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Review: Evidence-based Clinical Research of Anti-obesity Supplements in Japan

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Abstract: *Background:* The prevalence of obesity has increased dramatically throughout the world, and weight reduction through lifestyle management is urgently warranted. At present, numerous supplements advertised for their anti-overweight property are available in the Japanese market, but most of these lack proper evidence. Thus, we investigated dietary supplements that have been tested in clinical trials.

Search Strategy: We researched anti-obesity supplements in the Japanese market using the google search engine in Japanese with the key terms "anti-obesity supplements," "diet supplements," and "weight reduction supplements."

Results: We listed 49 companies that supply anti-obesity supplements. Of these, 11 had published clinical evidence of the anti-obesity efficacy of their supplements. These products contain the following active ingredients: *Angelica keiskei*, bofu-tsusho-san, capsaishin, DHA/EPA, forskohlii, garcinia cambogia, lactoferrin, L-carnitine, oligonol, tea catechin, and yeast hydrolysate.

Conclusion: We obtained 11 supplements for which clinical evidence was published in medical journals in English. We also found 10 products for which clinical or animal evidence was published in Japanese. We expect that many companies will produce evidence of the efficacy of their products in the near future, thereby validating the use of dietary anti-obesity supplements in Japan.

Keywords: Anti-obesity, clinical trial, dietary supplements, evidence-based, Japanese market, weight management.

INTRODUCTION

Globally, strategies to prevent the development of obesity are focused on lifestyle modifications that restrict caloric intake and increase physical activity[1]. Therefore, treatments for overweight and obesity have important medical implications. Food research has attracted attention to the potential of natural products as treatments for obesity [1-3]. These products contain dietary phytochemicals with high potential for health promotion and disease prevention [4-7]. The anti-obesity effects of these compounds are mediated by regulatory effects on various pathways, including lipid absorption, energy intake and expenditure, increased lipolysis, and decreased lipogenesis and differentiation. Dietary supplements have been proposed as stimulants of weight loss that alter body functions during low-calorie dieting. Some agents have anorectic effects that lead to decreased food intake, whereas others affect metabolic changes that cause weight loss by increasing energy output [8]. Complementary and alternative medicines (CAM) have long been used in eastern countries and are increasingly being used worldwide. Supplements for anti-obesity are an established CAM modality and have attracted attention as complementary medicines in recent years. However, rigorous scientific studies of these products are few, and in many cases safety and efficacy are subordinate to marketing.

The Japanese market for supplements recently reached 1.8 trillion yen[2], and many are advertised for their anti-overweight property on the internet and in newspapers. However, most of these lack sufficient evidence for medical professionals to prescribe them to patients with obesity and related complications. Evidence-based research regarding the efficacy and safety of anti-obesity supplements is required to make definite recommendations for lifestyle management. The purpose of this review was to evaluate the efficacy and safety of anti-obesity supplements currently available in the Japanese market.

In this study, we researched data pertaining to ingredients or supplements that are consumed for weight loss. Among marketed supplements in Japan, we only reviewed ingredients for which evidence is available. This review summarizes evidence of the effects and safety of anti-obesity supplements relevant for patients and medical professionals.

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[1]Global strategy on diet, physical activity and health. In *The Fifty-seventh World Health Assembly*, 2007; pp 38-55.

[2]Trends in the Market for Dietary Supplement, Health Ingredients and Production Technology. http://www.kenko-media.com/food_devlp/skpdf/1303-sd-01.pdf [Accessed on 3rd October 2013].

1875-5844/13 $58.00+.00

Table 1. List of Anti-obesity ingredients with company names, product names and the amount of active ingredients.

Material	Products	Active Ingredient	Sales Inc. (Representative)
Angelica keiskei (Ashitaba)	Ashitaba®	2850 mg/pack (3 g)	Takara Bio Inc.
Bofu-tsusho-san (an oriental herbal medicine)	Bofu-tsusho-san®	Clarified in Table 2	Tsumura Co. Ltd.
Capsinoids	Capsiate Natura®	3.0 mg/2 capsules (650 mg)	Ajinomoto Inc.
DHA/EPA	Imark S®	DHA 260 mg, EPA 600 mg/bottle (100 ml)	Nippon Suisan Kaisha, Ltd.
Forskohlii	DHC forskohlii®	500 mg/2 tablets	DHC Corp.
Garcinia cambogia	Perfect Slim α® (FANCL)	837 mg/6 tablets	FANCL Corp. LS Corporation Co. Ltd.
Lactoferrin	Nicelim essence Lactoferrin®	300 mg/3 tablets	Lion Corp.
L-carnitine	Carnipure™ ®	100% L-carnitine in the crystalline powder	Lonza Japan Co. Ltd.
Oligonol	Oligonol®	100 mg/capsule	Aminoup Chemical Co. Ltd.
Tea Catechin	Healthya® (Kao)	540 mg/bottle (500 ml)	Kao Corp. Itoen Co. Ltd.
Yeast hydrolysate	DNF-10®	1 g/2 pouches	BHN Co. Ltd.

MATERIALS & METHODS

We researched anti-obesity supplements in the Japanese market by performing a representative google search in Japanese on September 13, 2013, using the search terms "anti-obesity supplements," "Diet supplements," and "supplements for weight reduction." Although numerous marketed supplements were identified from the initial database search, we focused on best-seller products from databases of popular internet distributers in Japan. In addition, we contacted the major supplement manufacturing company, which markets its products on television. We also performed market research in supermarkets and drug stores.

Some dietary supplements were identified from evidence of current product sales. Manufacturers were contacted for evidence of supplement effects and safety, and evidence-based data for items were requested. However, data from other sources was also included in this study. When multiple products contained the same agent, we chose the most representative product.

We limited the main outcomes of anti-obesity effects to weight and body fat loss. Searches and analyses for impaired glucose tolerance (IGT), insulin resistance (IR) or appetite in participants did not include. All abstracts from human studies of changes in anthropometric measures such as body weight, body mass index (BMI) and body fat were included. Publications of *in vitro* experiments, review articles, and letters to editors were excluded. Unpublished data were also excluded.

We received responses from 41 of 49 listed companies [9]. Among these, 10 did not have evidence-based data and 2 others had products that lacked anti-obesity efficacy. Then, we excluded 12 products with evidence that was only published in Japanese. We also excluded 6 products that lacked characterization in human studies. Finally, we included 11 products (Table **1**) with published clinical evidence of anti-obesity effects of their supplements, as described in Table **2**.

RESULTS

Ashitaba (Angelica Keiskei)

Ashitaba is a green and yellow vegetable of the *Apiaceae Angelica* family and contains a rich balance of vitamin and mineral nutrients. Similar to kale, it is often used as a nutritious food ingredient, but has even higher contents of protein; carotene; potassium; vitamins E, K, and B; pantothenic acid; niacin; and dietary fiber. Zhang *et al.* (2013) demonstrated that ashitaba contains the two main phytochemicals 4-hydroxyderricin (4HD) and xanthoangelol (XAG) (chemical structures **1**), which have various biological effects that lead to anti-tumor, anti-inflammatory, and anti-diabetic activities. 4HD and XAG inhibited differentiation of 3T3-L1 (3T3 is a cell line derived from mouse and used in biological research on adipose tissue) adipocytes by suppressing the expression of cytidine-cytidine-adenosine-adenosine-thymidine enhancer-binding proteins (C/EBP)-β, C/EBP-α, and peroxisome proliferator-activated receptor (PPAR) γ. These effects lead to activation of AMP-activated protein kinase (AMPK), extracellular Signal-regulated kinase (ERK) 1/2, and c-jun N-terminal kinase (JNK) signaling pathways, indicating potential benefits of ashitaba 4HD and XAG in the prevention of obesity and obesity-related disorders [10]. Ohnogi. *et al.* (2012) reported that ingestion of ashitaba green juice (6.2 g/day) for 8 wks resulted in significant reduction in visceral fat areas (−25.5 cm^2, $p < 0.01$), body weight (−1.4 kg, $p < 0.05$), BMI (−0.5, $p < 0.05$), and body fat (−2.1%, $p< 0.01$) in nine adult subjects with metabolic syndrome [11].

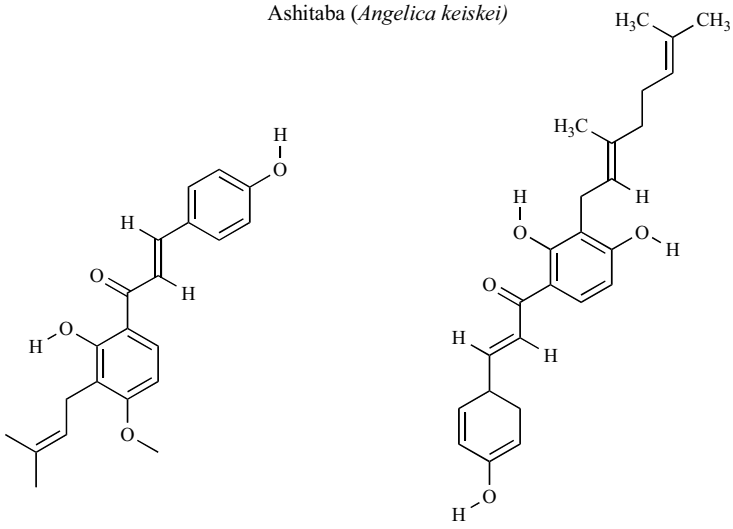
Table 2. Evidence list of active ingredients, references, study designs, numbers of subjects, intervention periods, and results.

Material	Representative Reference	Study Design	Subjects	Intervention Period	Results
Angelica keiskei (Ashitaba)	Hiromu Ohnogi.; Shoko Hayami.; Yoko Kudo (2012) Efficacy and Safety of Ashitaba (Angelica keisei) in Patients and Candidates with Metabolic Syndrome: A Pilot Study JJCAM, 9(1), 49-55.	Open-label pilot study	n = 9 with metabolic syndrome	8 weeks	Visceral fat area ($p < 0.01$) Body weight ($p < 0.05$) vs. 0 week
Bofu-Tsusho-san (an oriental herbal medicine)	Chizuko Hioki.; Kanji Yoshimoto.; Toshihide Yoshida (2004) Efficacy of Bofu-Tsusho-San, an oriental herbal medicine, in obese Japanese Women with Impaired Glucose Tolerance. Clin Exp Pharmacol Physiol, Sep;31(9), 614-9.	Randomized, double-blind, placebo study	n = 81 Obese women with impaired glucose tolerance and insulin resistance	24 weeks	Visceral fat area ($p < 0.01$) Body weight ($p < 0.01$) vs. 0 week
Capsinoid	Soren Snitker.; Yoshiyuki Fujishima.; Haiqing Shen (2008) Effects of novel capsinoid treatment on fatness and energy metabolism in humans: possible pharmacogenetic implications. Am J Clin Nutr, 2009, 89, 45-50.	Randomized, double-blind, placebo study	n = 80 with BMI of 30.4 ± 2.4	12 weeks	Abdominal adiposity ($p = 0.049$) vs. placebo
DHA/EPA	Alison M Hill.; Jonathan D Buckley.; Karen J Murphy.; *et al.* (2007) Combining of fish-oil supplements with regular aerobic exercise improves body composition and cardiovascular disease risk factors The American Journal of Clinical Nutrition, 85, 1267-74.	Randomized, double-blind Study (4 group)	n = 75 Over weight volunteers	12 weeks	Fish oil and exercise combination reduce body fat ($p < 0.05$) vs. 0 week
Forskohlii	Seika Kamohara.; Somboon Noparatanawong (2013) A Coleus Forskohlii extract improves body composition in healthy volunteers: An open-label trial Personalized Medicine Universe, 2, 25-27.	Open-label study	n = 15 Healthy volunteers	8 weeks	Fat content ($p = 0.0038$) Body weight ($p = 0.0038$) vs. 0 week
Garcinia cambogia	Kohsuke Hayamizu.; Yuri Ishii.; Izuru Kaneko (2003) Effect of Garcinia cambogia (Hydroxycitric Acid) on Visceral Fat Accumulation: A Double-Blind, Randomized, Placebo-Controlled Trial Current Therapeutic Research, 64, No.8.	Randomized, double-blind, placebo, parallel group study	n = 44 with visceral fat area of >90 cm^2	16 weeks	Visceral fat area ($p < 0.001$) Subcutaneous fat area ($p < 0.001$) vs. placebo
Lactoferrin	Tomoji Ono.; Michiaki Murakoshi.; Noriyuki Suzuki (2010) Potent anti-obesity effect of enteric-coated lactoferrin: decrease in visceral fat accumulation in Japanese men and women with abdominal obesity after 8-week administration of enteric-coated lactoferrin tablets. British Journal of Nutrition, 104, 1688-1695.	Randomized, double-blind, placebo study	n = 26 with visceral fat area of >100 cm^2 and BMI of >25	8 weeks	Body weight ($p = 0.032$) Visceral fat area ($p = 0.009$) Hip cicumference ($p = 0.041$) vs. placebo
L-carnitine	Klaus D. Wutzke.; Henril Lorenz (2004) The effect of L-Carnitine on Fat Oxidation, Protein Turnover, and Body Composition in Slightly Overweight Subjects Metabolism, 53, No.8, 1002-1006.	Randomized, double-blind, placebo study (4 groups)	n = 24 with overweight male volunteers	4 weeks	Body weight ($p < 0.01$) vs. 0 week

Table 2. contd…

Material	Representative Reference	Study Design	Subjects	Intervention Period	Results
Lychee Polyphrnol (Oligonol)	Jun Nishihira.; Maremi Sato-Ueshima.; Kentaro Kitadate.; *et al.* (2009) Amelioration of abdominal obesity by low-molecular-weight polyphenol (Oligonol) from lychee. Journal of Functional Foods I, 341-348.	Randomized, double-blind, placebo study	n = 18 with abdominal circumference of >85 cm	10 weeks	Waist circumference ($p < 0.01$) Visceral fat area ($p < 0.05$) Subcutaneous fat area ($p < 0.05$) vs. 0 week
Tea Catechin	Tomonori Nagao.; Yumiko Komine.; Shinichi Meguro *et al.* (2005) Ingestion of a tea rich in catechins leads to a reduction in body fat and malondialdehyde-modified LDL in men The American Journal of Clinical Nutrition, 81, 122-9.	Double-blind, placebo study	n = 38 with normal to over-weight male volun-teers	12 weeks	Body weight, Waist circumference ($p < 0.01$) vs. 0 week ($p < 0.05$) vs. placebo
Yeast hydrolysate	Eun Young Jung.; Mi Kyoung Cho.; Yang-Hee Hong (2013) Yeast hydrolysate can reduce body weight and the ab-dominal fat accumulation in obese adults Nutrition	Randomized, placebo study	n = 54 with BMI of ≥25	10 weeks	Body weight ($p < 0.001$) Energy intake ($p < 0.05$) vs. placebo

Ashitaba (*Angelica keiskei)*



4-hydroxyderricin (4HD) xanthoangelol (XAG)

Chemical Structures 1. Ashitaba(*Angelica keiskei*) [3].

Bofu-tsusho-san (An Oriental Herbal Medicine)

Bofu-tsusho-san (BF), a traditional Japanese herbal medicine "kampo" comprising 18 crude components (Table **3**), has been an effective treatment for obesity, constipation, and hypertension. In a clinical trial, BF reduced body weight and improved glucose tolerance [12]. In addition, several pharmacological studies have reported its ability to counter obesity, fatty liver, and arteriosclerotic diseases [13]. As in traditional Chinese medicine, BF was used to reduce fever after bouts of influenza and promote bowel movements. After administering BF, it was demonstrated that BF activates the brown adipose tissue (BAT) and promote the lipolysis in white adipose tissue (WAT). Furthermore, reports of thermogenic responses to BF components from *Ephedrae herba* (EH), *Glycyrrhizae radix* (GR), *Forsythiae fructus* (FF), and *Schizonepetae spica* (SS) extracts have been reported. These inhibit cyclic adenosine monophosphate (cAMP) phosphodiesterase as shown with caffeine [12]. Nakayama *et al.* (2007) also showed that BF extracts activated thermogenesis in BAT and inhibited phosphodiesterase activity, resulting in weight loss [14].

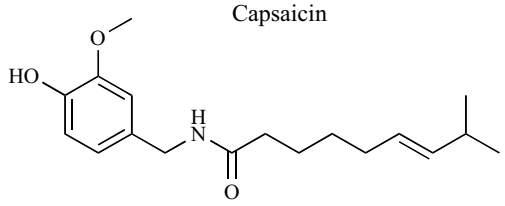
Hioki *et al.* (2004) conducted the randomized, double-blind, placebo-controlled study of BF. Eighty-one obese

[3] Chemical structures were drawn based on the Pub Chem Compound database.

Table 3. Composition of crude drugs preparations containing bofu-tsusho-san. The amount of each crude drug required to prepare 100 g of bofu-tsusho-san dry extract are presented.

Crude Drug	Content (g)
Scutellariae radix	44.4
Glycyrrhizae radix	44.4
Platycodi radix	44.4
Gypsum fibrosum	44.4
Atractylodis rhizoma	44.4
Rhei rhizoma	33.3
Schizonepetae spica	26.7
Gardeniae fructus	26.7
Paeoniae radix	26.7
Cnidium rhizoma	26.7
Angelicae radix	26.7
Menthae herba	26.7
Ledebouriellae radix	26.7
Ephedrae herba	26.7
Forsythiae fructus	26.7
Zingiberis rhizoma	6.7
Talcum	66.7
Natrium sulphuricum	15.6

Capsaicin



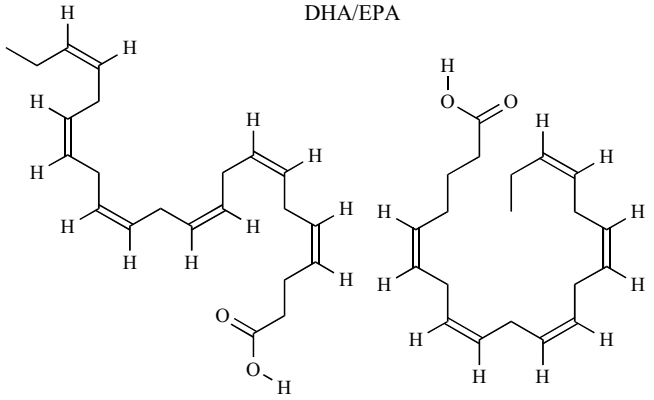
Chemical Structures 2. Capsaicin[4].

Japanese women (BMI 36.5 ± 4.8 kg/m^2) with IGT and IR were randomized to receive either placebo (n = 40) or BF (24 mg/day) treatments (n = 41). After 24 wks, the BF group had significantly reduced bodyweight (90.8 ± 17.9 to 80 ± 10.3, $p < 0.01$) and abdominal visceral fat (197.6 ± 69.7 to 104.4 ± 28.0, $p < 0.01$), without decreases in resting metabolic rates (1986.2 ± 402.5 to 1821 ± 420.6). Whereas the placebo group showed body weight loss (90.3 ± 12.2 to 83.4 ± 13.4, $p < 0.05$), with no significant changes in abdominal visceral fat (177.2 ± 73.3 to 140.9 ± 60.4) [12].

Capsinoids

Capsinoids are abundant in non-pungent chili peppers (*Capsicum anuum L.*; Solanacae or pepper fruit; variety CH-19 Sweet) (chemical structures **2**). Watanabe *et al*. (2011) researched the effects of capsinoids, increased basal metabolism, fatty acid oxidation and decreased body fat. These effects are mediated by transient receptor potential channels (TRP) and the sympathetic nervous system [15].

DHA/EPA



Docosahexaenoic Acid (DHA) Eicosapentaenoic Acid (EPA)

Chemical Structures 3. DHA & EPA[3].

BAT is a site for cold- and diet-induced thermogenesis, and therefore may be a target for body fat management. Yoneshiro *et al.* (2013) conducted a 6wk, placebo-controlled study and reported that cold-induced thermogenesis (CIT) was increased after administration of capsinoids (9 mg/day) (200.0 ± 33.9 vs 81.0 ± 32.5 kcal/d) [16]. Because CIT is proportional to BAT activity, these data suggest capsinoid-induced recruitment of BAT.

Orally administered capsiate activates transient receptor potential cation channel, subfamily V, member 1 (TRPV1) receptors on vagal afferents in the gut with equal potency to capsaicin, and results in increased sympathetic efferent activity and thermogenesis in animals [17].

Snitker *et al.* (2009) conducted a 12-wk, placebo-controlled, double-blind, randomized study in which 80 subjects (BMI 30.4 ± 2.4) were recruited and randomly assigned to capsinoid (6 mg/day) or placebo treatment groups. Capsinoids were well tolerated and mean ± SD weight changes of 0.9 ± 3.1 and 0.5 ± 2.4 kg were observed in capsinoid and placebo groups, respectively ($p = 0.86$). Abdominal adiposity was also significantly decreased ($p = 0.049$) in the capsinoid group [17].

DHA/EPA

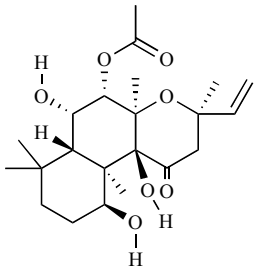
EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid) are essential fatty acids (chemical structures **3**). These essential omega-3 fatty acids are found in cold-water fish and are highly unsaturated, with 5 or 6 double bonds on their carbon chains. These polyunsaturated fats play important roles in human physiology[5].

Inoue *et al.* (2013) suggested that the ratio of EPA to arachidonic acid (EPA/AA ratio) may have a major role in obesity. The EPA/AA ratio, but not the DHA/AA ratio, was cor-

[4] Whiting, S.; Derbyshire, E.; Tiwari, B. K., Capsaicinoids and capsinoids. A potential role for weight management? A systematic review of the evidence. Appetite 2012, 59 (2), 341-8.

[5] Dr. Hoffman Home Page. What are EPA/DHA? http://www.drhoffman.com/page.cfm/84 [Accessed on 3rd October 2013].

Coleus forskohlii



Forskolin

Chemical Structures 4. CF[3].

related with visceral fat accumulation among men (n = 134) [18].

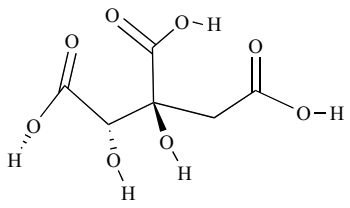
Some mechanisms by which EPA and DHA act against obesity have been proposed. Specifically, EPA is a ligand of PPARα and activates the expression of genes that encode key enzymes of fatty acid transport and β-oxidation. EPA also improves glucagon like peptide-1 (GLP-1) levels and enhances GLP-1 secretion from intestinal cells by activating G-protein-coupled receptor 120 (GRP120) [19]. GLP-1 also improves insulin secretion and satiety, and moderates post-prandial glucose levels. These actions of GLP-1 effectively facilitate visceral fat reduction.

Hill *et al.* (2007) recruited 75 overweight volunteers (BMI > 25) and investigated the effects of fish oil intake and regular exercise. Subjects were divided into fish oil (FO), FO and exercise (FOX), sunflower oil (SO, control), or SO and exercise (SOX) groups. Oil treatments comprised 6 g of tuna FO/d (including 1.9 g of n-3 fatty acid) or 6 g of SO/d and the exercise regimens involved walking for 45 min for 3 d/week. After the 12-wks intervention, FO supplementation lowered triacylglycerols, increased high density lipoprotein cholesterol (HDL), and improved endothelium-dependent arterial vasodilation ($p < 0.05$). Both fish oil and exercise independently reduced body fat compared with baseline measurements ($p < 0.05$) [20].

Forskohlii (South Asian herb)

Coleus forskohlii (CF) is a native Indian coleus plant of the *Lamiaceae* family that grows wild in arid and semi-arid regions of India and Thailand (chemical structures **4**). The rhizome part of the perennial CF plant has been traditionally used in Ayurvedic medicine as a remedy for heart disease, and respiratory, gastrointestinal, and central nervous systems disorders [21]. The active ingredients forskolin and diterpene act directly on adenylatecyclase, which activates cAMP and stimulates fat catabolism in human adipose cells [22]. CF regulates thermogenic responses to food, increases basal metabolic rates, and increases utilization of body fat. Theoretically, increased release of fatty acids from adipose tissue may also increase thermogenesis, facilitate body fat loss, and increase lean body mass. Enhanced lipolysis is associated with increased use of fat energy, and enhances fat loss without muscle mass loss [23].

Garcinia cambogia



Hydroxycitric Acid

Chemical Structures 5. GC[6].

Kamohara *et al.* (2013) performed an 8-wk open-label study of 15 healthy volunteers, who received 1000 mg of CF extract/d (10% forskolin). Subjects achieved significant decreases in BMI (24.92 ± 0.87 to 23.99 ± 0.86 kg/m^2, p = 0.0038), body weight (66.33 ± 3.00 to 63.96 ± 3.10 kg, p = 0.0038), fat content (29.64 ± 2.19 to 27.77 ± 2.27 kg, p = 0.0038), lean body mass (44.34 ± 2.98 to 43.93 ± 3.01 kg, p = 0.0044), and basal metabolic rates (1379.1 ± 74.4 to 1363.9 ± 77.5 kcal, p = 0.0254) [21].

Garcinia Cambogia

Hydroxycitric acid is an anti-obesity active ingredient found in rinds from the Indian fruit *Garcinia cambogia* (GC). GC derived hydroxycitric acid (chemical structure 5) decreases the synthesis and secretion of very low density lipoprotein (VLDL) in the liver by inhibiting citrate lyase, which ensures the availability of cytosolic acetyl-CoA after mobilization of citrate from mitochondria. As a precursor of malonyl-CoA, acetyl-CoA is the major *de novo* substrate for fatty acid biosynthesis. Under conditions of decreased fat secretion from the liver, increased plasma chylomicron levels may compensate by providing lipids derived from dietary sources, potentially under the influence of the hormone leptin [24]. Finally, hydroxycitric acid competitively inhibits the extramitochondrial enzyme adenosine triphosphate-citrate (pro-3S)-lyase, which may inhibit *de novo* lipogenesis as a citrate cleavage enzyme. Taken together, these mechanisms suggest that GC may lower body weight and reduce fat mass in humans [25].

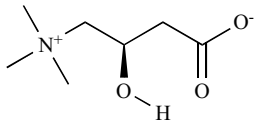
Various supplements contain GC with other components. However, GC is investigated in only one clinical study. Namely, Hayamizu (2003) *et al.* performed a double-blind, randomized, placebo-controlled, parallel-group design trial of 44 subjects (GC, n = 18; placebo, n = 21) aged 20–65 years with visceral fat areas of >90 cm^2. Subjects were randomly assigned to receive GC extract for 12 wks (1667.25 mg/9 tablets, containing 1000 mg of hydroxycitric acid). At 16 wk, the GC group had significantly reduced visceral, subcutaneous and total fat areas compared with placebo group ($p < 0.001$). However, neither body weight nor BMI were significantly lower in the GC group [26].

Lactoferrin

Lactoferrin (LF) is an iron-binding glycoprotein found in exocrine secretions such as breast milk, tears, sweat, and saliva. It is accepted that LF is a protective factor that prevents attacks from exogenous bacteria and viruses. LF has been shown to influence master regulators of adipocyte dif-

[6]Technical Resources International, GarciniaCambogia, http://ntp.niehs.nih.gov/ntp/htdocs/Chem_Background/ExSumPdf/GarciniaCambogiaExt_508.pdf [Accessed 25th November 2013].

L-Carnitine



Chemical Structure 6. LC[3].

ferentiation such as PPARγ, and inhibits the expression of genes encoding lipid synthesis enzymes, and hence lipid accumulation in preadipocytes. In recent experiments, LF increased cellular cAMP concentrations and reduced the expression of perilipin, further promoting lipolysis in mature adipocytes. Furthermore, the well-known lactoferrin receptor lipoprotein receptor related protein-1 (LRP1) is expressed in mesenteric fat and mediates accumulation of lactoferrin, suggesting that lactoferrin acts directly on adipocytes as visceral lactoferrin [27-28].

Ono *et al.* (2010) performed a double-blind, placebo-controlled design study of 22–60-year-old Japanese men and women (n = 26) with abdominal obesity (BMI > 25 kg/m^2 and visceral fat area > 100 cm^2). Subjects consumed enteric-coated LF (eLF) (300 mg/d as bovine LF) or placebo tablets for 8 wks and total visceral and subcutaneous fat areas were measured using computed tomography. In comparison with the placebo group, visceral fat area was significantly reduced in the eLF group (−1.8 vs. −14.6 cm^2, respectively, p = 0.009; ANCOVA). Decreases in body weight, BMI, and hip circumference in the eLF group (−1.5 kg, −0.6 kg/m^2, and −2.6 cm, respectively) were also significantly greater than those in placebo group (1.0 kg, 0.3 kg/m^2, and −0.2 cm; p = 0.032, 0.013, and 0.041, respectively). There was also a tendency for a reduced waist circumference in the eLF group (−4.4 cm) when compared with the placebo group (−0.9 cm; p = 0.073) [28].

L-Carnitine

L-Carnitine (LC) is a vitamin-like amino acid derivative (chemical structure 6) involved in metabolism of lipid and use of fat energy. LC promotes transport of long chain fatty acids across the selective inner membrane into the mitochondrial matrix for further β-oxidation. In addition to endogenous supply from liver, kidney, and other organs, LC is also ingested from foods such as lean meat [29].

Wutzke *et al.* (2004) showed that oral administration of LC to healthy human subjects for 10 days significantly facilitated fatty acid oxidation, indicating that LC may be a limiting factor for fat catabolism. Oyanagi *et al.* (2011) showed protective effects of LC vs. free fatty acid against mitochondrial membrane disruption, resulting in sustained β-oxidation functionally. These observations suggest that LC supplementation may attenuate obesity by improving rate limiting mitochondrial processes [30-31].

Odo *et al.* (2013) recruited 24 overweight (BMI 25.8–26.6 kg/m^2) male subjects for a double-blind randomized placebo-controlled study. In this trial, low-dosage (500 mg/day) LC supplementation and motivation training for 4 wks resulted in significant body weight loss (82.0 ± 2.2 to 80.9 ± 1.8 kg, p < 0.01) and decreased serum triglyceride levels (218 ± 45 to 145 ± 42, p < 0.01) compared with non-motivated placebo-treated subjects [32].

Oligonol (Lychee polyphenol)

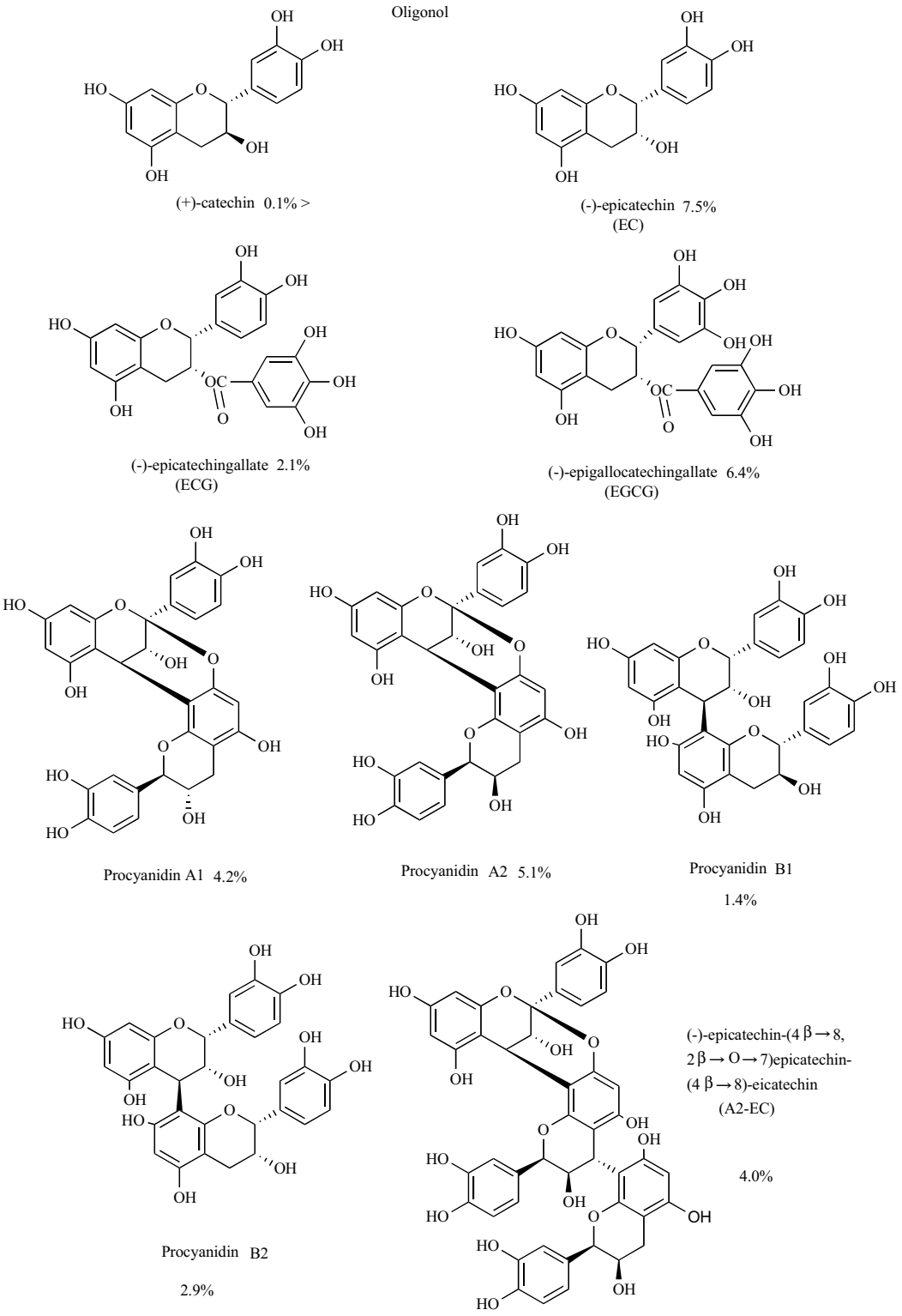
Oligonol is a lychee fruit-derived polyphenol that is oligomerized during manufacture of catechin-type monomers and proanthocyanidin oligomers (chemical structure **7**). Diabetes-induced hepatic damage is occasionally observed in patients with metabolic syndrome. Oligonol has been shown to protect against hepatic damage by regulating oxidative stress and lipid metabolism *in vitro* and *in vivo* [33]. Ogasawara *et al.* (2010) demonstrated a mechanism for oligonol-improved lipid metabolism that involves the mitogen activated-protein kinase (MAPK) signaling pathway. Oligonol stimulated lipolysis in primary adipocytes by activating Ras and phosphorylated (Raf-1) and MEK1/2 independent of autocrine/paracrine interleukin 6 (IL6), leading to significant activation of ERK1/2 proteins and decreased secretion of IL-6 from adipocytes [34].

Nishihira *et al.* (2009) performed a randomized double-blind, placebo-controlled clinical trial of oligonol in 18 adult volunteers with abdominal circumference of >85 cm. Subjects were enrolled and divided into groups treated with 50 mg oligonol or placebo/d for 10 wks. Clinical parameters such as waist circumference (p < 0.01), subcutaneous fat area (p < 0.05) and visceral fat area (80.5 ± 45.8 to 68.6 ± 36.5 cm^2, p < 0.05) were significantly decreased in the oligonol group compared with placebo treated subjects [35].

Tea Catechin

Polyphenol bioactivities have recently become topical in medicine and cosmetics. Green tea, which has been consumed in Asian countries for centuries, contains low-molecular-weight polyphenols comprising mainly flavanol (flavan-3-ol) monomers, which are referred to as catechins (chemical structure **8**) [36]. Green tea components have been shown to affect PPAR signaling pathways. Lee *et al*. (2004) reported that green tea and its main constituent epigallocatechin gallate (EGCG) increased the activation of PPAR [37]. Tea catechins also suppressed adipocyte differentiation and downregulated PPARγ and C/EBPα [38], which is a family of ligand-activated transcription factors of the nuclear receptor superfamily and is critical to fat metabolism and activation of PPARs.

Nagao *et al.* (2005) investigated the effects of tea catechin in 38 healthy normal to overweight men. Subjects were divided into 2 groups with similar BMI and waist circumference distribution, and ingested 1 bottle of oolong tea/d containing 690 mg of catechins (green tea extract group; n = 17) or 1 bottle of oolong tea/d containing 22 mg of catechins (control group; n = 18). After 12 wks, the green tea extract group achieved significant reduction in body weight (p < 0.01; vs. placebo p < 0.05), BMI (p < 0.01; vs placebo p < 0.05), waist circumference (p < 0.01; vs placebo p < 0.05), body fat mass (p < 0.01; vs placebo p < 0.05), and subcutaneous fat area (p < 0.01; vs placebo p < 0.05). Changes in the concentrations of malondialdehyde-modified LDL were positively associated with changes in body fat mass and total fat area in the green tea extract group [36].

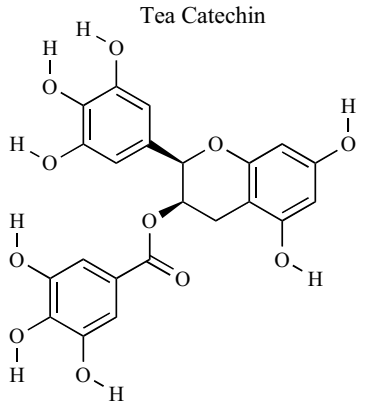


Chemical Structure 7. Oligonol (Content %).

Yeast Hydrolysate

The typical yeast *Saccharomyces cerevisiae* is used routinely in the production of sake and bread. Yeast hydrolysates (YH) from *S. cerevisiae* are solubilized using protein degradation enzymes. Jung *et al.* (2013) indicated that YH may act against obesity by suppressing appetite through appetite-related neurotransmitters in the central nervous system (CNS). YH is rich in cyclo-his-pro (CHP), which plays an important role in the regulation of leptin and has been associated with presynaptic dopaminergic mechanisms and leptin-like functions in CNS. Importantly, CHP reduces body weight by inhibiting food intake [39].

Jung *et al.* (2013) also conducted the first randomized, double-blind, placebo-controlled study of YH. They showed



Chemical Structure 8. Tea catechin[3].

obesity supplements in Japan. In addition, supplement–supplement and supplement–drug interactions remain largely unknown, despite the prevalent use of anti-hypertensive, anti-hyperlipidemia, and anti-diabetic drugs by obese patients.

Nonetheless, many people strive to decrease body weight using supplements that lack evidence. Thus, evidence-based research into the efficacy and safety of anti-obesity supplements is required for informed lifestyle management recommendations.

Accordingly, these products are marketed for weight reduction, but not for medical use, partly due to Japanese labeling regulations that prohibit health claims regarding anti-obesity effects of products, but recognize foods for specified

Table 4. List of anti-obesity materials, company names, and resons for exclusion from table 1.

Material	Sales Inc. (Representative)	Reasons for Exclusion from Table 1
Astaxanthin	AstaReal Inc.	data from mice
Chitosan	KOYO Chemical Co. Ltd.	data from rats
GCP (Genistein Combined Polysaccharide)	Aminoup Chemical Co. Ltd.	data published in Japanese
Germinated brown rice	FANCL Corp.	data published in Japanese
Maltitol	Ueno fine chamical industory Co. Ltd.	data from rats
Mixture of amino acids	Meiji Co. Ltd.	data from mice
Mulberry leaves	Ohta's Isan Co. Ltd.	data published in Japanese
Peucedanum japonicum	Macrobiotic Material Laboratory Inc.	data from rats
Phytosterol	Toyo Hakko Co. Ltd.	data from mice
Propolis	Yamada Bee Farm Co. Ltd.	data from rats
Rhamnan sulfate	Konan Chemical Co. Ltd.	data published in Japanese
Soy bean isoflavones	Sansho Pharmaceutical Co. Ltd.	data published in Japanese

that YH treatment for 10 wks inhibited abdominal fat accumulation in 54 obese (BMI > 25) men and women aged 20–50 years. From wk 6, energy intake in the YH (1 g/d) treatment group was significantly reduced compared with that in the control group (placebo 1 g/d; $P < 0.05$). Reduction in body weight and body mass index (BMI) between baseline and wk 10 were also significantly greater in the YH group than in the control group (body weight, -2.60 vs. +0.83 kg, $p < 0.001$; BMI: -0.90 vs. +0.29 kg/m^2; $p < 0.001$)[7].

DISCUSSION

Patients often inquire about anti-obesity supplements to medical professionals. However, due to lack of sufficient evidence, only few recommendations for anti-obesity supplements are possible. Nonetheless, most medical professionals fail to recognize the paucity of evidence for anti-health use (FOSHU; TOKUHO in Japanese)[8]. These regulations allow companies to produce supplements without clinical evidence and make it difficult for consumers to assess whether or not products have evidence. To solve this problem, the Japanese government is considering deregulation of dietary supplement labeling, which may encourage provision of evidence for anti-obesity supplements in the Japanese market.

CONCLUSION

Despite expectations, many companies have produced clinical evidence for their products regardless of labeling regulations in Japan. To improve the precision of this study, we only listed 11 products for which clinical trials were published in English journals (Table **1**). However, in addition to these, we found 10 more products with clinical trial evidence published in Japanese or with evidence from experimental

[7]Jung, E. Y.; Cho, M. K.; Hong, Y.-H.; Kim, J. H.; Park, Y.; Chang, U. J.; Suh, H. J., Yeast hydrolysate can reduce body weight and the abdominal fat accumulation in obese adults. *Nutrition* **2013**. *in press*

[8]Ministry of Health, Labor and Welfare. Food for Specified Health Uses (FOSHU). http://www.mhlw.go.jp/english/topics/foodsafety/fhc/02.html [Accessed 3rd October 2013].

studies using rodents (Table **4**). We expect that many companies will produce clinical evidence of international standard for their products in near future.

The Japanese market for dietary supplements is growing rapidly. However, the use of supplements remains more widespread in Western countries. Information regarding ingredients and products of supplements is more readily available in western counties, as indicated by the National Center for Complementary & Alternative Medicine (NCCAM) in America[9]. Thus, clinical evidence of supplement efficacy and safety should be more actively pursued in Japanese CAM.

CONFLICT OF INTEREST

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ABBREVIATIONS

4HD	=	4-hydroxyderricin
AA	=	Arachidonic acid
AMPK	=	AMP-activated protein kinase
BAT	=	Brown adipose tissue
BF	=	Bofu-tsusho-san
BMI	=	Body mass index
C/EBP	=	CCAAT enhancer-binding protein
CAM	=	Complementary and alternative medicines
cAMP	=	Cyclic adenosine monophosphate
CCAAT	=	Cytidine-cytidine-adenosine-adenosine-thymidine
CF	=	*Coleus forskohlii*
CHP	=	Cyclo-his-pro
CIT	=	Cold-induced thermogenesis
CNS	=	Central nervous system
DHA	=	Docosahexaenoic acid
EGCG	=	Epigallocatechin gallate
EH	=	*Ephedrae herba*
eLF	=	Enteric-coated LF
EPA	=	Eicosapentaenoic acid
ERK	=	Extracellular Signal-regulated kinase
FF	=	*Forsythiae fructus*
FO	=	Fish oil
FOSHU	=	Food for specified health use
FOX	=	FO and exercise
GC	=	*Galcinia cambogia*
GLP-1	=	Glucagon like peptide-1
GLP120	=	G-protein-coupled receptor 120
GR	=	*Glycyrrhizae radix*
HDL	=	High density lipoprotein
IGT	=	Impaired glucose tolerance
IL-6	=	Interleukin 6
IR	=	Insulin resistance
JNK	=	c-jun N-terminal kinase
LC	=	L-carnitine
LF	=	Lactoferrin
LRP1	=	Lipoprotein receptor related protein-1
MAPK	=	Mitogen activated-protein kinase
NCCAM	=	National center for complementary and alternative medicine
PPAR	=	Peroxisome proliferator-activated receptor
Pro-3S	=	Triphosphate-citrate
Raf-1	=	Ras and phosphorylated
SO	=	Sunflower oil
SOX	=	SO and exercise
SS	=	*Schizonepetae spica*
TOKUHO	=	Tokutei hokenyou shokuhin (in Japanese)
TRP	=	Transient receptor potential channels
TRPV1	=	Transient receptor potential cation channel, subfamily V, member 1
VLDL	=	Very low-density lipoprotein
WAT	=	White adipose tissue
XAG	=	Xanthoangelol
YH	=	Yeast hydrolysates

[9]National Center for Complementary & Alternative Medicine (NCCAM). Dietary and Herbal Supplements. http://nccam.nih.gov/health/supplements [Accessed 1st October 2013].

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