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New Dietary Supplements for Obesity: What We Currently Know

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Abstract Obesity and its associated cardiometabolic alterations currently are considered an epidemic; thus, their treatment is of major importance. The cornerstone for such treatment involves therapeutic lifestyle changes; however, the vast majority of cases fail and/or significant weight loss is maintained only in the short term because of lack of compliance. The popularity of dietary supplements for weight management has increased, and a wide variety of these products are available over the counter. However, the existing scientific evidence is insufficient to recommend their safe use. Hence, the purpose of this article is to review the clinical effects, proposed mechanism of action, and safety profile of some of the new dietary supplements, including white bean extract, *Garcinia cambogia*, bitter orange, *Hoodia gordonii*, forskolin, green coffee, glucomannan, β-glucans, chitosan, guar gum, and raspberry ketones.

Keywords Dietary supplements · Obesity · Weight loss

Introduction

The current overweight and obesity pandemic and its associated issues regarding adherence to treatment (i.e., lifestyle modification including a change in dietary patterns and exercise) have led to different interventional approaches, including pharmacologic therapy, surgery, and the use of dietary supplements. Dietary supplements represent an attractive adjuvant alternative to traditional therapy because most have a low-toxicity profile and are accessible to the general population. It is therefore not surprising that these supplements account for more than $37 billion in sales in the USA [1].

Dietary supplements are legally defined as products intended to supplement the diet (i.e., add further nutritional value), as they contain one or more "dietary ingredients" (e.g., vitamins, minerals, amino acids, herbs, metabolite, extract). Moreover, dietary supplements generally are taken orally; thus, they may be found as capsules, tablets, gelatin capsules, liquids, or powders [2, 3].

Considering the aforementioned definition, dietary supplements are not intended to either treat or prevent any disease; in fact, the clinical effects of most of these supplements have not been evaluated in sufficient double-blinded, randomized clinical trials. Although dietary ingredients may have demonstrated certain effects within preclinical and small clinical scenarios, the vast majority lack evidence when considering "the whole picture," including the purity grade of the supplement ingested, the overall lifestyle (i.e., diet and exercise) and other health-related conditions of the patient (e.g., nutritional status or concomitant diseases), food–drug interactions, excessive dosing, and potential side effects. Assessing the clinical effectiveness of dietary supplements is extremely difficult because regulation of these products differs from that of conventional pharmaceuticals. This situation has made dietary supplements widely available as over-the-counter (OTC) products, thus easily accessible to the general population. Because dietary supplements are not considered drugs, regulations based on their clinical effectiveness are not as "strict" as those of conventional drugs; therefore, they can be marketed and sold regardless of scientifically demonstrated clinical evidence. Furthermore, a recent study reported more than 23,000

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emergency department visits due to adverse events related to dietary supplements; interestingly, a quarter of these cases involved weight loss products [4•].

Because of the aforementioned situation, the objective this study is to review the bioactive ingredients, their—at least theoretical—molecular mechanisms, and any evidence-supported weight-loss effects of some of the commonly consumed dietary supplements.

Bitter Orange

Also known as *Citrus aurantium*, Seville orange, or sour orange, bitter orange has been used in traditional Chinese as well as South American folk medicine for a variety of conditions [5]. Its extracts have been used as supplements to treat obesity and to enhance exercise performance. It contains multiple phytochemicals, including octopamine, as well as alkaloids, particularly synephrine. These alkaloids may exert sympathomimetic effects [6, 7] that contribute to an oxidative metabolism—for example, by promoting lipolysis and stimulating β_3- and α-adrenergic receptors, as well as by inhibiting cyclic adenosine monophosphate (cAMP) production [6, 8].

Various clinical trials studying the effect of bitter orange extracts on weight loss reported significant results; however, these studies evaluated a combination of different products (*C. aurantium* extract, caffeine, and St. John's wort); thus, the individual effect of bitter orange could not be evaluated [9, 10]. On the other hand, in a small clinical trial evaluating the immediate effects of a single administration of synephrine, as well as of a combination of synephrine and flavonoids (naringin and/or hesperidin), an increase in basal metabolic rate (BMR) was observed after these compounds were ingested, either individually or in combination. Therefore, these results are presented as possible evidence for the use of isolated synephrine in treating obesity; however, further studies are needed to evaluate its long-term effects on BMR and weight loss [11].

It is important to consider that synephrine is not the only bioactive compound in *C. aurantium*; bitter orange also contains flavonoids, particularly hesperidin, naringin, limonene, and tangaretin [12], which have been studied and used to treat overweight and obesity.

In terms of safety, the administration of up to 98 mg of *C. aurantium*–derived synephrine for 60 days did not present any adverse effects [13, 14]. However, because of the sympathomimetic activity of synephrine, it has been proposed that its consumption might exert negative effects on the cardiovascular system. Indeed, from April 2004 through October 2009, the US Food and Drug Administration (FDA) received 22 adverse event reports related to products containing *C. aurantium* extract. The most common adverse events included chest pain, tachycardia, anxiety, dyspnea, and pain in the lower left quadrant [15].

In summary, most studies have not found significant weight loss effects from administration of *C. aurantium*; therefore, its effectiveness remains doubtful. In addition, certain predisposed individuals—e.g., those with hypertension, tachyarrhythmias, etc.—may present adverse events after ingesting. Thus, currently, there is not enough evidence to recommend the consumption of *C. aurantium* as an adjuvant in weight loss management.

Hoodia gordonii

Hoodia gordonii is a medicinal plant from the Apocynaceae family, native to South Africa, Botswana, and Namibia [16], and has been studied as a weight loss adjuvant because of its appetite suppression activity [17]. Several metabolites have been isolated from *H. gordonii*, particularly pregnane glycosides containing 6-deoxy and 2,6-dideoxy sugars. Although the active compound that causes its anorexigenic effect is unclear, the oxypregnane glycoside P57AS3 (also known as P57) is commonly accepted as the responsible metabolite [18].

Studies on the effects of P57 in vivo revealed that intraventricular injection of purified P57 in rats decreased food intake and significantly increased hypothalamic ATP production, which may decrease appetite response [19]. An in vitro study found that P57 initiated cholecystokinin secretion in human enteroendocrine cells; cholecystokinin has been studied for its effects on appetite suppression via the vagus nerve [20]. Nevertheless, it has been observed that oral administration of *H. gordonii* leads to an extensive gastric breakdown of P57; thus, *H. gordonii* extract must be consumed in high doses to achieve clinically significant effects [18].

To our knowledge, only one clinical trial evaluated the effects of *H. gordonii* on weight loss: Blom et al. [21] conducted a double-blind, placebo-controlled, parallel clinical trial lasting 15 days in 49 overweight women. They found that administration of an *H. gordonii* extract had no effect on body weight, body fat, or energy intake. Moreover, they reported adverse events in the *H. gordonii* group, including disturbance of skin sensation, headache, dizziness, nausea, increased systolic and diastolic blood pressure, increased pulse, electrocardiogram abnormalities (longer PR interval, higher ventricular heart rat, and a lower QT interval), and blood chemistry abnormalities (increase in total bilirubin and alkaline phosphatase, decrease in blood urea nitrogen) [21]. Given these results, it may be concluded that administration of *H. gordonii* is not effective for weight loss management and that it may lead to significant adverse events.

Irvingia gabonensis

Also known as African wild mango or African bush mango, *Irvingia gabonensis* is native to central and western Africa; its seed contains high amounts of lipids, mostly saturated fatty acids [22]. *I. gabonensis* is also rich in polyphenols, particularly flavonoids, although the specific flavonoids present in the seed have not been determined [23, 24]. An in vitro study, Oben et al. [25] used an adipocyte culture treated with an *I. gabonensis* extract. They observed an inhibition in the expression of peroxisome proliferator-activated receptor gamma (PPAR-γ) and leptin protein levels and up-regulation of adiponectin expression.

Randomized double-blind clinical trials evaluated the weight loss effects of the administration of an *I. gabonensis* extract [26, 27]. These studies were included in a systematic review by Onakpoya et al. [28], who reported that 200 to 3150 mg/day of an *I. gabonensis* extract given for 4 and 10 weeks resulted in both statistically and clinically significant reductions in body weight and waist circumference compared with placebo. The most common adverse events included headache, sleep difficulties, and flatulence; however, these events were not significantly different between the study groups.

Based on the available clinical trials, as well as the systematic review, the use of *I. gabonensis* as a dietary supplement represents an attractive adjuvant in weight loss strategies. It should be noted, however, that all the clinical trials were performed in Black Africans and in relatively small study samples; therefore, more research is needed to evaluate the effect of *I. gabonensis* in a larger, more diverse population.

Green Coffee

Green coffee extract is derived from green unroasted coffee beans and has been marketed in both decaffeinated and caffeinated forms. Within its bioactive substances, it contains chlorogenic acid, a polyphenol from the subfamily of phenolic acids [29, 30]. The mechanisms proposed for the effects of green coffee extract on weight loss include a lipolytic effect on adipocytes as well as a decrease in pancreatic lipase activity [31•, 32, 33]; inhibition of fatty acid synthase, hydroxymethylglutaryl-CoA reductase, and acyl-CoA-cholesterol acyltransferase; an increase in β-oxidation; and promotion of PPAR-α expression in the liver [34].

A meta-analysis reported a statistically significant weight loss of almost 2.5 kg after supplementation with green coffee extract in doses ranging from 180 to 200 mg/day over a treatment period of 4 to 12 weeks [35]. However, because of the moderate clinical magnitude and the significant heterogeneity of the reported clinical trials, the current evidence is insufficient to recommend green coffee as an adjuvant within weight management therapy. Given these results, though, green coffee extract should be studied in larger clinical trials to assess its effect.

Forskolin

Forskolin is the active compound of *Coleus forskohlii*, a member of the mint family. Because it is native to India, it has been used since ancient times in Ayurveda medicine to treat heart diseases, abdominal colic, and respiratory disorders, among other conditions [36]. Forskolin is a potent stimulator of cAMP, which activates the hormone-sensitive lipase, thus promoting the release of fatty acids from adipose tissue [37].

Small clinical trials have evaluated the effect of forskolin on weight loss and found different effects based on gender. In one double-blind, placebo-controlled clinical trial including 15 obese men, 500 mg/day of 10 % forskolin extract was administered for 12 weeks. At the end of this period, the forskolin group showed a significant decrease in body fat, together with an increase in lean body mass, but no changes in BMR [38]. Meanwhile, in a randomized clinical trial, 19 moderately overweight women were assigned to receive either placebo or 500 mg/day of 10 % forskolin extract for 12 weeks. At the end of this period, it was observed that forskolin administration tended to mitigate gains in body mass, but no significant differences were seen in body fat or fat-free mass. No significant adverse events were reported in this study [39].

Because of the conflicting results observed in men versus women, as well as the small number of participants in the studies, conclusions cannot be drawn regarding the effect of forskolin on weight loss management. The results from these clinical trials, however, lead to speculation that forskolin might be helpful in the management of overweight, although more evidence is needed.

Fucoxanthin

Fucoxanthin, a carotenoid widely distributed in nature, has been isolated from a variety of seaweeds and diatoms [40]. Multiple preclinical trials studied the possible mechanisms of fucoxanthin in the treatment of obesity and its associated cardiometabolic alterations. Fucoxanthin reduces both plasmatic and hepatic triglyceride concentrations. It also decreases acetyl-CoA carboxylase expression, thus decreasing malonyl-CoA formation, as well as the expression of fatty acid synthase, decreasing the synthesis of long-chain saturated fatty acids [41–44]. Studies have revealed that fucoxanthin downregulates the expression of the low-density lipoprotein receptor in the liver [41–43]. Moreover, fucoxanthin decreases the expression of PPAR-γ, CCAAT/enhancer-binding protein-α (C/EBPα), and sterol regulatory element-binding protein 1c (SREBP-1c) during the intermediate and late stages of adipocyte differentiation.

During the early stages of adipocyte differentiation, however, fucoxanthin increases the expression of PPAR-γ, C/EBPα, SREBP-1c, adipocyte-binding protein, lipoprotein lipase, and glucose transporter 4 (GLUT4) [45]. Fucoxanthin also has been shown to stimulate the expression of uncoupling protein1 (UCP-1) in white adipose tissue, thus increasing thermogenesis and energy expenditure [46, 47].

Regardless of the robust preclinical evidence available, however, few clinical trials have been conducted using fucoxanthin. In a double-blind, placebo-controlled clinical trial, 31 obese participants received supplementation with a combination of 100 mg of pomegranate seed oil and 0.8 mg of fucoxanthin or placebo for 16 weeks. No significant differences regarding weight loss or body fat were observed between the groups [48]. In another study, 151 obese premenopausal women received a supplement with pomegranate seed oil extract and/or brown seaweed extract containing fucoxanthin at different doses for 16 weeks. The investigators reported that the group receiving a dosage of 300 mg of pomegranate seed oil and 300 mg of seaweed extract containing 2.4 mg of fucoxanthin had a statistically significant reduction in body weight, body fat, and waist circumference. Furthermore, the group receiving 8 mg of fucoxanthin showed an increase in resting energy expenditure, measured by indirect calorimetry [49].

Based on the results from these clinical trials, no recommendations can be made regarding the consumption of fucoxanthin in the treatment of obesity.

Raspberry Ketone

Raspberry ketone [4-(4-hydroxyphenyl)-2-butanone] is an aromatic substance used by the food industry for flavoring [50]. In vitro studies using adipocytes have observed an increase in fatty acid oxidation, suppression in lipid accumulation, and increased secretion of adiponectin [51]. On a molecular basis, studies found that raspberry ketone downregulates the expression of transcription factors involved in adipogenesis, including PPAR-γ, C/EBPα, adipocyte fatty acid–binding protein2, acetyl-CoA carboxylase1, fatty acid synthase, and steroyl-CoA desaturase1, while increasing the expression of genes involved in fatty acid oxidation, including adipose triglyceride lipase, hormone-sensitive lipase, and carnitine palmitoyltransferase [52•]. Meanwhile, in vivo studies in rodents showed that raspberry ketone prevented high-fat diet–induced increases in body weight and visceral adipose tissues. Possible mechanisms of action include stimulation of the white and brown adipose tissues and inhibition of pancreatic lipase activity [53].

Although raspberry ketone has been considered within alternative weight loss management, no clinical evidence is available, and furthermore, raspberry ketone has the potential adverse effect of cardiotoxicity as well as a teratogenic effect, as identified in silico [50].

Glucomannan

Glucomannan, a hydrocolloid polysaccharide of the mannan family, is present naturally and abundantly in diverse products, such as softwoods, roots, tubers, and many plant bulbs [54]. The most used type of glucomannan comes from the tuber konjac (*Amorphophallus konjac*). It is composed of a β-1,4–linked D-mannose and D-glucose monomers, has a high molecular weight, and is considered a soluble fiber [55]. Glucomannan is one of the most viscous dietary fibers known, and it can absorb up to 50 times its weight in water. Because human salivary and pancreatic amylase cannot split β-1,4 linkages, glucomannan passes relatively unchanged into the colon, where it is fermented by the gut microbiota [56]. Konjac has been used in indigenous Asia as an herbal remedy and currently is being studied for its health-related effects on weight reduction, dyslipidemia, and blood glucose, among others [56, 57].

Different mechanisms have been proposed to explain the effects of glucomannan on weight loss, including promotion of satiety through increased mastication efforts, delayed gastric emptying, and reduced small bowel transit. Fecal energy loss also has been proposed as a mechanism, because soluble fibers reduce fat and protein absorption.

Glucomannan generally is well tolerated; the only serious adverse events reported were the result of ingestion of glucomannan tablets (which are no longer available) or jelly candies [56]. So far, two meta-analyses evaluated the efficacy of glucomannan as a weight loss dietary supplement. These studies analyzed nine clinical trials, six of which were included in both analyses. Both studies reported significant heterogeneity in their results [58, 59]. Sood et al. [59] found a statistically significant reduction in weight, −0.79 kg, among participants receiving glucomannan for a mean of 5.2 weeks. The more recent meta-analysis by Onakpoya et al. [58] revealed a non-statistically significant difference of −0.22 kg in weight loss between the glucomannan and placebo groups, contradicting the earlier meta-analysis. These conflicting results might be explained by the different inclusion criteria that the studies used to select the clinical trials analyzed. Although Sood et al. [59] found a statistically significant reduction in weight among study participants using glucomannan, this weight loss is not necessarily clinically significant; thus, the results should be interpreted carefully.

β-Glucans

Glucans are glucose polysaccharides classified according to their interchain linkage as α or β. β-Glucans consist of D-glucose monomers linked by β-glycosidic bonds, and their structure consists of linear β1-3,1-4-D-glucans. Glucans are present in cereal grains in the cell walls of the endosperm,

whereas in mushrooms, they are major structural components of the cell walls. β-Glucans are considered non-digestible dietary fiber, particularly soluble fiber, and are highly fermented in the cecum and colon by the gut microbiota; therefore, the effect of β-glucans as prebiotics has been proposed [60–62]. The weight loss effects attributed to β-glucans derive from their being a soluble fiber, which may increase satiety and total gastrointestinal transit time and slow glucose absorption. The effects of β-glucans in treating overweight and obesity have been studied mainly as secondary outcomes in clinical trials evaluating the effects of β-glucans on dyslipidemia, blood pressure, and insulin resistance as primary outcomes. Overall, most of these trials reported no or non-significant effects on weight loss from β-glucans administered at 3 to 10 g/day for 4 to 12 weeks [63–66]. Regarding satiety, most clinical trials have used subjective scores for satiety and appetite, reporting controversial results within the clinical trials, possibly as a result of the nature of the subjective scores used. Therefore, no conclusions can be drawn regarding the effects of β-glucan administration on satiety and/or appetite [67–71]. Given these results, it may be concluded that β-glucan administration does not appear useful in treating overweight or obesity.

Guar Gum

Guar gum, derived from the seeds of the *Cyamopsis tetragonoloba* plant, is a source of soluble fiber and is used as an emulsifier and thickener in diverse foods. It consists of high-molecular-weight polysaccharides of galactomannans in the form of a linear chain of β1-4–linked D-mannopyranosyl units with α1-6 D-galactopyranosyl residues as side chains [72]. Guar gum serves as a bulking agent; hence, its supplementation has been used to decrease food intake and to increase satiety [73].

Several studies evaluated the effect of guar gum on weight reduction. A meta-analysis of 11 randomized, double-blind, placebo-controlled clinical trials of guar gum given at dosages of 9 to 30 g/day for 3 weeks to 6 months found no significant difference in weight loss between patients receiving guar gum and the placebo group [74]. Since that study was published, few clinical trials regarding guar gum and weight loss have been reported. However, a clinical trial in patients with type 2 diabetes evaluated the effects of partially hydrolyzed guar gum on metabolic syndrome parameters; it found a significant reduction in waist circumference but no effect on weight loss [75]. Another study evaluated the effects of administering a combination of fibers, including guar gum, on appetite and energy intake in overweight humans and found no effect on appetite sensation or energy intake [76].

Therefore, current evidence does not support the use of guar gum as a dietary supplement for treating overweight or obesity.

Chitosan

Chitosans are a family of deacetylated chitins. Although not naturally present in human tissue, chitosan is biodegradable, nontoxic, nonimmunogenic, and biocompatible. Currently, chitosan may be found among OTC products for treating obesity, hypercholesterolemia, and hypertension.

The mechanism by which chitosan may exert a weight loss effect is by binding to negatively charged fat molecules within the intestinal lumen, thus preventing its absorption [77]. Chitosan is considered an insoluble fiber of animal origin and exerts a bile acid resin effect, decreasing cholesterol absorption [78]. Although several clinical trials and meta-analyses studied the effect of chitosan on weight loss, controversial results have been found. In the first published meta-analysis, Ernst and Pittler [79] reported a statistically significant weight loss of 2.38 kg after 28 days of treatment; however, more recent meta-analyses and systematic reviews have not found the same results. A Cochrane meta-analysis including 13 clinical trials found a weighted mean difference in body weight of −1.7 kg after chitosan supplementation vs placebo, which was statistically significant. However, when the inclusion standards were increased and only high-quality trials were analyzed, the reduction in estimated weight loss was only −0.6 kg, which nevertheless was still statistically significant [80].

Given the fact that chitosan is supposed to increase fecal fat excretion, clinical trials have evaluated this effect but have found only a non-significant difference in fecal fat excretion after chitosan administration [81, 82]. Finally, one clinical trial compared the effects of orlistat (a pancreatic lipase inhibitor) vs chitosan on fecal fat excretion, finding that the latter did not inhibit dietary fat absorption [83].

Given the aforementioned results, it may be observed that although chitosan might have an effect on weight loss, that loss is not clinically significant and therefore should be interpreted cautiously.

White Kidney Bean

Phaseolus vulgaris extract is marketed as an OTC dietary supplement for weight loss because of its so-called "carbohydrate blocker" actions, which refers to the fact that phaseolamin inhibits pancreatic amylase and thus digestion of dietary starches. Indeed, proof-of-concept studies have reported a dose-dependent decrease in glucose absorption [84].

However, effects from dosages ranging from 1.5 to 6 g/day were proven only in relatively small, short-term studies. For example, a clinical trial including 60 overweight subjects reported greater reductions in body weight, fat mass, and waist, hip, and thigh circumference in those taking white kidney bean extract versus the placebo group [85]. However, a meta-analysis found a statistically significant decrease in fat mass but a non-significant difference in weight loss between the two cohorts. Nevertheless, the authors acknowledge that the studies that they included clearly show heterogenicity and serious methodologic flaws [86].

In light of these results, accurate conclusions cannot be drawn, and more robust clinical evidence, together with long-term safety reports, is needed.

Garcinia cambogia

Native to Asia, Australia, Africa, and Polynesia, *Garcinia* has been associated with a wide variety of effects, including hypolipidemic, anti-inflammatory, antidiabetic, and antineoplasic properties. Because extracts of its exocarp have shown anorexigenic effects, *Garcinia* also has been studied within the weight management scenario. Moreover, *G. cambogia* contains high amounts of hydroxycitric acid—its proposed bioactive substance—whose mechanisms of action regarding weight loss include inhibition of extramitochondrial citrate lyase (thus, fatty acid and cholesterol synthesis) [87, 88].

Results from randomized clinical trials have been controversial, with some studies failing to show significant differences versus control groups [87] and others reporting significant weight loss [89].

More importantly, however, in vivo experiments found an association of *G. Cambogia* and isolated hydroxycitric acid with significant adverse effects, the clinically most important of which is hepatotoxicity, but also testicular atrophy, epididymal fat accumulation, hepatic collagen accumulation, lipid peroxidation, and increased hepatic transaminases [90–92].

Given the aforementioned findings, little evidence exists to support the long-term effectiveness of *G. cambogia* on weight management [93]. Moreover, its safety profile should be considered carefully, although the plant has not been confirmed as the sole culprit when used in multicomponent formulations [94].

Conclusions

Herein, we briefly review the available information regarding some of the new dietary supplements that are proposed as potential weight loss agents because of their molecular mechanisms of action, which might render them useful within obesity therapeutics (as opposed to creatine, L-arginine, carnitine, whey protein, etc., which actually are used as ergogenic aids). Nevertheless, these compounds need further investigation because no clear-cut evidence has been demonstrated in clinical practice and, moreover, because some are considered to exert potential side effects.

In conclusion, none of the dietary supplements reviewed here can be recommended for OTC use [95] and, moreover, both health professionals and their patients should acknowledge that therapeutic lifestyle changes remain the first-line treatment for weight loss, while other therapies are to be considered as coadjuvant/complimentary.

Compliance with Ethical Standards

Conflict of Interest Alejandro Ríos-Hoyo and Gabriela Gutiérrez-Salmeán declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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