Chapter 8
Nutraceuticals Supporting Body Weight Loss

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Introduction

Obesity and overweightness are major pandemic health problems and, in many cases, appear in close relationship with other cardiovascular disease (CVD) risk factors like glucose intolerance, type 2 diabetes mellitus (T2DM), dyslipidemia, hypertension, and kidney failure [1]. In addition, obesity and overweightness are associated with increased all-cause mortality [2].

According to World Health Organization (WHO) data, obesity has nearly tripled in the last 40 years. In 2016 more than 1.9 billion adults were overweight and, among these, over 650 million were obese, corresponding to 13% of the world's adult population (11% of men and 15% of women) [3].

Overweight and obesity are defined as abnormal or excessive fat accumulation. The calculation of body mass index (BMI) is the most commonly used tool for the classification of overweight and obesity. BMI is calculated as a person's weight in kilograms divided by the square of his height in meters (kg/m^2). For adults, WHO defines overweight as BMI $\geq$25 kg/m^2 and obesity as a BMI $\geq$30 kg/m^2. Furthermore,

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obesity is sub-classified into 3 subgroups – class I: BMI between 30–34.9 kg/m^2 (associated with moderate risk); class II: BMI between 35–39.9 kg/m^2 (associated with high risk) and class III: BMI ≥40 kg/m^2 (associated with very high risk). However, in many cases, BMI may not correspond to the same degree of adiposity in different individuals and should be used with caution. Therefore, the use of other indicators such as waist circumference and waist to hip ratio in association with BMI is recommended [4].

Early intervention, even at young ages, should be promoted as obesity prevention is fundamental. The first line treatment in weight management is lifestyle intervention including a hypocaloric diet and increased physical activity. When changing lifestyle fails, pharmacological management should be considered. Bariatric surgery might be recommended for individuals with a BMI ≥40 kg/m^{2}or BMI ≥35 kg/m^2 and other obesity-related comorbidities [5, 6].

Available drugs for weight management in obese patients have a broad mechanism of action including an increase in satiety as well as a decrease in hunger, or a reduction in calorie absorption. Very few drugs are approved for weight loss. At the same time, there are differences between the pharmacological treatments approved by the most important regulatory entities such as the Food and Drug Administration (FDA) and European Medicine Agency (EMA). Considering that the tolerability as well as the efficacy and the safety of anti-obesity drugs for long-term use are still controversial, the consumption of these drugs should be closely supervised [7]. Moreover, the possible interactions between nutraceuticals and other medications are as yet not well enough studied. On the other hand, there are many functional foods and nutraceuticals available for weight loss accessible over the counter and on the internet. The use of dietary supplements for weight loss is quite common and the data from a survey in US adults showed that more than 30% of the subjects who made a serious weight-loss attempt used dietary supplements. At the same time, of those interviewed, more than 60% of users and more than 40% of non-users respond that dietary supplements are effective for weight loss [8]. However, data from the scientific literature is contradictory and the use of these products should be carefully controlled due to increased numbers of documented adverse effects. Moreover, the efficacy of most of the dietary supplements used for weight loss is questionable.

This chapter will provide an overview of the most common nutraceuticals used for body weight management with available scientific data from clinical studies.

Fibers

Fibers are naturally present in the structure of some food plants including vegetables, fruits, grains, and legumes. Fibers are classified as soluble or insoluble, depending on its water-holding capacity or viscous characteristics in solution [9]. Fiber's mechanism of action on body weight is related to fiber proprieties of lowering the absorption of other caloric nutrients, especially carbohydrates and lipids. On the other hand, fibers could have an effect on appetite by increasing satiety while delaying gastric emptying, increasing glucagon-like peptide 1/2 (GLP-1/2) and cholecystokinin (CCK) hormones, as well as lowering ghrelin secretion and serotonin uptake. Generally, both soluble and insoluble fiber intake could increase satiety and hunger, and in obese subjects an intake of an additional 14 g/day of fiber could reduce energy intake by 82% with a further reduction in body weight of 2.4 kg [10]. In addition, the effect of fiber on appetite, acute and long-term energy intake as well as body weight differ depending on the different physicochemical properties of various fibers. For instance, more viscous fibers such as pectins, β-glucans and guar gum reduce appetite around 59%, while less viscous ones showed only a 14% appetite reduction [11].

Due to a low consumption of fiber rich foods like vegetables, fruits, and whole grains, in the USA the average fiber intake of adults does not even rich half of current recommendations. On the other hand, a positive correlation has been established between a low consumption of fiber and obesity. Furthermore, nutraceuticals containing dietary fiber could positively impact obesity [12–15]. Data derived from intervention studies strongly support the use of soluble fiber intake for weight management as well as for metabolic control in overweight and obese subjects. Results from a meta-analysis, including more than 600 patients, conclude a beneficial effect of different soluble fiber consumption (manno-oligosaccharides, galacto-oligosaccharides, fructo-oligosaccharides, β-glucan, flax-seed mucilage, mannans and dextrin) [15]. After 2–17 weeks of follow-up, at a mean dose of 18.5 g/day, overweight and obese subjects experienced reductions of 2.5 kg in weight and 0.4% of body fat.

Psyllium (Psyllium Husk Fiber)

Psyllium husk fiber is a water-soluble, gel-forming mucilage from *Plantago ovata*. As it is less readily fermented it provides less adverse effects than other fibers such as bloating and other gastro-intestinal dysfunction [16, 17]. Its main mechanism of action on body weight includes a delay in gastric emptying as well as increased satiety. Increased satiety at the central level is mediated by the inhibition of ghrelin secretion while up regulating GLP-1/2 and CCK hormones. On the other hand, hepatic cholesterol synthesis is reduced, and fecal excretion of cholesterol and bile salts are increased. Moreover, psyllium has been shown to modulate the gut microbiota by short-chain fatty acids (SCFA) produced by fermentation, lipolysis and lipoprotein lipase (LPL) upregulation [18].

Clinical evidence of psyllium supplementation showed either positive or no effect on weight loss. A very recent systematic review and meta-analysis analyzed the results of 22 randomized controlled trials (RCTs) and included a total 1458 adults [19]. The authors found no effect of psyllium supplementation on body weight, WC, and BMI. However, the results of this publication should be interpreted carefully as not all the participants were obese or overweight. Furthermore, subgroup analysis showed that the effect of psyllium supplementation on body weight and on BMI was significant in studies that used psyllium dosage of more than 10 g/day and with higher duration [19]. Another review concluded that dietary supplementation with psyllium could decrease appetite and has an effect on some components of the metabolic syndrome, such as hyperglycemia, insulin response and the lipid profile [20].

In other clinical studies, in overweight patients with T2DM, an improvement in glycemic control is observed, although there was no effect on BMI, after 8-week consumption of 10.2 g of psyllium daily [21]. In another study, after 7 weeks of high fiber food consumption, the lipid profile improved and there was a minimum reduction in body weight [22], while a 12 month supplementation period with a product containing 5 g of psyllium before meals had beneficial effects on body weight, WC, and body fat percentage [23]. Long-term supplementation with psyllium in addition to a caloric restricted diet showed better effects than short term use of this natural component on weight reduction [24].

Other health effects of soluble fiber, especially psyllium consumption as an adjuvant to a hypocaloric diet, shows that patients experience increased satiety and improvements in CVD related risk factors such as total and low-density lipoprotein (LDL) cholesterol, hypertension as well as an improvement in glycemic response and insulin sensitivity [24–26], findings also corroborated by a recent meta-analysis [27].

In clinical practice, psyllium supplementation could be used in addition to a healthy diet or weight loss plan at a minimum dose of 10 g twice a day for adults for a minimum duration of 10 weeks. Psyllium should be taken with 250 ml water or added to the meal while water consumption should be increased [24]. Psyllium could be a better choice for weight loss than other fibers as it has less adverse effects.

β-Glucans (Oats Bran)

Oats (Avena sativa) is a class of cereal grain belonging to the *Poaceae family*. Oats are rich in protein, lipids, vitamins, minerals, and fibers. Moreover, oats are considered functional food due to its high concentration in a soluble fiber, β-glucan [28]. β-glucan intake might contribute to body weight control and has other health-related beneficial effects such as hypolipidemic, hypoglycaemic, antioxidant and anti-inflammatory [29] efficacy, and could also reduce CVD risk [30]. In overweight subjects oat β-glucan could suppress hunger by increasing gastric emptying time, elevating post-prandial CCK, and decreasing the insulin response [31].

Even if it is largely recommended for obesity treatments, to our knowledge there is not much clinical evidence supporting the use of β-glucan for weight loss. Most of the studies concluded that β-glucan administration has no or has minimal effects on body weight. After 3-months supplementation with 0 g, 5–6 g or 8–9 g of β-glucan, in addition to dietary intervention in overweight women, no significant reduction in body weight was observed among intervention groups [32]. In several other studies investigating health-related benefits of β-glucans, weight loss was also assessed. After an administration of 3–9 g/day of β-glucan for up to 12 weeks, no effect was shown in body weight reduction [33–35]. In conclusion, β-glucan supplementation might not be a good option for treating overweight or obesity, although a recent meta-analysis shows that cereal β-glucan consumption seems to modestly decrease body weight (weighted mean difference (WMD) −0.77 kg, 95% CI: −1.49, −0.04) and BMI (WMD −0.62 kg/m^2, 95% CI: −1.04, −0.21), respectively, but has no effect on waist circumference and energy intake [36].

Chitosan

Chitosan is the second most abundant naturally occurring polysaccharide next to cellulose. Chitosan results from the deacetylation of chitin [37] and is categorized as an insoluble fiber from animal origin; it reduces cholesterol absorption [38]. The mechanism by which chitosan may exert a weight loss effect is by binding and trapping dietary fat and cholesterol, thus preventing its absorption in the intestinal lumen [39]. Moreover, chitosan might have an effect on the inhibition of adipogenesis in 3T3-L1 cells, as well as on the activation of 5′ adenosine monophosphate-activated protein kinase (AMPK) and by inhibiting lipogenesis-associated genes in the liver and adipose tissue [40]. A recent experimental study demonstrated that chitosan's weight-loss mechanism includes an increase in serum leptin levels, reduced inflammation, and a probiotic effect, leading to a change in gut microbiota by increasing the anti-obesity species such as *Clostridium leptum* and *Coprobacillus cateniformis* and by decreasing *Clostridium lactatifermentans* and *Clostridium cocleatum* [41].

A recent meta-analysis including 15 RCTs with 1130 subjects, studying chitosan consumption in adults, showed a significant reduction in weight (WMD −0.89 kg; 95% confidence interval (CI): −1.41 to −0.38; P = 0.0006) and body fat (WMD −0.69%; 95% CI: −1.02 to −0.35; P = 0.0001) in overweight and obese participants [42]. A meta-analysis by Moraru et al. [43] studying 14 RCT in 1101 individuals with a BMI ≥23.6 kg/m^2 concluded that the usage of chitosan supplementation might contribute to a slight short- and medium-term effect on weight loss. After an up to 52 week intervention, subjects included in the trials had a reduction of −1.01 kg, (95% CI: −1.67 to −0.34) and an improvement in cardiovascular factors [43]. Another meta-analysis included 13 trials with a total of 1219 participants, investigating the effect of chitosan after 1 to 6 months of supplementation, demonstrated a −1.7 kg (95% CI: −2.1 to −1.3 kg, $p < 0.00001$) change in weight, compared to placebo [44]. Other beneficial effects of chitosan supplementation includes a decrease in total cholesterol and a decrease in systolic and diastolic blood pressures [44].

The maximum intake recommended by The European Food Safety Authority (EFSA) Panel on Dietetic Products, Nutrition and Allergies (NDA) is 3 g chitosan per day [45].

Glucomannan

Glucomann is a soluble fiber derived from *Amorphophallus konjac*. Glucomaman is specially used for the treatment of constipation, being indicated even in children and during pregnancy [46, 47]. The mechanism of action of glucomanan in body weight loss includes increasing satiety, delaying gastric emptying, and a reduced transit time of food in the small intestine. Therefore, with blunted postprandial insulin excursions, cholesterol absorption is reduced, while there is an increase in fecal fat excretion as well as a reduction in small-bowel transit time [40].

Glucomannan consumption is associated with beneficial effects on body weight in various RCTs and meta-analyses, especially after long-term consumption [48, 49]. After analyzing the results of 14 RCTs on different parameters, Sood et al. [49] revealed that the intake of glucomannan could reduce body weight by −0.79 kg; (95% CI: −1.53, −0.05). On the other hand, a meta-analysis including 8 RCTs showed no difference in weight loss between patients consuming daily dosages ranging from 1000 to 3870 mg glucomannan or placebo (mean difference [MD]: −0.22 kg; 95% CI: −0.62, 0.19; I(2) = 65%) [50]. Some moderate weight loss was observed in obese and overweight subjects in another meta-analysis including results from 6 RCTs by Zalewski et al. [48].

Moreover, supplementation with a soluble viscous fiber complex containing konjac glucomannan, sodium alginate, and xanthan gum reduced the frequency of eating and induced a decrease of body weight and WC [51]. The complex was administered, in the context of a clinical trial, to 83 overweight/obese subjects for a period of 12 weeks. In order to achieve these effects the recommended dose is at least three doses of 1 g each of glucomannan daily with 1–2 glasses of water before meals associated with an energy-restricted diet [49].

*African Mango (***Irvingia gabonesis***)*

The soluble fiber of the seed of *Irvingia gabonensis* (IG), similar to other forms of water-soluble dietary fibers, is a "bulk-forming" laxative which delays stomach emptying, leading to a more gradual absorption of dietary sugar, but also can bind to bile acids in the gut and carry them in the feces, which stimulates the liver to convert more cholesterol into bile acids [52].

A double blind randomized study including 40 subjects (28) receiving IG (1.05 g three time a day for 1 month, while 12 were on placebo) was carried out in order to evaluate the efficacy of IG seeds in the management of obesity [53]. The mean body weight of the IG group was decreased by 5.26 +/− 2.37% ($p < 0.0001$) and that of the placebo group by 1.32 +/− 0.41% ($p < 0.02$). The difference observed between the 2 groups was significant ($p < 0.01$). In addition, in the IG group total cholesterol, LDL-cholesterol and triglycerides significantly decreased, while HDL-cholesterol increased [53]. In a 10 week randomized, double-blind, placebo-controlled trial involving 72 obese or overweight participants the Cissus quadrangularis/IF combination resulted in larger reductions in body weight, body fat, waist size; total plasma cholesterol, LDL-cholesterol and fasting glucose level compared to the Cissus quadrangularis-only group [54]. Similarly, in a randomized double-blind placebo controlled study where IG was administered 150 mg twice daily before meals to overweight and/or obese human volunteers, favorable effects on body weight and a variety of parameters of the metabolic syndrome were observed [55]. Finally, the latest meta-analysis including 5 RCTs [56], indicates good overall efficacy of IG seed extract supplementation on weight loss, but due to poor methodological quality and the insufficient clinical reports, further high quality RCTs are necessary.

Fucoxanthin

Among functional ingredients identified from marine algae (such as *Undaria pinnatifida* or *Laminaria japonica*, and microalgae such as *Phaeodactylum tricornutum* or *Cylindrotheca closterium*), fucoxanthin has received particular interest. Anti-obesity effects of fucoxanthin (a xanthophyll) have been reported. Fucoxanthin induces uncoupling protein 1 (an uncoupling protein dissipates protonmotive force without driving ATP biosynthesis) in abdominal white adipose tissue (WAT) mitochondria, leading to the increased oxidation of fatty acids and heat production in WAT; improves insulin resistance and decreases blood glucose levels through the regulation of cytokine secretions from WAT [57]. The carotenoid end of the polyene chromophore, which contains an allenic bond and two hydroxyl groups, has been suggested as the key structure for its anti-obesity effect. Such anti-obesity effects were primarily detected in murine studies, and further studies are needed in order to confirm all these promising scientific results in humans. Xanthigen-600/2.4 mg (300 mg pomegranate seed oil +300 mg brown seaweed extract containing 2.4 mg fucoxanthin) induces weight loss, reduces body and liver fat content, and improves liver function tests in obese non-diabetic women [58]. Finally, recent results suggest that fucoxanthin could be a promising microbiota-targeted functional-food ingredient as the composition of both cecal and fecal microbiota were significantly changed after 4 weeks of fucoxanthin supplementation [59].

Garcinia cambogia

Garcinia is a large genus in the family *Clusiaceae*, and *G. cambogiais,* a tree native to the forests of India, Nepal, and Sri Lanka, and is the most often used for medicinal purposes [60]. Although numerous chemicals have been isolated from G. cambogia fruit, hydroxycitric acid (HCA) is considered the active ingredient for weight loss. It is believed to have multiple sites of action, but primarily in the liver (where inhibits adenosine triphosphate citrate lyase, which cleaves citrate to acetyl coenzyme A (acetyl-CoA) and oxaloacetate), and brain (causes a decrease in serotonin reuptake). Dosages of *G. cambogia* for weight loss have ranged from 1667 to 4668 mg (taken in divided doses) daily [60].

Based on the available evidence from clinical studies published until February 2017, some authors suggest that *G. cambogia* is unlikely to be effective in obese subjects and even may cause harm [60]. On the other hand, the administration of *G. cambogia* and glucomannan for long-term weight loss in people with overweight or obesity led to reduced weight and improved lipid and glucose profiles [61]. Also, these authors suggested that the presence of several polymorphisms, including perilipin 4 (PLIN4), fat mass and obesity-associated (FTO) protein, and β-adrenergic receptor 3 (ADRB3) might hinder to some degree these effects.

Carnitine

In the human body carnitine can be found in almost every cell. Carnitine plays an important role in energy balance, mitochondrial β-oxidation, and in fatty acid metabolism. L-carnitine is the isomer used in weight loss [62]. Some preclinical findings suggest that the expression of microRNAs which play a role in the pathogenesis of obesity might be modulated by dietary agents and supplements including L-carnitine [63]. In human studies, carnitine supplementation as a weight-loss agent leads to increases in its intracellular concentration and triggers increased fat oxidation and a gradual reduction of the body's fat reserves [64].

Data from a systematic review meta-analysis of RCTs investigating the effect of carnitine on body weight loss concluded that carnitine might be an effective adjuvant for weight loss in adults. A daily intake of 1.8–4 g L-carnitine or levocarnitine showed a greater reduction in body weight and BMI. Subjects who received carnitine lost significantly more weight (MD: −1.33 kg; 95% CI: −2.09 to −0.57) and showed a decrease in BMI (MD: −0.47 kg m^{-2}; 95% CI: −0.88 to −0.05) compared with the control group [65]. The effect of carnitine supplementation on body weight decreases over time.

Green Tea

Both green tea and black tea are made from the leaves of the *Camellia sinensis* plant belonging to the *Theaceae family*. Green tea production is characterized by a rapidly steaming process that prevents fermentation, while during black tea production the leaves endure an extra enzymatic oxidation step during the processing [66]. In green tea there are naturally presented a series of components with biological activity, catechins, a class of polyphenols of low molecular weight. Catechins are present mainly as catechin, epicatechin, catechin gallate, gallocatechin, gallocatechin gallate, epicatechin gallate, epigallocatechin and epigallocatechin gallate [67]. The final concentration of these products in green tea drinks is largely variable depending on growing conditions, how the leaves are dried, harvesting and preparation conditions of the formulation that is consumed. Epigallocatechin-3-gallate (EGCG) was identified as the most abundant green-tea catechin and it is responsible for most of the biological properties of green tea [68]. EGCG reduces body weight by decreasing adipocyte differentiation and proliferation during lipogenesis [69]. Moreover, the anti-obesity mechanism of action of EGCG includes inhibition of pancreatic lipase, an increase in glucagon like peptide-1 (GLP-1) levels, and increased satiety (by enhancing serotonin/dopamine uptake) [70, 71]. Furthermore, high-dose green tea extract (EGCG) at a daily dosage of 856.8 mg may influence body weight by decreasing the secretion of ghrelin while increasing adiponectin levels [72]. In addition, green tea polyphenols also modulates the composition of gut microbiota [73].

There is much scientific literature describing the effect of green tea consumption on weight loss. A recent meta-analysis investigated the effect of green tea in 26 RCTs, including 1344 obese adults [74]. Subjects who consumed green tea had a reduction of around −1.78 kg (95% CI: −2.80, −0.75, p = 0.001), as well as a lower BMI WMD: −0.65 kg/m^2 (95% CI: −1.04, −0.25, p = 0.001). Moreover, there was a non-linear dose-response between dose and duration of green tea consumption and the most pronounced reduction in body weight was observed with 500 mg/day green tea for 12 weeks [74]. The effect of green tea extract on weight loss was recently investigated in a meta-analysis of 16 RCTs including 1090 subjects was analyzed [75]. After green tea extract consumption, the study revealed a reduction in BMI of −0.27 kg/m^2 (95% CI: −0.40 to −0.15, p < 0.0001). Moreover, this recent meta-analysis showed a beneficial effect on glycemic profile as well as an increase in high-density lipoprotein (HDL) levels, while all-cause adverse events were minimal [75]. On the other hand, obese women included in another study investigating the high-dose green tea extract intake, experienced significant weight, BMI, as well as WC reduction [72]. Even at a daily dosage of 856.8 mg EGCG for 12 weeks, subjects included in the study reported no side effects or adverse events. Furthermore, significantly lower ghrelin levels and elevated adiponectin levels were found in the active component study group.

For an optimal effect of green tea on weight loss it is essential that the final product contains in the range of 126–300 mg EGCG and 75–150 mg caffeine and

EGCG:caffeine ratio of 1.8:1 to 4:1 per day [76]. Therefore, we conclude that the use of green tea can be useful for the weight management of obese patients.

Hoodia gordonii

Hoodia gordonii (family *Apocynaceae*) is known for its claimed effects of appetite suppression and weight loss [77]. Future studies are needed to elucidate the mechanisms of action (p57 and Hoodigogenin A might not be the active agents responsible for the weight loss associated), as well as side-effects and appropriate doses. Few clinical trials are available, and these show that a 15 days regimen of repeated consumption of H. gordonii purified extract (HgPE) seems to be associated with significant adverse changes in some vital signs and laboratory parameters [78], while 40 days of repeated consumption resulted in statistically significant reductions in body weight, BMI and WC compared with the placebo group [79]. Thus, additional investigations are needed in order to assess safety and efficacy. Interestingly, a very recent randomized blinded controlled trial study, where a 4 weeks long supplementation with *H. Parviflora* at 9 mg + 200 mg of fructo-oligosaccharides was used in 30 overweight and obese patients, favorable effects were reported on weight loss, decreasing satiety, and improving fat mass, in particular visceral adipose tissue [80].

Pyruvate

The efficacy of pyruvate in reducing body weight was assessed in a meta-analysis including 6 RCTs [81] and the results do not convincingly support pyruvate to be efficacious in reducing body weight. However, it should be noted that there is limited evidence and future trials should be more rigorous and better-designed. In addition, pyruvate supplementation seems to be ineffective as a fat loss strategy in young athletes [82].

Caffeine

The daily consumption of coffee and caffeinated beverages between 494 weight loss maintainers and 2129 individuals from the general population controlling for sociodemographic variables, BMI and physical activity level were investigated [83] and the results indicate that weight loss maintainers consume significantly more cups of coffee and caffeinated beverages. Also, a recent meta-analysis demonstrated that caffeine intake might promote weight, BMI and body fat reduction (the overall pooled beta was 0.29 (95%CI: 0.19, 0.40; Q = 124.5, I^2 = 91.2%); 0.23 (95%CI:

0.09, 0.36; Q = 71.0, I^2 = 93.0%) and 0.36 (95% CI: 0.24, 0.48; Q = 167.36, I^2 = 94.0%), respectively) [84]. Thus, consumption of caffeinated beverages might support weight loss maintenance, but further studies are needed to investigate possible mechanisms.

Bitter Orange

Citrus aurantium L. (bitter orange) extracts that contain p-synephrine as the primary protoalkaloid are widely used for weight loss/weight management, appetite control, energy, and mental focus and cognition, although questions have been raised about the safety of p-synephrine as it has some structural similarity to ephedrine [85]. Mechanistic studies suggest that p-synephrine exerts its effects through multiple actions including its binding to β-3 adrenergic receptors that regulate lipid and carbohydrate metabolism, Neuromedin U Receptor 2 (NMUR2s), and AMP-activated protein kinase, cAMP, and Ca(2+)-dependent mechanisms, but also anti-inflammatory effects.

The consumption of bergamot polyphenol extract complex (BPE-C), a novel bergamot juice-derived formulation enriched with flavonoids and pectins, decreased body weight by 14.8% and BMI by 15.9% in obese participants at the dose of 1300 mg daily [86]. This further correlated with a significant, dose-dependent reduction of circulating hormones balancing caloric intake such as leptin and ghrelin, and upregulation of adiponectin. There has been concern that the consumption of orange juice may potentiate weight gain, particularly because of its sugar content. One randomized trial showed that when consumed concomitantly with a reduced-calorie diet, orange juice does not inhibit weight loss (body weight decreased-6.5 kg; p = 0.363 as well as BMI -2.5 kg/m^2; p = 0.34), and insulin sensitivity, the lipid profile, and inflammatory status all improved [87].

Chromium

Chromium (III) or trivalent chromium, is a trace element widely present in the human diet (around 1–2% of ingested chromium is absorbed from the diet), and food sources such as meat, nuts, cereal grains, molasses, and brewer's yeast provide an especially abundant source. The exact mechanism is not clear, but it is believed to be associated with carbohydrate and lipid metabolism, and may have roles in the action of insulin and serum glucose regulation, while its effects on weight loss is related to its ability to regulate eating behaviour and food cravings, suppress appetite, stimulate thermo-genesis, enhance resting energy expenditure and improve insulin sensitivity [88–90]. Current dietary recommendations suggest a daily intake range between 25 and 45 μg/d for adults [91].

Although the role of chromium supplementation as a weight loss agent remains questionable, recent meta-analyses have reported reductions in body weight (WMD −0.75 kg, 95% CI: −1.04, −0.45, $p < 0.001$), BMI (WMD -0.40, 95% CI: −0.66, −0.13, $p = 0.003$ and body fat percentage (WMD -0.68%, 95% CI: −1.32, −0.03, $p = 0.04$) in individuals with overweight/obesity [92]. Also, one previous meta-analysis [93] shows that chromium supplementation lead to statistically significant reductions in body weight (MD compared to placebo −0.50 kg; 95% CI: −0.97, −0.03). However, the magnitude of the effect is small, and the clinical relevance remains uncertain.

Conjugated Linoleic Acid (CLA)

CLA represents a group of unsaturated fatty acid isomers with several biological effects seen in animals (reduces body fat accumulation, influences lipid and glucose metabolism) and it has been proposed that the trans10-cis12 isomer is the active isomer associated with the anti-obesity and insulin-sensitizing properties, although the metabolic effects in humans in general, and isomer-specific effects specifically, are not well characterized [94]. Interestingly, the gut microbiota has been suggested as a potential mediator of CLA effects on obesity.

Preliminary results showed that CLA may slightly decrease body fat in humans, particularly abdominal fat, but there was no effect on body weight or BMI, lipid or glucose metabolism [95]. However, recent studies indicate that although body weight and BMI were not significantly decreased, the body fat mass ($p = 0.034$), body fat percentage ($p = 0.022$), and truncal fat ($p = 0.027$) as well as serum leptin levels ($p = 0.039$) decreased significantly during intervention with CLA (3 g administered in 3 daily doses for 3 months) [96]. In addition, CLA (3 g/d for 12 weeks) significantly decreased hip circumference compared to placebo ($p = 0.016$), but again had no effect on body weight, BMI, or WC [97]. On the other hand, the t10c12-CLA isomer had been suggested as the bioactive isomer of CLA potentially influencing the body weight changes observed in subjects with T2DM [98]. One very recent meta-analysis indicates that CLA significantly reduced body weight (WMD −0.52 kg, 95% CI: −0.83, −0.21; I^2: 48.0%, $p = 0.01$), BMI (WMD −0.23 kg/m^2, 95% CI: −0.39, − 0.06; I^2: 64.7%, $p = 0.0001$) in overweight and obese subjects compared to the placebo, while the effects on WC was not significant [99]. Additionally, its impact on body weight in subjects older than 44 years (WMD −1.05 kg, 95% CI: −1.75, −0.35; I^2: 57.0%, $p = 0.01$), with longer duration (more than 12 weeks) (WMD −1.29 kg, 95% CI: −2.29, −0.29; I^2: 70.3%, $p = 0.003$) and dosage more than 3.4 g/day (WMD −0.77 kg, 95% CI: −1.28, −0.25; I^2: 62.7%, $p = 0.004$) were greater than comparator groups. Thus, the metabolic effects of CLA seems to be complex and future, longer studies, especially evaluating isomer-specific effects, are warranted.

Coleus Forskohlii Extract Supplementation

Coleus forskohlii extract (CFE) contains forskolin, which plays a major role in mediating the pharmacological action, and it is a popular ingredient of weight loss dietary supplements in Japan [100]. Increased cAMP synthesis by CFE may be associated with enhancement of cAMP-dependent lipolysis in adipose tissue.

The effects of supplementation with CFE (250 mg) on key markers of obesity and metabolic parameters in 30 overweight and obese individuals were investigated in an RCT for 12 weeks [101]. Significant reductions in waist and hip circumference ($p = 0.02$; $p = 0.01$, respectively) as well as HDL-cholesterol increases were recorded in both experimental and placebo groups, while the experimental group showed a favorable improvement in insulin concentration and insulin resistance ($p = 0.001$ and $p = 0.01$, respectively) compared to the placebo group. The results of another randomized, double blind study suggest that CFE (250 mg of 10% CFE two times per day for 12 weeks) does not appear to promote weight loss but may help mitigate weight gain in overweight women with apparently no clinically significant side effects [102]. However, further investigation is needed to validate the effects of CFE/forskolin in humans.

White Kidney Bean (*Phaseolus vulgaris* L.)

White kidney beans, mostly known as common beans (*Phaseolus vulgaris* L.), originate from South America. White kidney beans are important source of energy and vegetarians' proteins. White kidney beans are used as a nutraceutical due to their enrichment in bioactive peptides, polyphenols, resistant starch, and oligosaccharides [103]. One proposed mechanism of action of white kidney beans in weight loss is through its content of alpha-amylase inhibitor with ability to reduce spikes in blood sugar caused by dietary carbohydrates intake [104]. Consequently, after the consumption of white kidney bean extract (WKBE), the absorption of carbohydrates is lowered.

In clinical studies, including one meta-analysis, few products containing white kidney beans extract with high quantities of α-amylase inhibitors for weight loss have been investigated. A meta-analysis analyzed the effect of one single product containing white kidney beans extract (Phase2®) for weight loss [105]. After analyzing data from 11 studies (573 subjects), *Phaseolus vulgaris* supplementation lead to a reduction in body weight by −1.08 kg (95% CI: −0.42 kg to −1.16 kg, $p < 0.00001$), compared to placebo. Moreover, an important reduction in body fat of –3.26 kg (95% CI: −2.35 kg to −4.163 kg, $p = 0.02$) was reported [105]. Other WKBE formulations have been also studied in the context of RCTs in overweight and obese participants. At a dosage between 445 and 3000 mg for 28–84 days of follow-up period, the reported weight loss ranged from 1.8 to 3.5 kg [106]. When comparing high (450 mg) vs low (300 mg) doses of WKBE for 9 months, no difference was observed between the 2 groups, therefore, prolonged supplementation may be equally effective at high or low doses of WKBE supplementation [107]. To our knowledge only 2 studies by Udani et al. [108, 109] reported a significant difference in weight loss in obese participants supplemented with WKBE vs placebo. The first study investigated the effect of 3000 mg/d WKBE (2 × 1500 mg/d) for 56-days, while the second one evaluated the administration of 2000 mg/d for 28-days. These investigators found that those subjects with a greater intake of carbohydrates might benefit more from WKBE supplementation for weight loss with WKBE. Moreover, WKBE could have an impact on other health-related parameters such as blood glucose, insulin, triglycerides, total cholesterol, LDL-cholesterol, oxidative stress markers, gut and microbiota composition [106] as well as antihypertensive, anticancer, antioxidant and anti-inflammatory proprieties [103]. In conclusion, WKBE might be a useful nutraceutical for weight reduction, but more solid clinical evidence including a meta-analysis with all available RCTs is needed.

Prebiotics and Probiotics

Modulation of gut microbiota could be a potential target in the fight against obesity and obesity related disorders [110]. There are differences between lean vs overweight vs obese subjects in terms of gut microbiota composition. Intervention with probiotics could produce changes in gut microbiota composition and therefore could trigger some mechanisms causally related to body weight and body fat. Gut microbiota can change the expression of host genes that are involved in the development of adiposity, fat storage, and oxidation. Moreover, gut microbiota can play an important role in energy metabolism, gastrointestinal hormone modulation, as well as in obesity-related inflammation [111, 112]. The Food and Agriculture Organization of the United Nations (FAO) and World Health Organization (WHO) defined a probiotic as "*live microorganisms that, when administered in adequate amounts, confer a health benefit on the host*", while prebiotic is defined as "*a substrate that is selectively utilized by host microorganisms conferring a health benefit*" [113]. A synbiotic is a combination of both probiotics and prebiotics offering beneficial effect on the host microbiota. Supplementation with prebiotics, probiotics and synbiotics have been demonstrated to possess anti-inflammatory, immunomodulatory, antioxidant, anti-cancer, and anti-aging properties, as well an improvement in the responses to clinical treatment against several diseases [71, 114, 115].

Probiotics and prebiotics can indirectly lead to weight loss by influencing a number of mechanisms. Prebiotics could induce weight loss by modulating gut microbiota and the production of lipopolysaccharide (LPS), that hinders the process of low-grade inflammation and modulates the endocannabinoid (eCB) system. Furthermore, prebiotics are also involved in hunger promoting mechanisms by stimulating release of satiety peptides from L cells in the gut [18]. Probiotic supplementation could also induce beneficial changes in gut microbiota that impact body weight. Some of the proposed mechanism of action also includes production of bioactive compounds by probiotic strains, reduction in fat storage, induction of fatty acid oxidation genes, reduced expression of pro-inflammatory cytokines, and stimulating the production of satiety-inducing peptides [18]. Furthermore, probiotics could influence cholesterol metabolism by metabolizing both cholesterol and bile acids [116].

The inulin type of prebiotics could induce satiety, increase breath-hydrogen excretion, and modulate gut peptides involved in satiety regulation, and prompted the study of bifidobacteria and lactobacilli. *Lactobacillus* spp. and *Bifidobacterium* spp. are two extensively studied probiotics that have provided anti-obesity effects in animal models and human studies [18]. A growing body of literature has examined the administration of prebiotics, probiotics and synbiotics for weight management and the findings are contradictory. A recent review of the literature on this topic and data from a meta-analysis of 19 RCTs including a total of 1412 participants were analyzed. Investigators conclude that supplementation with probiotics or synbiotics had no effect on body weight or BMI and just a small effect in reducing WC [117]. However, this is a general conclusion, as several types of probiotics were investigated as capsules, yogurt, fermented milk, and cheese. Indeed, the biological effect is dependent on the specific prebiotic and probiotic used, and not every probiotic will perform the same role. In addition, the health-related benefit of probiotic supplements is species- and strain-specific [118]. A meta-analysis including 4 RCTs concluded that there is no significant effect of probiotics on body weight and BMI, but the authors reported that due to a low quality of the RCTs analyzed no definitive conclusion could be established [119]. On the other hand, a meta-analysis by Zang et al. [120] investigated the results of 25 studies including 1931 patients. The authors reported that probiotic supplementation could reduce body weight and BMI. Moreover, the effect was greater in overweight and obese subjects, when multiple species of probiotics were administrated, and the duration of intervention was longer than 2 months.

Other Nutraceuticals and Healthy Dietary Patterns

Compared with placebo ($n = 25$), the consumption of dietary supplements containing 125 mg green tea, 25 mg capsaicin and 50 mg ginger for 8 weeks led to a significant decrease in body weight (-1.8 ± 1.5 vs. $+0.4 \pm 1.2$ kg, respectively, $p < 0.001$) and BMI (-0.7 ± 0.5 vs. $+0.1 \pm 0.5$ kg/m^2, respectively, $p < 0.001$) in 25 overweight women. Also, beneficial effects were seen on markers of insulin metabolism and plasma glutathione (GSH) levels [121].

An increased consumption of vegetables, fruits, nuts, legumes, whole grain, but also of fish, eggs, poultry, red meat as well as low to moderate amounts of wine (characteristics of the Mediterranean Diet) has favorable effects on obesity as shown in clinical studies [122], but also in a meta-analysis (where a decrease in body weight (−2.2 kg; 95% CI: −3.9 to −0.6 kg) and BMI (−0.6 kg/m^2; 95% CI: −1 to −0.1 kg/m^2) were reported [123]. It should be highlighted that the Mediterranean dietary model has been supported as a suitable model for T2DM (frequently associated with obesity) and that its beneficial health effects lie primarily in the synergy among various nutrients and foods rather than on any individual component [124]. Furthermore, in a parallel design study of 39 overweight hyperlipidaemic men and postmenopausal women advised to consume either a low-carbohydrate vegan diet (containing increased protein and fat from gluten and soy products, nuts and vegetable oils) or a high-carbohydrate lacto-ovo vegetarian diet for 6 months after completing 1 month metabolic (all foods provided) versions of these diets [125]. The metabolic treatment lead to an approximate 4 kg weight loss that was increased to −6.9 kg on low-carbohydrate and −5.8 kg on high-carbohydrate *ad libitum* treatments (treatment difference (95% CI) −1.1 kg (−2.1 to 0.0), p = 0.047). One meta-analysis of RCTs with 1369 participants assessed the effects of low-carbohydrate diets vs low-fat diets on weight loss and risk factors of CVD [126] and showed a greater reduction in body weight (WMD −2·17 kg; 95% CI −3·36, −0·99) in participants on low-carbohydrate diets.

A multi-ingredient supplement containing primarily raspberry ketone, caffeine, capsaicin, garlic, ginger and *Citrus aurantium* (Prograde Metabolism™ [METABO]) as an adjunct to an 8-week weight loss program, in a randomized, placebo-controlled, double-blind study resulted in significant differences vs. placebo in body weight (−2.0% vs. -0.5%, p < 0.01), but also fat mass (−7.8 vs. -2.8%, p < 0.001), lean mass (+3.4% vs. +0.8%, p < 0.03), waist girth (−2.0% vs. −0.2%, p < 0.0007), hip girth (−1.7% vs. −0.4%, p < 0.003), as well as energy levels [127].

Four-month treatment with a dietary supplement containing cinnamon, chromium and carnosine (1.2 g/day) had no significant effects on body weight and energy, but significantly decreased fasting plasma glucose and increased fat-free mass in overweight or obese pre-diabetic subjects [128]. These beneficial effects might open new avenues in the prevention of diabetes.

In conclusion, nutraceuticals and functional food have a beneficial effect on obesity and body weight. However, the current evidence is limited and still there are controversial findings, while the studies often differ among them (by the length of interventions, the dose used, the methodology, the population selected, etc). Consequently, their direct comparation is not possible. Future, well-designed, and longer-term studies are needed to further support the use of nutraceuticals in the prevention and/or management of obesity as well as obesity-related complications, but also to better understand their underlying mechanisms of action.

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