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Natural Products in the Management of Obesity

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Abstract

Treating overweight and obesity with medications generally offers initial advantages but can result in weight regain after stopping the drugs, as well as in medication-related side effects, and the potential for substance misuse. The allure of herbal products lies in their natural origin, thus leading individuals towards these products in search of a healthier and more sustainable approach to weight loss. Understanding how herbal products interact with biological systems is crucial for assessing their therapeutic potential. Anti-obesity herbal products and their compounds can act through different mechanisms, such as: appetite suppression, digestion and absorption blocking, stimulation of thermogenesis, inhibition of adipogenesis, and modulation of these processes through gene expression. The physiological effects and therapeutic properties exhibited by herbal products are ascribed to the presence and activity of their active components, such as polyphenols, tannins, flavonoids, anthocyanins, stanols, sterols and alkaloids. Furthermore, the synergistic effects of various phytochemicals have been explored to enhance their anti-obesity properties.

Key words: overweight, obesity, anti-obesity treatment, herbal products

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Introduction

An inequity in energy intake versus expenditure, combined with genetic influences, reduced physical activity, high-calorie food intake and increased redistribution of body fat with increasing age, usually leads to additional fat mass and an increase in body weight. According to the WHO (World Health Organization), the human condition in which the individual's body mass index (BMI) exceeds 25 kg/m^2 is defined as overweight, while a BMI over 30 kg/m^2 is declared as obesity. Overweight and especially obesity are considered to be metabolic disorders, and are the main factors for cardiovascular diseases, diabetes and cancer, leading to decreased life expectancy. They not only affect physical health, but also take a toll on mental well-being. Rapid weight loss methods, such as extreme diets or excessive exercise, can indeed be unhealthy, as they may result in adverse health effects. Promoting weight loss through lifestyle changes, including physical activity and dietary modifications, is generally recommended, but in some cases medicament intervention becomes necessary. Treating overweight and obesity with medications generally offers initial advantages but can result in weight regain after stopping the drugs, as well as in medication-related side effects, and the potential for substance misuse (1). As a result, interest in alternative approaches to weight management has increased sharply worldwide, with a special focus on reducing side effects. This heightened curiosity is notably directed towards herbal products as a potential solution to achieve weight management goals with a reduced risk of adverse effects. The allure of herbal products lies in their natural origin, which attracts individuals towards these products in search of a healthier and more sustainable approach to weight loss. Without stringent oversight, consumers face the risk of encountering products that lack standardized formulations, accurate labeling, or scientific validation of claimed benefits. Exploring the challenges posed by the lack of oversight, the aim is to shed light on the potential pitfalls and uncertainties associated with the current state of herbal products used for weight management. Navigating through the issue's complexities, it becomes clear that addressing regulatory gaps is essential to ensure the reliability and efficacy of anti-obesity herbal treatments in the pursuit of healthier lifestyles (2). The aim of the study is to provide new insights into the role and mechanism of action of prominent phytochemicals, as well as to explore the herbal products and their preparations, identifying certain plants as potential sources which can be used in contemporary overweight and anti-obesity management.

Mechanisms of action of anti-obesity phytochemicals

Plants employed in the management of obesity are commercially available in various products, including dietary supplements, teas, etc. The preparation and administration of herbal products are crucial, as these processes can significantly impact their bioavailability and absorption. Effective preparation methods, such as extraction techniques and formulation into specific delivery systems, can enhance the bioavailability and absorption of herbal products, mainly phytochemicals, thereby optimizing their biochemical interactions and therapeutic effectiveness within human physiology.

Understanding how these phytochemicals interact with biological systems and modulate physiological processes is paramount in assessing their therapeutic potential and clinical utility. Thus, while formulation practices are relevant, the critical focus lies in comprehending how phytochemicals bring about their therapeutic effects. Anti-obesity herbal products and their compounds can act through different mechanisms, such as: appetite suppression, digestion and absorption blocking, stimulation of thermogenesis, inhibition of adipogenesis and modulation of these processes through gene expression (3).

Appetite suppression - Appetite regulation is a complex interaction of neurological and hormonal factors that includes approximately 40 anorexigenic and orexigenic neuropeptides, hormones, enzymes, cell signaling molecules, and their corresponding receptors. Elevated satiety is facilitated by increased noradrenaline level, which subsequently activates the sympathetic nervous system. This activation enhances satiety, boosts energy expenditure, suppresses hunger, and promotes increased fat oxidation. Satiety and hunger regulators are synthesized not only in the hypothalamus, but also in various parts of the digestive tract and adipose tissue. When individuals consume ingredients that enhance fatty acid oxidation within the liver, it often leads to a decrease in food intake among human subjects (3, 4, 5).

Digestion and absorption blocking - A promising therapeutic approach for addressing obesity involves targeting fat absorption directly in the gastrointestinal tract, without affecting the central nervous system. Since dietary fat contributes significantly to excess calorie deposition compared to carbohydrates and proteins, fat absorption inhibition represents a crucial strategy to decrease overall energy intake. The main principle of this approach is to inhibit pancreatic lipase, the enzyme responsible for breaking down dietary fat into monoacylglycerols and fatty acids during digestion in the human intestine. The modulation of pancreatic lipase activity serves as a critical parameter in evaluating the anti-obesity efficacy of natural products. Since carbohydrates also contribute to excessive calorie intake, interventions targeting carbohydrate digestion are another important target in weight management. In this way, amylase inhibitors, commonly referred to as starch blockers, interfere specifically with carbohydrate digestion, offering another avenue for weight reduction strategies (3, 6).

Inhibition of adipogenesis - Human adipose tissue consists of two primary types: brown and white adipose tissues. White adipocytes are primarily involved in the storage of fat. The structural composition of adipose tissue encompasses macrophages, fibroblasts, as well as pre and mature adipocytes (7). The suppression of transcription factors, specifically peroxisome proliferator-activated receptor gamma (PPARγ) and cytosine-cytosine-adenosine-adenosine-thymidine (CCAAT) enhancer-binding protein alpha (C/EBPα), inhibits the development of white adipose tissue. This inhibition regulates adipogenesis and adipocyte differentiation, highlighting their significance in the formation and function of adipose tissue. When energy intake exceeds expenditure, extra energy accumulates as triglycerides in white adipose tissue. During periods of low energy availability or starvation, the body releases triacylglycerols to make up for the energy deficit. Herbal compounds that induce apoptosis in adipocytes lead to a reduction in body

fat mass. This phenomenon, known as preadipocyte apoptosis, offers the potential for longer-lasting effects compared to body fat reduction solely through lipolysis and lipid mobilization (3).

Stimulation of thermogenesis - In contrast to white adipose tissue, brown adipose tissue plays a crucial role in energy expenditure by generating energy in the form of heat through a process known as thermogenesis. Mitochondria play a crucial role in adaptive thermogenesis, which is a metabolic pathway regulated by a protein called peroxisome proliferator-activated receptor γ coactivator-1alpha (PGC-1α). In this process, the mitochondria are involved in the oxidation of lipids (fat molecules), which releases energy in the form of heat. This heat dissipation occurs through a mechanism known as uncoupling of the mitochondrial electron transport chain, facilitated by a protein called uncoupling protein 1 (UCP1). Essentially, UCP1 'uncouples' the usual energy production process in mitochondria from ATP synthesis, allowing energy to be released as heat instead. This increased heat production in the process is called thermogenesis, which contributes to maintaining body temperature and can also play a role in metabolic regulation (3, 4).

Modulation of adipogenesis, thermogenesis and lipolysis through gene expression - Increased lipolysis rate stimulates triglyceride hydrolysis. Hence, substances capable of mimicking lipolysis become a crucial aspect in the creation of anti-obesity products. Activation of β-adrenergic receptors proactively activates lipolysis in white adipocytes and induces thermogenesis in brown fat (8). An activation of adenosine monophosphate-activated protein kinase (AMPK) leads to the improvement of fatty acid utilization and glucose delivery in skeletal muscles (9, 10). AMPK, as a regulator of metabolic energy, plays essential roles in both white and brown adipogenesis. Activating AMPK contributes to the expression of UCP1, enhancing thermogenesis, and promoting brown adipocyte differentiation. Lipases, including adipose triglyceride lipase (ATGL), hormone sensitive lipase (HSL), fatty acid synthase (FAS) and lipoprotein lipase (LPL), also influence the synthesis and breakdown of fatty acids, closely linking them to obesity (11). Leptin, a circulating protein derived from adipocytes and the placenta, controls the extent of fat stores in the body, thereby regulating the prevalence of obesity. The expansion of adipose tissue mass can occur through either the creation of new fat cells via adipogenesis or the increased accumulation of cytoplasmic triglycerides or lipid droplets within existing cells (12). In the process of adipogenesis, the proliferation of preadipocytes or precursor fat cells is followed by their differentiation into mature adipocytes. The predominant feature contributing to obesity is increased lipid accumulation within mature adipocyte cells. Peroxisome proliferator-activator receptor gamma (PPAR-γ), primarily expressed in adipocytes, serves as a crucial determinant in adipogenesis. Additionally, it is recognized that PPAR-α plays a significant role in regulating lipolysis by controlling lipid metabolic enzymes, including lipoprotein lipase (12).

Phytochemicals in anti-obesity management

The physiological effects and therapeutic properties exhibited by herbal products are ascribed to the presence and activity of their active components.

A broad range of research, covering *in vitro*, animal, and clinical studies, has explored the potential anti-obesity properties of various polyphenols (3). Certain polyphenols have a range of effects, including inhibiting the transformation of preadipocytes into adipocytes, inducing apoptosis in adipocytes, lowering fat absorption in the intestines, reducing glucose uptake by skeletal muscles, suppressing lipid production, and supporting catabolism in adipose tissue, the liver, and other organs. Furthermore, they can potentially boost the synthesis of anti-inflammatory compounds in adipose tissue (13).

Tannins as polyphenolic compounds are also recognized as effective in anti-obesity management because of their free-radical scavenging activity and ability to reduce lipid peroxidation (14).

Flavonoids may also be beneficial, as they play a helpful role in preventing and reducing the oxidative inflammatory status associated with obesity (15). Flavonoids achieve this through the regulation of various molecular signaling pathways, including mitogen activated protein kinase (MAPK), adenosine monophosphate-activated protein kinase (AMPK), peroxisome proliferator-activated receptor alpha (PPARα), and sterol regulatory element-binding protein-1c (SREBP-1) pathway (16). Research by Wu et al. demonstrated that a flavonoid-rich extract of lotus leaf (*Nelumbo nucifera*), with rutin and gallic acid as primary components, targeted lipid-controlled enzymes and showed potential effectiveness in blocking lipid storage in obese mice. (17)

Flavonoids as quercetin, apigenin, and kaempferol have gained attention due to their anti-obesity properties. Quercetin suppresses the expression of PPARy gene, which regulates fat accumulation in the liver induced by a high-fat diet (18). Apigenin demonstrated the ability to activate adenosine monophosphate-activated protein kinase (AMPK), effectively suppressing adipocyte differentiation and reducing intracellular lipid accumulation (19). In the maturation of human preadipocytes into mature adipocytes, apigenin lowers triglyceride storage by stimulating lipolysis (11). Kaempferol has been found to modulate 3T3-L1 adipogenic differentiation of cells by regulating PPARα and C/EBPα (20, 21, 20). Additionally, it exhibits preventive effects against palmitic acid-induced ectopic lipid deposition in rat clonal pancreatic beta-cells via AMPK-mediated lipophagy. These results indicate that kaempferol might serve as a promising therapeutic candidate for averting obesity and associated diabetic complications (22).

Genistein and daidzein, isoflavones found in legumes, soybeans, and soy products, exhibit phytoestrogenic activity and modulate multiple pathways to regulate adipocyte differentiation. The anti-adipogenic effects of genistein and daidzein are closely linked to their potential to trigger or block PPARα signaling pathways in adipose cells. Daidzein

plays a positive influence not just in adipogenic differentiation, but also in triglyceride synthesis (11).

Anthocyanins represent a major group of components present in plants, which showed suppressive effects on obesity development in induced obese mice. Furthermore, it was demonstrated that anthocyanins possess therapeutic potential in regulating adipocyte function and influence adipocytokine expression in that way (3).

Resveratrol, a polyphenolic compound belonging to the class of stilbenes, exhibits potential as an anti-obesity agent due to its significant impacts on lipolysis and glucose transport in human fat cells. Resveratrol enhances isoprenaline stimulation while impeding insulin's antilipolytic action in human subcutaneous fat tissue, consequently impairing glucose uptake and reducing triglyceride synthesis within these adipocytes. The cumulative outcome is an increase in β-adrenergic-stimulated lipolysis and an inhibition of lipogenesis, which ultimately leads to a reduction in fat cells (23). Resveratrol exerts negative regulation on white adipogenesis by suppressing PPARα and C/EBPα. Moreover, resveratrol enhances brown thermogenesis through uncoupling protein 1 (UCP1), promotes lipolysis, and increases fatty acid oxidation in skeletal muscle and liver tissue by stimulating PPARα activities. Additionally, resveratrol influences lipogenesis and lipolysis mediated by β-adrenergic receptors and cyclic adenosine monophosphate (cAMP) levels in both rat and human adipocytes (23, 11).

Phytosterols, which are plant-derived sterols and stanols, have been shown to block the absorption of intestinal fatty acids, contributing to a reduction in body weight gain in animal tests (24, 25).

Some alkaloids exhibit anti-obesity activity. Capsaicin and caffeine, for example, can markedly increase energy expenditure, decrease appetite, and suppress both adipocyte transformation and pancreatic lipase activity (3). Moreover, the thermogenic effect of capsaicin is achieved by increasing catecholamine secretion from the adrenal medulla in a dose-dependent manner (3).

Plants in obesity management

Camellia sinensis L., (Theaceae) commonly known as green tea, is rich in phenolic compounds, catechins. The leading catechin component in the *C. sinensis* leaf is epigallocatechin gallate (EGCG), which inhibits the growth and maturation in primary human visceral preadipocytes and suppresses the absorption of triglycerides (26). Moreover, EGCG was also reported as an appetite suppressant and inhibitor of pancreatic lipase activity. The inhibitory effects of EGCG are comparable to those of well-known synthetic fatty acid synthase inhibitors such as cerulenin and C75 (3). Furthermore, green tea catechins demonstrate the ability to enhance sympathetic nervous system activity at the fat cell adrenoreceptor level. At the same time, the presence of flavonoids, which are present in smaller quantities (quercetin, kaempferol), and alkaloids such as caffeine and theobromine, displayed an additional anti-obesity effect. *In vitro* studies revealed that a green tea extract containing both catechins and caffeine exhibited more potency in

stimulating thermogenesis in brown adipose tissue compared to equimolar concentrations of caffeine alone (27).

While green tea is often associated with health benefits, numerous studies have investigated the potential toxicity of green tea products, revealing concerns primarily related to high doses or certain physiological conditions. Specifically, EGCG at elevated concentrations has been shown to induce reactive oxygen species in mitochondria (28). This heightened production of reactive oxygen species can lead to oxidative damage, resulting in the degradation of cellular DNA (29, 30). Moreover, consuming large amounts of green tea on an empty stomach can also lead to gastrointestinal irritation in certain individuals, or other side effects such as headaches or irregular heartbeats, primarily due to its caffeine content (3).

Arachis hypogaea L., (Fabaceae) commonly known as peanut, is a versatile and globally consumed legume, celebrated for its culinary applications, nutritional value, and potential health benefits. Peanut shells contain bioactive molecules such as luteolin, certain fatty acids, caffeic, ferulic and benzoic acid, which are capable of inhibiting lipases, particularly pancreatic lipase (31, 32). This inhibition results in increased fecal lipid content and decreased digestibility of dietary fat (33). The anti-obesity activity of the peanut may be attributed to its effect on the expression of PPARγ, leading to lower epidermal fat and reduced weight gain (7). Peanut is rich in resveratrol, which activates the mitochondrial sirtuin proteins and subsequently promotes thermogenesis, resulting in regulating sugar and fat metabolism (34).

Herbal products based on *Garcinia cambogia* L. (Clusiaceae) fruit are among the most popular agents for the treatment of obesity, primarily due to their main component, hydroxycitric acid (HCA). HCA is one of the 16 isomers of citric acid and stands out as the only inhibitor of the enzyme citrate lyase (35). By inhibiting ATP citrate lyase, HCA redirects carbohydrates and fatty acids into hepatic glycogen, subsequently triggering satiety signaling to the brain and leading to the suppression of appetite (36). In the rat brain cortex, HCA increases accessibility of serotonin, which is also involved in appetite control (3). *G. cambogia* fruit is generally well tolerated; however, notable adverse effects may include increased hepatic transaminases and hepatotoxicity (37). Minor side effects reported include headaches, nausea, upper respiratory tract symptoms, and gastrointestinal discomfort (38).

Zingiber officinale L., (Zingiberaceae) commonly known as ginger, possesses a wide spectrum of health-beneficial activities. The primary bioactive compounds in ginger rhizome, contributing to its diverse pharmacological properties, include zingerone, gingerols, shogaols, and paradols (39). Specifically, the main active compounds responsible for its anti-obesity effects are 6-gingerol and 6-shogaol. Research indicates that 6-gingerol and 6-shogaol are effective in suppressing the differentiation of preadipocytes into adipocytes, as well as reducing triglyceride levels. These compounds inhibit lipid accumulation and decrease glycerol-3-phosphate dehydrogenase (GPDH) activity. Furthermore, they lower the mRNA expression levels of adipogenesis-related transcription factors such as PPARγ, C/EBPα, and key lipogenic enzymes, including fatty

acid synthase (FAS) and acetyl-CoA carboxylase (ACC). Additionally, 6-gingerol and 6-shogaol suppress the activity of pancreatic lipase and amylase, resulting in a reduction in plasma and tissue lipids. However, large amounts of ginger rhizome may potentially exacerbate certain heart conditions and increase the risk of bleeding, particularly in individuals with pre-existing cardiovascular issues or those taking anticoagulant medications. Further research in humans is needed to confirm these effects (40-43).

Extracts of the *Hibiscus sabdarifa* L. (Malvaceae) flower rich in phenolic acids (protocatechuic acid), organic acids (hydroxycitric and hibiscus acid), and anthocyanins (delphinidin-3-sambubioside and cyanidin-3-sambubioside), showed anticholesterol, antidiabetic, antihypertensive and antioxidants effects. These compounds contribute to the inhibition of *α*-glucosidase and *α*-amylase. Extracts from *H. sabdarifa* flowers were also able to reduce lipid and triglyceride levels in rats and inhibit adipogenesis in preadipocyte cell lines. The anti-obesity properties of hibiscus extracts were manifested through the inhibition of adipocyte differentiation, modulating phosphoinositide 3 kinase (PI3-K) and mitogen activated protein kinase (MAPK) pathways critical for adipogenesis. The hibiscus flower is commonly consumed in various foods, and is considered safe when utilized in medicinal amounts. Although infrequent, potential adverse reactions may include mild stomach upset and flatulence (3).

The leaf of rosemary (*Rosmarinus officinalis* L., Lamiaceae) is rich in bioactive compounds, including antioxidants like carnosic and rosmarinic acid, as well as monoterpenes, diterpenes, and other phenolics. The primary polyphenols identified in rosemary are caffeic acid derivatives, such as rosmarinic acid and its hydrolyzed metabolites. One of the main reported anti-obesity mechanisms of rosemary leaf is its ability to increase the elimination of fat in feces without reducing food intake (7). Additionally, rosemary has been found to inhibit the activity of hormone-sensitive lipase and pancreatic lipase, further contributing to its anti-obesity effects. Moreover, rosemary exhibits anti-adipogenic activity, as evidenced by the ability of carnosic acid to inhibit the differentiation of 3T3-L1 preadipocytes cell lines. Clinical studies have shown that the consumption of rosemary leaves powder at a dose of 10 g/day for 4 weeks resulted in significant reductions in serum glucose concentration during fasting, total cholesterol, LDL, triglycerides, and malondialdehyde levels compared to the control group, in both male and female participants aged from 20 to 57 years (44).

In the global sphere of anti-obesity treatment, the common bean (*Phaseolus vulgaris* L., Fabaceae) has garnered attention for its potential therapeutic properties and effects on weight management. The seeds of *P. vulgaris* are rich in quercetin, kaempferol, *p*-coumaric, ferulic, *p*-hydroxybenzoic and vanillic acid (45). *P. vulgaris* bean extract has demonstrated the ability to inhibit the activity of α-amylase and various other intestinal enzymes involved in digestion, such as maltase and lactase. By inhibiting the metabolism of complex carbohydrates into easily digestible sugars, common bean extract may contribute to weight loss by potentially reducing carbohydrate-derived calories (46). Short-term dietary supplementation with *P. vulgaris* beans, as described by Zhu et al., has shown a decreasing effect on total cholesterol and low-density lipoprotein (LDL) without

affecting high-density lipoprotein (HDL) (47). Additionally, the lectins derived from *P. vulgaris* have been observed to exhibit suppressive activity on the appetite, suggesting their potential role in modulating hunger signals and influencing overall food intake regulation. Individuals with diabetes should be cautious when considering supplements containing the common bean, as it has been associated with potential blood sugar-lowering effects (3).

The fruit of pomegranate (*Punica granatum* L., Punicaceae) is widely recognized for its antioxidant activity and is also acknowledged for its anti-obesity properties (48). Pomegranate leaf extract (PLE) exhibits anti-obesity effects comparable to the synthetic drugs orlistat and sibutramine. PLE has demonstrated a reduction in energy intake and the inhibition of dietary fat absorption in the intestine by effectively blocking pancreatic lipase. This results in higher levels of fat excretion in feces. The compounds responsible for these effects are ellagic and tannic acid (49). Additionally, individuals who consumed pomegranate fruit juice for one year exhibited reduced oxidation of both HDL and LDL cholesterol. Consuming pomegranate juice has been associated with a slight reduction in blood pressure. However, individuals with pre-existing low blood pressure should be cautious, as excessive intake of pomegranate juice may potentially increase the risk of blood pressure dropping to excessively low levels (3).

When discussing weight loss, the *Rutaceae* family emerges as a crucial mention. Lemon (*Citrus limon*), orange (*Citrus aurantium*), and grapefruit (*Citrus paradisi*) within this family are rich sources of phenolic compounds, primarily flavonoids, along with vitamins, minerals, and dietary fiber. The anti-obesity activity of lemon is attributed to flavonoids such as hesperidin, eriocitrin, and naringin. These compounds contribute to decreased plasma and hepatic cholesterol and triacylglycerol levels by inhibiting the function of liver enzymes involved in their production. On the other hand, these compounds affect the genetic regulation of glucose-controlling enzymes, enzymes involved in hepatic fatty acid oxidation, and improve the levels of serum insulin, glucose and leptin, affecting decreased insulin sensitivity (3). Sesquiterpene compound nootkatone, responsible for the aroma and slightly bitter taste of grapefruit, stimulates AMP-activated protein kinase through different mechanisms in the liver and skeletal muscles, thus enhancing energy metabolism. While grapefruit juice and products have possible health advantages, their consumption is associated with interactions with certain medications, including antihistamines, calcium channel blockers, and immunosuppressants. The primary route for these interactions involves the inhibition of cytochrome P450 3A4 activity by furanocoumarins, which increases the rate of drug absorption that substrates post-administration (3). Protoalkaloid *p*-synefrine from bitter orange (*C. aurantium* subsp. *amara*) immature fruit is widely used in weight loss products, especially since such use of ephedrine is prohibited. Its thermogenic and lipolytic activities are obtained through the activation of β-adrenergic receptors. Synephrine also possesses α-adrenergic affinity that is responsible for cardiovascular adverse effects (hypertension, tachyarrhythmia, ventricular fibrillation, myocardial infarction, and sudden death) associated with its intake (50).

Olives and olive oil obtained from *Olea europea* L. (Oleaceae) are the main components in the Mediterranean diet and have proven health benefits. Central to their health-promoting properties is the secoiridoid compound oleuropein, principally abundant in leaves and unprocessed fruits (51). Side by side with other phenolics such as verbascoside, luteolin, rutin, and catechin, oleuropein reduces the increase in body weight through adipogenesis and thermogenesis and by inhibiting intestinal glucose absorption (3). In fact, studies conducted on mice fed with a high-fat diet and administered olive leaf extracts have demonstrated reduced accumulation of intracellular lipids in preadipocyte cell lines, inhibition of PPARγ and C/EBPα, decreased levels of triglycerides, glucose, and total cholesterol, as well as a reduction in leptin levels. (51, 52, 53). Experimental data pointed out oleuropein as an autophagy inducer. Autophagy appears to participate in hypothalamic agouti-related peptide neurons in controlling food intake and energy balance, suggesting potential new treatments for obesity and metabolic syndrome (54).

The primary bioactive components of *Panax ginseng* L. (Araliaceae) root, namely ginseng saponins and polysaccharides, play a crucial role in its health benefits (1). Anti-obesity effects are attributed to ginsenosides, their key constituents. Ginseng has demonstrated an impact on hormone levels, including leptin, ghrelin, and adiponectin, influencing appetite regulation. Furthermore, ginseng is believed to inhibit pancreatic lipase activity, hindering the digestion and absorption of fat and carbohydrates, resulting in decreased blood glucose levels and increased fecal weight. Through the regulation of PPARγ/C/EBPα, PPARα, and AMPK pathways, ginseng exerts an antiadipogenic effect, promoting improved fat oxidation and energy expenditure (55).

Research articles extensively support the pharmacological potential of berberine found in *Berberis vulgaris* L. (Berberidaceae). Classified as an alkaloid, berberine exerts activity against white adipocyte differentiation through a variety of mechanisms. It induces AMPK (11) and promotes white adipose tissue browning by activating thermogenesis (56). Clinical studies have revealed that oral administration of berberine tablets results in decreased levels of triglycerides, total cholesterol, and LDL, while in other studies HDL levels either increase or remain unchanged (57, 58).

Capsicum annuum L. (Solanaceae), with the variety commonly known as chili pepper, has been a widely utilized herbal supplement used in anti-obesity treatments. Capsaicinoids, as main components, can influence metabolic activation of transient receptor potential vanilloid 1 (TRPV1) receptors. This activation is believed to enhance energy expenditure and reduce body fat by promoting catabolic processes in adipose tissues (59). It also activates metabolic modulators such as AMPK and PPARα (60). Additionally, capsaicin has been found to decrease lipid accumulation by reducing the expression of PPARγ, C/EBPα, and leptin proteins, while increasing adiponectin expression in 3T3-L1 adipocytes (61). Several studies in mice have indicated that capsaicin and other capsaicinoids stimulate sympathetically mediated brown adipose tissue thermogenesis, leading to a decrease in body fat (62). Research suggests that capsaicin-induced thermogenesis is probably due to β-adrenergic

activation. Capsaicin administration also increases lipid mobilization and a reduction in adipose tissue mass (63).

Capsaicin is generally considered safe, with reported adverse effects including gastrointestinal distress, sweating, flushing, and rhinorrhea (63). Acute ingestion of a large quantity of chili peppers has been documented to induce a severe hypertensive crisis in some cases (64).

Synergism between phytochemicals in anti-obesity management

It is evident that certain herbal products and their constituents exhibit significant anti-obesity effects, often obtained through multiple and overlapping mechanisms. Thus, their collaborative effects have been explored to enhance their anti-obesity properties. For instance, a combination of resveratrol, genistein, and quercetin has demonstrated synergistic inhibition of adipogenesis and induction of adipocyte apoptosis, surpassing the effects observed with individual treatments with resveratrol, genistein, or quercetin (10). When resveratrol is combined with berberine, it shows improved cholesterol-lowering effects in mice on a high-fat diet, achieving a lower level of lipid accumulation compared to monotherapies (55, 65). Likewise, the combination of resveratrol and quercetin exhibits superior effects in lowering lipid storage in rat white adipose tissue compared to individual feeding (66). Additionally, a blend of quercetin, crocin, chlorogenic acid, and geniposide displays an enhanced reduction of lipid deposition in human hepatoma when compared to individual administrations (67). Supplementation with a combination of citrus polymethoxyflavones, green tea extract, and lychee (*Litchi chinensis* Sonn., Sapindaceae) fruit extract has shown potential to inhibit obesity and hepatic steatosis by activating AMPK signaling and lipid catabolism in mice (68).

As described by Zhu et al., the combination of a low dose of EGCG and caffeine showed synergism in the anti-obesity effect and suppressed fat accumulation as well as a high dose EGCG (69). Moreover, the study of Nakadate et al. revealed that the consumption of both catechin and β-cryptoxanthin, an antioxidant carotenoid, resulted in a decreased inflammatory response of adipocytes. The combination of green tea and mandarin oranges, both rich in β-cryptoxanthin, for a short duration of 4 weeks, is expected to produce an anti-obesity effect while requiring a lower intake of green tea catechins compared to earlier studies. Given that this amount can be easily incorporated into a daily diet, this strategic approach holds promise for effectively addressing and reducing obesity (70). Treatment with 6-gingerol and quercetin has demonstrated significant reductions in serum cholesterol and triglyceride levels in hyperlipidemic rats, indicating an improved lipid metabolism. The observed lipid level decrease attributed to 6-gingerol and quercetin is likely a result of their separate functions being enhanced by insulin's control of lipoprotein lipase, leading to increased degradation of triglycerides and simultaneous suppression of lipolysis. This dual action results in a diminished supply of free fatty acids necessary for triglyceride biosynthesis. Previous studies have shown that 6-gingerol, in a dose-dependent manner, inhibits LDL oxidation, while quercetin

effectively inhibits triglyceride synthesis, thereby preventing atherosclerotic progression in animals (71). However, in some cases, desirable synergistic interactions against obesity can exacerbate adverse reactions beyond what would be expected from each component individually. The combination of ephedrine and caffeine for weight loss was shown to be very effective, increasing lipolysis, energy expenditure and decreasing energy intake, but is associated with high cardiovascular risks (72). Similarly, the combination of synephrine and caffeine should also be avoided (50). As with many other treatments, meticulous dosage determination and adherence to the recommended amounts are crucial to mitigate the risk of adverse effects associated with synergistic interactions.

Conclusion

The usage of phytochemicals and herbal products in the management of obesity is becoming more and more relevant. Most of the examined herbal sources show positive outcomes in overweight and anti-obesity management, mainly without the occurrence of serious side effects. While herbal products may present themselves as appealing due to the perceived natural origin of the phytochemicals, it's important to note that the effectiveness as well as safety of usage of herbal supplements for anti-obesity management is still limited, and that a wide-ranging approach to weight management that includes lifestyle changes, dietary modifications, and regular exercise remains a key component of any comprehensive strategy. Before considering any alternative treatments, including herbal substances, individuals should consult with healthcare professionals to ensure not only safety, but also appropriateness of the treatment for their specific health conditions.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author contributions

Conceptualization, Iskra Davkova and Jelena Kukić-Marković; Data curation, Iskra Davkova and Jelena Kukić-Marković; Formal analysis, Zoran Zhivikj and Ivana Cvetkovik Karanfilova; Supervision, Marija Karapandzova; Writing - original draft, Iskra Davkova; Writing - review & editing, Ivana Cvetkovik Karanfilova, Gjoshe Stefkov, Svetlana Kulevanova and Marija Karapandzova.

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Biljni proizvodi u lečenju gojaznosti

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Kratak sadržaj

Lečenje prekomerne težine i gojaznosti lekovima obično je od kratkoročne koristi i često je povezano sa povećanjem telesne težine nakon prestanka terapije, neželjenim efektima lekova i rizikom od njihove zloupotrebe. Popularnost biljnih proizvoda potiče od njihovog prirodnog porekla, što navodi pojedince da ih upotrebljavaju u cilju zdravijeg i održivijeg pristupa mršavljenju i regulaciji telesne težine. Razumevanje načina na koji biljni proizvodi stupaju u interakciju sa biološkim sistemima je ključno za procenu njihovog terapeutskog potencijala. Biljne droge protiv gojaznosti i njihova jedinjenja mogu delovati kroz različitim mehanizmima, kao što su: suzbijanje apetita, blokiranje varenja i apsorpcije, stimulacija termogeneze, inhibicija adipogeneze i modulacija ovih procesa kroz ekspresiju gena. Fiziološki efekti i terapijska svojstva biljnih droga pripisuju se njihovim aktivnim sastojcima, kao što su polifenoli, tanini, flavonoidi, antocijanini, stanoli, steroli i alkaloidi. Takođe, analizirani su sinergistička delovanja različitih biljnih sastojka kako bi se poboljšali njihovi efekti protiv gojaznosti.

Ključne reči: prekomerna telesna masa, gojaznost, tretman protiv gojaznosti, biljni proizvodi