Dietary Supplements for Weight Loss

Fact Sheet for Health Professionals

Table of Contents

Introduction

This fact sheet provides information on weight-loss dietary supplements*, including summaries of research on the safety and efficacy of several of the most commonly used ingredients in these products.

More than two-third of adults and almost one-third of children and adolescents in the United States are overweight or obese [1,2]. Forty-five percent of overweight Americans and 67% of those who are obese are trying to lose weight [3].

Health experts agree that making lifestyle changes—including following a healthy eating pattern, reducing caloric intake, and engaging in physical activity—is the basis for achieving long-term weight loss [4-7]. But because making diet and lifestyle changes can be difficult, many people turn to dietary supplements promoted for weight loss in the hope that these products will help them more easily achieve their weight-loss goals.

Approximately 15% of U.S. adults have used a weight-loss dietary supplement at some point in their lives; more women report use (21%) than men (10%) [8]. Americans spend about $2.1 billion a year on weight-loss dietary supplements in pill form (e.g., tablets, capsules, and softgels) [9], and one of the top 20 reasons why people take dietary supplements is to lose weight [10].

Dietary supplements promoted for weight loss encompass a wide variety of products and come in a variety of forms, including capsules, tablets, liquids, powders, and bars [11]. Manufacturers market these products with various claims, including that these products reduce macronutrient absorption, appetite, body fat, and weight and increase metabolism and thermogenesis. Weight-loss products can contain dozens of ingredients, and some contain more than 90 [11]. Common ingredients in these supplements include botanicals (herbs and other plant components), dietary fiber, caffeine, and minerals.

In its report on dietary supplements for weight loss, the U.S. Government Accountability Office concluded that "little is known about whether weight loss supplements are effective, but some supplements have been associated with the potential for physical harm" [12]. Many weight-loss supplements are costly, and some of these products' ingredients can interact or interfere with certain medications. So it is important to consider what is known—and not known—about each ingredient in any dietary supplement before using it.

People who are considering using weight-loss supplements should talk with their healthcare provider to discuss these products' potential benefits and risks. This is especially important for those who have medical conditions, including high blood pressure, diabetes, and liver or heart disease. Yet, according to a large national survey, less than one-third of U.S. adults who use weight-loss dietary supplements discuss this use with a healthcare professional [8].

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*Dietary supplements are labeled with a Supplement Facts panel and do not include meal replacement shakes or prescription or over-the-counter medications.

Regulation of Weight-Loss Dietary Supplements

The U.S. Food and Drug Administration (FDA) regulates dietary supplements, including those promoted for weight loss [13]. Like other dietary supplements, weight-loss supplements differ from over-the-counter or prescription medications in that the FDA does not classify them as drugs. Unlike drugs, dietary supplements do not require premarket review or approval by the FDA. Supplement manufacturers are responsible for determining that their products are safe and their label claims are truthful and not misleading. If the FDA finds a supplement to be unsafe, it may take enforcement action to remove the product from the market or ask the manufacturer to recall the product. The FDA and the Federal Trade Commission can also take regulatory actions against manufacturers that make unsubstantiated weight-loss claims about their products. The FDA does not permit dietary supplements to contain pharmaceutical ingredients, and manufacturers may not promote dietary supplements to diagnose, treat, cure, or prevent any disease [13].

For more information about dietary supplement regulation, see the Office of Dietary Supplements (ODS) publication, Dietary Supplements: What You Need to Know.

Common Ingredients in Weight-Loss Dietary Supplements

Weight-loss dietary supplements contain a wide variety of ingredients. Not surprisingly, the amount of scientific information available on these ingredients varies considerably. In some cases, evidence of their purported benefits consists of limited data from animal and laboratory studies, rather than data from human clinical trials. In other cases, studies supporting a given ingredient's use are small, of short duration, and/or of poor quality, limiting the strength of the findings. In almost all cases, additional research is needed to fully understand the safety and/or efficacy of a particular ingredient [3].

Complicating the interpretation of many study results is the fact that most weight-loss dietary supplements contain multiple ingredients, making it difficult to isolate the effects of each ingredient and predict the effects of the combination. Evidence may exist for just one of the ingredients in a finished product, and no evidence may be available for an ingredient when it is combined with other ingredients. Furthermore, dosages and amounts of active components vary widely among weight-loss supplements, and a product's composition is not always fully described in published studies [14]. Studies might also use different and sometimes inappropriate assessment techniques to measure the effectiveness of a given treatment. All of these factors can make it difficult to compare the results of one study with those of another.

Table 1 briefly summarizes the findings discussed in more detail in this fact sheet on the safety and efficacy of the most common ingredients of weight-loss dietary supplements. These ingredients are listed and discussed in the table and text in alphabetical order. Dosage information is provided when it is available. However, because ingredients might not be standardized and many products contain proprietary blends of ingredients, the active compounds and their amounts might not be comparable among products [15].

Table 1: Common Ingredients in Weight-Loss Dietary Supplements*

Ingredient	Proposed Mechanism of Action	Evidence of Efficacy**	Evidence of Safety**
African mango (*Irvingia gabonensis*)	Inhibits adipogenesis and reduces leptin levels	Few clinical trials, all with small sample sizes **Research findings**: Possible modest reduction in body weight and waist circumference	No safety concerns reported for up to 3,150 mg/day for 10 weeks **Reported adverse effects**: Headache, difficulty sleeping, flatulence, and gas
Beta-glucans	Increase satiety and gastrointestinal transit time, and slow glucose absorption	Several clinical trials with weight loss as a secondary outcome **Research findings**: No effect on body weight	No safety concerns reported for up to 10 g/day for 12 weeks **Reported adverse effects**: Flatulence
Bitter orange (*Citrus aurantium* L.)	Increases energy expenditure and lipolysis, acts as a mild appetite suppressant. Synephrine is the proposed active constituent.	Small clinical trials of poor methodological quality **Research findings**: Possible increase in resting metabolic rate and energy expenditure; inconclusive effects on weight loss	Some safety concerns reported, especially for combinations with other stimulants **Reported adverse effects**: Chest pain, anxiety, headache, musculoskeletal complaints, and increased blood pressure and heart rate
Caffeine (as added caffeine or from guarana, kola nut, yerba maté, or other herbs)	Stimulates central nervous system, increases thermogenesis and fat oxidation	Short-term clinical trials of combination products **Research findings**: Possible modest effect on body weight or decreased weight gain over time	Safety concerns not usually reported at intakes less than 400–500 mg/day for adults, significant safety concerns at higher doses **Reported adverse effects**: Nervousness, jitteriness, vomiting, and tachycardia
Calcium	Increases lipolysis and fat accumulation, decreases fat absorption	Several large clinical trials **Research findings**: No effect on body weight, weight loss, or prevention of weight gain based on clinical trials	No safety concerns reported at recommended intakes (1,000–1,200 mg/day for adults) **Reported adverse effects**: Constipation, kidney stones, and interference with zinc and iron absorption at intakes above 2,000–2,500 mg for adults
Capsaicin and other capsaicinoids	Increase energy expenditure and lipid oxidation, increase satiety, and reduce energy intake	Several clinical trials, mostly focused on energy intake and appetite **Research findings**: Might reduce energy intake but no effect on body weight	Few safety concerns reported for up to 33 mg/day for 4 weeks or 4 mg/day for 12 weeks **Reported adverse effects**: Gastrointestinal distress, increased insulin levels, and decreased high-density lipoprotein (HDL) levels
Carnitine	Increases fatty acid oxidation	Several clinical trials with weight loss as a secondary outcome **Research findings**: Possible modest reduction in body weight	No safety concerns reported for up to 2 g/day for 1 year or 4 g/day for 56 days **Reported adverse effects**: Nausea, vomiting, diarrhea, abdominal cramps, and a “fishy” body odor; might increase trimethylamine N-oxide (TMAO) levels, which are linked to greater cardiovascular disease risk

Ingredient	Proposed Mechanism of Action	Evidence of Efficacy**	Evidence of Safety**
Chitosan	Binds dietary fat in the digestive tract	Small clinical trials, mostly of poor methodological quality **Research findings**: Minimal effect on body weight	Few safety concerns reported for 0.24–15 g/day for up to 6 months; could cause allergic reactions **Reported adverse effects**: Flatulence, bloating, constipation, indigestion, nausea, and heartburn
Chromium	Increases lean muscle mass; promotes fat loss; and reduces food intake, hunger levels, and fat cravings	Several clinical trials of varying methodological quality **Research findings**: Minimal effect on body weight and body fat	No safety concerns reported for recommended intakes (20–45 mcg/day for adults) **Reported adverse effects**: Headache, watery stools, constipation, weakness, vertigo, nausea, vomiting, and urticaria (hives)
Coleus forskohlii	Enhances lipolysis and reduces appetite. Forskolin is the proposed active constituent.	Few short-term clinical trials **Research findings**: No effect on body weight	No safety concerns reported at typical doses of 500 mg/day for 12 weeks **Reported adverse effects**: More frequent bowel movements, loose stools
Conjugated linoleic acid	Increases lipolysis, reduces lipogenesis, and promotes apoptosis in adipose tissue	Several clinical trials **Research findings**: Minimal effect on body weight and body fat	Few safety concerns reported for 2.4–6 g/day for up to 12 months **Reported adverse effects**: Abdominal discomfort and pain, constipation, diarrhea, loose stools, dyspepsia, and (possibly) adverse effects on blood lipids and glucose homeostasis
Fucoxanthin	Increases energy expenditure and fatty acid oxidation, suppresses adipocyte differentiation and lipid accumulation	Studied only in combination with pomegranate-seed oil in one trial in humans **Research findings**: Insufficient research to draw firm conclusions	No safety concerns reported from one clinical trial that used 2.4 mg/day for 16 weeks, but not rigorously studied **Reported adverse effects**: None known
Garcinia cambogia (hydroxycitric acid)	Inhibits lipogenesis, suppresses food intake. Hydroxycitric acid is the proposed active constituent.	Several short-term clinical trials of varying methodological quality **Research findings**: Little to no effect on body weight	Some safety concerns reported **Reported adverse effects**: Headache, nausea, upper respiratory tract symptoms, gastrointestinal symptoms, mania, and liver damage
Glucomannan	Increases feelings of satiety and fullness, prolongs gastric emptying time	Several clinical trials of varying methodological quality, mostly focused on effects on lipid and blood glucose levels **Research findings**: Little to no effect on body weight	Significant safety concerns reported for tablet forms, which might cause esophageal obstructions, but few safety concerns with up to 15.1 g/day of other forms for several weeks **Reported adverse effects**: Loose stools, flatulence, diarrhea, constipation, and abdominal discomfort

Ingredient	Proposed Mechanism of Action	Evidence of Efficacy**	Evidence of Safety**
Green coffee bean extract (*Coffea arabica, Coffea canephora, Coffea robusta*)	Inhibits fat accumulation, modulates glucose metabolism	Few clinical trials, all of poor methodological quality **Research findings**: Possible modest effect on body weight	Few safety concerns reported for up to 200 mg/day for as long as 12 weeks, but not rigorously studied; contains caffeine **Reported adverse effects**: Headache and urinary tract infections
Green tea (*Camellia sinensis*) and green tea extract	Increases energy expenditure and fat oxidation, reduces lipogenesis and fat absorption	Several clinical trials of good methodological quality on green tea catechins with and without caffeine **Research findings**: Possible modest effect on body weight	No safety concerns reported for use as a beverage, contains caffeine; some safety concerns reported for green tea extract **Reported adverse effects (for green tea extract)**: Constipation, abdominal discomfort, nausea, increased blood pressure, and liver damage
Guar gum	Acts as bulking agent in gut, delays gastric emptying, increases feelings of satiety	Several clinical trials of good methodological quality **Research findings**: No effect on body weight	Few safety concerns reported with currently available formulations containing up to 30 g/day for as long as 6 months **Reported adverse effects**: Abdominal pain, flatulence, diarrhea, nausea, and cramps
Hoodia (*Hoodia gordonii*)	Suppresses appetite, reduces food intake	Very little published research in humans **Research findings**: No effect on energy intake or body weight based on one study	Some safety concerns reported, increases heart rate and blood pressure **Reported adverse effects**: Headache, dizziness, nausea, and vomiting
Probiotics	Alter gut microbiota, affecting nutrient and energy extraction from food and altering energy expenditure	Few clinical trials **Research findings**: Little to no effect on body fat, waist and hip circumference, or body weight	No safety concerns reported **Reported adverse effects**: Gastrointestinal symptoms, such as gas
Pyruvate	Increases lipolysis and energy expenditure	Few clinical trials, all of weak methodological quality **Research findings**: Possible minimal effect on body weight and body fat	Few safety concerns reported for up to 30 g/day for as long as 6 weeks, but not well studied **Reported adverse effects**: Diarrhea, gas, bloating, and (possibly) decreased HDL levels
Raspberry ketone	Alters lipid metabolism	Studied only in combination with other ingredients **Research findings**: Insufficient research to draw firm conclusions	No safety concerns reported in one 8-week study, but not well studied **Reported adverse effects**: None known

Ingredient	Proposed Mechanism of Action	Evidence of Efficacy**	Evidence of Safety**
Vitamin D	None proposed; associations exist between low vitamin D status and obesity	Several clinical trials **Research findings**: No effect on body weight	No safety concerns reported at recommended intakes (600–800 IU/day for adults); toxic at very high intakes; tolerable upper intake level of 4,000 IU/day for adults **Reported adverse effects**: Anorexia, weight loss, polyuria, heart arrhythmias, and increased calcium levels leading to vascular and tissue calcification
White kidney bean (*Phaseolus vulgaris*)	Interferes with breakdown and absorption of carbohydrates by acting as a "starch blocker"	Several clinical trials of varying methodological quality **Research findings**: Possible modest effect on body weight and body fat	Few safety concerns reported for up to 3,000 mg/day for as long as 12 weeks **Reported adverse effects**: Headache, soft stools, flatulence, and constipation
Yohimbe (*Pausinystalia yohimbe*)	Has hyperadrenergic effects. Yohimbine is the proposed active constituent.	Very little research on yohimbe for weight loss **Research findings**: No effect on body weight; insufficient research to draw firm conclusions	Significant safety concerns reported, especially for yohimbine doses of 20 mg or higher **Reported adverse effects**: Headache, anxiety, agitation, hypertension, and tachycardia, myocardial infarction, cardiac failure, and death

* References to support statements in Table 1 are provided in subsequent text.
**The evidence of efficacy and safety is for the individual ingredients. The efficacy and safety of these ingredients might be different when they are combined with other ingredients in a product.

African Mango [*Irvingia gabonensis* (Aubry-Lecomte ex O'Rorke) Baill.]

African mango, or *Irvingia gabonensis*, is a fruit-bearing tree that is native to western and central Africa [16]. *Irvingia gabonensis* seed kernel extract has been proposed to promote weight loss by inhibiting adipogenesis, as demonstrated in vitro [17]. In addition, a proprietary extract of *Irvingia gabonensis*, IGOB131®, reduces serum levels of leptin [18], a hormone that is positively correlated with body weight and percentage body fat [19]. IGOB131® might also reduce total cholesterol and low-density lipoprotein (LDL) levels [18].

Efficacy: Studies have examined the effects of *Irvingia gabonensis* on weight loss to only a limited extent in humans. A clinical trial conducted in Cameroon randomized 102 overweight or obese adults (body mass index [BMI] >25) to receive either 150 mg IGOB131® or placebo 30–60 minutes before lunch and dinner (300 mg total daily dose) for 10 weeks [18]. Participants who received the extract had significantly lower body weight, body fat, and waist circumference at the end of the trial than those taking a placebo. This trial, along with two others, was included in a 2013 systematic review whose authors reported that *Irvingia gabonensis* extract causes statistically significant reductions in body weight and waist circumference [19]. The authors noted, however, that the trials included in the review used different study methodologies, small samples, short intervention periods, and varying daily doses of *Irvingia gabonensis* extract (300 mg to 3,150 mg); in addition, the trials were all conducted by the same authors. Additional trials with larger samples and diverse populations are needed to determine whether *Irvingia gabonensis* extract is effective for weight loss [19].

Safety: *Irvingia gabonensis* extract appears to be well tolerated. No adverse effects have been found in rats at doses up to 2,500 mg/kg body weight per day [20], but its safety has not been rigorously studied in humans. Most reported adverse effects are mild, including headache, difficulty sleeping, flatulence and gas [19]. However, *Irvingia gabonensis* has been associated with renal failure in a patient with chronic kidney disease [21].

Beta-Glucans

Beta-glucans are glucose polysaccharides found in bacteria, yeasts, fungi, and cereal grains (such as oats and barley). As soluble dietary fibers, beta-glucans are proposed to increase satiety and gastrointestinal transit time and to slow glucose absorption [16]. Consumption of beta-glucans from barley has been shown to reduce energy intake and appetite in humans [22].

Efficacy: Several studies have investigated the effects of beta-glucans on blood lipids, blood pressure, and insulin resistance, with weight loss as a secondary outcome. In one of these studies, 66 overweight women followed a low-calorie diet (designed to produce a 0.5 kg/week weight loss) for 3 months that was supplemented with 5–6 g/day beta-glucan (from oat bran), 8–9 g/day beta-glucan, or no beta-glucan (control) [23]. At the end of the trial, all groups lost weight and had a smaller waist circumference, but there were no significant differences between groups. Similarly, other trials have found that 3–10 g/day beta-glucans for 4–12 weeks does not have a significant effect on weight loss [16].

Safety: Beta-glucans appear to be well tolerated. Reported adverse effects include increased flatulence, but not changes in stool consistency, stool frequency, or bloating [24].

Bitter Orange [(*Citrus aurantium* L.); zhi qiao]

Bitter orange is the common name for the botanical *Citrus aurantium*. The fruit of this plant is a source of p-synephrine (often referred to simply as “synephrine”) and other protoalkaloids [25- 28]. As alpha-adrenergic agonists, synephrine alkaloids can mimic the action of epinephrine and norepinephrine. However, the extent to which bitter orange and synephrine cause similar cardiovascular and central-nervous-system effects to epinephrine and norepinephrine (e.g., increased heart rate and blood pressure) is not clear [25-27].

Studies suggest that bitter orange increases energy expenditure and lipolysis and that it acts as a mild appetite suppressant [25,27]. After the FDA banned the use of ephedrine alkaloids in dietary supplements in 2004 [see section on ephedra (má huáng)], manufacturers replaced ephedra with bitter orange in many products; thus, bitter orange became known as an “ephedra substitute” [29]. Although synephrine has some structural similarities to ephedrine, it has different pharmacological properties [27,30].

Efficacy: Several small human studies have examined whether bitter orange is effective for weight loss [30]. Interpreting the results of these studies is complicated by the fact that bitter orange is almost always combined with other ingredients in weight-loss supplements.

In one study, 20 healthy overweight adults (BMI >25) took a product containing 975 mg bitter orange extract (6% synephrine alkaloids), 528 mg caffeine, and 900 mg St. John’s wort; a placebo; or nothing (control) each day for 6 weeks [31]. All participants also took part in a circuit-training exercise program and were counseled to consume 1,800 kcal/day. At the end of the study, participants taking the combination bitter orange product had a significantly greater reduction in percent body fat and fat mass and a greater increase in basal metabolic rate than those in the placebo and control groups. Participants in all groups lost weight, but the authors did not report whether the mean reduction in body weight in the treatment group (1.4 kg) was significantly greater than that in the placebo group (0.9 kg) or control group (0.4 kg) [32].

In another study, 8 healthy overweight or obese people (BMI 25–40) received counseling to follow a 1,200–1,500 kcal/day diet and were randomized to take either an herbal supplement containing bitter orange (18 mg synephrine/day) and other ingredients, including guarana extract as a source of caffeine (396 mg caffeine/day), or placebo [33]. The peak rise in resting metabolic rate at baseline was significantly higher in participants taking the herbal supplement than those in the placebo group, but the difference was not significant at the end of the 8-week study. Participants taking the herbal supplement had a significant *increase* in mean body weight (1.13 kg) compared with those taking a placebo (0.09 kg) at the end of the study. However, this increase in body weight did not significantly affect body fat and lean tissue levels or waist circumference. The authors noted that the weight gain might have occurred by chance because the trial was insufficiently powered to detect this small difference.

The authors of a 2012 review of 23 small human clinical studies involving a total of 360 participants concluded that synephrine increases resting metabolic rate and energy expenditure [30]. The authors of an earlier review of animal studies, clinical trials, physiologic studies, and case reports concluded that synephrine alkaloids have a "suggestion of some benefit to weight loss," but the available data are very limited and cannot be considered conclusive [25]. Similarly, a 2011 systematic review of four weight loss trials (including the two described above) concluded that the evidence of efficacy for bitter orange/synephrine is contradictory and weak [34]. According to all of these reviews, longer-term clinical trials with rigorous designs and large samples are needed to determine the value of bitter orange for weight loss.

Safety: Products containing bitter orange may have significant safety concerns. Reported adverse effects include chest pain, headache, anxiety, elevated heart rate, musculoskeletal complaints, ventricular fibrillation, ischemic stroke, myocardial infarction, and death [34,35]. However, many of the products with these effects contain multiple herbal ingredients, and the role of bitter orange in these adverse effects cannot be isolated. Some studies indicate that bitter orange and synephrine—as bitter orange extract or pure synephrine—raise blood pressure and heart rate, but other studies show that they do not have these effects [25-27,31,36-39]. For example, a single dose of 900 mg bitter orange standardized to 6% (54 mg) synephrine significantly increased heart rate as well as systolic and diastolic blood pressure for up to 5 hours compared to placebo in 15 healthy men and women [38]. However, in an 8-week clinical trial in 80 healthy, resistance-trained adult men, a dietary supplement containing bitter orange extract (providing 20 mg synephrine/day), 284 mg caffeine, and other ingredients did not increase resting heart rate, systolic or diastolic blood pressure, or reported side effects at 4 and 8 weeks compared to placebo or the same supplement formulation without synephrine [40]. Some researchers have suggested that synephrine might not act directly as a cardiovascular stimulant [27,37,39]. Instead, caffeine, other stimulants in multicomponent formulations, and other constituents of bitter orange or adulterants (such as m-synephrine, which is not naturally present in bitter orange) might be responsible for its observed effects.

Caffeine, Including Caffeine from Guarana, Kola Nut, Yerba Maté, or Other Herbs

Many dietary supplements promoted for weight loss contain added caffeine or an herbal source—such as guarana (*Paullinia cupana*), kola (or cola) nut (*Cola nitida*), and yerba maté (*Ilex paraguariensis*)—that naturally contains caffeine. Green tea and other forms of tea also contain caffeine (see section on green tea). Some weight-loss supplement labels do not declare the amount of caffeine in the product and only list the herbal ingredients. As a result, consumers might not be aware that the presence of certain herbs means that a product contains caffeine and possibly other stimulants [41].

Caffeine is a methylxanthine that stimulates the central nervous system, heart, and skeletal muscles. It also increases gastric and colonic activity and acts as a diuretic [42,43]. Caffeine has a half-life of about 6 hours; blood levels increase within 15–45 minutes of consumption, and they peak at around 60 minutes [44]. Caffeine increases thermogenesis in a linear, dose-dependent fashion in humans [45]. A 100 mg dose of caffeine, for example, increased energy expenditure by a mean of 9.2 kcal/hr more than placebo in healthy humans, and this effect lasted for three hours or more. Caffeine might also contribute to weight loss by increasing fat oxidation through sympathetic activation of the central nervous system and by increasing fluid loss [41,45]. Habitual use of caffeine however, leads to caffeine tolerance and a diminishment of these effects [41,43].

Efficacy: Caffeine increases energy expenditure and fat oxidation [44]. However, the extent to which these effects affect weight loss is less clear, partly because clinical trials examining the effects of caffeine on weight loss have all been short and have used combination products. In one study, 167 overweight or obese participants (BMI 25–40) took a supplement containing kola nut (192 mg/day caffeine) and ma huang (90 mg/day ephedrine) or placebo [46]. Participants were counseled to eat a normal diet except for limiting dietary fat to 30% of calories and to exercise moderately. After 6 months, those in the treatment group lost significantly more weight (mean weight loss 5.3 kg) than those in the placebo group (2.6 kg) and had significantly greater body fat reduction. A product containing caffeine plus glucosyl hesperidin (G-hesperidin, a flavonone glycoside found mainly in citrus fruits) reduced abdominal fat and BMI in a clinical trial in Japan [47]. In this study, 75 healthy, overweight men and women (BMI 24–30) received one of five treatments daily for 12 weeks while maintaining their regular lifestyle and eating habits. The five treatments were placebo and four formulations of 0, 25, 50, or 75 mg caffeine plus 500 mg G-hesperidin. The 75 mg caffeine plus G-

hesperidin significantly reduced BMI by a mean of 0.56 vs. 0.02 for placebo. The 50 or 75 mg caffeine plus G-hesperidin also significantly reduced abdominal fat compared to placebo, whereas the G-hesperidin alone or with only 25 mg caffeine did not significantly affect BMI or abdominal fat. These findings indicate that the higher doses of caffeine might be responsible for the observed effects.

In another study, 47 overweight adults (BMI 26–30) were randomized to take a combination product containing 336 mg yerba maté (1–1.5% caffeine), 285 mg guarana (3–6% caffeine), and 108 mg damiana (a botanical extract that contains essential oils, resins, and tannins but not caffeine) or placebo 15 minutes before each main meal for 45 days while maintaining their normal eating habits [48]. At the end of the study, participants taking the herbal product lost a mean of 5.1 kg compared to 0.3 kg for those taking the placebo.

Data from a 12-year prospective observational study provide some insight into the long-term association between caffeine intake and body weight [49]. In this study, researchers followed 18,417 healthy men and 39,740 healthy women enrolled in either the Nurses' Health Study or the Health Professionals Follow-Up Study. On average, participants gained some weight during the study, but men who increased their caffeine intake during the 12 years of follow-up gained a mean of 0.43 kg less than those who decreased their caffeine consumption. For women, the corresponding mean difference in weight gain was 0.35 kg less. In a cross-sectional study, German adults who had lost weight and maintained the weight loss (n = 494) reported significantly higher consumption of coffee and other caffeinated beverages (mean intake 3.83 cups/day) than the general population (n = 2,129, mean intake 3.35 cups/day), suggesting that caffeine might help with weight loss maintenance [50]. However, further research is needed to confirm this finding.

Safety: For healthy adults, the FDA and the European Food Safety Authority (EFSA) state that up to 400 mg/day caffeine does not pose safety concerns [51,52], whereas the American Medical Association recommends a limit of 500 mg/day [53]. For comparison, an 8-ounce cup of brewed coffee contains about 85–100 mg caffeine . The FDA and EFSA have not set a safe level of intake for children, but the American Medical Association recommends that adolescents consume no more than 100 mg/day, and the American Academy of Pediatrics discourages children and adolescents from consuming caffeine and other stimulants [51-54].

Caffeine can cause sleep disturbances and feelings of nervousness, jitteriness, and shakiness. Caffeine can be toxic at doses of 15 mg/kg (about 1,000 mg for a 150-lb adult), causing nausea, vomiting, tachycardia, seizures, and cerebral edema [42]. Doses above 150 mg/kg (about 10,000 mg for a 150-lb adult) can be fatal. Combining caffeine with other stimulants, such as bitter orange and ephedrine, can potentiate these adverse effects. According to an analysis, 47% of calls to the California Poison Control System in 2006 reporting adverse effects or toxicities potentially caused by dietary supplements involved products containing caffeine [55]

Calcium

Calcium is an essential mineral that is stored in the bones and teeth, where it supports their structure and function. Calcium is required for vascular contraction and vasodilation, muscle function, nerve transmission, intracellular signaling, and hormonal secretion [56]. The Recommended Dietary Allowance (average daily level of intake sufficient to meet the nutrient needs of 97–98% of healthy individuals) for calcium ranges from 1,000 to 1,300 mg/day for children and adults aged 4 years and older.

Several studies have correlated higher calcium intakes with lower body weight or less weight gain over time [57-61]. Two explanations have been proposed. First, high calcium intakes might reduce calcium concentrations in fat cells by decreasing the production of parathyroid hormone and the active form of vitamin D. Decreased intracellular calcium concentrations, in turn, might increase fat breakdown and discourage fat accumulation in these cells [59]. Second, calcium from food or supplements might bind to small amounts of dietary fat in the digestive tract and prevent absorption of this fat [59,62,63]. Dairy products, in particular, might contain additional components that have even greater effects on body weight than their calcium content alone would suggest [60,64-67]. For example, protein and other components of dairy products might modulate appetite-regulating hormones [61].

Efficacy: A 2014 randomized crossover trial in 15 healthy young men found that diets high in milk or cheese (supplying a total of 1,700 mg/day calcium) significantly increased fecal fat excretion compared to a control diet that

supplied 500 mg calcium/day [68]. However, the results from clinical trials examining the effects of calcium on body weight have been largely negative. For example, supplementation with 1,500 mg/day calcium (from calcium carbonate) was investigated in 340 overweight or obese adults (BMI ≥25) with mean baseline calcium intakes of 878 mg/day (treatment group) and 887 mg/day (placebo group) [69]. Compared to placebo, calcium supplementation for 2 years had no clinically significant effects on weight.

The authors of four reviews of published studies on the effects of calcium from supplements or dairy products on weight management reached similar conclusions [70-73]. These reviews include a 2009 evidence report from the Agency for Healthcare Research and Quality whose authors concluded that, overall, clinical trial results do not support an effect of calcium supplementation on weight [70]. In addition, a 2015 meta-analysis of 41 randomized controlled trials found no benefit of calcium supplementation or increased dairy food consumption for body weight or body fat [73]. A 2016 meta-analysis of 33 randomized trials and longitudinal studies lasting 12 weeks to 6 years found that calcium from foods or supplements had no overall effect on body weight [74]. However, in subgroup analyses, calcium did reduce body weight in some groups, including children, adolescents, adult men, premenopausal women, women older than 60, and people with normal BMI [74]. Overall, the results from clinical trials do not support a clear link between higher calcium intakes and lower body weight, prevention of weight gain, or weight loss.

Safety: The Tolerable Upper Intake Level (UL; maximum daily intake unlikely to cause adverse health effects) for calcium established by the Institute of Medicine of the National Academies (now the Academy of Medicine at the National Academies of Sciences, Engineering, and Medicine) is 2,500 mg/day for adults aged 19–50 years and 2,000 mg for adults aged 51 and older [56]. High intakes of calcium can cause constipation and might interfere with the absorption of iron and zinc, although this effect is not well established. High intakes of calcium from supplements, but not foods, have been associated with an increased risk of kidney stones [56,75-77].

Capsaicin and Other Capsaicinoids

Capsaicinoids give chili peppers their characteristic pungent flavor. Capsaicin is the most abundant and well-studied capsaicinoid [78]. Capsaicin and other capsaicinoids have been proposed to have anti-obesity effects via their ability to increase energy expenditure and lipid oxidation, attenuate postprandial insulin response, increase satiety, and reduce appetite and energy intake [78-82]. Other research suggests that capsaicin increases satiety by inducing gastrointestinal distress (e.g., pain, burning sensation, nausea, and bloating, which could all reduce the desire to eat) rather than by releasing satiety hormones [82].

Efficacy: Most research on capsaicin and other capsaicinoids focuses on their effects on energy intake and appetite, rather than body weight. A meta-analysis of eight randomized, placebo-controlled clinical trials evaluated the effects of capsaicinoids on *ad libitum* energy intake in a total of 191 participants who had a normal body weight or were moderately overweight [78]. Doses of capsaicinoids ranged from 0.2 mg in a single meal to 33 mg/day for 4 weeks (via chili powder, chili-containing foods, or chili capsules). Overall, consuming capsaicinoids significantly reduced energy intake by a mean of 74 kcal per meal; body weight was not assessed, so the impact of this calorie reduction on weight loss cannot be quantified. The authors noted that the results suggest that at least 2 mg capsaicinoids are needed to reduce calorie intake but that the studies were very heterogeneous.

A 2017 clinical trial compared 2 mg/day and 4 mg/day capsaicinoid supplements for 12 weeks in 77 overweight adults [83]. At the end of the trial, participants receiving 4 mg/day capsaicinoids reported a mean intake of 252 fewer calories per day than those receiving placebo and a mean of 140 fewer calories per day than those receiving 2 mg/day capsaicinoids. However, the calorie reductions did not significantly affect body weight at either 6 weeks or 12 weeks.

Safety: Supplementation with 4 mg/day capsaicinoids can cause gastrointestinal distress [83]. It might also increase serum insulin and reduce high-density lipoprotein (HDL) cholesterol levels. Otherwise, capsaicin and other capsaicinoids appear to be safe. Research is underway to reduce the pungency and “chili taste” associated with capsaicin while retaining its potential biological effects [81].

Carnitine

Carnitine is the generic term for several compounds, including L-carnitine itself, several acylcarnitines (e.g., acetyl-L-carnitine), and propionyl-L-carnitine. It is composed of the amino acids lysine and methionine [84]. Carnitine is naturally present in animal products such as meat, fish, poultry, and milk and dairy products; small amounts are present in some plant foods. Humans synthesize carnitine from its constituent amino acids, so dietary carnitine intake is not necessary. Almost all cells of the body contain carnitine, which transports fatty acids into the mitochondria and acts as a cofactor for fatty acid beta-oxidation [85]. Because of these effects, carnitine has been proposed as a weight-loss agent.

Efficacy: Studies have primarily evaluated carnitine's effects on lipid levels, cardiovascular disease, and type 2 diabetes; weight loss has been a secondary outcome in most studies. In a clinical trial in 258 patients with uncontrolled type 2 diabetes, 2 g/day L-carnitine plus the pharmaceutical ingredient orlistat (360 mg/day) for 1 year significantly increased weight loss compared to orlistat alone [86]. However, 2 g/day L-carnitine alone for 6 months did not affect weight loss in 94 overweight men and women with newly diagnosed type 2 diabetes [87]. A 2016 systematic review and meta-analysis combined the results from nine carnitine supplementation clinical trials in adults (including the two described above) that assessed weight loss [85].The trials included a total of 911 participants. In eight trials, the daily carnitine doses ranged from 1.8 to 4 g/day L-carnitine or levocarnitine for 30 to 360 days; in one trial, the dose of L-carnitine was 15 mg/kg/day for 182 days. Overall, study participants who received carnitine supplements lost an average of 1.33 kg more weight than those who received a placebo. Additional research on carnitine for weight loss is warranted.

Safety: Carnitine supplements are well tolerated and generally safe at doses up to about 4 g/day, although they can cause nausea, vomiting, abdominal cramps, diarrhea, and a "fishy" body odor [88-90]. Rarer side effects include muscle weakness in patients with uremia and seizures in those with seizure disorders.

Some research indicates that intestinal bacteria metabolize carnitine to form trimethylamine N-oxide (TMAO), a substance that might increase the risk of cardiovascular disease [91]. This effect appears to be more pronounced in people who consume meat than in vegans or vegetarians. The implications of this effect are not well understood and require more research.

Chitosan

Chitosan is a manufactured polysaccharide that is commercially prepared from the exoskeletons of crustaceans. It is purported to promote weight loss by binding to some dietary fat in the digestive tract, preventing its absorption [16,41]. Chitosan might also decrease cholesterol absorption [16].

Efficacy: In a small study, 12 healthy men and 12 healthy women (BMI 20–36) followed the same diet for 12 days (five meals per day with 38% of energy from fat) [92]. Chitosan capsules taken before meals (total of 2.5 g/day) slightly increased fecal fat excretion in the men compared to the control group. However, the amount of fat that the chitosan trapped would result in a loss of only 1 lb body fat over about 7 months. Chitosan had no significant effect on fecal fat excretion in the women compared to the control group.

One clinical trial randomly assigned 59 overweight or obese women (BMI 27–40) to receive either chitosan (3 g/day divided between the two largest meals) or placebo for 8 weeks while continuing their normal dietary and exercise habits [93]. At the end of the study, those in the treatment group lost a mean of 1 kg body weight compared to a mean weight gain of 1.5 kg in the placebo group. The effect of chitosan (3 g/day) with or without ascorbic acid (2 g/day) was evaluated in an 8-week study in overweight women aged 20–30 who followed their regular diet and exercise habits [94]. In this study, chitosan treatment reduced body weight (mean weight loss about 2.5 kg) compared to placebo (mean weight loss about 1 kg); the addition of ascorbic acid led to additional body weight reductions of about 1.5 kg compared to chitosan alone. In contrast, in a 28-day trial, chitosan (2 g/day divided into two equal doses) failed to reduce body weight compared to placebo in 28 overweight women and 6 overweight men who maintained their normal diet during the study [95]. The authors of a Cochrane review that included 13 trials examining the effect of chitosan on body weight found that chitosan, when taken for 4 weeks to 6 months, reduced body weight by a mean of 1.7 kg compared with placebo [96]. They concluded that chitosan appears to be more effective than placebo for short-term weight loss, but most studies have been of poor quality. The authors also noted that results from high-

quality trials indicate that chitosan has minimal effects on body weight, and these effects are probably clinically insignificant.

Safety: The adverse effects of chitosan are minor and primarily involve the gastrointestinal tract. They include flatulence, bloating, mild nausea, constipation, indigestion, and heartburn [93,95,96]. Because chitosan is derived from shellfish, people who are allergic to shellfish could theoretically be allergic to chitosan [97].

Chromium

The trivalent form of chromium (chromium III) is an essential trace mineral that potentiates the action of insulin. The Institute of Medicine of the National Academies (now the Academy of Medicine at the National Academies of Sciences, Engineering, and Medicine) has established an Adequate Intake for chromium of 20–35 mcg/day for non-pregnant, non-lactating adults [98]. Dietary supplements commonly contain chromium in the form of chromium picolinate, which consists of chromium and picolinic acid, although they might also contain other forms, including chromium nicotinate and chromium yeast [99]. Poor chromium status might contribute to impaired glucose tolerance and type 2 diabetes [98]. Researchers have hypothesized that chromium supplements increase lean muscle mass and promote fat loss, but study results have been equivocal [41,100]. Some research indicates that these supplements might also reduce food intake, hunger levels, and fat cravings [101], although data on these effects are sparse.

Efficacy: Several studies have evaluated the effects of chromium supplements, usually in the form of chromium picolinate, on weight loss. A 2013 Cochrane review analyzed the results from 9 randomized controlled trials of chromium picolinate supplements in a total of 622 overweight or obese participants (BMI ≥25) [100]. Trial durations ranged from 8 weeks to 6 months, and doses of chromium picolinate were 200 to 1,000 mcg/day. Six of the trials included resistance or weight training, and three did not. Chromium picolinate supplementation reduced body weight by 1.1 kg more than placebo, but the amount of weight loss did not correlate with the dose of chromium picolinate. The authors stated that the effect is of “debatable clinical relevance” and the overall quality of the evidence is low.

Also in 2013, a systematic review and meta-analysis of 11 randomized controlled trials (including most of the trials evaluated in the Cochrane review) examined the effects of chromium supplementation in a total of 866 overweight or obese individuals [99]. The authors concluded that daily doses of 137 to 1,000 mcg chromium for 8 to 26 weeks reduce body weight by 0.5 kg and percent body fat by 0.46%. Like the authors of the Cochrane review, these authors noted that the effect is small and of “uncertain” clinical relevance. Similar findings were reported from an earlier meta-analysis of 12 trials [102].

Safety: Trivalent chromium appears to be well tolerated. Adverse effects from clinical trials include watery stools, headache, weakness, nausea, vomiting, constipation, vertigo, and urticaria (hives) [99,100]. Chromium does not have an established UL because few serious adverse effects have been linked to high intakes [98]. Hexavalent chromium (chromium IV) is toxic and not found in food or dietary supplements.

Cola (or kola) nut *(see section on caffeine above)*

Coleus forskohlii

Forskolin is a compound isolated from the roots of *Coleus forskohlii*, a plant that grows in subtropical areas, such as India and Thailand. Forskolin is purported to promote weight loss by enhancing lipolysis and reducing appetite [103,104], possibly by stimulating cyclic adenosine monophosphate (cAMP) production. This increased cAMP production, in turn, is thought to activate lipase and promote the release of fatty acids from adipose tissue [16].

Efficacy: Although animal studies indicate that forskolin reduces food intake [103,105], research in humans is very limited and inconclusive. In a small randomized double-blind trial, 19 overweight or obese women (BMI 25–35) aged 18–40 years took either a placebo or an extract of *Coleus forskohlii* (250 mg standardized for 10% forskolin [ForsLean™]) before breakfast and dinner for a total daily dose of 500 mg while continuing their usual diet for 12 weeks [106]. Compared to placebo, *Coleus forskohlii* extract had no effect on body weight, appetite, caloric intake, or macronutrient intake. The same *Coleus forskohlii* extract and dose were evaluated in another 12-week randomized

double-blind trial involving 30 overweight men (BMI ≥26) [104]. In this study, *Coleus forskohlii* extract did not affect body weight, but it did significantly decrease mean body fat by about 4% compared with about 1% for placebo. A similar extract of *Coleus forskohlii* (500 mg/day standardized for 10% forskolin) also failed to reduce body weight compared to placebo in a 12-week trial in 30 overweight or obese adults (BMI >25) consuming a hypocaloric diet, although it significantly reduced plasma insulin concentrations [107].

Safety: In a study in mice, *Coleus forskohlii* extract caused dose-dependent hepatotoxicity, but pure forskolin did not have this effect, suggesting that other component(s) of *Coleus forskohlii* extract might be responsible for the hepatotoxicity [108]. In humans, forskolin might increase the frequency of bowel movements and cause loose stools [107], but doses of 500 mg/day (standardized for 10% forskolin) for 12 weeks have not been reported to cause more serious adverse events [104,106,107]. Forskolin has not been evaluated in longer-term trials. Additional research is needed to better understand the safety and side effects of both short- and long-term use.

Conjugated Linoleic Acid

Conjugated linoleic acid (CLA) is a mixture of linoleic acid isomers containing conjugated double bonds that is present mainly in dairy products and beef. The various isomeric forms of CLA include c9t11-CLA and t10c12-CLA, and it is available in dietary supplements as a triacylglycerol or as a free fatty acid [109]. Researchers have suggested that CLA enhances weight loss by increasing lipolysis and fatty acid oxidation in skeletal muscle, reducing lipogenesis, and promoting apoptosis in adipose tissue [17,110].

Efficacy: Although CLA appears to reduce body fat mass in animals [17], results from human studies suggest that its effects are small and of questionable clinical relevance [111]. One double-blind, placebo-controlled trial evaluated the effects of CLA supplementation (as a 50:50 mixture of c9t11-CLA and t10c12-CLA) in 180 overweight male and female volunteers (BMI 25–30) consuming an ad libitum diet [109]. Participants received CLA as a free fatty acid (3.6 g CLA isomers), CLA as a triacylglycerol (3.4 g CLA isomers), or placebo daily for 1 year. At the end of the study, body fat mass dropped by significant amounts with both forms of CLA compared with placebo; reductions, on average, were 6.9% with CLA as a free fatty acid and 8.7% with the triacylglycerol form. Supplementation with CLA as a free fatty acid (but not as a triacylglycerol) also increased lean body mass compared with placebo.

In another double-blind crossover trial, daily supplementation with CLA oil (6.4 g CLA isomers—approximately equal amounts of c9t11-CLA and t10c12-CLA) for 16 weeks significantly reduced BMI and total body fat compared with safflower oil in 35 obese postmenopausal women (BMI >30) with type 2 diabetes [112]. These findings are similar to those from a 2012 randomized, double-blind, placebo- controlled trial in 63 overweight or obese adults (BMI 24–35) that found statistically significant, but small, reductions in mean weight (0.69 kg) and body fat (0.49 kg) compared to baseline after 12 weeks of CLA use (3.4 g/day, 50:50 mixture of c9t11-CLA and t10c12-CLA) [113]. In contrast, those in the placebo group did not lose a significant amount of body weight (0.09 kg) or body fat (0.1 kg) compared to baseline. However, 3.2 g/day CLA (isomer mixture, mainly c9t11-50% and t10c12-80%) combined with aerobic exercise for 8 weeks did not reduce body fat compared to placebo in 28 obese young women [114]. The authors of a systematic review and meta-analysis of seven randomized controlled trials concluded that taking 2.4–6 g/day CLA for 6–12 months reduces body weight by a mean of 0.7 kg and body fat by a mean of 1.33 kg compared to placebo [111]. However, the authors noted that the “magnitude of these effects is small, and the clinical relevance is uncertain.”

Safety: CLA appears to be well tolerated. Most reported adverse effects are minor, consisting mainly of gastrointestinal disturbances, such as abdominal discomfort and pain, constipation, diarrhea, loose stools, nausea, vomiting, and dyspepsia [3,109,111,113,115,116]. CLA might also increase some markers of oxidative stress and decrease breastmilk fat levels, but additional research is needed to confirm these effects [117].

CLA has been linked to hepatitis in three case reports [118-120]. However, whether CLA caused this toxicity cannot be definitively established because the products were not analyzed to rule out the presence of a contaminant.

CLA might adversely affect lipid profiles, although results from studies are inconsistent. Some research indicates that CLA has no major effect on lipid profiles, but other research shows that certain CLA isomers might decrease HDL

cholesterol and increase lipoprotein(a) levels [109,110,116,121-124]. The CLA isomer t10c12-CLA has also been reported to increase insulin resistance and glycemia in obese men with metabolic syndrome [110,124].

Fucoxanthin

Fucoxanthin is a carotenoid in brown seaweed and other algae. Results from laboratory and animal studies suggest that fucoxanthin might promote weight loss by increasing resting energy expenditure and fatty acid oxidation as well as by suppressing adipocyte differentiation and lipid accumulation [125,126].

Efficacy: Only one clinical trial has been conducted on the possible weight-loss effects of fucoxanthin. This 16-week trial used Xanthigen®, a dietary supplement containing brown seaweed extract and pomegranate-seed oil [127]. In one arm of this study, 110 obese (BMI >30) premenopausal women, 72 of whom had non-alcoholic fatty liver disease (NAFLD), received either a placebo or Xanthigen® three times a day before meals for a total daily dose of 2.4 mg fucoxanthin and 300 mg pomegranate-seed oil. Participants followed a controlled diet that limited total energy intake to 1,800 kcal/day. Compared to the placebo group, those receiving Xanthigen® lost significantly more body weight by the end of the trial (mean loss of 6.9 kg vs. 1.4 kg for placebo in participants with NAFLD; mean loss of 6.3 kg vs. 1.4 kg for placebo in those without NAFLD). Because this is the only clinical trial on a dietary supplement containing fucoxanthin, additional research is needed to understand the supplement's potential effects on body weight and the role of fucoxanthin versus that of the combination or pomegranate oil alone.

Safety: The safety of fucoxanthin has not been thoroughly evaluated in humans. Although participants using Xanthigen® in the clinical trial described above reported no adverse effects [127], further investigation of the safety and potential side effects of fucoxanthin at various levels of intake is required.

Garcinia cambogia

Garcinia cambogia is a fruit-bearing tree that grows throughout Asia, Africa, and the Polynesian islands [128]. The pulp and rind of its fruit contain high amounts of hydroxycitric acid (HCA), a compound that has been proposed to inhibit lipogenesis, increase hepatic glycogen synthesis, suppress food intake, and reduce weight gain [6,15,109,128,129].

Efficacy: Studies in rats have found that *Garcinia cambogia* suppresses food intake and inhibits weight gain [3]. In humans, however, the evidence on whether *Garcinia cambogia* or HCA is effective for weight loss is conflicting, and any effects it has appear to be small [6,17,128-130].

In one randomized, placebo-controlled trial, 89 mildly overweight women (mean BMI 28.6) received *Garcinia cambogia* (800 mg 30–60 minutes before meals for a total daily dose of 2.4 g/day [1,200 mg HCA]) or placebo and followed a 1,200 kcal diet for 12 weeks [131]. Women receiving *Garcinia cambogia* lost significantly more weight (3.7 kg) than those receiving placebo (2.4 kg). However, *Garcinia cambogia* did not alter appetite, and the study produced no evidence that the supplement affected feelings of satiety. In another double-blind, placebo-controlled trial, 135 overweight men and women (BMI 27–38) received either *Garcinia cambogia* (1,000 mg 30 minutes before each meal for a total daily dose of 3,000 mg/day [1,500 mg HCA]) or placebo and followed a high-fiber, low-energy diet for 12 weeks [132]. Participants in both groups lost weight, but the between-group weight-loss differences were not statistically significant. HCA also had no effect on body fat loss.

A 2011 review and meta-analysis of 12 randomized controlled trials with a total of 706 participants examined the effects of *Garcinia cambogia* on weight loss [130]. The findings from nine of the trials (those that had data suitable for statistical pooling) indicate that when taken for 2–12 weeks, *Garcinia cambogia* (1,000–2,800 mg/day HCA) reduces body weight in the short term by a mean of 0.88 kg compared to placebo. However, the authors noted that most of the studies had methodological issues; when they considered the two rigorously designed trials only (which used 1,500 mg/day and 2,800 mg/day HCA), the effect was no longer statistically significant. Therefore, the effect of *Garcinia cambogia* on body weight remains uncertain. The authors of a 2013 review reached similar conclusions, noting that whether *Garcinia cambogia*/HCA is effective for obesity "remains to be proven in larger-scale and longer-term clinical trials" [133].

Safety: The reported adverse effects of *Garcinia cambogia* and HCA are generally mild and include headache, nausea, upper respiratory tract symptoms, and gastrointestinal symptoms [128,130,132]. However, dietary supplements containing *Garcinia cambogia* have been implicated in three cases of mania, which might have been caused by the serotonergic activity of HCA [134]. Symptoms included grandiosity (an unrealistic sense of superiority), irritability, pressured speech, and decreased need for sleep. Reports have also described 10 cases of liver toxicity, resulting in one death and two liver transplants, in people taking products containing *Garcinia cambogia* [43,135-137]. In most of these cases, the products contained other botanical ingredients and minerals as well, so the toxicity cannot be definitively attributed to *Garcinia cambogia*. Because all clinical trials of *Garcinia cambogia* and HCA have been short, its long-term safety is unknown.

Glucomannan

Glucomannan is a soluble dietary fiber derived from konjac root (*Amorphophallus konjac*) that can absorb up to 50 times its weight in water [16]. Like guar gum, glucomannan has been proposed to increase feelings of satiety and fullness and prolong gastric emptying by absorbing water in the gastrointestinal tract [16,138,139]. It might also reduce fat and protein absorption in the gut [16].

Efficacy: Glucomannan appears to have beneficial effects on blood lipids and glucose levels [139], but its effects on weight loss are inconsistent. In one study in Italy, 2 g/day glucomannan in two divided doses in 60 obese children (mean age 11.2 years) for 2 months did not significantly affect weight loss compared to placebo [140]. In a small study conducted in the United States, 20 obese women (weighing ≥20% more than ideal body weight) consumed 3 g/day glucomannan (1 g before each meal) or placebo for 8 weeks [141]. At the end of the study, glucomannan produced significantly greater weight loss (mean loss of 2.5 kg) than placebo (mean gain of 0.7 kg). In another study conducted in the United States, supplementation with glucomannan (3.9 g/day) for 4 weeks in 63 healthy men did not significantly reduce body weight compared with placebo [142]. Eight weeks of glucomannan supplementation (1.33 g before each meal for a total of 3.99 g/day) also failed to significantly reduce body weight compared to placebo in 53 overweight or obese adults who continued their usual dietary and physical activity habits [143].

The authors of a 2015 systematic review of six randomized controlled trials with a total of 293 participants concluded that 1.24 to 3.99 g/day glucomannan for up to 12 weeks does not have a significant effect on body weight compared to placebo [144,145]. Similarly, a 2014 meta-analysis of eight trials that included 301 participants found that glucomannan did not significantly affect weight loss compared to placebo [146]. The authors of an older meta-analysis of 14 studies designed primarily to investigate glucomannan's effect on lipid and blood glucose levels concluded that 1.2 to 15.1 g/day glucomannan reduces body weight by a small but statistically significant amount (mean loss 0.79 kg more than placebo) over about 5 weeks [139].

Safety: Little is known about the long-term safety of glucomannan. Glucomannan appears to be well tolerated for short-term use, with minor adverse effects, including belching, bloating, loose stools, flatulence, diarrhea, constipation, and abdominal discomfort [139,143,144,146]. The use of tablet forms of glucomannan was reported to be associated with seven cases of esophageal obstruction in 1984–1985 in Australia [99]. Users should therefore be cautious when taking glucomannan tablets. Powdered and capsule forms have not been associated with this effect [147].

Green Coffee Bean Extract (*Coffea arabica, Coffea canephora, Coffea robusta*)

The seeds (or beans) of the coffee plant (*Coffea arabica, Coffea canephora, Coffea robusta*) are green until they are roasted. Compared to roasted beans, green coffee beans have higher levels of chlorogenic acid. Green coffee extract, probably because of its chlorogenic acid content, inhibits fat accumulation in mice and humans by regulating adipogenesis. Green coffee extract also modulates glucose metabolism [148-150], perhaps by reducing glucose absorption in the gut [151]. Green coffee beans contain caffeine (see section on caffeine above) [152], although decaffeinated forms are available [16].

Efficacy: In mice, green coffee bean extract in combination with a high-fat diet significantly reduced body weight gain and fat mass [149,150]. Only a few clinical trials have examined the effects of green coffee bean on weight loss in humans, and all were of poor methodological quality. Onakpoya and colleagues conducted a meta-analysis of three

trials in which overweight participants received either 180 or 200 mg/day green coffee extract for 4 to 12 weeks [151]. The researchers concluded that green coffee extract has a moderate but significant effect on body weight (mean weight loss of 2.47 kg more than placebo), but they noted that the methodological quality of all studies included in the meta-analysis was poor.

The authors of another small clinical trial claimed to show a benefit of green coffee extract for weight loss [153], but the study was strongly criticized by the Federal Trade Commission for having several critical flaws in its design [154,155]. Two of the three study authors subsequently retracted the journal publication.

Safety: Green coffee extract appears to be well tolerated, but its safety has not been rigorously studied. Reported adverse effects include headaches and urinary tract infections [151]. The caffeine naturally present in green coffee beans acts as a stimulant and can cause adverse effects, depending on the dose and whether it is combined with other stimulants (see section on caffeine above).

Green Tea (*Camellia sinensis*) and Green Tea Extract

Green tea (*Camellia sinensis*) is a popular beverage consumed worldwide that has several purported health benefits [156]. Green tea is present in some dietary supplements, frequently in the form of green tea extract. The active components of green tea that are associated with weight loss are caffeine (see section on caffeine above) and catechins, primarily epigallocatechin gallate (EGCG), which is a flavonoid [41,156]. A typical brewed cup of green tea has about 240–320 mg catechins [156] and 45 mg caffeine. It has been suggested that green tea and its components might reduce body weight by increasing energy expenditure and fat oxidation, reducing lipogenesis, and decreasing fat absorption [41,157-160]. Green tea might also decrease carbohydrate digestion and absorption [161]. Available green tea extracts cover the range from minimally processed tea leaves to highly processed, manufactured concentrates of single constituents, such as EGCG.

The authors of a meta-analysis of six randomized controlled trials with a total of 98 participants found that caffeine alone or in combination with catechins significantly increases energy expenditure in a dose-dependent fashion compared with placebo [157]. This effect might be important for maintaining weight loss by helping counteract the decrease in metabolic rate that can occur during weight loss. Catechins combined with caffeine also significantly increase fat oxidation, but caffeine alone does not. Other human research indicates that EGCG alone does not increase resting metabolic rate, fat oxidation, or the thermic effect of feeding (the increase in metabolic rate associated with the digestion and absorption of food) [162,163].Taken together, these findings suggest that green tea catechins and caffeine might act synergistically [41,157,158].

Efficacy: Several human studies have examined the effects of green tea catechins on weight loss and weight maintenance. A 2012 Cochrane review analyzed the results from 14 randomized controlled trials of green tea preparations in a total of 1,562 overweight or obese participants [164]. The trials lasted from 12 to 13 weeks, and doses of green tea catechins ranged from 141 to 1,207 mg; in 10 of the 14 trials, the green tea preparations contained caffeine. Green tea supplementation reduced body weight by a mean of 0.95 kg more than placebo. However, when the authors analyzed the six studies that were conducted outside of Japan (where study methodologies were less heterogeneous than in the Japanese studies), they found no statistically significant difference in weight loss for green tea compared to placebo.

Another systematic review and meta-analysis included 15 randomized controlled trials, 6 of which examined the effects of caffeine (39–83 mg/day) with and without green tea catechins (576–690 mg/day) on anthropometric measurements. The authors reported that green tea catechins combined with caffeine over a median of 12 weeks modestly yet significantly reduced body weight by a mean of 1.38 kg and waist circumference by a mean of 1.93 cm compared with caffeine alone [165]. Only two studies in this meta-analysis examined the effects of green tea catechins alone. Their results suggest that green tea catechins alone do not affect body weight or other anthropometric measurements. A subsequent trial also found that decaffeinated green tea extract containing EGCG (1,315 mg/day total catechins) for 12 months had no overall effect on body weight, BMI, or waist circumference in 121 overweight or obese postmenopausal women [166].

A meta-analysis of 11 randomized controlled trials found that people who took EGCG combined with caffeine for 12–13 weeks lost a mean of 1.31 kg more body weight (or gained 1.31 kg less weight) than those in control groups [167]. In 2010, EFSA examined health claims related to green tea and concluded that "a cause and effect relationship has not been established between the consumption of catechins (including EGCG) from green tea…and contribution to the maintenance or achievement of a normal body weight" [168]. Taken together, the findings of these studies suggest that if green tea is an effective weight-loss aid, any effect it has is small and not likely to be clinically relevant [164,165].

Safety: No adverse effects have been reported from the consumption of green tea as a beverage [156]. For green tea extract, most reported adverse effects are mild to moderate, and they include nausea, constipation, abdominal discomfort, and increased blood pressure [164]. Toxicology studies in rats and mice show that green tea extract does not cause cancer but does cause nonneoplastic lesions in many areas of the body, including the nose, liver, and bone marrow [169]. Other evidence in mice shows that high doses of catechins cause liver toxicity. There is also increasing evidence in humans that green tea extract might cause liver damage, though the underlying mechanism is not well understood [170]. An analysis of 1,021 postmenopausal women participating in the Minnesota Green Tea Trial found that women who consumed green tea extract containing 1,315 mg total catechins (including 843 mg EGCG) and 15.8 mg caffeine daily for 12 months had significantly increased liver enzymes compared to those taking a placebo, and some women developed moderate or more severe liver function abnormalities [170]. Other research indicates that green tea polyphenols do not elevate liver enzymes or cause liver dysfunction when consumed by healthy men for 3 weeks at a dose of 714 mg/day [171].

Consumption of some green tea extracts—primarily ethanolic extracts of green tea—has also been linked to liver damage in at least 50 case reports since 2006 [43,172]. In 2008, the U.S. Pharmacopeia (USP) systematically reviewed the safety of green tea products [173]. Based on 34 of the liver damage case reports and animal pharmacological and toxicological information, the USP concluded that the consumption of green tea products "probably" caused 7 cases of liver damage and "possibly" caused 27 cases. The USP noted that problems are more likely when green tea extract is taken on an empty stomach and, therefore, advises taking green tea extracts with food to minimize the possible risk of liver damage. Other researchers and medical experts advise using dietary supplements containing green tea extract only with caution [156].

Guarana *(see section on caffeine above)*

Guar Gum

Guar gum is a soluble dietary fiber derived from seeds of the Indian cluster bean *Cyamopsis tetragonolobus* [16,174]. Guar gum is present in certain dietary supplements and is an ingredient in some food products, especially gluten-free baked goods, because it helps bind and thicken these products. Like glucomannan, guar gum is purported to promote weight loss by acting as a bulking agent in the gut, delaying gastric emptying, increasing feelings of satiety, and, theoretically, decreasing appetite and food intake [16,174].

Efficacy: The authors of a review of guar gum's effects on appetite control concluded that a dose of 2–5 g increases satiety and reduces the frequency of between-meal snacking [175]. However, guar gum does not appear to enhance weight loss. In a 2001 meta-analysis of 20 randomized, double-blind, placebo-controlled trials that statistically pooled data from 11 trials, Pittler and colleagues evaluated the effects of guar gum for body weight reduction in a total of 203 adults [174]. Trial participants included people with hypercholesterolemia, hyperlipidemia, or type 1 or type 2 diabetes; menopausal women; and healthy volunteers. Doses of guar gum ranged from 9 to 30 g/day for 3 weeks to 6 months; most participants followed their usual diet, and some received dietary advice. Compared with placebo, guar gum had no significant effect on weight loss. The authors concluded that guar gum is not effective for body weight reduction. More recently, a randomized study in 44 adults with type 2 diabetes who followed their usual diet found that 10 g/day guar gum significantly reduced waist circumference after 4 and 6 weeks compared to baseline, but it did not affect weight loss [176].

Safety: Reported adverse effects for guar gum are primarily gastrointestinal and include abdominal pain, flatulence, diarrhea, increased number of bowel movements, nausea, and cramps [174,176,177]. Case reports indicate that guar

gum can cause severe esophageal and small-bowel obstruction if taken without sufficient fluid [178,179]. However, these reports were about a guar gum product that is no longer available [178]. In their meta-analysis, Pittler and colleagues concluded that given the adverse effects associated with the use of guar gum, the risks of taking it outweigh its benefits [174].

Hoodia (*Hoodia gordonii*)

Hoodia gordonii is a succulent plant that grows in the Kalahari Desert of southern Africa. The San people have traditionally used hoodia as an appetite suppressant during long hunts. This anecdotal evidence, combined with results of a few animal studies indicating that hoodia reduces food intake [180], led to the widespread marketing of hoodia as a weight-loss supplement in the United States in the early 2000s.

Scientists have not determined the exact mechanism whereby hoodia might suppress appetite. A glycoside commonly called P57, which may have central nervous system activity [181], is widely believed to be the main active ingredient, although not all researchers agree [16,182].

Efficacy: Despite its popularity as a weight-loss supplement, very little scientific research on hoodia has been conducted in humans [183]. In a randomized controlled trial, 49 healthy women (mean BMI 25) aged 18–50 years were randomized to receive *Hoodia gordonii* purified extract (2,220 mg/day in two divided doses taken 1 hour before breakfast and dinner) or placebo combined with an ad libitum diet for 15 days [184]. Compared to placebo, hoodia extract had no significant effect on energy intake or body weight.

Safety: Hoodia has been reported to cause significant increases in heart rate and blood pressure [184]. It also raises bilirubin and alkaline phosphatase levels (which may indicate impaired liver function), although the clinical significance of these findings is unclear because hoodia has not been reported to affect levels of other liver enzymes. Other side effects include headache, dizziness, nausea, and vomiting.

In the past, some hoodia products were found to contain little or no hoodia [185]. According to a report released in 2007, only 30–60% of hoodia products contained adequate amounts of hoodia, although the authors did not indicate whether “adequate” referred to a therapeutic dose or whether the quantity of hoodia matched the label claim [186]; no more recent data on hoodia content in supplements is available.

Maté *(see section on caffeine above)*

Probiotics

The human microbiota, which outnumber human cells by up to 10-fold, have myriad roles in human health [187,188]. Although microbes are found throughout the human body, the vast majority inhabit the colon. The gut microbiota play an important role in nutrient and energy extraction from food. Research in mice suggests that the gut microbiota affect not only energy utilization from the diet, but also energy expenditure and storage within the host [189]. Whether these effects translate to humans is not yet clear. However, manipulating the gut microbiota has been proposed as a method to prevent or treat obesity in humans, and probiotics might provide a way to accomplish this. Probiotics are in foods such as yogurt as well as dietary supplements. The many different strains of probiotics include lactobacilli, streptococci, and bifidobacteria, which all have widely varying effects in the body [188,189].

Efficacy: Most of the research on probiotics and its influence on the gut microbiota and obesity has been in mice, and the results have been promising. For example, probiotic supplementation reduced body weight gain and fat accumulation in obese mice fed a high-fat diet [190].

A limited number of human clinical trials have been conducted and have had inconsistent results. One 12-week clinical trial randomized 210 adults to consume 200 g/day fermented milk containing 10^7, 10^6, or 0 (control) colony-forming units of *Lactobacillus gasseri* SBT2055 (LG2055) per gram of milk [191]. Participants who received 10^7 or 10^6 colony-forming units/g milk of *Lactobacillus gasseri* experienced significant reductions in abdominal fat area (mean reductions of 8.5% and 8.2%, respectively), BMI, waist and hip circumference, and body fat mass compared to the control group. However, a systematic review and meta-analysis of four randomized controlled trials (including the one described above) found no significant effect of probiotics on body weight or BMI [192]. The researchers noted

that the limited number of trials, small samples, and poor methodological quality of the trials limited their ability to draw firm conclusions. Additional research is needed to fully understand the potential effects of probiotics on body weight and obesity in humans.

Safety: Probiotics from foods or dietary supplements are safe in healthy people. No serious adverse effects have been reported in clinical trials [191,192], and side effects are usually minor, consisting of gastrointestinal symptoms, such as gas [193].

Pyruvate

Pyruvate is a three-carbon compound that is generated in the body through glycolysis [194]. Pyruvate is also available as a dietary supplement, frequently in the form of calcium pyruvate. Researchers have suggested that pyruvate enhances exercise performance and reduces body weight and body fat, possibly by increasing lipolysis and energy expenditure [6,195,196].

Efficacy: Only a few studies have examined the effects of pyruvate supplementation in humans. Although some of these studies suggest that pyruvate decreases body weight and body fat, others do not. In a double-blind, placebo-controlled trial, 26 overweight men and women (BMI ≥25) were given 6 g/day pyruvate or placebo for 6 weeks [194]. All participants received counseling to follow a 2,000 kcal/day diet and completed 45–60 minutes of circuit training three times per week. At the end of the trial, the pyruvate group had significant decreases in body weight (mean loss of 1.2 kg), body fat, and percent body fat compared to baseline but no significant changes in lean body mass. In the placebo group, these measurements did not change significantly compared to baseline.

Another small study of 14 obese women (BMI 28–53) found that 30 g/day pyruvate produced greater weight loss and fat loss when isoenergetically substituted for a glucose placebo for 21 days as part of a liquid low-energy diet [197]. However, a double-blind, placebo-controlled trial in 23 overweight women (mean BMI 27.4) who followed their normal diets and participated in weight training and 30 minutes of walking three times per week had a different outcome [196]. In this trial, supplementation with 5 g/day calcium pyruvate for 30 days did not significantly affect body weight, body fat, percent body fat, or lean body mass compared with placebo. The authors of a systematic review and meta-analysis of 6 randomized controlled trials in a total of 203 participants concluded that 5–30 g pyruvate for 3–6 weeks reduces body weight by a mean of 0.72 kg and body fat by a mean of 0.54 kg compared to placebo [195]. However, the authors noted that the methodological quality of all trials is weak, preventing them from drawing firm conclusions.

Safety: The safety of pyruvate has not been rigorously studied. Pyruvate causes gas, bloating, diarrhea, and borborygmus (rumbling noise in intestines resulting from gas) but has no serious adverse effects when taken at doses up to 30 g/day for as long as 6 weeks [194,195,197]. Pyruvate might also increase LDL levels and decrease HDL levels [195,196]. Additional research is needed to better understand the safety and possible side effects of this compound.

Raspberry Ketone

Raspberry ketone is the primary aroma compound found in red raspberries (*Rubus idaeus*), and it is added to some foods as a flavoring agent [16,198]. In vitro and animal studies suggest that raspberry ketone might help prevent weight gain by increasing fatty acid oxidation, suppressing lipid accumulation, and inhibiting pancreatic lipase activity [16]. Although it has been touted on the Internet and national television as an effective way to burn fat, little evidence exists to support this claim.

Efficacy: In mice fed a high-fat diet, raspberry ketone supplementation reduced food intake and body weight compared to the same diet without raspberry ketone [199].

Only one randomized controlled trial has examined the effects of a dietary supplement containing raspberry ketone on weight loss. In this trial, 70 overweight men and women aged 21–45 (BMI >27) received daily supplementation with either a placebo or a weight-loss product, Prograde Metabolism™ (METABO) [200]. This product contained 2,000 mg of a proprietary blend of raspberry ketone, caffeine, bitter orange, ginger, garlic, cayenne, L-theanine, and pepper extract along with B- vitamins and chromium. During the 8-week study, participants followed a calorie-

restricted diet (approximately 500 calories less per day than estimated needs) and engaged in moderate exercise (60 minutes 3 days per week). Compared to the placebo group, those receiving METABO lost significantly more body weight (mean loss of 1.9 kg vs. 0.4 kg for placebo) and fat mass. However, 25 of the 70 participants dropped out of the study, and results were reported for only the 45 participants who completed the study (i.e., the authors did not complete an intention-to-treat analysis). Furthermore, the product contained many ingredients in addition to raspberry ketone, making it impossible to determine the effects of raspberry ketone alone.

Safety: Typical diets provide only a few mg of raspberry ketones a day. Doses contained in dietary supplements typically range from 100 to 1,400 mg, and the safety of such doses has never been evaluated in humans [198]. Participants in the METABO study described above had no serious adverse effects [200]. However, additional research on raspberry ketone is needed to better understand its safety and side effects.

Vitamin D

Vitamin D, which is fat soluble, is present in a few foods, such as fatty fish, cheese, egg yolks, and vitamin D-fortified milk. It is also available in many dietary supplements, and humans synthesize it naturally when their skin is exposed to sunlight. Vitamin D promotes calcium absorption in the gastrointestinal tract and is needed for proper bone growth and remodeling [56].

Observational studies indicate that greater body weights are associated with lower vitamin D status, and obese individuals frequently have marginal or deficient circulating levels of vitamin D [201]. Although obesity does not affect the skin's capacity to synthesize vitamin D, greater amounts of subcutaneous fat sequester more of the vitamin and alter its release into the circulation. Nevertheless, the association between vitamin D and obesity raises the question of whether increasing vitamin D concentrations might reduce body weight [201,202].

Efficacy: Despite the association between low vitamin D levels and obesity, scientific evidence does not support a cause-and-effect relationship. A systematic review and meta-analysis of 15 weight-loss intervention studies that used caloric restriction and/or exercise, but not necessarily vitamin D supplementation or other treatment, found that people who lost weight had a significantly greater increase in serum vitamin D concentrations than those who maintained their weight [202]. The authors commented that the cause of this finding might have been stored vitamin D in body fat and skeletal muscle that was released during weight loss. In another study, 400 IU/day vitamin D and 1,000 mg/day calcium supplementation slightly, but significantly, reduced weight gain compared to placebo in postmenopausal women, especially those with a baseline total calcium intake of less than 1,200 mg/day [203]. However, according to a meta-analysis of 12 vitamin D supplementation trials (including 5 in which body composition measurements were primary outcomes), vitamin D supplements without calorie restriction did not affect body weight or fat mass compared to placebo [204]. Overall, the available research suggests that consuming higher amounts of vitamin D or taking vitamin D supplements does not promote weight loss.

Safety: Vitamin D from both foods and dietary supplements is safe at recommended intakes of 600–800 IU/day for adults [56]. Vitamin D toxicity can cause anorexia, weight loss, polyuria, and heart arrhythmias. It can also raise calcium blood levels, which can cause vascular and tissue calcification. The UL for vitamin D is 4,000 IU/day for adults and children 9 aged years and older [56].

White Kidney Bean/Bean Pod (*Phaseolus vulgaris*)

White kidney bean or bean pod (*Phaseolus vulgaris*) is a legume that is native to Mexico, Central America, and South America and is cultivated worldwide [140]. *Phaseolus vulgaris* extract is an ingredient in some weight-loss dietary supplements marketed as carbohydrate- or starch-absorption "blockers." Laboratory research indicates that *Phaseolus vulgaris* extract inhibits alpha-amylase activity, so experts have hypothesized that the plant interferes with the breakdown and absorption of carbohydrates in the gastrointestinal tract [16,205-208]. *Phaseolus vulgaris* might also act as an appetite suppressant [205,209].

Efficacy: The effect of *Phaseolus vulgaris* on weight loss and body fat has been examined in a few clinical trials, which had inconsistent results. In a randomized, double-blind, placebo-controlled trial in Italy, 60 mildly overweight women (mean BMI 26) aged 20–45 followed a 2,000–2,200-calorie meal plan and took a tablet containing

approximately 445 mg dried aqueous extract of *Phaseolus vulgaris* (Phase 2® Starch Neutralizer IV) or a placebo once daily before eating a carbohydrate-rich meal [210]. After 30 days, those receiving *Phaseolus vulgaris* extract lost significantly more weight (mean weight loss 2.93 kg) than those receiving placebo (mean weight loss 0.35 kg). Those in the *Phaseolus vulgaris* group also experienced a significantly greater reduction in fat mass, adipose tissue thickness, and waist–hip–thigh circumference. However, in a similar trial in the United States in 39 obese adults (mostly women, BMI 30–43) aged 20–69, those who consumed 1,500 mg Phase 2® starch neutralizer twice daily with lunch and dinner (total daily dose 3,000 mg) for 8 weeks with a high-fiber/low-fat diet did not experience significantly greater weight loss than those receiving a placebo [206].

The authors of a 2011 review of six trials (including the two trials described above) with a total of 247 participants concluded that 445 to 1,500 mg/day *Phaseolus vulgaris* for 4–13 weeks significantly reduced body fat (mean difference 1.86 kg compared to placebo) but did not significantly affect weight loss [205]. However, the authors noted that the quality of the trials included in their review was poor, making it impossible to draw firm conclusions.

After the publication of that review, a 12-week clinical trial in 123 overweight and obese men and women showed that *Phaseolus vulgaris* modestly yet significantly reduced body weight and body fat [211]. Participants consumed either a placebo or 1,000 mg *Phaseolus vulgaris* (IQP-PV-101; marketed under the Phase 2®, Starchlite®, and Phaselite™ brands) three times per day before meals for a total daily dose of 3,000 mg while following a mildly hypocaloric diet (500 kcal/day less than basal energy needs). Compared to those taking placebo, those receiving *Phaseolus vulgaris* lost significantly more body weight (mean loss of 2.91 kg vs. 0.92 kg for placebo) and body fat (2.23 kg vs. 0.65 kg for placebo).

Safety: Reported adverse effects for *Phaseolus vulgaris* are minor and include headaches, soft stools, flatulence, and constipation [205]. No serious adverse effects of *Phaseolus vulgaris* have been reported in clinical trials, but no trials have lasted longer than 13 weeks.

Yerba Maté *(see section on caffeine above)*

Yohimbe (*Pausinystalia yohimbe*)

Yohimbe (*Pausinystalia yohimbe, Pausinystalia johimbe*) is a West African evergreen tree. The tree's bark contains several indole alkaloids, including yohimbine, which is the main active constituent of yohimbe [212]. Yohimbine has hyperadrenergic physiological effects because it acts as an alpha-2 receptor antagonist [6,213]. Yohimbe extract is an ingredient in some dietary supplements that are promoted for libido enhancement, body building, and weight loss [212], but it is used primarily as a traditional remedy for sexual dysfunction in men.

Efficacy: Very little research has been conducted on the use of yohimbe for weight loss and/or its effect on body mass. In a small clinical trial, 5 mg yohimbine taken four times/day resulted in greater weight loss (mean weight loss 3.55 kg) than placebo (mean weight loss 2.21 kg) in 20 obese females (mean BMI 40 for placebo group and 43 for yohimbine group) who followed a low-energy diet (1,000 kcal/day) for 3 weeks [214]. However, in another clinical trial in 47 men (weighing >20% more than ideal body weight), high-dose yohimbine (peak dose 43 mg/day) for 6 months had no effect on body weight or body fat compared with placebo [215]. The authors of a 2011 review of yohimbe concluded that no conclusive evidence indicates that yohimbe affects body weight or body mass [213]. The author of a 2010 review of yohimbe reached similar conclusions, noting that results from small human trials of yohimbine for weight loss are contradictory and the evidence base is insufficient to support a weight loss claim for this compound [212].

Safety: Yohimbe can be dangerous. Taking 20 to 40 mg of yohimbine has been reported to increase blood pressure slightly, whereas doses of 200 mg or higher can cause headaches, hypertension, anxiety, agitation, tachycardia, myocardial infarction, cardiac failure, and death [43,177,212,213,216]. According to an analysis of calls to the California Poison Control System in 2006, 18% of calls reporting an adverse effect or toxicity potentially caused by dietary supplements involved products containing yohimbe [55]. More recently, dietary supplements containing yohimbe accounted for 1,818 self-reports to U.S. poison control centers between 2000 and 2012 [217]. Of these, 30% caused adverse effects deemed "moderate or major," 3.2% required admission to a critical care unit, and one led to a death. Although yohimbe is generally well tolerated at low doses [213], no safe dose has been established for it.

A 2015 analysis determined that only 22% of 49 dietary supplements containing yohimbe or yohimbine listed the quantity of yohimbine on the product label [218]. Many of these amounts were not accurate, and the actual content of yohimbine ranged from 23% to 147% of the labeled amount.

Yohimbe should only be used under medical supervision because of its potential to produce serious adverse effects [219].

Ephedra (Má Huáng), an Ingredient Banned from Dietary Supplements

Ephedra (also known as má huáng), a plant native to China, is the common name for three main species: *Ephedra sinica, Ephedra equisentina, and Ephedra intermedia* [220]. The active compounds, which are in the plant's stem and account for about 1.32% of the plant's weight, are the alkaloids ephedrine, pseudoephedrine, norephedrine, and norpseudoephedrine [221,222].

In the 1990s, ephedra—frequently combined with caffeine—was a popular ingredient in dietary supplements sold for weight loss and to enhance athletic performance. The FDA no longer permits the use of ephedra in dietary supplements because of safety concerns that are detailed below, but information is provided here in response to continued interest in this ingredient.

Efficacy: Ephedrine acts as a stimulant in the central nervous system [223,224], and it might increase thermogenesis and act as an appetite suppressant [225]. The authors of a meta- analysis that included 20 clinical trials concluded that ephedrine and ephedra are modestly effective for short-term weight loss (6 months or less), but no studies have assessed their long-term effects [226].

Safety: While ephedra was available as a dietary supplement ingredient in the United States, its use with or without caffeine was associated with numerous reported adverse effects, including nausea, vomiting, psychiatric symptoms (such as anxiety and mood change), hypertension, palpitations, stroke, seizures, heart attack, and death [226,227]. Although these reported adverse effects could not be linked with certainty to the use of ephedra-containing dietary supplements, the FDA deemed the safety concerns serious enough to prohibit the sale of dietary supplements containing ephedrine alkaloids in 2004 [228]. As a result of this ruling, manufacturers are no longer permitted to sell dietary supplements containing ephedrine alkaloids in the United States.

Safety Considerations

Like all dietary supplements, weight-loss supplements can have side effects and might interact with prescription and over-the-counter medications. In some cases, the active constituents of botanical or other ingredients promoted for weight loss are unknown or uncharacterized [29]. Furthermore, many weight-loss supplements contain multiple ingredients that have not been adequately tested in combination with one another.

Pittler and Ernst noted that for ingredients lacking convincing evidence of effectiveness, "even minor adverse events shift the delicate risk-benefits balance against their use" [6]. People need to talk with their healthcare providers about the use of weight-loss dietary supplements to understand what is known—and not known—about these products.

Fraudulent and adulterated products

The FDA and FTC warn consumers to beware of fraudulent claims about weight-loss dietary supplements [229,230]. Messages like "magic diet pill!", "melt your fat away!", and "lose weight without diet or exercise!" that sound too good to be true usually are. At best, products with claims like these do not live up to them, and even worse, they could be dangerous.

Weight-loss products marketed as dietary supplements are sometimes adulterated or tainted with prescription-drug ingredients; controlled substances; or untested/unstudied, pharmaceutically active ingredients that could be harmful [231].

Between January 2004 and December 2012, 237 dietary supplements were subject to a Class I recall by the FDA, indicating a reasonable probability that use of or exposure to these products would cause serious adverse health

consequences. Of these products, 27% were weight-loss dietary supplements [232]. In most cases, the recall was due to the presence of undeclared drug ingredients. In 2016, the FDA issued 36 public notifications warning consumers not to purchase specific weight-loss products because they contained a hidden drug ingredient—often sibutramine, a weight-loss medication that was withdrawn from the U.S. market in 2010 because of safety concerns [231]. A product represented as a dietary supplement that contains one or more drug ingredients, whether or not these ingredients are declared on the label, is considered an unapproved drug and is therefore subject to enforcement action by the FDA. The FDA maintains a webpage listing public notifications about tainted weight-loss products.

Interactions with medications

Some ingredients in weight-loss dietary supplements can interact with certain medications. For example, glucomannan and guar gum might decrease the absorption of many drugs that are taken orally [147,179]. Glucomannan has been reported to lower blood glucose levels [139] and, therefore, could interact with diabetes medications [147]. Chitosan might potentiate the anticoagulant effects of warfarin [233]. Green tea could interact with chemotherapy drugs [234,235]. *Garcinia cambogia* was associated with serotonin toxicity in a patient taking the supplement together with two selective serotonin reuptake inhibitor medications [236]. Other ingredients, such as caffeine and bitter orange, could have an additive effect if taken with other stimulants. Bitter orange has also been shown to inhibit CYP3A4 activity, leading to increased blood levels of certain drugs, such as cyclosporine and saquinavir [43].

These are just a few examples of interactions between ingredients of weight-loss dietary supplements and medications. Individuals taking dietary supplements and medications on a regular basis should discuss their use with their healthcare provider.

Choosing a Sensible Approach to Weight Loss

As this fact sheet shows, the evidence supporting the use of dietary supplements to reduce body weight and stimulate weight loss is inconclusive and unconvincing, and the cost of these products can be considerable [6,14,29,41]. The best way to lose weight and keep it off is to follow a sensible approach that incorporates a healthy eating plan, reduced caloric intake, and moderate physical activity under the guidance of a heath care provider. For some individuals with a high BMI who have additional health risks, physicians may prescribe adjunctive treatments, including FDA- approved prescription medications or bariatric surgery, in addition to lifestyle modifications [7]. Lifestyle changes that promote weight loss might also improve mood and energy levels and lower the risk of heart disease, diabetes, and some cancers [5].

The Weight-control Information Network, a service of the National Institute of Diabetes and Digestive and Kidney Diseases at the National Institutes of Health, provides several helpful publications on weight control, obesity, physical activity, and related nutritional issues.

The federal government's 2015-2020 *Dietary Guidelines for Americans* notes that "Nutritional needs should be met primarily from foods. … Foods in nutrient-dense forms contain essential vitamins and minerals and also dietary fiber and other naturally occurring substances that may have positive health effects. In some cases, fortified foods and dietary supplements may be useful in providing one or more nutrients that otherwise may be consumed in less-than-recommended amounts."

For more information about building a healthy diet, refer to the *Dietary Guidelines for Americans* and the U.S. Department of Agriculture's MyPlate.

The *Dietary Guidelines for Americans* describes a healthy eating pattern as one that:

- Includes a variety of vegetables, fruits, whole grains, fat-free or low-fat milk and milk products, and oils.
- Includes a variety of protein foods, including seafood, lean meats and poultry, eggs, legumes (beans and peas), nuts, seeds, and soy products.
- Limits saturated and trans fats, added sugars, and sodium.

- Stays within your daily calorie needs.

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