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REVIEW ARTICLE



# Nutritionist and obesity: brief overview on efficacy, safety, and drug interactions of the main weight-loss dietary supplements

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## Abstract

Over the past 20 years the use of dietary supplements as adjuvant therapy for weight loss gained growing favor among consumers and dietician–nutritionists, with the subsequent astounding increase in health costs. Despite the reassuring label of natural remedy for losing weight, dietary supplements contain a wide variety of ingredients on which available information is rather scanty and scientifically incomplete. Currently, there is little evidence that weight-loss supplements offer effective aids to reduce weight and meet criteria for recommended use. Robust, randomized, placebo-controlled studies to provide clear-cut scientific evidence of their efficacy and potential side effects in clinical practice are still lacking. Understanding the evidence for the efficacy, safety, and quality of these supplements among nutritionists and physicians is critical to counsel patients appropriately, especially considering the risk of serious adverse effects and interference with concomitant therapies. Detailed information on the efficacy and safety of the most commonly used weight-loss dietary supplements has been recently published by the National Institutes of Health (NIH). However, in this report the thorny issue that may result from drug interactions with weight-loss dietary supplements has been not sufficiently addressed. The aim of this review was to provide a synthetic, evidence-based report on efficacy and safety of the most commonly used ingredients in dietary supplements marketed for weight loss, particularly focusing on their possible drug interactions.

## Introduction

Obesity, whose prevalence is highly variable throughout the world [1], is involved in the development of several non-communicable diseases, including heart disease, stroke, some type of cancer, and chronic respiratory disease [2]. In addition, obesity contributes to reducing the quality of life [3] and increasing both mortality and morbidity rates [4] and, as a result, it leads to high costs for the national health services [5].

Treatment strategies to achieve optimal weight loss include both diet and lifestyle changes. There is an overall agreement that making lifestyle changes, including the promotion of healthy diet with reduced total energy intake, and engaging in physical activity, are the basis for achieving weight loss [6]. However, to make sustained healthy lifestyle changes for managing body weight might represent a frustrating experience for some patients, especially considering that dieting per se can lead to multiple adaptations in the homeostatic system that controls body weight. Thus, weight regain after weight loss might be unfortunately a common occurrence in obesity therapeutics [7]. In that respect, dietary weight-loss supplements may be perceived to satisfy the common need for a "magic bullet" that is less demanding than lifestyle changes [8]. Despite the fact that many weight-loss supplements are costly, over the past 20 years dietary supplement use [9], especially as adjuvant therapy for weight loss and for the prevention of weight regain after weight loss [10], has increased greatly, thereby becoming of considerable interest among consumers and nutritionists [11]. Considering the growing pace of the obesity epidemic in the Eurozone, the Europe weight loss and weight management diet market is estimated to increase from $2534 million (2190 million €) in 2016 to $3120 million (2696 million €) by 2025. Blanck et al. [12] reported that about 15% of U.S. adults have used a weight-loss dietary supplement during their life, with more women

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reporting their use (21%) than men (10%). The use of dietary supplements raised many serious questions about the scientific consensus on the research on dietary supplements, their effectiveness or on safety issues [13]. Regulation of nutritional supplements, health foods and herbal medicines, including those promoted for weight loss, have been recently revised in both United States and European Union. The term "dietary supplement was defined by the Dietary Supplement Health and Education Act as a product (other than tobacco) intended to supplement the diet that bears or contains 1 or more of the following dietary ingredients: (a) a vitamin, (b) a mineral, (c) an herb or other botanical, (d) an amino acid, (e) a dietary substance for use by man to supplement the diet by increasing the total dietary intake, or (f) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E)." [14]. Dietary supplements are therefore products intended to supplement the diet, generally taken orally, and found as capsules, tablets, liquids, or powders [10].

Dietary supplements are not drugs and, therefore, are not intended to treat, diagnose, mitigate, prevent, or cure diseases. Nevertheless, due to their low toxicity profile and easy availability for the general population, these compounds might represent an attractive adjuvant alternative to conventional therapies. Therefore, several patients might turn to dietary weight-loss supplements to achieve and maintain their weight-loss goals, with the a priori assurance of safety and efficacy associated with the term 'natural remedy'. Unfortunately, there is scant information on the intereference of ingredients of weight-loss dietary with certain medications [15, 16]. Nevertheless, the thorny issues that may result from drug interactions with weight-loss dietary supplements have been not sufficiently addressed. Unraveling the efficacy and safety of weight-loss dietary supplements to increase the compliance and the adherence to healthy dietary recommendations could be of strategic relevance in the management of obese patients [https://ods.od.nih.gov/factsheets/WeightLoss-HealthProfessional/].

Detailed information on the efficacy and safety of the most commonly used weight-loss dietary supplements has been recently published by the National Institutes of Health (NIH) [17]. However, in this report the issue of potential drug interactions with weight-loss dietary supplements has been not sufficiently addressed.

This review aims to briefly summarize the information from the evidence-based studies on some of the most commonly used weight-loss dietary supplements and their ingredients particularly focusing on their possible drug interactions. As it is missing a global consensus in terminology for the nutritional supplements, herbal medicines and traditional medicines, in this review the term "dietary supplement" will be used to refer to this category of products.

## β-glucans

### Experimental studies

β-glucans, known for their cholesterol and glucose-lowering effect, are natural soluble fibers that may increase satiety and total gastrointestinal transit time [17]. In diet-induced obesity mice models β-glucan induces the activation of the gut-hypothalamic axis, a significant increase of plasma peptide YY (PYY), with suppression of neuropeptide Y (NPY) messenger RNA (mRNA) in the hypothalamic arcuate nucleus, with consequent increase in satiety and weight loss [18].

### Clinical studies

Besides their effects on glucose levels, several studies have investigated the effects of β-glucans in treating overweight and obesity as a secondary outcome; however they report non-significant effects on weight loss. One study in overweight women that followed a low-calorie diet plus a supplementation of β-glucans or placebo showed that all patients lost weight and had a smaller waist circumference, but without significant differences between groups [19]. Controversial data have been reported regarding the correlation between β-glucans and satiety [10]. Therefore, there is still insufficient evidence that demonstrated that β-glucans administration may be useful in treating obesity.

### Safety and drug interactions

β-glucans administration is well tolerated and the most frequent reported adverse effects include flatulence [20]. No limiting doses are suggested. A possible negative effect of β-glucans is the interference with absorption of other nutrients from the diet. It has also been reported that β-glucans might act as an immune system activator, thereby interacting with medications that decrease the immune system, such as cyclosporine, tacrolimus, sirolimus together with prednisone and corticosteroids [20]. Moreover, β-glucans interact with several non-steroidal anti-inflammatory, including diclofenac, ibuprofen, ketoprofen, naproxen, and aspirin [20].

## Bitter orange

### Experimental studies

Bitter orange, the fruit of the *Citrus aurantium*, is a source of multiple phytochemicals including *p*-synephrine, a primary protoalkaloid widely used for weight-loss management as suppressor of appetite and stimulator of energy expenditure and lipolysis [21, 22]. Its anorexic effect has been shown to prevent weight gain in a ketotifen-induced

obesity mice model [23]. Moreover, bitter orange promotes lipolysis in mice, due to its action on β3-receptors, and increases thermogenesis and β-oxidation [22]. Very recently Maldonado et al. [24] reported *p*-synephrine decreases the pyruvate dehydrogenase activity, thus inhibiting the transformation of carbohydrates into lipids, and increases the adenosine triphosphate-adenosine diphosphate pool, with beneficial effect on the cellular energetics in perfused liver.

### Clinical studies

Several clinical trials have demonstrated positive outcomes regarding the correlation between the consumption of bitter orange and weight loss [25, 26]. However, in these studies the bitter orange has been studied in a combination of different products and its individual effect could not be evaluated [22]. An increase in basal metabolic rate has been observed in a small clinical trial, either as a single administration of p-synephrine or as a combination of p-synephrine and flavonoids [27]. Currently, there is not enough evidence to recommend the consumption of bitter orange as an adjuvant in weight-loss management [22].

### Safety and drug interactions

*p*-Synephrine is chemically similar to ephedrine, the main chemical in the Herb Ephedra, which is banned by the U.S. Food and Drug Administration due to its cardiovascular adverse effects, including heart attack, stroke, seizures, and sudden death. *p*-Synephrine might exert as well effects on the cardiovascular system due to its sympathomimetic activity, and The National Collegiate Athletic Association placed *p*-synephrine on its current list of banned drugs; nevertheless, the World Anti-Doping Agency (WADA) does not ban this compound and ephedra-free weight-loss dietary supplements containing bitter orange at a dose of up to 98 mg for 60 days did not present any adverse effects [10, 28]. Among the side effects, rarely it has been reported to occur chest pain, tachycardia, anxiety, dyspnea, and pain in the lower left quadrant, but the combinations with other stimulants containing multiple herbal ingredients makes it difficult to isolate the role of bitter orange in these adverse effects [22]. Thus, the risk for high blood pressure and cerebrovascular diseases increases when bitter orange extract is taken with stimulants such as caffeine or caffeine-containing herbs. A recent, placebo-controlled, cross-over, double-blinded study however evidenced that bitter orange and *p*-synephrine were without stimulant (cardiovascular) and hemodynamic effects although the caffeine consumed by the participants varied markedly [29]. Owing to the inhibition of cytochrome P450 (CYP) 3A4 activity, bitter orange can increase blood levels of drugs, such as cyclosporine, an immunosuppressant medication, and saquinavir, an antiretroviral protease inhibitor [16]. Additive effects with antidepressant monoamine oxidase inhibitors (MAOIs) and anti-diabetic drugs have also described [30].

## Caffeine

### Experimental studies

Experimental evidence on the sympathomimetic effect of caffeine as a potent inhibitor of cyclic adenosine monophosphate (cAMP) phosphodiesterase is robust, although the doses which can be consumed in humans do not give a high enough tissue concentration to be associated with meaningful phosphodiesterase inhibition [31]. As it competitively and nonselectively inhibits adenosine receptors in the presynaptic nerve terminals in vitro, caffeine increases fat oxidation through sympathetic activation of the central nervous system and decreases the energy intake, as evidenced in adenosine A ($2_A$) receptor knockout mice [31]. Moreover, studies in animal models provide evidence that caffeine influences energy balance by up-regulating the expression of uncoupling protein (UCPs) in brown adipose tissue and skeletal muscles, with an increase in thermogenesis in a dose-dependent fashion [31].

### Clinical studies

A recent cross-sectional study reported that adults who maintained their weight after weight-loss significantly consumed more cups of coffee and caffeinated beverages compared with the general population sample, suggesting that caffeine might help with weight-loss maintenance [32]. Nordestgaard et al. [33] demonstrated that a higher coffee consumption was associated with a low risk of obesity, metabolic syndrome and type 2 diabetes, suggesting that caffeine might prevent also comorbidity of obesity. However, clinical trials investigating the effect of caffeine alone on body weight are missing and further research is needed to confirm these findings.

### Safety and drug interactions

The Food and Drug Administration (FDA), the European Food Safety Authority (EFSA) and the American Medical Association recommend for adults a limit of caffeine between 400–500 mg/day [34]. Doses of caffeine of 15 mg/kg can be toxic for an adult and can cause nausea, vomiting, tachycardia, seizures and cerebral edema and the combination of caffeine with other stimulants, such as bitter orange, can potentiate these effects [35]. The concomitant administration of caffeine and other drugs metabolized by the CYP1A2, including selective serotonin reuptake inhibitors,

antiarrhythmics, MAOIs, lithium, bronchodilators and quinolones, may cause pharmacokinetic interactions causing toxic effects [36]. Caffeine also reduces the bioavailability of [37] alendronate (~60%) [35]. Estrogen drugs decrease clearance of caffeine up to 50–65%, thereby increasing possible adverse effects and possible drug interactions [16].

## Calcium

### Experimental studies

Data from animal studies suggest that calcium intake may affect both lipogenesis and lipolysis within adipocytes via modulation of calcitropic hormones, such as vitamin D and parathyroid hormone [38]. High dietary calcium intake seems to reduce its intracellular concentrations in adipose cells, thereby improving fat degradation and reducing fat accumulation [38]. Decreased dietary calcium also decreases saponification of fatty acids in the gut bound to calcium, thus increasing the fat absorption [38]. In spontaneous hypertensive rats high-calcium diet induces a lower net weight gain than rats fed a low-calcium diet; in addition, diets high in dietary calcium and sodium induces favorable changes in total body fat in both spontaneous hypertensive rats and its normotensive genetic control Wistar-Kyoto rats [38].

### Clinical studies

A meta-analysis of randomized controlled trial (RCTs) concluded that an increased calcium intake impaired the absorption of dietary fat and resulted in increased excretion of fecal fat [39]. Observational studies demonstrated that dietary calcium intake is inversely correlated to body weight and body fat mass [38]. Results deriving from two recent meta-analyses did not confirm the link between higher calcium intakes and lower body weight [40, 41]. The meta-analysis by Booth et al. [40] including 41 RCTs showed that calcium supplementation or an increased dairy food intake did not significantly affect body weight or body fat. The second meta-analysis including 4733 participants found that calcium supplements could reduce body weight only in some groups of subjects who have a normal body mass index (BMI) or in children and adolescents, adult men, or premenopausal women [41].

### Safety and drug interactions

The Recommended Dietary Allowance (RDA) for calcium ranges from 700 to 1300 mg/day for children and adults aged 1 years and older [42]. High intakes of calcium can cause constipation and increased risk of kidney stones. Calcium supplementation interacts with several drugs through different mechanisms [43]. It reduces the absorption of bisphosphonates (including alendronate, etidronate, risedronate, tiludronate), levothyroxine and antibiotics (including quinolones and tetracyclines), thereby reducing the efficacy of these drugs [43]. Moreover, calcium supplementation together with thiazide diuretics may increase the total amount of calcium in the body, causing hypercalcemia, metabolic alkalosis, and renal failure. It may cause also cardiotoxicity when administrated together with digoxin, as calcium increases the effect of this drug leading to arrhythmia and cardiovascular collapse. In association with verapamil, calcium may cause a reversal of the hypotensive effects [43].

## Capsaicin

### Experimental studies

Weight-loss effects on lipid oxidation and energy expenditure of capsaicin, a major active compound from chili peppers, have been extensively reported [44]. In addition, capsaicin acts by activating transient receptor potential vanilloid (TRPV)-1 (nonspecific calcium channel) that has a key role in the regulation of body weight, glucose and lipid metabolism, and the cardiovascular system [44]. In particular, experimental studies provide evidence that capsaicin induces thermogenesis by increasing the expression of metabolically important thermogenic genes in brown adipose tissue, including UCP-1, suppresses appetite and increases satiety by regulating neuronal circuits involved in the hypothalamic control of food intake, and modulates the gut microbiome. In the 3T3-L1 pre-adipocytes and in adipocytes from an obese mouse model (C57BL/6J), the capsaicin decreases body fat accumulation by inhibiting adipogenesis through the down-regulation of the expression of peroxisome proliferator-activated receptor (PPAR)-γ and TRPV-1, and increased adiponectin expression [45]. In male C57BL/6 mice it has been reported that capsaicin, at the level of the hypothalamus, can suppress appetite, increase satiety and reduce leptin resistance, via the signal transducer and activator of transcription-3 (STAT-3) [44]. In the gastrointestinal tract and gut microbiome of wild-type and TRPV-1−/− mice, capsaicin can stimulate glucagon-like peptide 1 (GLP-1) secretion and increase specific gut bacteria populations [44]. In addition, capsaicin might act in a TRPV-1-independent manner, by inactivating nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), activating PPARγ, modulating the adipocyte function of adipose tissues in obese mouse and suppressing the inflammatory responses of adipose tissue macrophages [44].

### Clinical studies

The consumption of foods containing capsaicin is associated with a lower prevalence of obesity [44]. However, a recent meta-analysis of eight studies (191 participants) reports that a dose of 2 mg capsaicin ingestion prior to a meal reduced energy intake by 74 kcal, thereby concluding that its consumption may contribute to weight management through reductions in total energy intake [46].

### Safety and drug interactions

Capsaicin appears to be safe. The adverse effects might be gastrointestinal distress, sweating, flushing, rhinorrhea [47]. Capsaicin induces a triphasic pressure response exhibiting an immediate decrease, intermediate increase, and delayed prolonged decrease in blood pressure that can be due to the activation of adrenergic or angiotensinergic mechanisms, but the acute ingestion of large quantity of chili peppers has been reported to produce a severe hypertensive crisis in a patient [48]. Capsaicin increased absorption and bioavailability of theophylline [49]. In addition, capsaicin compounds can interfere with antihypertensive [48], antidiabetic, anti-anticoagulant drugs (capsaicin has antiplatelet effects), and antilipemic drugs [50]. Capsaicin inhibits CYP2C19, thus affecting the intracellular concentration of drugs metabolized by this enzyme, and induces CYP3A4, which may increase the clearance of drugs metabolized *via* this route when used concomitantly [51].

## Carnitine

### Experimental studies

Carnitine, a quaternary ammonium compound synthetized in human cells from the essential amino acids L-lysine and L-methionine, has been proposed as a weight-loss compound since it presents a critical role in the mitochondrial β-oxidation, which includes fatty acid metabolism and energy balance [52]. The effect in vitro of L-carnitine on adipogenic differentiation has been previously examined in several studies [52]. In one study, the exogenously added carnitine had an inhibitory role in 3T3-L1 cell differentiation [52]. In addition, mice fed with a carnitine-supplemented high-fat diet for 12 week showed a lower body weight due to increased lipolysis by enhancing carnitine palmitoyltransferase I mRNA expression [52].

### Clinical studies

Recently, a systematic review and meta-analysis of nine RCTs, including 911 participants, evaluated the effect of carnitine supplementation on adult weight loss [53]. The study showed that subjects who received carnitine (1.8 to 4 g/day L-carnitine or levocarnitine) significantly lost more weight and had higher decrease in BMI compared with the placebo control group. However, the effect of carnitine supplementation significantly decreased over time [53].

### Safety and drug interactions

Carnitine supplementation up to 4 g/day is well tolerated [54]. Side effects, such as muscle weakness in patients with uremia and seizures in those who suffer from epilepsy, are rare. Several in vitro studies and RCTs demonstrated that L-carnitine antagonized the peripheral action of thyroid hormones [55]. Thus, carnitine decreases the effectiveness of the supplemented thyroid hormone and may have additive anticoagulant effects when co-administered with warfarin [56].

## Chitosan

### Experimental studies

"Chitosan is a biodegradable and biocompatible polysaccharide, found in the exoskeleton of crustaceans and insects, derived by deacetylation of chitin" [57]. The proposed weight-loss mechanism is the binding and trapping of dietary fat, with decrease in cholesterol absorption, increase in fat excretion and weight loss also without caloric restriction [10]. Recent studies have suggested that exposure of pre-adipocytes to chitosan modulates adipokine secretion and inhibits adipogenesis in vitro [57]. The inhibition of adipogenesis was also reported in mouse 3T3-L1 cells at day 8 post-induction of differentiation in the presence of chitosanin association with the upregulation of the interleukin (IL)-6 gene and the prostaglandin-endoperoxide synthase 2 gene, thereby concluding that IL-6 is a signaling molecule in the chitosan-mediated inhibition of adipogenesis in 3T3-L1 cells [58]. Finally, Chiu et al. [59] have reported that the supplementation of chitosan decreases high-fat diet-enhanced lipogenesis in obese rats via the activation of 5′ adenosine monophosphate-activated protein kinase (AMPK) and the inhibition of lipogenesis-associated genes in liver and adipose tissue.

### Clinical studies

The results of a Cochrane review that included 13 trials provided evidence that the supplementation with chitosan preparations for 4 weeks to 6 months reduced body weight of 1.7 kg compared to placebo [60]. More recently, Pokhis et al. [61] have evaluated the efficacy of chitosan for weight loss in

a randomized double-blind, placebo-controlled clinical investigation on 115 in obese patients. All participants followed a low-calorie diet and they were randomized to receive standard treatment plus placebo or standard treatment plus chitosan, respectively. After 25 weeks, the obese patients treated with chitosan showed a significant amount of weight loss, compared to placebo (−1.8 kg) [61]. Considering the limited studies available, chitosan supplementation cannot be recommended at this time for weight loss.

### Safety and drug interactions

The chitosan appears to be safe in short-term studies, but it should be avoided in individuals with a shellfish or mushrooms allergy. Adverse effects could be: flatulence, bloating, constipation, indigestion, nausea, and heartburn [60]. Chitosan might potentiate the anticoagulant effects of warfarin and prevents some absorption of the fat-soluble vitamins A, D, E, and K [62].

## Chromium

### Experimental studies

Chromium may affect body weight by enhancing insulin sensitivity and stimulating thermogenesis; in addition, chromium modulates the food intake through insulin-sensitive glucoreceptors in the brain, as intracerebroventricularly administered chromium in fasted rats suppressed the food intake at all doses [63]. Salt forms including chromium picolinate, niacin-bound chromium, and chromium chloride, potentiate the activity of molecules involved in insulin signaling and resistance, including insulin receptor (IRS-1), phosphatidylinositol 2-kinase (PI3K) and protein kinase B (Akt) and glucose transporter type 4 (GLUT4) [63]. In particular, treatment of CHO-IR cells with chromium picolinate led to enhance the tyrosine phosphorylation of insulin receptors that increases insulin sensitivity [63]. In in vitro culture of differentiated myotubes chromium also downregulates endoplasmic reticulum stress within the cells, rescuing insulin receptor substrate from Jun NH(2)-terminal kinase (JNK)-mediated serine phosphorylation and subsequent ubiquitination with leads to increased glucose uptake [63].

### Clinical studies

The results of a Cochrane review that included nine trials evidenced that chromium supplementation exerts an effect on body weight of debatable clinical relevance across all doses investigated (200, 400, 500, 1000 µg) after 12 to 16 weeks of treatment [64]. The efficacy of chromium picolinate on weight loss is limited [65, 66]. In particular, Pittler et al. [65] in a meta-analysis of randomized, double-blind and placebo-controlled, have reported a relatively small but significant effect (−1.1 kg) of the chromium picolinate supplementation compared with placebo on reducing body weight. In addition, Lukaski et al. [66] have evaluated in a double-blind, randomized trial the supplementation of 200 µg of chromium picolinate compared with an equivalent amount of picolinic acid and placebo on body weight and body composition in 83 women. After 12 weeks, the chromium picolinate did not affect body weight or fat mass [66].

### Safety and drug interactions

Chromium is well tolerated. The adverse effects include skin irritation, headaches, dizziness, nausea, vomiting, mood changes, watery stools, and weakness [64, 67]. Chromium picolinate has been reported to decrease serum thyroxine concentration, thus it should be administered with caution in subjects taking levothyroxine [68]. Aspirin and non-steroidal anti-inflammatory drugs might increase circulating levels of chromium and increase the risk of adverse effects. Chromium picolinate in combination with insulin or anti-diabetes drugs might cause hypoglycemia [69].

## *Coleus forskohlii*

### Experimental studies

*Coleus forskohlii* is a diterpene and acts directly on adenylatecyclase that activates cAMP and stimulates fat oxidation in animal fat cells [67]. Forskolin further stimulates lipolysis and release of free fatty acids by directly activating hormone-sensitive lipase by phosphorylation of protein kinase A [67]; in addition, it increases thermogenesis and basal metabolic rate [67]. Animal studies have shown that administration with *C. forskohlii* significantly reduces food intake. In particular, administration of *C. forskohlii* extracts in ovariectomized rats reduced the body weight, food intake, and fat accumulation, thus suggesting that *C. forskohlii* may be useful in the treatment of obesity [70].

### Clinical studies

Despite evidence in animal studies [67], researches on humans are limited and inconclusive. Although the administration of extract of *C. forskohlii* 250–500 mg/day standardized for 10% forskolin for 12 weeks [71] did not significantly affect body weight, it has been reported to modify body composition, thereby reducing total fat and improving insulin resistance [72].

### Safety and drug interactions

In in vivo studies, *C. forskohlii* extract causes dose-dependent hepatotoxicity and markedly induced hepatic drug metabolizing enzymes, especially CYP [73]. The reported adverse effects of forskolin in human are increased frequency of bowel movements and loose stools, headache [72]. *C. forskohlii* decreased the anticoagulant action of warfarin through the enhancement of hepatic CYP2C [74]. Forskolin may have additive hypotensive effects with beta-blockers, vasodilators, calcium channel blockers [75]. Finally, forskolin can induce CYP3A gene expression thus potentially increasing the metabolism of CYP3A substrate drugs [76].

## Conjugated linoleic acid

### Experimental studies

Conjugated linoleic acid (CLA), a fatty acid found naturally in the milk and meat of ruminant animals, reduces the lipogenesis in in vitro culture of human adipocytes by inhibition of adipocyte differentiation and induction of apoptosis in adipose tissue; in addition it potentiates the lipolysis and the β-oxidation of fatty acid in the skeletal muscle via different mechanisms, including the increased activity of carnitine palmitoyltransferase-1 and the expression of the UCP-1, and the interaction with PPARγ [77, 78]. In particular, CLA interacts with the co-activator complex PPAR stimulating target genes transcription by binding to specific DNA sequence related to the differentiation of adipocytes, leading to increased lipolysis, β-oxidation, mitochondrial biogenesis and insulin sensitivity [77]. A recent review by Lehnen et al. [77] reported that the weight-loss effect of CLA is not the same in all animal models, as after supplementation with CLA, rats presented a small, but fast reduction of body fat compared with mice.

### Clinical studies

Onakpoya et al. [79] in systematic review and meta-analysis of RCTs, have reported a small significant difference in fat loss with long-term CLA supplementation in overweight and obese individuals vs. placebo (−1.33 kg). The evidence from RCTs does not convincingly show that CLA can have clinically relevant effects on weight loss on the long term [79].

### Safety and drug interactions

CLA appears to be safe. Few adverse effects are reported, such as gastrointestinal disturbances, abdominal discomfort and pain, constipation, diarrhea, loose stools, nausea, vomiting, and dyspepsia [80]. The CLA has also been shown to have anticoagulant/antiplatelet activities. It may increase the effect of drugs with similar properties [81].

## Fucoxanthin

### Experimental studies

Fucoxanthin, a marine carotenoid, is a potent antioxidant compound, and has potential application as anti-diabetic and anti-obesity effects in several animal models, including diabetic mice, Wistar rats, and diet-induced obese C57BL/6J mice [82, 83]. In particular, as reported in a recent review [83], fucoxanthin enhances β-oxidation and reduces lipogenesis in an obese mouse model by increasing the activities of key enzymes in lipid metabolism, such as AMPK and acetyl-CoA carboxylase in adipose tissue. In addition, mice fed with capsules containing fucoxanthin showed increased mRNA expression of UCP-1 in white adipose tissue, with enhanced dissipation of energy through oxidation of fatty acids and heat production [82]. Furthermore, in obese mouse models feeding of fucoxanthin reduces the levels of inflammatory markers, including IL-1β, increased expression of tumor necrosis factor (TNF)-α, and decreases serum levels of adiponectin and expression of leptin [83], and activates the peroxisome proliferator-activated receptor γ co-activator-1α (PGC-1α), a strong promoter of mitochondrial biogenesis and oxidative metabolism through nuclear respiratory factor, modulating the energy balance in mouse white adipose tissues [82].

### Clinical studies

An RCT including 151 non-diabetic, obese premenopausal women who received supplementation with brown marine algae fucoxanthin and/or pomegranate seed oil at different doses, demonstrated that those receiving 300 mg of pomegranate seed oil and 2.4 mg of fucoxanthin significantly reduced body weight and waist circumference increase in resting energy expenditure, measured by indirect calorimetry compared to placebo [84]. However, since this is the only clinical trial that investigated the role of fucoxanthin in the treatment of obesity, no recommendations can be made.

### Safety and drug interactions

No safety dosages, as well as adverse effects, have been reported for fucoxanthin administration in humans [82, 84]. The only known side effect of fucoxanthin supplementation is the risk of thyroid function disorders caused by increased intake of iodine [82, 84]. No drug interactions have been reported.

## *Garcinia cambogia*

### Experimental studies

The key active ingredient found in the rind of garcinia cambogia is a negative isomer of hydroxycitric acid ((−)-HCA) [85]. In experimental animals, HCA may promote weight reduction through the suppression of de novo fatty acid synthesis, an increase in lipid oxidation and reduction in food intake [85]. In particular, HCA is a potent competitive inhibitor of adenosine triphosphate-citrate lyase, an extramitochondrial enzyme catalyzing the cleavage of citrate to oxaloacetate and acetyl-CoA reducing fatty acid and cholesterol biosynthesis [85]. In addition, Saito et al. [82] investigated the effect of garcinia cambogia supplementation to suppress body fat accumulation in male Zucker obese (fa/fa) rats. After 6 weeks of dietary supplementation with HCA there was a significant suppression of epididymal fat accumulation in developing male Zucker obese rats [82].

### Clinical studies

Results of RCTs are controversial [86]. Some studies failed to show significant differences between groups treated with garcinia cambogia supplementation vs. control [87], whereas other studies reported significant weight loss after its supplementation [88]. In particular, the supplementation with 2.4 g/day of garcinia cambogia (1.2 g of HCA) for 12 weeks, reported a significant beneficial effect on weight loss vs. placebo ($3.7 \pm 3.1$ kg vs. $2.4 \pm 2.9$ kg; $p < 0.002$) [89].

### Safety and drug interactions

*Garcinia cambogia* appears to be well tolerated. The most important adverse effects include increased hepatic transaminases and hepatotoxicity[10], while minor adverse effects are headache, nausea, upper respiratory tract symptoms, and gastrointestinal symptoms [90]. Garcinia cambogia might interact with anti-diabetic drugs, as it decreases both plasma glucose and insulin levels [91], and with antidepressants due to an increase in serotonin release [92]. *G. cambogia* extract could modulate the pharmacokinetics of CYP2B6 substrate drugs, including antitumor drugs (cyclophosphamide, ifosphamide, and sorafenib), antimalarials (artemisinin), antivirals (efavirenz) analgesics (methadone, meperidine), and anticonvulsants (valproic acid) [93]. Antilipemic agents such as 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase inhibitors should be avoided due to an increased risk of rhabdomyolysis [16].

## Glucomannan

### Experimental studies

Glucomannan, a soluble fiber obtained from the Konjac root, is contained in several foods and food additives [10]. In rats fed on a hyperlipidic diet, glucomannan lowered liver cholesterol by a viscosity-mediated interference of cholesterol absorption with fecal energy loss as a possible weight-loss mechanism [10, 94]. Weight-loss mechanisms of glucomannan include also slowed absorption of food in the small intestine, with blunted postprandial insulin excursions, increased fecal energy loss, and "promotion of satiety due to the combined effects of increased mastication efforts associated with eating fiber, delayed gastric emptying, reduced small-bowel transit time due the increased viscosity of the gastrointestinal contents, and elevated levels of plasma cholecystokinin, which induce cephalic- and gastrointestinal-phase satiety signals" [10, 94].

### Clinical studies

"In order to obtain the claimed effect, the recommended dose was at least three doses of 1 g each of glucomannan daily, with 1–2 glasses of water before meals, associated with an energy-restricted diet" [95]. A meta-analysis published in 2014 showed that the administration of 1.2 to 15.1 g/day of glucomannan has beneficial effects on blood glycemic and lipid profile, with only a slight effect on body weight over a period of 5 weeks [95]. This effect was not confirmed by Onakpoya et al. [96] that found no convincing evidence suggesting an association between glucomannan and weight loss. Contrasting results were also reported by Zalewski et al. [97].

### Safety and drug interactions

Glucomannan is generally well tolerated for short time periods, but there is scant evidence of its long-term safety. Reported adverse effects are similar to those of other water-soluble, fermentable fibers and include abdominal discomfort, bloating, diarrhea, loose stools, belching and flatulence [95–97]. There are relatively few reported interferences with absorption of some drugs, especially regarding patients taking antihypertensives, antilipemics, antidiabetics, liposoluble vitamins and anti-obesity agents [16]. Glucomannan has been used as an adjunctive therapeutic agent in the treatment of thyrotoxicosis by increasing the enterohepatic circulation of thyroid hormones [16]. Therefore attention should be paid to hyperthyroid patients, but also to diabetic patients for the possible interaction with diabetes medications as glucomannan has been reported to lower blood glucose levels [16].

## Guar gum

### Experimental studies

Guar gum is a gel-forming galactomannan derived from the leguminous plant *Cyamopsis tetragonolobus* and primarily used as a food thickener [98]. Owing to its bulking properties, guar gum has been proposed to promote weight loss, to lower dietary lipids absorption and to increase satiety because of slow gastric emptying [10]. In addition, guar gum acts in vitro as a barrier between starch and starch hydrolyzing enzymes, thereby significantly decreasing its digestion [99].

### Clinical studies

Besides its effects in lowering cholesterol levels and improving insulin sensitivity in healthy subjects [100], there is no evidence of the efficacy of guar gum supplementation on weight loss. A meta-analysis published in 2001 evaluated the effect of guar gum as a weight-loss supplement in a total number of 203 subjects. No significant effect was observed for a supplementation of 9–30 g/day of guar gum up to 6 months [100]. A recent review confirmed the effect of guar gum on increasing satiety and reducing by about 20% daily energy intake via snacking, but no effect on weight loss was found [101].

### Safety and drug interactions

Guar gum supplementation seems to have more risks than benefits. Frequent adverse effects for 9–30 g of guar gum supplementation include abdominal pain and cramps, nausea, diarrhea, flatulence, increased number of bowel movements. Guar gum can decrease the absorption of several drugs, including digoxin, aspirin, paracetamol, rosuvastatin, oral diabetes medications, corticosteroids, and multivitamins [16].

## *Hoodia gordonii*

### Experimental studies

A very comprehensive review reports that *Hoodia gordonii* acts as an appetite suppressant in rodents by possibly increasing adenosine triphosphate content of hypothalamic neurons [102]. The anorectic activity might be also mediated by the suppression of adrenal steroidogenesis *via* the inhibition of the steroidogenic CYP enzymes activity in human adrenocortical H295R cells [103]. In addition it exerts anti-inflammatory effects, including reduced IL-6 and increased leptin levels, with possible favorable effects on obesity-related meta-inflammation [102].

### Clinical studies

There is little clinical evidence on the efficacy of *H. gordonii* supplementation for weight loss in humans [104, 105]. To date, only one double-blind, placebo-controlled, parallel clinical trial analyzed its impact of a dose of 2220 mg/day of *H. gordonii* purified extract or placebo administered in two divided doses for 15 days on weight loss in 49 healthy women. No significant effect on energy intake or body weight relative to the placebo was observed [105].

### Safety and drug interactions

There is little evidence on *H. gordonii* supplementation safety. No "adequate" or therapeutic dose has been established. Adverse events reported included dizziness, nausea, paresthesia, "headache, systolic and diastolic hypertension, tachycardia, ECG abnormalities, including longer PR interval, and a lower QT interval, and blood chemistry abnormalities, such as increase in total bilirubin and alkaline phosphatase, decrease in blood urea nitrogen" [10]. *H. gordonii* may interact with anti-diabetic drugs as well as some blood clotting medications including warfarin, and inhibit CYP3A4, thus potentially affecting the intracellular concentration of drugs metabolized by this enzyme [16].

## *Irvingia gabonensis*

### Experimental studies

The soluble fiber of the seed of *I. gabonensis* acts as a "bulk-forming" laxative and delays gastric emptying, leading to a more gradual absorption of dietary sugars [106]. In murine 3T3-L1 adipocytes *I. gabonensis* acts by reducing the enzyme glycerol-3-phosphate dehydrogenase involved in converting glucose to stored fat; in addition, in the same model it inhibits adipogenesis through the downregulated expression of the adipogenic transcription factor PPAR-γ and adipocyte-specific proteins, such as leptin, and the upregulated expression of adiponectin [107, 108].

### Clinical studies

Randomized double-blind clinical trials evaluated the effect on weight loss of *I. gabonensis* and its fruit African mango [106, 109]. These studies were included in a systematic review by Onakpoya et al. [106] that reported that variable doses of African mango extract (200 to 3150 mg/day) for 4 and 10 weeks resulted in both statistically and clinically

significant reductions in body weight compared to placebo (−0.88 kg; 95% CI: −1.75, −0.00). However, due to the paucity and poor reporting quality of these RCTs, additional trials are required to determine whether African mango extract could be recommended as a weight-loss aid.

### Safety and drug interactions

Adverse events have been reported in some studies, such as headache, xerostomia, gastrointestinal complaints, sleep disorder, and flu-like symptoms [106]. There is at present little information on drug interactions, but African mango may enhance the side effects of anti-diabetic drugs and statins. Due to the delay in stomach emptying, African mango should be co-administered with prescription medications with caution [106].

## *Phaseolus vulgaris*

### Experimental studies

*P. vulgaris* contains a moderate amount of non-fiber products (2–4 g/kg) that interfere with body metabolism and nutrient availability. Experimental studies in obese animals have reported that the administration of *P. vulgaris* reduces food intake, body mass, lipid accumulation and may potentially reduce the consumption of highly palatable foods, such as butter cookies and chocolate-flavored beverages [67]. Two mechanisms of action have been proposed for the effect of *P. vulgaris* extracts. Both of these mechanisms are based on the presence of two lectins, such as pancreatic α-amylase inhibitors and phytohemoagglutinin; [67]. In vivo and in vitro studies on α-amylase inhibition have suggested that dietary supplements of *P. vulgaris* decreases postprandial hyperglycemia by delaying carbohydrate digestion and reduces gastric emptying, which in turn prolongs satiety and reduces food intake. On other side, in the rat gastrointestinal tract the lectin phytohemoagglutinin binds to the stomach epithelial cells and intestinal brush border of the small intestine, cecum and colon, which results in the stimulation of cholecystokinin and GLP-1 release which are involved in the modulation of food intake [67].

### Clinical studies

The evidence of association between *P. vulgaris* supplementation and weight loss is inconsistent. A systematic review and meta-analysis revealed a significant reduction in body fat after the administration of *P. vulgaris* for 4–13 weeks; however, any firm conclusion was prevented because of the poor quality of the analyzed RCTs [110]. A randomized controlled study demonstrated that a total daily dose of 3000 mg of *P. vulgaris* extract for 12 weeks significantly reduced body weight and body fat compared to placebo (−2.91 kg ± 2.63 vs. −0.92 kg ± 2.00; $p < 0.001$) in 123 overweight and obese subjects following a mildly hypocaloric diet [111]. Very recently Udani et al. [112] have investigated the effectiveness α-amylase inhibitor from *P. vulgaris* supplementation on body weight and fat mass modification in 11 studies for a total of 573 subjects of weight loss and three studies of body fat reduction for a total of 110 subjects. The authors concluded that *P. vulgaris* supplementation showed statistically significant effects on body weight and body fat, in particular the reduction of 1.08 kg (11 studies, 314 patients) and 3.26 kg (3 studies, 60 patients), respectively [112].

### Safety and drug interactions

Current literature reports no serious adverse effects for 445–3000 mg/day of *P. vulgaris* over a period of 13 weeks. Known minor side effects include flatulence, constipation or soft stools and headaches [113]. *P. vulgaris* could interact with oral hypoglycemic drugs and insulin due to its effect in reducing glucose levels [114].

## Pyruvate

### Experimental studies

Pyruvate, a key molecule of several metabolic pathways including lipid synthesis, might induce weight loss by increasing lipolysis and energy expenditure via increased metabolic rate in muscle tissue [17]. The supplementation with pyruvate and dihydroxyacetone to the diet of rats increases energy expenditure accompanied by an increase in thyroxine levels, a key hormone in regulating energy metabolism, and decreased insulin levels and body fat [115]. An increased of "futile" cycling in glycolytic pathways, in particular the phosphorylation of pyruvate to phosphoenolpyruvate and dephosphorylation back to pyruvate, may have played a role in increased energy expenditure in this experimental model [115].

### Clinical studies

In humans, it is unclear how pyruvate works to promote weight loss. To date, there are only few and contradictory findings on the impact of the pyruvate supplementation on weight loss. A meta-analysis including 6 RCTs showed a significant reduction of body weight and fat mass after pyruvate supplementation for 3–6 weeks (−0.72 kg) [116]. Despite these results, the Authors concluded that the

**Table 1** Brief overview on compound, mechanism of action, main clinical studies, adverse effects, and drug interactions of the main weight-loss dietary supplements

| Compound | Mechanism of action | Main clinical studies | Adverse effects | Drug interactions | Usefulness |
|---|---|---|---|---|---|
| β-glucans | Increases satiety and total gastrointestinal transit time; slow cholesterol and glucose absorption | [19] | Abdominal pain, bloating, and disturbed defecation, such as urgent diarrhea and/or episodes of chronic constipation | Interaction with immunosuppressants, non-steroidal anti-inflammatory, and antihypertensive drugs | Not significant weight loss |
| Bitter orange | Increases energy expenditure and lipolysis, acts as a mild appetite suppressant | [25, 26] | Chest pain, tachycardia, anxiety, dyspnea; increases the risk for hypertension and cerebrovascular diseases when taken with stimulants such as caffeine or caffeine-containing herbs | Increase in blood levels of immunosuppressants, antiretroviral agents, drugs metabolized by the liver (CYP3A4); additive effect with antidepressant depression (MAOIs) and anti-diabetic drugs | Not enough evidence to recommend the consumption as an adjuvant in weight-loss management |
| Caffeine | Stimulates thermogenesis and central nervous system, increases fat oxidation and decreases the energy intake | [32, 33] | Nausea, vomiting, tachycardia, seizures, and cerebral edema | Toxic effects for the concomitant administration of caffeine and other drugs metabolized by the CYP1A2, including selective serotonin reuptake inhibitors, antiarrhythmics, MAOIs, lithium, bronchodilators, and quinolones; decrease the effectiveness of alendronate | The effect of caffeine alone on body weight are missing and further research is needed to confirm these findings |
| Calcium | Increases lipolysis and fat accumulation, decreases fat absorption by increasing fecal fat excretion | [38–41] | Constipation, increased risk of kidney stones, and interference with zinc and iron absorption | Reduces the absorption of bisphosphonates, levothyroxine, and antibiotics; induces hypercalcemia in association with thiazides cardiotoxicity in association with digoxin | Calcium supplementation did not significantly affect body weight or body fat |
| Capsaicin | Increases thermogenesis and energy expenditure; enhances lipolysis in adipocytes, glycogenolysis in the liver, and fat oxidation in muscle; increases satiety by increasing GLP-1 secretion, and reduce energy intake | [46] | Gastrointestinal distress, sweating, flushing, and rhinorrhea | Interferes with antihypertensive, anti-diabetic, anti-anticoagulant drugs, and simvastatin; reduces the efficacy of drugs metabolized by CYP2C19 and CYP3A4 | Its consumption may contribute to weight management through reductions in total energy intake |
| Carnitine | Increases mitochondrial β-oxidation of fatty acids and lipolysis; reduces adipogenesis | [53] | Muscle weakness in patients with uremia and seizures in those suffer of epilepsy | Decreases the effectiveness of the supplemented thyroid hormone; increases anticoagulant effects of warfarin | Its consumption may temporarily contribute to weight loss |
| Chitosan | Prevents fat absorption, decreases cholesterol absorption, and increases fecal fat excretion | [60, 61] | Allergic reactions, flatulence, bloating, constipation, indigestion, nausea, and heartburn | Potential increase of the anticoagulants; reduces the absorption of fat-soluble vitamins (A, D, E, and K) | Considering the limited studies available, chitosan supplementation cannot be recommended at this time for weight loss |
| Chromium | Increases the activity of insulin, regulates eating behavior, mood and food cravings, and stimulates thermogenesis | [65, 66] | Skin irritation, headaches, dizziness, nausea and vomiting, mood changes, watery stools, and weakness | Decreases the serum thyroxine concentration; aspirin and non-steroidal anti-inflammatory drugs increase the risk of adverse effects; potentiates insulin or anti-diabetic drugs | Not enough evidence to recommend the consumption as an adjuvant in weight-loss management |

**Table 1** (continued)

| Compound | Mechanism of action | Main clinical studies | Adverse effects | Drug interactions | Usefulness |
|---|---|---|---|---|---|
| Coleus forskohlii | Stimulates cAMP levels, fat oxidation, and thermogenesis, activates the hormone-sensitive lipase, reduces appetite | [71, 72] | Increased frequency of bowel movements and loose stools, headache | Decreases the effect of anticoagulant drugs; potentiates the effects of hypotensive drugs; stimulates metabolism of CYP3A substrate drugs | Not enough evidence to recommend the consumption as an adjuvant in weight-loss management |
| Conjugated linoleic acid | Increases lipolysis and fatty acid oxidation in skeletal muscle, reduces lipogenesis, promotes apoptosis in adipose tissue, increases UCP-1 and energy expenditure | [79] | Abdominal discomfort and pain, constipation, diarrhea, loose stools, nausea, vomiting, and dyspepsia | Potential interactions with anticoagulant drugs | Not enough evidence to recommend the consumption as an adjuvant in weight-loss management |
| Fucoxanthin | Increases energy expenditure, fatty acid oxidation and thermogenesis, inhibits adipocytes differentiation | [84] | Potential risk of thyroid disorders | No drug interactions have been reported | Considering the limited studies available, fucoxanthin cannot be recommended at this time for weight loss |
| Garcinia cambogia | Exerts anorexigenic effects, stimulates fatty acid and inhibits cholesterol synthesis | [86–89] | Headache, nausea, upper respiratory tract, and gastrointestinal symptoms | Interacts with anti-diabetic, serotonin-norepinephrine reuptake inhibitors and CYP2B6 substrate drugs; increases risk of rhabdomyolysis with HMG-CoA reductase inhibitors | Garcinia cambogia did not significantly affect body weight or body fat |
| Glucomannan | Promotes satiety, delays gastric emptying, and reduces small-bowel transit and cholesterol absorption | [95–97] | Abdominal discomfort, bloating, flatulence, diarrhea, loose stools, and belching and flatulence | Reduces with absorption of antihypertensives, antilipemics, antidiabetics, liposoluble vitamins and anti-obesity agents; increases the enterohepatic circulation of thyroid hormones | Not enough evidence to recommend the consumption as an adjuvant in weight-loss management |
| Guar gum | Reduces dietary lipids absorption and gastric emptying, increases satiety | [100] | Abdominal pain and cramps, nausea, diarrhea, flatulence, and increased number of bowel movements | Decreases the absorption of digoxin, aspirin, paracetamol, rosuvastatin, anti-diabetic drugs, corticosteroids, and multivitamins | Guar gum did not significantly affect body weight |
| Hoodia Gordonii | Suppresses appetite and adrenal steroidogenesis, exerts antinflammatory | [105] | Dizziness, nausea, disturbance of skin sensation, headache, hypertension, tachycardia, electrocardiogram abnormalities, and blood chemistry abnormalities | Interactions with anti-diabetic drugs and anticoagulants; inhibits CYP3A4 substrate drugs | Hoodia Gordonii did not significantly affect body weight |
| Irvingia gabonensis | Reduces fat storage, food intake and gastric emptying; inhibits adipogenesis | [106, 109] | Headache, xerostomia, gastrointestinal complaints, sleep disorder, and flu-like symptoms | May enhance the side effects of anti-diabetic drugs and statins | Considering the limited studies available, Irvingia gabonensis cannot be recommended at this time for weight loss |
| Phaseolus vulgaris | Reduces food intake, gastric emptying, carbohydrate digestion and fat storage; stimulates cholecystokinin and GLP-1 release | [110, 111] | Flatulence, constipation or soft stools and headaches | Interactions with anti-diabetic drugs and insulin | Phaseolus vulgaris supplementation showed statistically significant effects on body weight and body fat |

**Table 1** (continued)

| Compound | Mechanism of action | Main clinical studies | Adverse effects | Drug interactions | Usefulness |
|---|---|---|---|---|---|
| Pyruvate | Increases lipolysis, energy expenditure, thyroxine levels, and 'futile' cycling in glycolytic pathways | [116] | Gas, bloating, and diarrhea | Not available | Not enough evidence to recommend the consumption as an adjuvant in weight-loss management |
| Raspberry ketone | Reduces adipogenesis, fat storage and appetite | [122] | Cardiotoxicity as well as a teratogenic effect | Interactions with anti-diabetic drugs and anticoagulants | Considering the limited studies available, raspberry ketone cannot be recommended at this time for weight loss |

evidence was not strong enough to claim the efficacy of pyruvate in enhancing weight loss because of the methodological weaknesses of all the analyzed trials and the low magnitude of the weight-loss effect. The evidence from RCTs does not support that pyruvate is efficacious in reducing weight loss [116].

### Safety and drug interactions

Evidence on the safety of pyruvate supplementation is scant and limited to a short treatment period (6 weeks). Pyruvate supplementation at doses of 5–44 g/day seems to cause no serious adverse effects. Frequent side effects could be gastrointestinal bloating and diarrhea [110]. Pyruvate might also cause an alteration of the lipid profile [117, 118].

## Raspberry ketone

### Experimental studies

The weight-loss efficacy of raspberry ketone, a volatile aroma compound contained in the red raspberry (*Rubusidaeus*), has been reported in preclinical and cell culture models [119, 120]. The results of animal studies suggest that raspberry ketone inhibits lipid accumulation by regulating autophagy [121] and reduces significant food intake in rats [120]. In particular, very recently Leu et al. have reported that raspberry ketone reduces lipid accumulation in 3T3-L1 cells and its daily administration in ovariectomy-induced obese Wistar rats has led to body weight, fat mass and fat cell size reduction via reduction the expression of light chain 3B, autophagy-related protein 12 and sirtuin 1 and the increase of phosphorylated-mammalian target of rapamycin (mTOR) [121].

### Clinical studies

To date, there is only one clinical trial showing a significant reduction of body weight and fat mass in 70 obese subjects after supplementation with primarily raspberry ketone as a component of a multi-ingredient weight-loss product or a placebo for 8 weeks [122]. In this randomized, placebo-controlled, double-blind design, the subjects supplemented with multi-ingredient containing raspberry ketone showed a reduction of body weight, fat mass, serum resistin and elevated serum leptin compared to placebo [122].

### Safety and drug interactions

Dietary supplements provide doses of raspberry ketone that range from 100 to 1400 mg/day. This dosage is far higher than the usual dietary intake from fruits and flavorings (1.8–

3.8 mg/day). Due to the lack of clinical evidence, there is a need for further investigations to evaluate safety and side effects of such supplementation [123]. The raspberry ketone has the potential adverse effect of cardiotoxicity, as well as a teratogenic effect [123]. Raspberry ketone may interact with anti-diabetic drugs as well as with some blood clotting medications including warfarin [124].

## Conclusions

We have briefly examined the best and up-to-date available evidence-based information regarding the efficacy and safety of the most commonly used ingredients in dietary supplements marketed for weight loss. In particular, we focused on the possible drug interactions of weight-loss dietary supplements, which can be a common occurrence in obesity therapeutics, summarized in Table 1. The take-home messages on the possible use of weight-loss dietary supplements are the following: (i) The use of weight-loss dietary supplements is still inconclusive, and the cost of these products can be considerable; (ii) Both Nutritionists and their patients should acknowledge that therapeutic lifestyle changes, in particular healthy diet and physical activity, remain the first-line intervention for weight loss, while weight-loss dietary supplements are to be considered as adjuvant/complimentary; (iii) Considering their potential side effects, habitual consumers of dietary supplements should discuss carefully their use in light of the risk-benefit profile with their healthcare provider; (iv) All dietary supplements for weight-loss might interact with other prescription medications; (v) Many bioactive constituents remain unknown, uncharacterized, or not adequately tested in combination with one another, possibly shifting their risk-benefits balance against their use. Weight-loss dietary supplements need robust, randomized, placebo-controlled studies to provide clear-cut scientific evidence of their efficacy, potential side effects and drug interaction in clinical practice.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.



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