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Anti-obesity properties and mechanism of action of genistein

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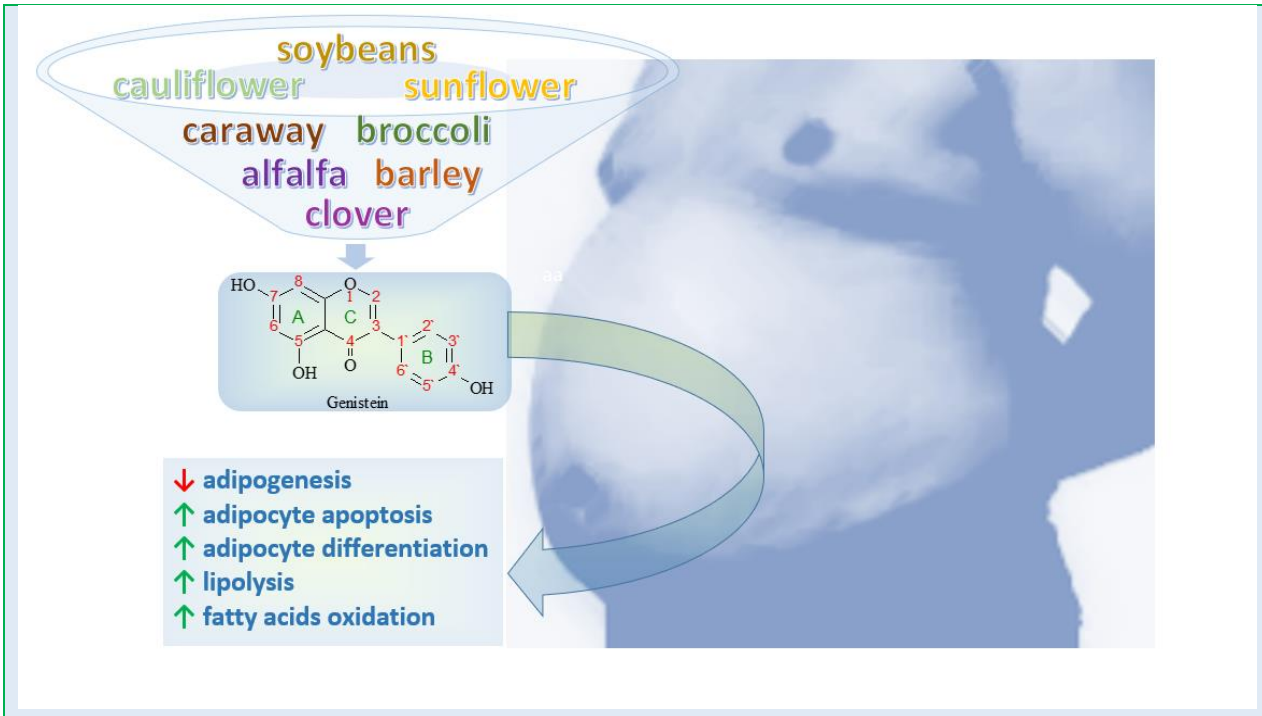
ABSTRACT

Obesity is considered a major health problem worldwide with a constantly increasing incidence, representing a significant public health issue affecting all genders and all ages, even children. The WHO reports alarming information that in 2016, 39% of adults were overweight, 13% were obese, and more than 340 million children and adolescents were overweight or obese. Information from 2020 states that 39 million children under 5 years of age were overweight or obese. With the occurrence of obesity, the risk of obesity-related disease incidence, for example, hypertension, stroke, myocardial infarction, diabetes mellitus, fatty liver, osteoarthritis, obstructive sleep apnoea, dementia, and several types of cancer, greatly increases.

Recent evidence shows the beneficial effects of natural compounds - flavonoids in preventing and treating obesity. Flavonoids, found in various plants, represent active biocompounds that are associated with many beneficial effects on human health, including their noticeable effect in obesity treatment due to their ability to reduce food intake and increase energy expenditure, reduce fat absorption and fat mass, decrease levels of triacylglycerides and cholesterol, and modulate the metabolism of lipids. Our review summarizes the antiobesity effect of genistein, a flavonoid that belongs to isoflavones subgroups. Genistein, a naturally occurring compound, is one of the most known and studied isoflavones that shows many beneficial antiobesity properties. Genistein has the ability to reduce body weight and food intake, increase lipolysis, increase oxidation of fatty acids, decrease adipogenesis, stimulate adipocyte differentiation, and induce adipocyte apoptosis.

Keywords: Obesity, Flavonoids, Isolavone, Genistein



Graphical Abstract: Mechanism of action of genistein

INTRODUCTION

Obesity is considered a major health problem worldwide. According to World Health Organization (WHO), obesity is defined as abnormal or excessive fat accumulation associated with various other health problems [1]. Obesity arises due to an imbalance in the ratio of energy intake and expenditure, leading to an overabundance of nutrients and adipose tissue dysfunction [2]. Obesity increases the risk of obesity-related diseases such as hypertension, stroke, myocardial infarction, diabetes mellitus, osteoarthritis, fatty liver, obstructive sleep apnea, dementia, and several types of cancer. Obesity could shorten the average life expectancy and contribute to socio-economic disadvantage [3]. Precisely because of this broad impact of obesity on human life, its prevention and treatment are crucial.

In the scientific community, there is evidence of the beneficial effects of natural compounds in preventing and treating obesity. Natural compounds could inhibit adipogenesis, modify different stages of the adipocyte life cycle, and research shows that these compounds can induce adipocyte apoptosis [4]. Natural compounds are responsible for many health benefits and are considered important dietary supplements that support human health and the prevention of diseases. Recently, there has been an increasing interest in using plant-based products to prevent and treat various diseases through proper and appropriate nutrition within the new discipline of nutrition science, Functional Food Science. The Functional Food Center (FFC) has agreed on the current definition for functional foods as: "Natural or processed foods that contain biologically active compounds, which, in defined, effective, non-toxic amounts, provide a clinically proven and documented health benefit utilizing specific biomarkers, to promote optimal health and reduce the risk of chronic/viral diseases and manage their symptoms" [5]. FFC, together with the Academic Society of Functional Foods and Bioactive Compounds (ASFFBC) in collaboration with the FDA and other governmental agencies, decided to bring a definition and classification of Functional Foods [6].

Plants contain bioactive compounds (phytochemicals, secondary plant metabolites), which are required to sustain life, and for normal physiological functions, but are also important in preventing and treating diseases [7]. Flavonoids represent the most abundant, isolated, and studied secondary plant metabolites belonging to the phenolic class of phytochemicals. They have different chemical structures and show multiple beneficial effects on the human body [8-9]. Flavonoids act as antioxidants, anticarcinogens, antiinflammators, and antimutagens. The flavonoid class is subdivided into subgroups: flavones, flavonols, flavanones, flavanonols, flavanols or catechins, anthocyanidins, and chalcones [9].

Our review summarizes the antiobesity effect of genistein, a flavonoid that belongs to isoflavones subgroups. Genistein is one of the most investigated isoflavones, with various beneficial effects on the human body. It is well known for its beneficial effects on reducing osteoporosis, cardiovascular diseases, and diabetes, as well as on obesity treatment [10].

METHODOLOGY

Literature searches were performed without a specific timeframe using Google Scholar, PubMed, and the Functional Food Center's journal database. Both research articles and review articles were searched. Articles unavailable in English were excluded. Keywords for the literature search included: obesity, obesity causes, obesity treatment, flavonoids, genistein, and genistein in obesity.

OBESITY

Obesity is characterized as a complex multifactorial disease. It is a global health problem with increased incidence in the last 50 years. The global prevalence of obesity and overweight has doubled since 1980. Nowadays, obesity is considered the fifth leading cause of death worldwide [11-13]. Obesity is a complex health problem caused by a combination of genetic, environmental, and behavioral factors, as well as psychosocial factors, including eating habits, sedentary lifestyles, and cultural influences [11,14-15]. According to World Health Organization (WHO), overweight and obesity are abnormal or excessive fat accumulation that leads to many health problems [16]. A general and very simple index commonly used for classifying adults into four categories, namely underweight, normal weight, overweight, and obese, is body mass index (BMI). The BMI (Table 1) is defined as a person's weight in kilograms divided by the square of his height in meters (kg/m^2) [11,17]. BMI was initially developed in the 1830s by a Belgian mathematician and sociologist; it is still widely used to define overweight and obesity in epidemiological studies [11]. It is an overall classification, a simple weight-for-height index, inexpensive, and very quick to perform, making it practical for use in clinical conditions.

Table 1: Body mass index (BMI) for adults, BMI =Weight in kg/(Height in meters)^2 [18]

BMI (kg/m^2)	Nutritional status
Below 18.5	Underweight
18.5 – 24.9	Normal weight
25.0 – 29.9	Overweight
30.0 – 34.9	Mild obesity (class I)
35.0 – 39.9	Moderate obesity (class II)
Above 40	Morbid obesity (class III)

According to WHO, adults with BMI over 25 are considered overweight, and adults with BMI over 30 are considered obese [16]. There are three classes of obesity defined, class I of obesity is defined for BMI between 30 and 34.9, and this class of obesity is associated with a moderate risk of mortality. Obesity class II is defined when BMI is between 35 and 39.9 and is associated with a high mortality risk. Class III obesity is defined as when BMI is 40 or above and is associated with a very high risk of mortality [19].

The key facts from the WHO are alarming; there is stated that in 2016, 39% of adults (18 years and older) were overweight, and 13% were obese. In the same year, over 340 million children and adolescents (5-19 years) were overweight or obese. In 2020, 39 million children younger than 5 years of age were overweight or obese [16].

Only BMI does not provide information about the distribution of body fat or the type of obesity. Therefore, it is crucial to consider other measurements, namely the amount of body fat, waist circumference, waist/hip ratio, and waist/height ratio [20-21]. Obesity and overweight are associated with an increased probability of occurrence of various diseases and conditions such as type 2 diabetes, cardiovascular diseases, hypertension, metabolic syndrome, chronic kidney disease, dyslipidemia, nonalcoholic fatty liver disease, cancer, gallstones, stroke, dementia, obstructive sleep apnea, depression [2-4,11,13,22-24]. Obesity is also associated with economic and social problems; it could be linked to social disadvantage, unemployment, and reduced socioeconomic productivity [3].

Obesity and overweight are major public health problems affecting all ages, genders, and races. Prevention of obesity is essential, as well as its targeted and successful treatment, which is not easy and should include an individual approach. Obesity treatment includes modification of lifestyle (which includes diet and physical activity), pharmacotherapy (that is recommended for individuals with BMI ≥30 that are not able to lose weight only by lifestyle modification), bariatric surgery (recommended for individuals with BMI > 40 or BMI > 35 with comorbidities, not able to lose weight by lifestyle modification or pharmacotherapy), and fecal microbiota transplantation (transplantation of microbes from healthy individuals to obese patients could also be an option in the treatment and maintenance of weight loss) [13]. Although most of the studies have been done on animals, there are also clinical studies on humans, but it can be said that they are rare. Promising results have been seen in human studies in patients with metabolic syndrome who were transplanted with fecal intestinal microflora from lean donors [25-27].

Weight reduction seems to be associated with overall improvement in the life quality of obese people [28]. Essential in obesity prevention and treatment is a diet rich in natural bioactive compounds – polyphenols. Polyphenols are divided into two groups: flavonoids and non-flavonoids [29]. Flavonoids, according to their structure, are divided into subgroups, namely flavones, flavonols, flavanones, flavanonols, flavanols or catechins, anthocyanidins, chalcones, isoflavones, neoflavonoids [9]. Flavonoids are the most abundant secondary plant metabolites found in various plants, including vegetables, fruits, nuts, seeds, stems, juices, beer, and wine. They represent active biocompounds associated with many beneficial effects on human health [2]. It was shown their noticeable effect in obesity treatment, thanks to the ability to lower fat mass, body weight, plasma triglycerides, and cholesterol. Flavonoids act on obesity by reducing food intake, increasing energy expenditure, reducing fat absorption, modulating lipid metabolism, and regulating gut microbiota profile [30-31].

Genistein [5,7-dihyroxy-3-(-4-hydroxyphenyl)-4H-1-benzopyran-4-one]: Genistein is a naturally occurring compound that belongs to the flavonoid family, in the isoflavones subgroup (Figure 1). Genistein is one of the most known and most studied isoflavones. The structure of genistein is formed from 15 carbons organized into two aromatic rings (ring A and ring B);

those two rings are linked to the carbon pyran ring (ring C). Genistein in its structure contains one double bond between carbons in positions two and three, an oxo group in ring C: position four, and three hydroxyl groups, two of them in ring A: in positions five and seven, and one in B ring: position four. Its molecular formula is $C_{15}H_{10}O_5$, molecular weight is 270.241 g/mol [32]. Genistein structure is similar to the structure of mammalian estrogens; it can be said that genistein is a naturally occurring phytoestrogen. Genistein could be used as a natural estrogen supplement in post-menopausal women [33].

Genistein is mainly derived from legumes, predominantly from soy products, such as soybeans [32,34]. Naturally occurring dietary source of genistein is the glucoside form of genistein - genistin. During the digestion or fermentation of soy products or soybeans, the β-glycosyl bond of genistin cleavage to form genistein. Genistein has also been found in alfalfa, barley meal, cauliflower, broccoli, clover sprouts, clover seeds, sunflower, and caraway [35]. Genistein is absorbed in the small or large intestine. Isoflavones, and thus also genistein, are generally absorbed after the cleavage of sugar chains by the activity of intestinal bacteria and enzymes. Subsequently, they are transformed into glucuronic acid or sulfate conjugates, and then they are modified into metabolites during circulation in the body [36].

Genistein shows many beneficial effects on the human body. It has been shown its anticancer properties, positive effect in the reduction of the risk of cardiovascular disease, neurodegenerative diseases, protection against osteoporosis, reduction of the symptoms of postmenopause, reduce the incidence of diabetes and obesity [33-34]. Genistein plays a critical role in controlling body weight, shows antiadipogenic properties, and shows an important role in lipid metabolism, reducing lipogenesis and triglyceride accumulation [37-38].

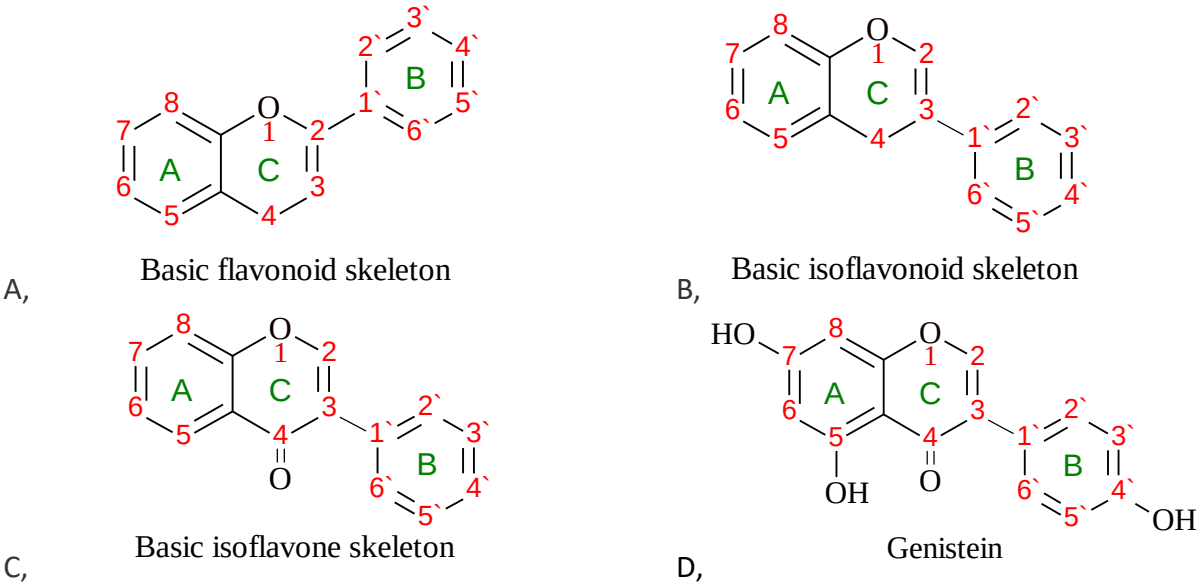


Figure 1: The structure of: A, Flavonoid; B, Isoflavonoid; C, Isoflavone; D, Genistein

Genistein effect in obesity treatment: It was confirmed that genistein reduces body weight and food intake. Rockwood et al., in their study, administrated a genistein-containing diet (600 mg genistein/kg diet) to mice (male and female). They observed a significant reduction in body weight. Genistein supplementation also improved serum glucose levels. An improvement was also observed in the value of serum triacylglycerides, in which genistein administration returned to lean levels [37]. Similar results were observed in the study of Kim et al. Genistein (1500 mg/kg) administrated to ovariectomized female mice

decreased food intake, reduced body weight, fat pad weight, and induced adipose tissue apoptosis. The effect of genistein on adipose tissue apoptosis was also observed in 3T3-L1 adipocytes, where a dose-related increase in apoptosis was observed in mature adipocytes [39]. A study by Chen et al. proved that high-fat diet mice supplemented with 0.2% genistein (high-fat diet + genistein) indicated increased metabolic homeostasis, which included a reduction in obesity, improved glucose uptake and insulin sensitivity, and attenuated hepatic steatosis. Their study indicates that improvements observed after genistein administration are associated with the phenomenon of beiging in white adipose tissue, reversal of brown adipose tissue bleaching, and body temperature modulation [38]. Gan et al. administrated genistein to high-fat diet mice; inhibition in body weight gain was observed in their study. Also, hyperglycemia, adipose, and hepatic lipid imposition were inhibited. Their results summarized that genistein could inhibit gluconeogenesis in obese mice by glycerol kinase and glucose-6-phosphatase expression regulation through miR451 [40].

Another possible effect of genistein in obesity treatment is its ability to increase lipolysis and oxidation of fatty acids. Treatment with high or low doses of genistein could influence metabolic disorders through changes in the composition and metabolism of fatty acids. The administration of genistein can upregulate the expression of genes involved in fatty acid metabolism. Genistein may concurrently activate peroxisome proliferator-activated receptors PPARα and PPARγ and support β-oxidation of fatty acids. Genistein has also been shown to upregulate fatty acid transporters [41]. Kim et al. evaluated the effect of genistein on the expression of a hepatic form of carnitine palmitoyltransferase 1 (CPT1) and PPARα in HepG2 cells [42]. The authors evaluated the effect of genistein on PPARα expression since genes involved in fatty acid catabolism are regarded as putative downstream target genes of PPARα. According to their results, genistein induced expression of liver CPT1 in HepG2 cells and induced expression of PPARα at the mRNA and protein levels [42]. Similar results were observed in the study of Yang et al., where an effect of genistein itself and the synergistic effect of genistein in combination with L-carnitine in high-fat diet C57Bl/6J mice was determined. The authors concluded that genistein induced the liver's expression of acyl-coenzyme A synthetase (ACS) and carnitine palmitoyltransferase 1 (CPT1). Induction of expression increased when the combination of genistein with carnitine was used, thus, their synergistic effect was demonstrated [43]. In the study by Weigt et al., genistein was administered to ovariectomized female high-fat diet Wistar rats. It was demonstrated that genistein reduced lipogenesis and triglyceride accumulation in the liver and muscle. Hepatic and muscular PPARγ expression increased and correlated with increased hepatic glucose uptake in obese animals [44]. Seidemann et al. studied the effect of genistein administration on hepatic lipid metabolism in an in vitro model of hepatic steatosis. Their results showed that administration of genistein in steatotic primary human preadipocytes induced expression of PPARα protein; simultaneously, an increase in CPT1 and ACS mRNA was observed. In steatotic hepatocytes, genistein also suppressed the activation of SREBP-1c (Sterol regulatory element binding protein 1). PPARα and SREBP-1c are signaling pathways considered key transcription factors related to the de novo synthesis of lipids as well as to lipid degradation [45]. Qin et al. investigated the function of estrogen receptor β in genistein-induced regulation of hepatic lipid metabolism in HepG2 cells. Their results showed that genistein significantly reduced the levels of triglycerides reduced the levels of genes and proteins that participated in lipogenesis (specifically, fatty acid synthase, stearoyl-coenzyme A desaturase 1, and SREBP-1c). Their study also reported that genistein supplementation upregulated gene and protein levels of regulatory factors liable for the β-oxidation of fatty acids (specifically, carnitine palmitoyltransferase 1α and PPARα) [46].

There is evidence about the possibility of the effect of natural compounds, including genistein, as inhibitors of adipogenesis through regulating the expression of PPARγ or through its transcriptional activity. PPARγ, considered a key regulator of adipogenesis, has been widely studied as an important molecular target for natural bioactive compounds in obesity treatment [47]. Zhang et al. reported an effect of genistein on adipogenesis in 3T3-L1 cells. In their study, genistein treatment inhibited the accumulation of lipids and reduced the amount of nonesterified fatty acid. Their results also showed that genistein inhibited the expression of fatty acid synthase and suppressed the expression of adipocyte differentiation marker - CCAAT/enhancer binding protein alpha (C/EBPα) [48]. Harmon et al. demonstrated an inhibitory effect of genistein on adipogenesis in 3T3-L1 cells by blocking the DNA binding and transcriptional activity of CCAAT/enhancer-binding protein beta (C/EBPβ). Inhibition of the transcriptional activity of C/EBPβ leads to the inhibition of the differentiation induced PPARγ and C/EBPα protein expression and a significant decrease in the accumulation of lipids [49]. Szkudelska et al. studied the effect of genistein on lipogenesis and lipolysis in adipocytes isolated from male Wistar rats. Their results showed that genistein limited glucose conversion to total lipids, decreased adipogenesis, and increased basal lipolysis in adipocytes. Their study demonstrated the inhibitory effect of genistein on protein kinase A and hormone-sensitive lipase activity in lipolysis [50]. The study of Shen et al. investigated the effect of genistein on white adipose tissue in high-fat diet ovariectomized female Wistar rats. Genistein supplementation decreased body weight, reduced the plasma levels of cholesterol and triacylglyceride, and inhibited the lipogenic proteins (acetyl-CoA carboxylase, fatty acid synthase, SREBP-1, and CD36) in the liver. Genistein increased the white adipose tissue browning, which was observed by increasing brown adipose tissue markers as uncoupling protein-1, PR domain containing 16, peroxisome proliferator-activated receptor gamma coactivator 1α, and cell death-inducing DFFA like effector [51].

Genistein administration also affects adipocyte differentiation and apoptosis. Grossinni et al. studied the effect of genistein on the differentiation and viability of human visceral adipocytes. Genistein enhances the differentiation and browning of human visceral preadipocytes, and genistein is also involved in the improvement of the viability of the cell and mitochondrial membrane potential in a dose-dependent manner. Genistein increased AMP-activated protein kinase signaling, which protects cells against oxidative stress and increases and preserves mitochondrial function in human preadipocytes [53]. The study of Yang et al. supports the findings about the antiobesity effect of genistein supplementation. In their study, genistein administrated in 3T3-L1 cells caused apoptosis, increased Bax expression, procaspase-3 cleavage, cytochrome 3 release, and proteolytic cleavage of poly (ADP-ribose) polymerase [53].

CONCLUSION

Interest in using natural compounds in many areas of medicine is constantly growing, and new studies dealing with the impact of bioactive substances on the human body are constantly being published. Foods rich in flavonoids are proven to have multifunctional health benefits, including treating obesity. The future of using natural substances for weight loss in the treatment of obesity looks very promising. When using natural substances, knowing their metabolism, mechanism of action, side effects, and synergistic effects is vital. The presented study summarizes the beneficial effect of genistein intake in the prevention of obesity in several model systems, where it appears to be a promising molecule in the treatment of obesity at several levels. It is worth noting that no clinical studies show genistein's effectiveness for weight loss in humans, even though it is the most studied isoflavone. Genistein is a naturally occurring phytoestrogen, and its

administration may be beneficial in postmenopausal women in many aspects, including menopause-related obesity treatment.

List of Abbreviations: WHO: world health organization, BMI: body mass index, PPARα: peroxisome proliferator-activated receptor alpha, PPARγ: peroxisome proliferator-activated receptor gamma, CPT1: carnitine palmitoyltransferase 1, ACS: acyl-coenzyme A synthetase, SREBP-1c: Sterol regulatory element binding protein 1, C/EBPα: CCAAT/enhancer binding protein alpha, C/EBPβ: CCAAT/enhancer-binding protein beta.

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