and 4 g/d were also significant (-3,1 cm p <0.001). There were no further changes between placebo and 4g/d. **-Group 2:** Significant decrease (-2,7 cm) after 4 g/d (p <0,01). Treatment with 6g/d was associated with a further 3 cm decrease, which was significant when compared to 4g/d (p <0.01) and when compared to baseline (p<0.001). No associated changes in **body weight** or **BMI** were observed. **SBP:** Changes were observed in people with high blood pressure (> 130 mmHg). **-Group 1:** Significant decrease in the placebo treated participants, which became insignificant on 4 g seaweed daily. **-Group 2:** There was a decrease in the 4g/d seaweed group, which reached significance when the dose increased to 6g/d (-10,5 mmHg (95%IC -4,1-16,8 mmHg; p <0.05).
6	Randomized double-blind, placebo- controlled with parallel-group design	N=20 **Inclusion criteria:** Diabetes controlled by diet and (or) oral hypoglycemic agents. BMI <35, FPG>150 mg/dl (150-300 mg/dl), no consumption of lipid-lowering drugs, and being 40 to 70 years of age. **Exclusion criteria:** Good general health and had no clinical or laboratory evidence of renal, hepatic, or cardiovascular disease.	(n=10) Male/Female 04/06 Age: 54.4 ± 3.1 years Pill with equal parts of dry powdered sea tangle and sea mustard were provided 3 times a day (48g/d). The mean total dietary fiber intake in seaweed group was 2,5 times higher than in the control group (p<0.001).	(n=10) Male/Female 05/05 Age: 54.8 ± 2.5 years Placebo	4 weeks	CT TG LDLc HDLc FPG Postprandial Glucose HbA_{1c}(%)	**CT:** No significant difference was observed **TG:** Significant decrease in seaweed group (from 171.2 ± 36.7 to 111.8 ± 17.6) (p<0.05), but there were no significant differences in controls. **LDLc:** No significant difference was observed. **HDLc:** Significant increase in seaweed group (from 37,1 ±3,2 to 44,6 ±2,9)(p <0.05), but there were no significant differences in controls. **FPG:** Significant decrease in patients receiving seaweed supplementation (from 181.7 ± 8.2 to 151,8 ± 8.2)(p <0,01), but there were no significant differences in controls. **Postprandial Glucose:** Significant decrease in patients receiving seaweed supplementation (from 263,2 ± 13 to 203,1,8 ± 12.3)(p <0.05), but there were no significant differences in controls. **HbA_{1c}(%):** No significant difference was observed.
7	Randomized placebo-controlled with crossover design.	N=12 **Inclusion criteria:** Subjects with normal BMI. Fasting plasma glucose were lower than 92 mg/dl and serum insulin concentrations were within the normal range for healthy subjects.	Characteristic of the subjects (n=12): Male/Female: 08:04 Age: 25,4± 1.3 years 200 g de white rice, 50 g boiled soybeans, 60 g potatoes y 40 g broccoli with Wakame or Mekabu.	200 g de white rice, 50 g boiled soybeans, 60 g potatoes y 40 g broccoli with placebo	Single dose	Postprandial Glucose	**Postprandial Glucose:** Plasma glucose levels at 30 minutes after the Mekabu meal were significantly lower (approximately 130 mg / dL) than those obtained after the control meal (approximately 160 mg / dL)(p <0,05) No differences were observed between the placebo group and the Wakame group.
8	Randomized, single blinded, single centre, controlled clinical trial.	N=60 **Inclusion criteria:** BMI>22 Kg/m₂ **Exclusion criteria:** Pregnant women or breastfeeding, and those unable to give consent were excluded.	-(n=19) Fucoxanthin 1mg/d 32% Male Age: 57.5± 2.9 -(n=20) Fucoxanthin 2 mg/d 45% Male Age: 55.2 ±3.2 One capsule every dary after dinner. Each capsule contained Fx-enriched akamoku oil.	(n=20) 20% Male Fucoxanthin 0 mg/d (placebo) Age: 53.0 ± 2.2	8 weeks	CT HDLc LDLc TG HbA_{1c}(%) Weight BMI	Lipid metabolism (**TG, CT, HDLc** and **LDLc**) did not differ between treatment groups. **HbA_{1c}(%):** Significant decrease (-0,14%) in Fucoxanthin 2 mg/d group compared with 0 mg/d group(0,06%)(p <0.05) **Weight:** No significant difference was observed. **BMI:** No significant difference was observed.
9	Randomized placebo- controlled with crossover design.	N=10	Characteristic of the subjects (n=10) Male/Female 04/06 Age: 25,6± 3.83 years Experimental *Arroz caldo*: The same, except for the addition of 1,75% carraguenano and 10% more chicken broth.	Control *Arroz caldo*: It was prepared from boiled rice, boiled chicken meat, ginger, onion and garlic	Single dose	Postprandial Glucose	**Postprandial Glucose:** Significant decrease at 15, 45 and 90 mn (p<0,05); and at 30 mn (p<0,01) after consuming the experimental sample.
10	Randomized double- blind, placebo- controlled with parallel-group design	N=110 **Inclusion criteria:** Obese (BMI >30 kg/m₂), premenopausal non-diabetic females who were recruited through the National Academy of Natural Sciences in Russia. **Exclusion criteria:** Positive pregnancy test or diabetes were excluded from the study. Exclusion criteria for the latter were fasting glucose above >100 mg/dl and mailing results of a standard oral glucose tolerant test with 75 g of glucose. Women taking medications known to influence fat metabolism or women with a history of excessive alcohol consumption were excluded	NLF (n=19): Liver fat content below 6,5% Age: 35.7 ± 3.52 years NAFLD (n=36) Liver fat content above 11%, ALT ≥42 U/l, AST ≥46 U/l, GGT ≥44 U/l, y CRP ≥6.0 mg/ Age: 36.1 ± 2.1 years	NLF (n=19) Age: 34.7 ± 3.5 yr NAFLD (n=36) Age: 37.4 ± 2.8 yr	16 weeks	TG Weight Waist SBP DBP	**TG:** -NAFLD: In the Xanthigen group, decreased from, 195 ± 19 to 158 ± 21 mg/ dL (p <0.05, compared to placebo) **Weight:** -NAFLD: The volunteers in the Xanthigen group lost 5.5 ± 1.4 Kg more than in the placebo group (p <0.05) -NLF: The participants in the Xanthigen group lost 4.9 ± 1.2 Kg more than in the placebo-NLF group (p <0.05) There was no statistically significant difference in body weight loss between Xanthigen-NAFLS and Xantighen-NLF groups. **Waist:** -NAFLD: In the Xanthigen group, waist decreased from 110.6 ± 1.6 to 105.0 ± 5.6 cm (p <0.05). In the placebo group waist was maintained. **SBP and DBP:** -NAFLD: In the Xanthigen group, SBP decreased from 138 ± 6 to 119 ± 6 mmHg, and DBP decreased from 91 ± 4 to 79 ± 3 mmHg. Changes in both systolic and diastolic blood pressure were statistically significant compared to the placebo group (p <0,05). -NLF: In the Xanthigen group, SBP decreased from 128 ± 6 to 112 ± 6 mmHg and DBP decreased from 93 ± 2 to 77 ± 3 mmHg. Changes in both systolic and diastolic blood pressure were statistically significant compared to the placebo group (p <0,05).
11	Double-blind, placebo-controlled, randomized cross-over trial.	N=38 **Inclusion criteria:** Volunteers, aged 18 to 65 years, with a BMI from 18.5 to 28 Kg/m₂, a FPG<5.5 mmol / L and blood pressure within the normal range (SBP≤140 mmHg, DBP≤90 mmHg). **Exclusion criteria:** If they were taking other natural health products known to impact on polyphenols, were breastfeeding or pregnant; had liver, thyroid or gastrointestinal issue; had hypertension, had undergone recent major surgery, consumed >4 drinks per day or 9 per week; cigarette smoker, or had implanted cardiac defibrillator. If they were unable to consume any of the study food due to dietary requirements. For all menstruating female participants, testing sessions were avoided in the seven-day period prior to beginning the menstruation.	Characteristic of the subjects (n= 38) Male/Female 9/29 Age: Median (Interquartile range) 23 (11) years Low dose (500 mg) and high dose (2000 mg) of the brown seaweed (Fucus vesiculosus) extract.	Cellulose placebo (2000 mg)	Single dose	FPG	**FPG** Placebo: 79,27 (5,4) mg/dL Low dose (500 mg): 81.07 (7,21) mg/dL High dose (2000 mg): 79,27 (7,21) mg/dL p=0.157 No significant differences between placebo group and low/high dose seaweed supplement
12	Randomized double-blind, placebo-controlled with parallel-group design	N=33 **Inclusion criteria:** Participants registered with the monitor bank of TES Holdings Co., Ltd. Aged 20 to 59 years with BMI>25 and <30Kg/m₂, with abdominal circumference being at least 85 cm for men and 90 cm for women. **Exclusion criteria:** Current medication for chronic symptoms or taking medication that may influence test results; previous allergic reaction to food or medicine; Current or previous cardiovascular disease, nephritis, hepatitis and other disorders. Participants with AST, ALT o γ-GTP more than 2.5 times the upper limit of normal, or serum uric acid more than 9.0 mg / dL, severe anemia, or breastfeeding women. Regular alcohol intake of 60 gr or more almost every day. Subjects participating in another clinical trial, or determined to be unsuitable for this study by the attending pshysician.	-(n= 11) Fucoxanthin 1 mg/d group. Age: 45.4±6.7 years -(n=11) Fucoxanthin 3 mg/d Age: 40.2±9.6 years	-(n=11) Fucoxanthin 0 mg/d (Placebo) Age: 42.6±6.4 years	4 weeks	CT HDLc LDLc TGL Glucose BMI Waist Weight SBP DBP	**LDLc:** Significant decrease in the 3 mg/d fucoxanthin group compared to placebo. No signifant differences in **CT, HDLc** and **TGL** was observed **Glucose:** No significant difference was observed. **BMI:** Significant decrease -0,5(-1,7) Kg/m₂ in the 3 mg/d fucoxanthin group compared to placebo group and the values before ingestion. **Weight:** Significant decrease -1.3 (-1,7) kg in the 3 mg/d fucoxanthin group compared to placebo and the values before ingestion. **Waist:** Decreased significantly after ingestion in both placebo and 3mg/d fucoxanthin group compared to the values before ingestion. In the 1 mg / d fucoxanthin group, waist increased significantly compared with befote ingestión. **SBP** and **DBP:** Significant decrease in the 3 mg/d fucoxanthin group compared to placebo.

CONCLUSION

There are indications of the potential benefits of marine algae in the components of the metabolic syndrome; however, the absence of coherent and reproducible data from human studies is evident in most cases. Large-scale well- designed randomized controlled trials are needed in order to support the reported results.