# Dietary supplements for weight loss control

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The market offers supplements containing food plant-derived molecules (e.g., primary and secondary metabolites, vitamins, and fibers), microbes (probiotics), and microbial-derived fractions (postbiotics). They can control lipid and carbohydrate metabolism, reduce appetite (interacting with the central nervous system) and adipogenesis, influence intestinal microbiota activity, and increase energy expenditure. Unfortunately, the copious choice of products and different legislation on food supplements worldwide can confuse consumers.

Keywords: antiobesity ; food-derived moieties ; antiobesity phytochemicals ; prebiotics ; microbial-derived moieties ; probiotics ; metabiotic ; parabiotic ; postbiotic

## 1. Obesity

The body mass index (BMI) values body fat based on a person's weight and height. A person whose BMI is over 25 is considered to be overweight, and obese if it is over 30 (**Figure 1**). Family genetics (a propensity to accumulate fat), psychological factors, and lifestyle (poor exercise or dietary habits) can result in obesity [21]. In living organisms, lipids and fatty acids are formed from glucose. Successively, fatty acids are esterified into triglycerides and stored in adipose tissue. Amylases and glucosidases are the key enzymes that metabolize carbohydrates into glucose [22]. Increased glucose levels determine the insulin release from pancreatic cells and induce glycogenesis, glycolysis, and lipogenesis [23].

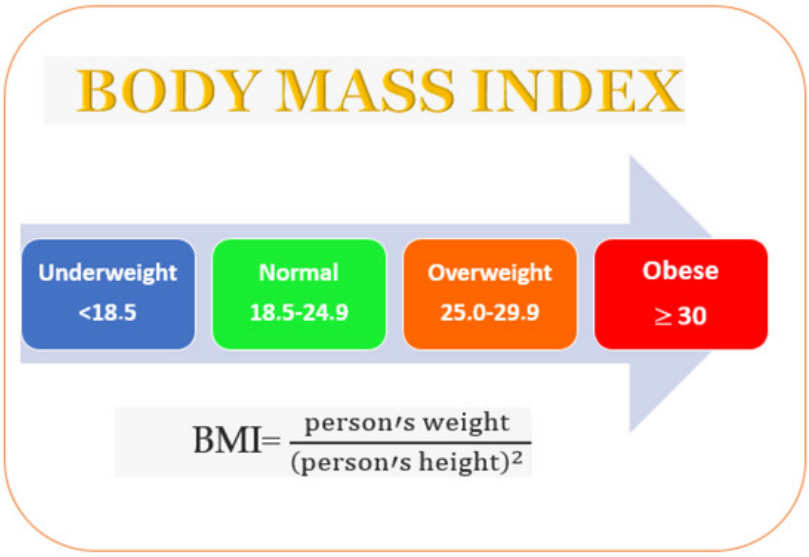


**Figure 1.** Overweight incidence evaluated by the body mass index.

Pancreatic lipase is a critical enzyme in dietary fat digestion. It reduces the fat deposition into adipose tissue and controls the digestion and absorption of triglycerides [24]. This lipase is upregulated by glucagon and epinephrine and downregulated by insulin [25]. Adipose tissue regulates obesity. Adipocytes act as energy storage, detect energy demands, and produce paracrine factors to regulate other metabolic tissues. In obesity, adipose tissue becomes severely dysfunctional, does not store excess energy, causes ectopic fat deposition [26], enhances the levels of free fatty acid metabolites (e.g., ceramide, long-chain fatty acyl Coenzyme A, and di-acyl glycerol) [27], and regulates insulin resistance by constraining the protein-kinase B (PKB) pathway [28].

Hyperinsulinemia increases the ATP level and downregulates the AMP-activated protein kinase (AMPK) pathway [29]. In obesity, preadipocyte differentiation into mature adipocytes is promoted [30], as is the production of inflammatory cytokines (such as the Tumor necrosis factor alpha (TNF-α) and some interleukins such as IL-6, IL-1, and IL-18) [31].

TNF-α downregulates insulin sensitivity (improving IκB kinase/NF-κB signaling), glucose uptake (preventing the GLUT-4 transporter), the 5′ AMP-activated protein kinase (AMPK) pathway, lipogenesis (reducing PPARγ expression), and increases lipolysis [32]. Some hormones (e.g., leptin, insulin, adiponectin, and ghrelin) are involved in the etiopathogenesis of obesity. Leptin is released by white adipose tissue (WAT) and regulates the brain–gut axis. It controls appetite and metabolism by impeding the synthesis and release of neuropeptide Y in the arcuate nucleus. The leptin isoform b (LEP-Rb) regulates the energy balance and body mass in the ventromedial hypothalamic nucleus, arcuate nucleus, lateral hypothalamic nuclei, and dorsomedial hypothalamic nucleus and decreases appetite [33]. Insulin (secreted from pancreatic beta cells) converts signals to the brain and decreases food intake (over the long term) and rapid energy outflow. Brain insulin signaling regulates systemic and organ-specific metabolism, often in a complementary manner [34] (**Figure 2**). Signals from leptin and insulin communicate to reduce food and energy intake [35], the metabolisms of carbohydrates and lipids [36], fatty acid oxidation, and glucose uptake in the skeletal muscle and liver [37]. Adiponectin can activate the adenosine monophosphate-activated protein kinase (AMPK) and decrease acetyl CoA carboxylase and malonyl CoA activities [38,39].

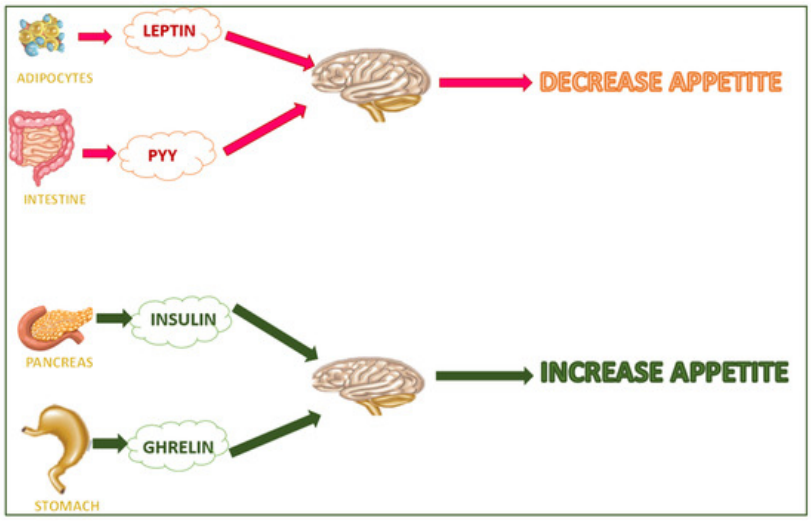


**Figure 2.** Hunger/satiety-regulating hormones.

Adiponectin is secreted from adipose tissue and controls energy homeostasis and the metabolisms of carbohydrates and lipids [36]. It improves the fatty acid oxidation, hepatic insulin activity, and glucose uptake in the skeletal muscle and liver [37]. Adiponectin can activate the adenosine monophosphate-activated protein kinase (AMPK) and decrease acetyl CoA carboxylase and malonyl CoA activities [38,39]. The stomach secretes ghrelin (the hunger hormone), which stimulates food intake and adiposity [40]. Finally, endoplasmic reticulum stress can affect insulin resistance, activating the Jun N-terminal kinase (JNK) and inhibitory kappa B kinase (IKK) pathways [41].

## 2. Supplement Regulation

Urbanization and income growth worldwide have increased the demand for products that control weight management. This segment is expected to grow significantly in the coming period due to the prevalence of obesity among adults and children worldwide linked to changing food habits [42]. The global dietary supplements market will probably reach 327.4 billion USD by 2030. Dietary supplements are regulated differently around the world. In the USA, they are regulated as food by the FDA (Food and Drug Administration) under the DSHEA of 1994 (Dietary Supplement Health and Education Act) [43]. In the United Kingdom, food supplements are regulated by the Department of Health and Social Care (England), Food Standards Scotland (Scotland), Welsh Government (Wales), and Food Standards Agency (Northern Ireland). They are defined as “food whose purpose is to supplement the normal diet and which is a concentrated source of a vitamin or mineral or other substance with a nutritional or physiological effect, alone or in combination and is sold in dose form” [44]. In other jurisdictions, they are considered to be therapeutic goods, food supplements, prescription medicines, or controlled substances [45]. In Italy, the Directive 2002/46/EC and Legislative Decree 21 May 2004 n. 169 regulate dietary supplements as “food products that can supplement the common diet. They are a source concentrate of nutrients, such as vitamins and minerals, or other substances having an effect nutritional or physiological, in particular—but not exclusively—amino acids, essential fatty acids, probiotic microorganisms, fibers, and extracts of vegetable origin, both mono-compound and multi-compound” [46]. The uneven legislation on the marketing of these products around the world can confuse consumers. It is hoped that convergence on this matter can be achieved as soon as possible.

## 3. Weight Management Supplements

Dietary supplements can control being overweight by inhibiting the appetite [47], lipid and carbohydrate absorption [48], adipogenesis and lipogenesis [49], regulating lipid metabolism and the gut microbiota [50], and improving energy consumption [51] and obesity-related inflammation (**Figure 3**) [52].

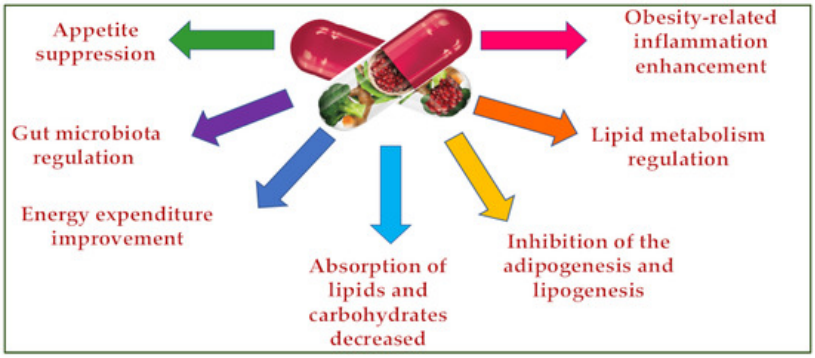


**Figure 3.** Dietary supplements' antiobesity action mechanisms.

### 3.1. Plants Extract in Supplements for Weight Control Management

Usually, weight loss supplements are multi-ingredient preparations (an average of 10 ingredients are enclosed) [53]. It is difficult to determine their effects on the body due to the recipes' complexity and different dosages, extract types, and administration times used in studies. Some food or medicinal plants are employed in weight control treatments. Their effects are mainly linked to secondary metabolites (e.g., polyphenols and saponins, etc.) [54,55], unsaturated fatty acids, and fibers. Natural products that are in used in weight control management include green tea, garcinia cambogia, turmeric, ginger, coffee, chili pepper, spirulina, licorice, hibiscus sabdariffa, white bean, and yerba maté, etc.

Green tea (GT) extract decreases waist circumference (WMD: −2.06 cm) when GT of ≥800 mg/day for <12 weeks or GT of <500 mg/day for 12 weeks is consumed [56]. The consumption of green tea extract for up 14 weeks decreases body weight (BW: 1.8 kg) and body mass index (BMI: 0.65 kg/m$^2$) [56]. Unfortunately, some studies have reported that green tea extract can cause liver damage [57,58]. Dexaprine (a multi-ingredient supplement with green tea extract) has caused some consumers emesis, anxiety, and tachycardia [59]. The Linea Detox (with green tea extract) has produced anaphylactic reactions [60].

### 3.2. Dietary Supplements Able to Decrease the Appetite

Appetite control can reduce weight gain [76]. They can contain grains (e.g., wheat, oats, corn, rice, rye, or barley) [77], prebiotics (e.g., fructosan and inulin) [78], secondary metabolites such as saponins (e.g., pregnane glycosides and stavarosides) [79], methylxanthines (e.g., caffeine, theobromine, and theophylline) [80], and hydrolyzed yeast proteins [81].

### 3.3. Dietary Supplements Able to Interact with the Central Nervous System

Some supplements can promote antiobesogenic effects, interacting with the central nervous system and determining the release of hormones, such as the neuropeptide Y (that can delay satiety and promote food intake), norepinephrine (that can increase lipolysis), the POMC/CART (that can regulate food consumption) [82], the melanocortins and α-melanocyte-stimulating hormone (that can regulate the appetite and are affected by leptin and insulin) [83], and serotonin (that can regulate food intake). The plant secondary metabolites that can interact with the hormones released by the central nervous system are ephedrine (that acts as a sympathomimetic agent) [84], the red ginseng's saponins (protopanaxadiol and protopanaxatriol type that act by downregulating leptin and neuropeptide Y) [85,86], the garcinia's hydroxy citric acids (that control the glucose and uptake of serotonin level) [87,88], the amines in citrus with aromatic rings (that improve serotonin levels) [89], and fucoxanthin isolated from brown seaweed (that impacts insulin levels) [90].

### 3.4. Dietary Supplements That Interact with the Hormones in the Digestive System and Adipose Tissue

Some dietary supplements suppress the appetite by regulating the secretion of hormones in the digestive system (e.g., the ghrelin in the stomach) and adipose tissue (e.g., leptin, secreted by adipocytes [91], the AMP-activated protein kinase that controls energy metabolism [92], and the carnitine palmitoyl transferase 1A and cofactor for the beta-oxidation of fatty acids that enhance the fatty acid oxidation) [93].

### 3.5. Prebiotics in Weight Control Supplements

Prebiotics are non-viable food components (e.g., non-digestible carbohydrates, peptides, proteins, and lipids) [94] that can positively impact beneficial bacteria's activity (e.g., *Lactobacillus* and *Bifidobacterium*) and/or growth in the gut microbiota [95]. They are not hydrolyzed by gastric acidity and mammalian enzymes. Moreover, prebiotics do not get absorbed into the gastrointestinal tract, are fermented by the gut microbiota, and are beneficial to a host's health [96]. The prebiotic, non-digestible carbohydrates include resistant starch, non-starch polysaccharides, and oligosaccharides composed of three–nine sugar units [97,98], which endogenous enzymes cannot hydrolyze [99]. By imitating intestinal binding sites, some prebiotics impede the pathogenic microbiota's adhesion to the gastrointestinal tract [100]. These prebiotics can modulate the immune system by upregulating interleukins and immunoglobulins, downregulating proinflammatory interleukins [101,102], and improving short-chain fatty acids' (SCFAs) production [103]. The SCFAs improve the intestinal barrier integrity, are an essential indicator of bacterial fermentation in the colon [104], protect against inflammation, regulate mucus production [105], and constrain obesity [106].

### 3.6. Probiotics in Weight Control Supplements

Probiotics are live microorganisms that affect human health when consumed adequately [107]. They control being overweight, enhancing the gut barrier function, decreasing metabolic endotoxemia, systematic inflammation, gut permeability, energy hemostasis, and appetite regulation. They can deconjugate the bile acids interfering with lipid absorption, increase SCFAs, and stimulate intestinal peptide synthesis [108,109,110]. The probiotic *L. rhamnosus* GG strain can constrain obesity via the upregulation of adiponectins [111]. A mix containing *Bifidobacterium*, *Lactococcus*, and *Propionibacterium* showed a significant reduction in the total body and visceral adipose tissue [112].

### 3.7. Symbiotics in Weight Control Supplements

Synbiotics are "a mixture comprising live microorganisms and substrate(s) utilized by host microorganisms that confer a health benefit on the host" [113]. The complex mixtures of bacterial strains and different dosages of prebiotic fibers in symbiotics can modulate the metabolic activity in the intestine, upregulate microbiota development, short-chain fatty acid, carbon disulfides, ketones, and methyl acetate concentrations, decrease pathogens, and inactivate nitrosamines and other cancerogenic substances [114].

### 3.8. Postbiotics in Weight Control Supplements

Postbiotics are products (microbial cells or cellular factors that have been attenuated with or without metabolites) or metabolites produced by bacteria or liberated after bacterial lysis, which have a beneficial role in human health [117,118]. Gut bacteria secrete low-molecular-weight metabolites that regulate their growth, promote cell-to-cell communication, and protect against environmental stresses [119,120,121]. The *Lactobacillus*, *Bacillus*, *Bifidobacterium*, *Faecalibacterium*, and *Streptococcus* genera can produce postbiotics [122,123]. These postbiotics emulate probiotics' actions and have a better shelf-life, easier packaging, and minor transport requirements. SCFA, enzymes, peptides, vitamins, and teichoic acids exemplify postbiotics [124]. Acetate, propionate, and butyrate are the most rapresentative SCFAs [124,125]. Butyrate and propionate can positively downregulate the gut hormones and decrease food intake [126]. Acetate acts as a lipogenic substrate propionate that can moderate lipogenesis by downregulating the fatty acid synthase (in the liver). Therefore, the acetate/propionate ratio is crucial for de novo lipogenesis [127].