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REVIEW ARTICLE

The Health-Promoting Properties of Seaweeds: Clinical Evidence based on *Wakame* and *Kombu*

Eric Wei Chiang Chan[1*], Mio Kezuka[2], Hung Tuck Chan[2] and Siu Kuin Wong[3]

[1]Faculty of Applied Sciences, UCSI University, 56000 Cheras, Kuala Lumpur, Malaysia; chanwc@ucsiuniversity.edu.my

[2]Secretariat of International Society for Mangrove Ecosystems (ISME), Faculty of Agriculture, University of the Ryukyus, Okinawa 903-0129, Japan

[3]School of Foundation Studies, Xiamen University Malaysia, 43900 Sepang, Selangor, Malaysia

Abstract

In this review, the botany, uses, bioactive metabolites, and health-promoting benefits of *Undaria pinnatifida* (*wakame*) and *Saccharina japonica* (*kombu*) are highlighted. Their clinical evidence is focused on clinical studies conducted in Japan and in other countries. These two species are brown seaweeds (Phaeophyta). In Japan, *wakame* and *kombu* seaweeds are popular food items consumed almost daily. Laboratory evidence shows that carotenoids (fucoxanthin and fucoxanthinol), polysaccharides (fucoidan) and sterols (fucosterol) are bioactive metabolites in *wakame* and *kombu*. *Wakame* displays antioxidant, anti-inflammatory, anticancer, antihypertensive, antidiabetic, antiviral, anticoagulant, antiosteoporotic, hepatoprotective, and antiobesity properties. *Kombu* possesses anticoagulant, antithrombotic, anticancer, hypolipidemic, hypoglycemic, antiobesity, antithrombotic, antiatherosclerosis, renal protective, vascular protective, antioxidant, antimicrobial, anti-inflammatory, immunomodulatory, gut biota regulatory, hypoglycemic, hypolipidemic, and neuroprotective activities. Clinical evidence on the effects of *wakame* intake was based on eight studies in Japan and eight studies in other countries. Clinical evidence on the effects of *kombu* intake was based on five studies in Japan. One case study on *kombu* dealt with severe alopecia areata. Some areas for future research on *wakame* and *kombu* are suggested. Information and data used in this review were from databases such as Google, Google Scholar, PubMed, PubMed Central, Science Direct, J-Stage, PubChem, China Academic Journals, and ClinicalTrials.gov.

Keywords: Brown Algae, Clinical Trials, *Saccharina japonica*, *Undaria pinnatifida*

1. Introduction

Seaweeds are macroalgae that can be classified into brown algae (Phaeophyceae), red algae (Rhodophyceae) and green algae (Chlorophyceae)[1]. Being diverse and wide-ranging in biochemical composition, seaweeds are a valuable source of bioactive compounds with commercial potential in the food, nutraceutical, pharmaceutical, and cosmeceutical industries. In countries of East Asia, especially Japan and Korea, brown algae are a staple food item, and they include *Undaria pinnatifida* (*wakame*), *Saccharina japonica* (*kombu*), and *Sargassum fusiforme* (*hijiki*)[2].

Seaweeds are a main food item of the Japanese cuisine, and their intake contributes to health-promoting benefits such as life-longevity and prevention of lifestyle-related diseases[3]. Seaweeds are served in 20% of Japanese meals with each person consuming 1.3–1.5 kg/year[4], or 5.3 g/day[5], at a frequency of 3–5 times/week[6]. Consumption of seaweeds has been associated with lower incidence of chronic diseases such as obesity, diabetes, cardiovascular,

*Author for correspondence

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and inflammatory disorders[5,7]. The Japanese people have the lowest rate of cardiovascular diseases[8].

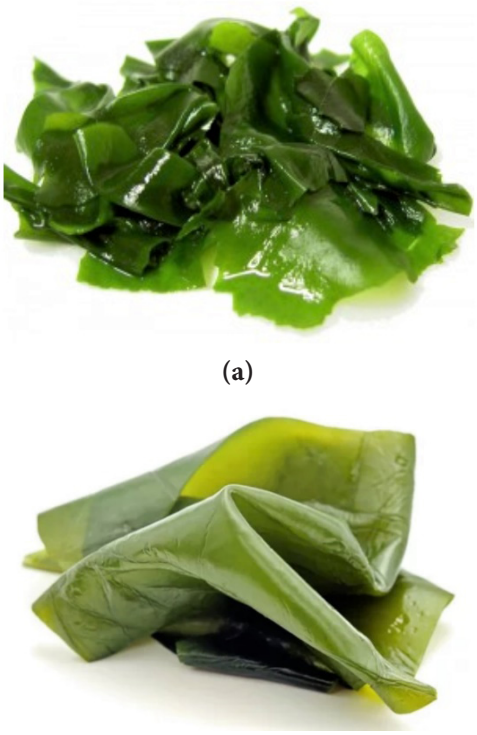
While the consumption of seaweeds has health-promoting benefits, one should also take cognition that seaweeds contain arsenic metabolites that can have harmful effects when consumed in large quantities[3]. *Wakame* (soaked in 10 min) and *kombu* (soaked in 1 min) have an arsenic content of 34.7 and 51.2 µg/g, respectively[9]. The detection of arsenic metabolites in humans after ingesting *wakame* has been reported[10].

2. Botany and Uses

Undaria pinnatifida or sea mustard (family Laminariaceae) is a brown seaweed (Phaeophyta) consisting of the frond, midrib, sporophyll and haptera as plant parts[11]. The thallus is attached to a fibrous holdfast, and the plant is 60–120 cm long, reaching 2–3 m in length at maturity[12]. In Japan, *U. pinnatifida* is cultivated in Sanriku and Naruto[13]. The species is also cultivated in China and Korea and has been introduced into France, Australia, and New Zealand. Edible parts of *U. pinnatifida* are the edible frond (*wakame*) and sporophyll (*mekabu*).

Saccharina japonica or sweet kelp (family Laminariaceae) is another brown seaweed. Previously named as *Laminaria japonica*, the species is now named as *S. japonica*[14]. The phenotypically diverse, *kombu* inhabits the coastal waters of the northwest Pacific region[15]. The typical form is 2.0–3.5 m in length, inhabiting the littoral zone at depths of 5–11 m, and widely distributed. In East Asia, *S. japonica* is cultivated in northern Hokkaido, Japan[16]. The species is also cultivated along the east and south coast of Korea, and in the coastal waters of Shandong and Liaodong in China[17]. North of East Asia, *S. japonica* is cultivated in southern Sakhalin and Primorye of Russia[16].

In Japan, *wakame* and *kombu* (Figure 1) are popular cuisines used in miso soup, salad, or consumed as a side dish. Dried *wakame* needs to be softened by boiling in water and then pickled in vinegar or dressed in soy sauce before consumption. *Wakame* is green in colour when cooked, and has a subtle sweet flavour and satiny texture[18]. *Wakame* has also been used as food products such as additives, colorants, animal feeds, nutraceuticals, and functional food[12]. In Japan, *kombu* is used as seasoning, condiment, and tea. Besides its wide applications as a traditional and functional food and medicine, *kombu* has been developed into natural food preservatives and whitening agents[17].



(a)

(b)

Figure 1. Processed *wakame* (a) and *kombu* (b) seaweeds are popular food items in Japan.

3. Bioactive Metabolites

Bioactive metabolites of *wakame* and *kombu* include carotenoids (fucoxanthin and fucoxanthinol), polysaccharides (fucoidan), and sterols (fucosterol) (Figure 2). Fucoxanthin is a xanthophyll carotenoid with a molecular formula of $C_{42}H_{58}O_6$ and a molecular weight of 659 g/mol[19]. This red- or orange-coloured pigment accounts for more than 10% of the total carotenoids in marine algae. Fucoxanthinol $C_{40}H_{56}O_5$ is a derivative of fucoxanthin[20,21]. Lacking the acetyl group, fucoxanthinol is considered the active form of fucoxanthin. Fucoidan is a polysaccharide containing monosaccharides that are linked by glycosidic bonds and saccharide bonds with sulphate substitutions[22,23]. Fucosterol has sterol moieties with an allyl methyl[24]. The molecular formula of fucosterol is $C_{29}H_{48}O$ and its molecular weight is 413 g/mol.

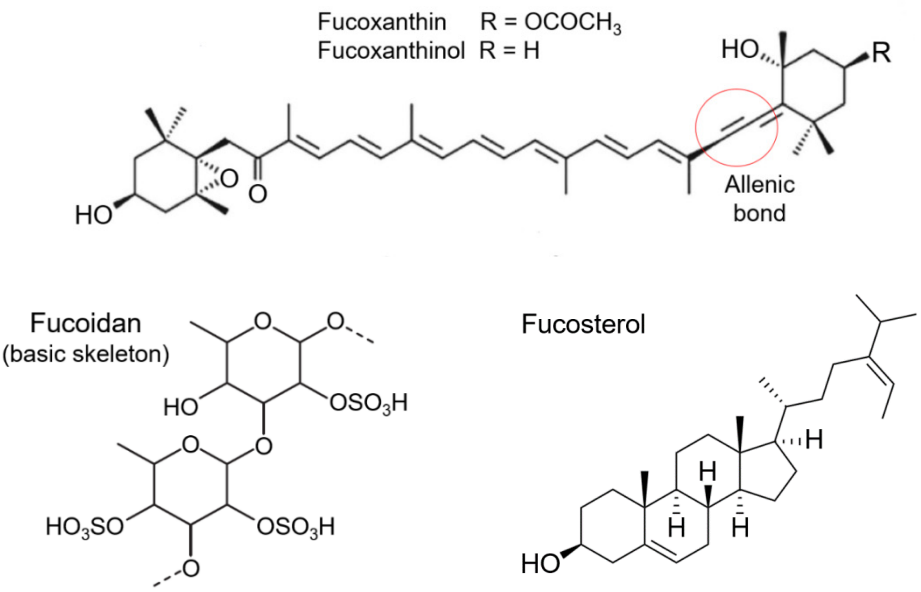


Figure 2. Chemical structures of fucoxanthin, fucoxanthinol, fucoidan, and fucosterol.

4. Health-Promoting Properties

Extracts and bioactive metabolites of *wakame* and *kombu* have been reported to possess a wide spectrum of health-promoting properties. *Wakame* possesses bioactivities such as antioxidant, anti-inflammatory, anticancer, antidiabetic, antihypertensive, antiviral, and antiobesity properties[25,26]. *Kombu* possesses pharmacological properties such as antioxidant, antimicrobial, anticoagulant, anticancer, antithrombotic, hypolipidemic, hypoglycemic, antiobesity, antithrombotic, antiatherosclerosis, vascular protective, neuroprotective, renal protective, anti-inflammatory, hypoglycemic, hypolipidemic, and gut biota regulatory activities[17,27].

Among the bioactive metabolites, fucoxanthin possesses antioxidant, anti-inflammatory, anticancer, antiobesity, antidiabetic, antiangiogenic, and antimalarial properties[19,20,28]. The carotenoid has protective effects on the human liver, brain, heart, bone, skin, and eye. Fucoxanthinol, a derivative fucoxanthin, has been reported to have antioxidant, anticancer, anti-inflammatory, antidiabetic, antiangiogenic, lipid-lowering, and antiobesity activities[19,20,29]. Fucoidan possesses anticancer, antioxidant, antimicrobial, anti-inflammatory, immunomodulatory, anticoagulant, neuroprotective, cardioprotective, and growth-promoting properties[18,30]. Fucosterol also possesses antioxidant, anticancer, antidiabetic, hypotensive, antiobesity, hypolipidemic, and hepatoprotective activities[31].

5. Clinical Studies

5.1 *Wakame*

5.1.1 In Japan

In Japan, eight clinical studies were undertaken to investigate the effects of *wakame* intake on antibody response[32], blood pressure[33,34], diabetes[35,36], intestinal environment[37], and post-prandial glycemia[38,39] of subjects.

A clinical trial was conducted to investigate antibody production after influenza vaccination in elderly Japanese men and women, with and without the intake of *mekabu* fucoidan, a bioactive metabolite from *wakame*[32]. The trial (Registration: UMIN000006394) was conducted from October 2009 to May 2010 at a nursing (old folks') home in Osaka, Japan, with 70 volunteers more than 60 years of age. They were assigned to group 1 (given 300 mg/day of fucoidan) and group 2 (placebo) for four weeks and then injected with a seasonal influenza vaccine. Serum was sampled at week 5 and week 20 to determine

hemagglutination inhibition and killer cell activity. The fucoidan group had higher antibodies against all three strains of influenza virus in the vaccine than the placebo group. In the fucoidan group, killer cell activity increased from week 9 after fucoidan intake. In the placebo group, no such activities were observed. The study concluded that fucoidan intake increased antibody production in the elderly after vaccination, thus preventing influenza[32].

A clinical trial was conducted at the outpatient clinic of Kyroin University Hospital in Tokyo, Japan, to test the effects of the intake of *wakame* capsules on Blood Pressure (BP) and other metabolic disorders in hypertensive patients[33]. The study of eight-week duration involved 36 elderly patients with hypertension. They were divided into the *wakame* group (6 males, 12 females and a mean age of 72 years) and the control group (6 males, 12 females and mean age of 71 years). The patients of the treatment group were given capsules, each containing 0.4 g of *wakame* powder. Given three doses with meals, 6, 2, 6, and 3 patients took 12, 8, 6, and 3 capsules per day. At each hospital visit (once in four weeks), the BP and clinical chemistry of each patient were examined. Results showed that both systolic and diastolic BP of the *wakame* group decreased significantly with stronger effects observed after four weeks than after eight weeks. The study concluded that ingestion of *wakame* capsules has beneficial effects in the treatment of hypertension with or without high cholesterol[33]. Side effects were minimal.

In October and November, 2006, a study was conducted to investigate whether *wakame* intake was inversely associated with BP levels of preschool children. Preschool children, aged 3–6 years, from two preschools in Aichi Prefecture, Japan, participated in the study[34]. Information on BP, pulse, and intake of *wakame* was recorded from 223 boys and 194 girls for two consecutive weekdays and one weekend day. Data on their heights and weights were provided by their parents. Results showed that *wakame* intake was negatively related to diastolic BP in the boys and to systolic BP in the girls[34]. This suggests that *wakame* has beneficial effects on BP among children.

A study on the antidiabetic effects of *wakame* and *mekabu* was conducted at the University of Tokushima Graduate School in Tokushima, Japan, involving 12 healthy subjects (eight men, four women, and ~25 years mean age)[35]. For three days, separated by weekly intervals, the subjects were given different breakfast meals. The effects of intake of 70 g *wakame* with 200 g of white rice; 70 g of *mekabu* with 200 g of white rice; 50 g of boiled soybeans; 60 g of potatoes; and 40 g of broccoli on post-prandial glucose, insulin, and free fatty acid levels in healthy subjects were analyzed. The plasma glucose levels of subjects given the *mekabu* meal were significantly lower than those given the control meal, but not in values of insulin and free fatty acid[35]. The consumption of *mekabu* with white rice reduced post-prandial glucose concentration. Lower plasma glucose levels and other parameters were not observed in the *wakame* group.

The effects of *wakame* on post-prandial blood glucose and insulin levels were investigated among 26 subjects recruited by TES Holdings Co., Ltd. in Tokyo, Japan[36]. The trial (Registration: UMIN000031050) was conducted for two days (a week apart) on 31 January, 2018 and 7 February, 2018. Blood samples were taken to determine glucose and insulin levels after subjects have consumed 200 g of rice or 200 g of rice with 4 g of *wakame*. The study revealed that the levels of blood glucose and insulin were significantly lower in subjects after consuming rice with *wakame* than after consuming rice alone[36]. *Wakame* intake, therefore, improved post-prandial glucose homeostasis.

A clinical study was conducted to test the feasibility of using *wakame* as a probiotic based on the frequency of defecation and the type of intestinal microbiota[37]. A total of 22 healthy subjects (20–49 years of age) with low defecation frequency were recruited by Souken Co., Ltd., and the study was conducted at Shiba Palace Clinic in Tokyo, Japan. Each subject was given 4 g of dried *wakame* per day for two weeks. Results showed that defecation frequency (times, days and volume per week) significantly increased following *wakame* intake[37]. The population of gastro-intestinal *Bifidobacterium longum* increased significantly, suggesting that *wakame* had prebiotic properties.

The study (Registration: UMIN000047854) was aimed at determining the effects of *wakame* on post-prandial glycaemia in humans[38]. Conducted at Fuji Women's University in Hokkaido, Japan, 12 young-healthy adults were given 150 g of rice with or without *wakame* soup (2 g or 4 g of dried *wakame*). After 5 min of ingestion, the blood glucose levels of participants were significantly lower after consuming rice with 2 g of *wakame* soup than participants who consumed only rice. Another 16 participants ingested 150 g of rice with or without 4 g of *wakame* salad. All participants who consumed *wakame* soup or salad had significantly lower blood glucose levels after meals[38]. The study concluded that *wakame*

soup or salad may be used as a functional food item with hypoglycemic properties.

The effects of the intake of *mekabu* on levels of post-prandial blood glucose and related hormones in young-healthy women were investigated at Wayo Women's University in Chiba, Japan[39]. The subjects comprised 10-young-healthy adult women (20–23 years of age). Blood samples taken at 0, 15, 30, 90, and 120 min after consuming *mekabu* followed by rice, were measured for blood glucose level and related hormones. Results indicated that consuming *mekabu* before rice resulted in a significant reduction of glucose and insulin at 30 min after ingestion[39]. The level of Glucagon-Like Peptide-1 (GLP-1) in the plasma was higher 30, 60, and 120 min after *mekabu* consumption. Ingestion of *mekabu* suppressed post-prandial blood glucose levels and supported secretion of GLP-1.

5.1.2 In Other Countries

Eight clinical studies were undertaken in other countries to determine the effects of *wakame* intake on herpes[40], metabolic syndrome[41], obesity[42], Human Immunodeficiency Virus (HIV)[43], breast cancer[44], cholesterol[45,46], menopausal syndrome[47], and post-prandial glucose metabolism[48].

A clinical trial on herpetic infection was conducted at Marine Biomedical Research in Tasmania, Australia[40]. Patients (ranging from 10 to 72 years of age) with active (15 subjects were given four *wakame* capsules per day for four days) or latent (six subjects were given two *wakame* capsules per day for four days) herpetic infections participated in the study. The capsules contained 560 mg of *wakame* each. The subjects were tested for human T cell mitogenicity and antiherpes activity. Results showed that the intake of *wakame* capsules inhibited the growth of herpes viruses and was mitogenic towards human T cells[40].

A clinical study that assessed the effects of *wakame* on metabolic syndrome was carried out at the University of San Francisco de Quito in Quito, Ecuador[41]. The participants were 13 men (average age of 47.4 years) and 14 women (average age of 45.6 years) with at least one symptom of metabolic syndrome. They were assigned to group 1 (placebo, followed by 4 g/day of *wakame*) or group 2 (4 g/day of *wakame* followed by 6 g/day of *wakame*) over a period of one month. BP, body weight, waist girth, inflammation biomarkers and lipids were monitored monthly. After one month, a 2.4 cm decrease in waist girth was observed among the women in group 1[41]. Similarly, women in group 2 showed a decrease of 2.1 cm and 1.8 cm in the waist. In group 2, systolic BP decreased by 10.5 mm Hg in both men and women.

A clinical trial (Registration: NCT03420989) analyzed the effects of two different snacks enriched with *wakame* on obese subjects with metabolic syndrome in the Endocrinology and Clinical Nutrition Research Centre at Universidad de Valladolid in Spain[42]. Patients were assigned to Group 1 (given snacks enriched with *wakame*, n = 16) or Group 2 (given control snacks, n = 16). Each patient received two packets of 25 g/day of either snack over a period of two months. After two months, results revealed that the *wakame*-enriched snack induced a significant decrease in total cholesterol, Low-Density Lipoprotein (LDL)-cholesterol and resistin levels, compared to the control snack[42].

Another clinical trial (Registration: NCT01195077) was conducted at the Palmetto Health Hospital and University of South Carolina in Columbia, USA, to study the effects of consumption of algae on HIV/acquired immunodeficiency syndrome (AIDS)[43]. African Americans (three females and two males) with HIV 1 participated in Phase I study. Subjects were given 5 g/day of *wakame*, spirulina or a combination of both. They were analyzed for HIV viral load, blood count, metabolic and lipid traits, and questionnaire data. No short-term toxicities were detected in Phase I. Subsequently, another five African Americans and one Latina (four females and three males) were recruited for Phase II study to evaluate short- and long-term toxicities[43]. No toxic effects were observed for the 11 subjects, and their quality-of-life indicators improved after three weeks. There were no significant changes in blood count and metabolic and lipid traits. CD4 cells and HIV-1 viral load were stable in the first three months of phase II. One subject continued for 13 months of the study showed significant improvement in CD4 cells and a decrease in HIV viral load. This pilot study showed that *wakame* combined with spirulina is safe to use in a Phase III study to test for their efficacy against HIV/AIDS.

At Royal Hobart Hospital and the University of Tasmania in Tasmania, Australia, a study was undertaken to assess the effect of fucoidan from *wakame* on the pharmacokinetics of letrozole and tamoxifen in patients with breast cancer[44]. In this study, patients on letrozole or tamoxifen (n = 10 per group) took fucoidan extract at 500 mg twice daily for three weeks. Results showed that

the consumption of fucoidan by breast cancer patients had no effect on the plasma concentration of letrozole or tamoxifen, and there were no adverse effects that could be attributed to *wakame* as a dietary supplement[44].

At Maastricht University Medical Centre in the Netherlands, a clinical study (Registration: NCT03380611) was carried out to determine the effects of *wakame* consumption on cholesterol absorption and serum lipid concentration in non-hypercholesterol (non-HC) men and women[45,46]. A total of 35 healthy non-HC men and women consumed 4.8 g of *wakame* or placebo for 17 days. Results showed no difference in total cholesterol, LDL, High-Density Lipoprotein (HDL), and triacylglycerol. The study concluded that consumption of wakame did not affect serum lipid, plasma glucose concentration, and BP in non-HC men and women[45,46].

At Chonnam National University and Korea University College of Medicine in Korea, a clinical study (Registration: KCT0004025) investigated whether menopausal symptoms were alleviated *via* a marine healing program with additional *wakame* intake[47]. A total of 42 menopausal women participated, with $n = 22$, in a marine group and $n = 20$ in a city group. Consisting of 11 women who took 15.4 g of *wakame* per day while another 11 women served as control, the marine group participated in a healing program consisting of balanced diet, exercises, and mind-body practices using coastal resources for five days. Participants of the city group received no interventions[47]. No effect of *wakame* was detected in the marine group although the marine healing program was maintained for two weeks. However, this study did not project the beneficial effects of *wakame* towards alleviation of menopausal symptoms.

A study (Registration: NCT02608372) was conducted at the University of Copenhagen and Technical University of Denmark to investigate the effects of *wakame* on post-prandial glucose metabolism and appetite[48]. A total of 20 healthy subjects received a meal comprising 30 g of starch with 5 g of *wakame* or a control meal of pea protein. Analysis showed lower blood glucose level, insulin and C-peptide response, followed by decreased appetite sensation after *wakame* intake. Results showed that the ingestion of *wakame* improved post-prandial glycemic and appetite control in adults, depending on the dosage used[48].

The clinical trials and findings on the health-promoting properties of *wakame* and *mekabu* are summarized in Table 1.

Table 1. Summary of clinical trials and findings of *wakame* and *mekabu*

Sr. No.	Location	Objective and finding of clinical trial	Ref.
1	Osaka, Japan	Objective: To investigate antibody production after influenza vaccination in elderly Japanese men and women, with and without intake of *mekabu* fucoidan. Findings: Fucoidan intake increased antibody production in elderly men and women after vaccination, thus preventing influenza.	32
2	Tokyo, Japan	Objective: To test the effects of intake of *wakame* capsules on blood pressure and other metabolic disorders in hypertensive patients. Findings: Ingestion of *wakame* capsules has beneficial effects in treating patients with hypertension with or without high cholesterol.	33
3	Aichi Prefecture, Japan	Objective: To investigate whether *wakame* intake was inversely associated with BP levels of preschool children. Findings: Results showed that *wakame* intake was negatively related to diastolic BP in the boys and to systolic BP in the girls. This suggests that *wakame* has beneficial effects on BP among children.	34
4	Tokushima, Japan	Objective: To study the antidiabetic effects of *wakame* and *mekabu*. Findings: Subjects given *mekabu* had significantly lower PG levels but not in insulin and free fatty acids. The consumption of *mekabu* with white rice reduced PP glucose concentration. Lower PG levels and other parameters were not observed in the *wakame* group.	35
5	Tokyo, Japan	Objective: To assess the effects of *wakame* on the PP blood glucose and insulin levels of subjects. Findings: The levels of blood glucose and insulin were significantly lower in subjects after consuming rice with *wakame*. Intake of *wakame,* therefore, improved PP glucose homeostasis.	36

Table 1 to be continued...

Sr. No.	Location	Objective and finding of clinical trial	Ref.
6	Tokyo, Japan	Objective: To test the feasibility of using *wakame* as a probiotic based on the frequency of defecation and the type of intestinal microbiota. Findings: Results showed that defecation frequency significantly increased following *wakame* intake. Gastro-intestinal *Bifidobacterium longum* bacterial population increased significantly, suggesting that *wakame* had prebiotic properties.	37
7	Hokkaido, Japan	Objective: To determine the effects of *wakame* on PP glycaemia in young healthy adults. Findings: All participants who consumed *wakame* soup or salad had significantly lower blood glucose levels. *Wakame* soup or salad may be used as a functional food item with hypoglycemic properties.	38
8	Chiba, Japan	Objective: To study the effects of *mekabu* intake on levels of the PP blood glucose and related hormones in young healthy women. Findings: The consumption of *mekabu* before rice resulted in significant reduction of glucose and insulin. The level of plasma GLP-1 was higher and PP blood glucose level was suppressed.	39
9	Tasmania, Australia	Objective: To assess the antiherpes activity of wakame on subjects with latent or active herpetic infections. Findings: Intake of *wakame* capsules inhibited the growth of herpes viruses and was mitogenic towards human T cells.	40
10	Quito, Ecuador	Objective: To assess the effects of *wakame* on metabolic syndrome of subjects. Findings: After one month, a 2.4 cm decrease in waist girth was observed among the women in group 1. Similarly, women in group 2 showed a decrease of 2.1 cm and 1.8 cm in the waist. In group 2, systolic BP decreased by 10.5 mm Hg in both men and women.	41
11	Valladolid, Spain	Objective: To analyze the effects of snacks enriched with *wakame* on obese subjects with metabolic syndrome. Findings: After two months, the *wakame*-enriched snack induced a significant decrease in total cholesterol, LDL-cholesterol and resistin levels, compared to the control snack.	42
12	Columbia, USA	Objective: To study the effects of the consumption of algae on African Americans with HIV/AIDS. Findings: No toxic effects were observed. There were no significant changes in blood and in metabolic and lipid traits. *Wakame*, combined with spirulina are safe to use in a Phase III study to test for their efficacy against HIV/AIDS.	43
13	Tasmania, Australia	Objective: To assess the effect of fucoidan from *wakame* on the pharmacokinetics of letrozole and tamoxifen in patients with breast cancer. Findings: The consumption of fucoidan by breast cancer patients had no effect on the plasma concentration of letrozole or tamoxifen, and there were no adverse effects that could be attributed to *wakame* as a dietary supplement.	44
14	Maastricht, Netherlands	Objective: To determine the effects of *wakame* consumption on cholesterol absorption and serum lipid concentration in non-HC subjects. Findings: There was no difference in total cholesterol, LDL, HDL, and triacylglycerol. The study concluded that consumption of wakame did not affect serum lipid, plasma glucose concentration, and BP in non-HC men and women.	45,46
15	Chonnam, Korea	Objective: To investigate whether MS was alleviated *via* a marine healing program with additional *wakame* intake. Findings: No effect of *wakame* was detected in the marine group. This study did not project the beneficial effects of *wakame* towards the alleviation of MS.	47
16	Copenhagen, Denmark	Objective: To investigate the effects of *wakame* on post-prandial glucose metabolism and appetite. Findings: The ingestion of *wakame* improved PP glycemic and appetite control in adults, depending on the dosage used.	48

Abbreviations: AIDS = acquired immunodeficiency syndrome, BP = blood pressure, GLP-1 = glucagon-like peptide-1, HC = hypercholesterol, HDL = high-density lipoprotein, HIV = human immunodeficiency virus, LDL = low-density lipoprotein, MS = menopausal symptoms, PG = plasma glucose, and PP = post-prandial.

5.2 *Kombu*

Five clinical studies and one case study were carried out in Japan to assess the effects of *kombu* intake. The clinical studies were on post-prandial glucose metabolism[48], thyroid function[49], health effects[50], abnormally high serum triglyceride levels[51,52], and overweight body fat[53]. The case study involved a 36-year-old woman with severe alopecia areata[54].

The study (Registration: NCT02608372) located at the University of Copenhagen, Denmark, investigated the effects of *wakame* on post-prandial glucose metabolism and appetite had also included *kombu*[48]. A total of 20 healthy subjects received a meal containing 30 g of starch with 5 g of *kombu* or a meal of pea protein as a control. Similar results were obtained as with *wakame*. Analysis showed lower insulin and C-peptide response, blood glucose level, and appetite sensation in subjects following intake of *kombu*. Results also showed that the ingestion of *kombu* improved post-prandial glycemic and appetite control in adults, depending on the dosage used[48].

The effect of *kombu* ingestion on thyroid function in normal Japanese adults was studied at the College of Nutrition, Koshien University, Hyogo in Japan[49]. A total of 13 adults (average age of 27 years) ingested 15 g and 30 g of *kombu* (iodine content of 35 mg and 70 mg, respectively) daily for 7–10 days. Results showed a significant increase in thyrotropin levels in the serum. Thyroxine and 3,5,3'-triiodothyronine levels were slightly decreased. For daily ingestion of 15 g of *kombu* for 55–87 days, serum thyrotropin levels were elevated and sustained, while thyroxine and 3,5,3'-triiodothyronine levels remained unchanged. Urinary iodine significantly increased but returned to initial levels 7–40 days after *kombu* ingestion was discontinued. These findings showed that ingestion of *kombu* suppressed thyroid function, though the effect was reversible[49]. The study recommended that Japanese people should avoid ingesting *kombu* in excessive amounts.

This clinical study (Registration: UMIN000030418) carried out at Hokkaido Information University in Japan, assessed the effects of *kombu* intake on adiponectin levels and body fat[50]. The study recruited 70 healthy Japanese subjects with a body mass index of 22–30 kg/m^2 and LDL cholesterol levels of 120–160 mg/dL. Subjects were assigned to either the *kombu* group (given nine *kombu* capsules per day for six weeks) or the placebo group. Interviews, examinations and blood sampling were conducted at weeks 0, 2, and 6. Body composition was analyzed at weeks 0 and 6. Results showed that *kombu* intake significantly reduced body fat and improved adiponectin levels but did not improve the lipid profile. The study concluded that *kombu* intake had beneficial effects including reduction in body fat and improvement in adiponectin levels[50]. *Kombu* was deemed safe to ingest at the dosage used in this study.

At the Kobe University Graduate School of Medicine in Japan, a pilot study investigated the effects of *kombu* on lifestyle-related diseases[51]. In the study, 48 subjects ingested 6 g of roasted *kombu* a day for 4 weeks. Results suggested that the frequent intake of *kombu* may relieve constipation, diarrhoea and hard stools. Blood tests also indicated a decrease in serum triglyceride levels. A follow-up study found that lipid alterations might be related to the health benefits of *kombu* and that the quality as well as the quantity of lipids are important indicators[52].

At the Department of Food Science, Otsuma Women's University in Tokyo, Japan, a study investigated the effect of iodine-reduced *kombu* powder intake on body fat composition in overweight Japanese subjects[53]. The study (Registration: IRB15000088) recruited 48 Japanese subjects having body mass index of 25–30 kg/m^2. One group (12 males and 12 females) consumed 10 capsules of *kombu* powder, three times/day while another group (13 females and 11 males) ingested *kombu*-free powder (placebo) for eight weeks. Body fat, body weight, and body mass index were significantly decreased in male subjects. No significant changes were observed in female subjects. The study concluded that the intake of iodine-reduced *kombu* powder resulted in a safe and significant reduction in body fat in overweight male subjects[53].

A woman (36 years of age) in Osaka, Japan, suffered from severe alopecia areata (extensive hair loss) and was treated by intravenous corticosteroid pulse therapy[54]. During her follow-up visit to the Graduate School of Medicine at Osaka University, the doctors detected that she had thyroid swelling. She had been taking *kombu* supplements by herself for a year, on the belief that *kombu* can stimulate or maintain hair growth. It was diagnosed that thyroid inflammation by iodine from the seaweed supplement was the likely cause and the doctors advised her to stop its intake. Two months later, her blood tests showed normalized results in thyroid hormone synthesis[54].

The clinical trials and findings on the health-promoting properties of *kombu* are summarized in Table 2.

Table 2. Summary of clinical trials and findings of *kombu*

Sr. No.	Location	Objective and finding of clinical trial	Ref.
1	Copenhagen, Denmark	Objective: The study investigated the effects of *kombu* on post-prandial glucose metabolism and appetite. Findings: Results showed that the ingestion of *kombu* improved post-prandial glycemic and appetite control in adults.	48
2	Hyogo, Japan	Objective: To assess the effect of *kombu* ingestion on thyroid function in normal Japanese adults. Findings: Results showed a significant increase in serum thyrotropin and urinary iodine. Although the effect of thyroid function suppression was reversible, the study recommended that Japanese people should avoid ingesting *kombu* in excessive amounts.	49
3	Hokkaido, Japan	Objective: To assess the effects of *kombu* intake on adiponectin levels and body fat. Findings: *Kombu* intake significantly reduced body fat and improved adiponectin levels but did not improve the lipid profile.	50
4	Kobe, Japan	Objective: To investigate the effects of *kombu* on lifestyle-related diseases. Findings: Results suggested that the frequent intake of *kombu* may relieve constipation, diarrhea, and hard stools, and decrease serum triglyceride levels. A follow-up study found that lipid alterations might be related to the health benefits of *kombu*.	51,52
5	Tokyo, Japan	Objective: To investigate the effect of iodine-reduced *kombu* powder intake on body fat composition in overweight Japanese subjects. Findings: Body fat, body weight, and body mass index were significantly decreased in male subjects. No significant changes were observed in female subjects.	53
6	Osaka, Japan	Case study: A 36-year-old woman suffered from severe alopecia areata or extensive hair loss. Doctors detected that she had thyroid swelling due to thyroid inflammation by iodine from *kombu* supplement she was taking. They advised her to stop its intake. Two months later, her blood tests showed normalized results in thyroid hormone synthesis.	54

6. Conclusion

Wakame and *kombu* seaweeds are popular food items in Japan. There is ample evidence that their extracts and bioactive metabolites possess a wide range of promising health-promoting benefits. Out of 16 clinical trials on *wakame* intake presented in this review, eight were conducted in Japan and eight outside Japan. Two studies outside Japan did not project the beneficial effects of *wakame* intake. Out of five clinical trials and one case study on *kombu* intake, one clinical trial and the case study revealed the negative effects of excessive consumption of *kombu*. More clinical trials are needed for bioactive metabolites such as fucoxanthin, fucoxanthinol, fucoidan, and fucosterol. Detailed studies are needed on the bioavailability, metabolism, pharmacokinetics, and toxicity of *wakame* and *kombu*, before they can be developed into useful nutraceutical and pharmaceutical products. Albeit the consumption of seaweeds has many health-promoting benefits, one should also take cognition that seaweeds contain arsenic metabolites that can have harmful effects when consumed in large quantities.

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