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The effects of different fatty acids on nesfatin-1, omentin-1, adropin, leptin and ghrelin levels

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Abstract

There are many studies on nesfatin-1, omentin, adropin, leptin, and ghrelin. However, data on the effects of long, medium, and short chain fatty acids on serum/tissue concentrations of nesfatin-1, omentin, adropin, leptin, and ghrelin are scarce. This study aims to investigate the effects of butyric acid, caprylic acid, and oleic acid alone or in combination on nesfatin-1, omentin, adropin, leptin, and ghrelin secretion. In the study, 49 male Wistar rats were used. The rats were randomly divided into 7 groups as control (CONT), butyric acid (BA), caprylic acid (CA), oleic acid (OA), butyric acid+caprylic acid (BA+CA), butyric acid+oleic acid (BA+OA) and caprylic acid+oleic acid (CA+OA) groups. The rats were orally administered fatty acids for twenty-one days. At the end of the study, the levels of nesfatin-1, omentin, adropin, leptin, and ghrelin were determined by the ELISA method. When the groups were compared in terms of nesfatin-1, omentin, adropin, leptin, and ghrelin levels, the butyric acid group had higher nesfatin-1, omentin, adropin, leptin, and ghrelin levels than the other groups ($p<0.05$). No statistically significant difference was found in the other groups ($p>0.05$). In conclusion, it was observed that butyric acid use caused an increase in serum nesfatin-1, omentin, adropin, leptin, and ghrelin levels.

Keywords: Fatty acids, nesfatin-1, omentin-1, leptin, ghrelin, adropin

Introduction

Fatty acids are classified according to chain length, the presence or absence of double bonds and the position of double bonds. Those with five or fewer carbon atoms are called short-chain fatty acids (SCFA), those with 6-12 carbon atoms are called medium-chain fatty acids (MCFA), and those with 13-20 carbon atoms are called long-chain fatty acids (LCFA) [1]. In addition to being a simple source of energy, fatty acids also act as intracellular and extracellular signaling molecules [1]. During fasting, short, medium, and long-chain fatty acids hydrolyzed from adipose tissue stores are used to provide energy to tissues. In particular, SCFAs are the main metabolites produced by bacterial anaerobic fermentation of indigestible polysaccharides and proteins in the large intestine [1]. Short- and medium-chain fatty acids are important substrates of energy metabolism and anabolic processes in mammals.

Butyrate demonstrates strong impacts on diverse functions within the colonic mucosa. These include suppressing inflammation and carcinogenesis by enhancing different elements of the colon's protective barrier and diminishing oxidative stress. Additionally, it finds utility in managing ulcerative colitis, a condition arising from insufficient metabolism of butyric acid in humans, as well as in treating individuals with Crohn's disease affecting the digestive tract [2].

Caprylic acid is produced in trace amounts in the human body but is abundant in coconut oil and goat milk. It lowers blood sugar by blocking glycolysis in liver cells. When combined with ghrelin (caprylate ghrelin), it also controls other physiological pathways such as growth hormone secretion, appetite stimulation (orexigenic effect), glucose homeostasis and adiposity [3].

Oleic acid constitutes 70-80% of the fatty acids in olive oil. The beneficial health effects of olive oil are generally associated with its high content of oleic acid. Oleic acid, which is a monounsaturated fatty acid, contributes to the antioxidant effect

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of olive oil due to its lower susceptibility to oxidation [4].

Nesfatin-1 is produced in the central and peripheral nervous systems through the processing of the precursor peptide NEFA/nucleobindin 2 (NUCB2), and it crosses into the brain via transmembrane diffusion. NUCB2 mRNA is expressed in the gastric mucosa, white adipose tissue, and to a lesser extent in other peripheral organs such as the pancreas and testes [5]. The circulating levels of Nesfatin-1 increase after food intake and decrease during fasting. Its appetite-suppressing effect is independent of the leptin pathway and acts through the melanocortin signaling pathway. It has been found that Nesfatin-1 mRNA expression is 10 times higher in the gastric mucosa compared to the brain, indicating that the stomach is a key source of circulating Nesfatin-1. The intracerebroventricular (ICV) injection of Nesfatin-1 can inhibit food intake in rats with leptin receptor mutations, suggesting that the inhibition of food intake is assumed to be independent of the leptin pathway [6].

Also known as Intelectin-1, omentin-1 is a recently identified novel adipokine. It is primarily expressed in visceral fat. Plasma levels of omentin-1 in females are higher than in males. Circulating levels of omentin-1 have a negative correlation with free testosterone, androgens, leptin, tumor necrosis factor-alpha (TNF-α), and interleukin-6 levels, but they show a positive correlation with adiponectin levels. While its regulation is suppressed by glucose and insulin, omentin-1 secretion is stimulated by fibroblast growth factor-21 and dexamethasone [7]. However, it has also been observed that high omentin concentration is associated with an increased risk of cardiovascular events in diabetic patients. Omentin is positively correlated with adiponectin while being inversely proportional to leptin [8].

Adropin is a 76-amino acid protein that plays a significant role in the regulation of energy metabolism [9]. The active portion of adropin is located in residues 34-76, encoded by the energy homeostasis-related gene (ENHO), which is associated with energy homeostasis [10,11]. Adropin is expressed in various tissues and organs, especially the liver. Adropin, which has numerous metabolic effects, controls the metabolism of glucose and lipids in skeletal muscles. It suppresses hepatic glucose production and enhances insulin sensitivity in the liver. Additionally, circulating adropin has a therapeutic effect on numerous cardiovascular diseases. It can protect against hepatocyte damage and improve liver function. Furthermore, the expression of the adropin-associated gene ENHO decreases in obese individuals induced by long-term high-fat diets [10].

Leptin is a hormone secreted by adipose tissue that regulates appetite and represents a key factor in the development of obesity [12]. Despite its ability to effectively reduce food intake and body weight, circulating leptin levels are elevated in obese individuals, and they are insensitive to exogenous leptin administration. The condition where leptin does not exhibit anorexigenic effects and lacks clinical utility in obese individuals is referred to as leptin resistance [12].

Ghrelin is a 28-amino acid hunger hormone. It is secreted by endocrine cells classified as P/D1 type in the gastric mucosa [13]. Among the gastrointestinal hormones that regulate appetite and food intake, only ghrelin has an orexigenic effect. Ghrelin synthesis and secretion are influenced by various conditions such as hunger and pathological states. It reaches its highest levels during periods of fasting, intensifying the sensation of hunger. After a meal, its levels drop and a feeling of satiety develops. Prolonged high-fat diet and obesity lead to decreased ghrelin production in the stomach. Ghrelin has vasodilator effects in healthy individuals, causing a decrease in mean arterial pressure without altering heart rate [14].

This study aims to investigate the impact of fatty acids such as butyric acid, caprylic acid, and oleic acid on the levels of serum nesfatin-1, omentin, adropin, leptin, and ghrelin.

Material and Methods

Animals

The animals used in the study were obtained from the Düzce University Laboratory Animal Application and Research Center. A total of 49 male Wistar rats, aged 2-3 months and weighing 230±30 grams, were used in the study. The rats were housed in the laboratory under optimal conditions of 23°C room temperature, 60±5% humidity, and a 12:12 light-dark cycle, with free access to food and water. This investigation received ethical clearance from the Düzce University Animal Experiments Local Ethics Committee, under Decision No: 2021/04/01."

Substances and doses

The butyric acid, caprylic acid, and oleic acid used in the study were obtained from Sigma Aldrich (Sigma Aldrich Chemical Co., St. Louis, Missouri, US). Each of these fatty acids was applied orally at a dose of 100 mg/kg. Anesthesia was induced using 90 mg/kg ketamine hydrochloride (Keta-Control, Mefar İlaç Sanayi A.Ş., Istanbul, Turkey) and 10 mg/kg xylazine hydrochloride (Vetaxyl, VET-AGRO Sp. z o.o., ul. Lublin, Poland). All drugs were prepared daily.

Experimental groups and routes of administration of the substances

Rats were randomly divided into 7 subgroups as Control (CONT), Butyric Acid (BA), Caprylic Acid (CA), Oleic Acid (OA), Butyric Acid+Caprylic Acid (BA+CA), Butyric Acid+Oleic Acid (BA+OA), Caprylic Acid+Oleic Acid (CA+OA). In the control group, only saline was administered orally at 1 ml/kg for 21 days. The fatty acid groups were administered 100 mg/kg fatty acid orally for 21 days.

Termination of the study

After the last administration, blood was taken from the heart of the rats by cardiac puncture method under ketamine/xylazine anesthesia. The animals were then sacrificed by cervical dislocation under anesthesia. Blood samples were centrifuged at 4000 rpm for 15 minutes. Afterward, the obtained serums were stored at -80 °C.

Determination of biochemical parameters

Nesfatin-1, omentin, adropin, leptin and ghrelin levels were

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measured by ELISA method in the collected serum samples. ELK (ELK biotechnology CO., LTD, Hubei, CHINA) brand ELISA kits for nesfatin-1 (Cat. ELK4864), omentin-1 (Cat: ELK2005), adropin (Cat: ELK9286, leptin (Cat: ELK1244)) and ghrelin (Cat: ELK7752) were obtained. All parameters were measured with an ELISA reader (Epoch, BioTek Instruments, Inc., VT, USA) according to the kit procedure.

Statistical analysis

The ANOVA test was used to compare the groups in terms of serum nesfatin, omentin, adropin, leptin and ghrelin levels, and the homogeneous subgroups multiple comparison method was used to determine the groups that were different. GraphPad Prism (version 9.0, La Jolla, California, USA) program was used for analysis.

Results

The effects of SCFA, MCFA, and LCFA on Nesfatin-1 levels

A statistically significant difference was detected among the groups when comparing nesfatin-1 levels (P=0.0002) (Figure 1).

Upon further detailed examination of the results, it was determined that the nesfatin-1 level values of the BA group were statistically higher than those of the CA, OA, BA+CA, BA+OA, and CA+OA groups (p=0.0007, p=0.0006, p=0.0005, p=0.0029, and p=0.0391, respectively).

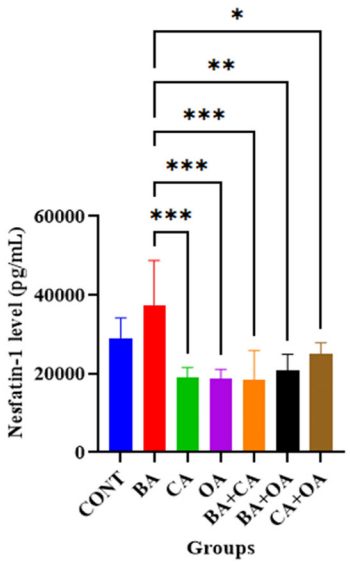

Figure 1. The effect of short, medium, and long-chain fatty acids on nesfatin-1 levels (*p<0.05, **p<0.001 and ***p<0.001)

The effects of SCFA, MCFA, and LCFA on omentin-1 levels

A statistically significant difference was detected among the groups when comparing omentin-1 levels (P=0.0043) (Figure 2).

Upon further detailed examination of the results, it was determined that the mean omentin-1 level of the BA group was higher than the CONT, KA, OA, BA+CA, BA+OA, and CA+OA groups (p=0.0154, p=0.0488, p=0.0334, p=0.0037, p=0.0120, and p=0.0084, respectively). Although the omentin level values of the CA and OA groups were higher than the other groups (except the BA group), it was not different (p>0.05).

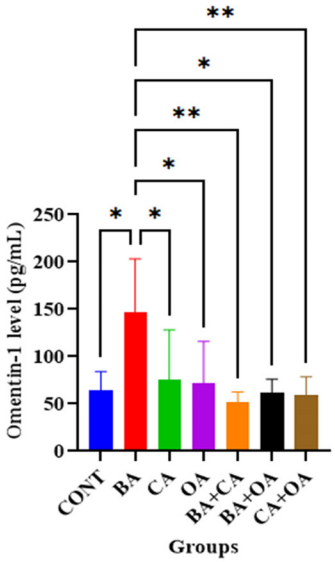

Figure 2. The effect of short, medium, and long-chain fatty acids on omentin-1 levels (*p<0.05, **p<0.001)

The effects of SCFA, MCFA, and LCFA on adropin levels

A statistically significant difference was detected among the groups when comparing adropin levels (P<0.0001) (Figure 3).

Upon further detailed examination of the results, it was determined that the mean adropin level of the BA group was statistically higher than CONT, KA, OA, BA+CA, BA+OA, and CA+OA groups (p=0.0085, p<0.0001, p=0.0159, p<0.0001, p=0.0081, and p=0.0081, respectively). Adropin level values of CA and BA+CA groups were lower than the other groups, but not significant (p>0.05).

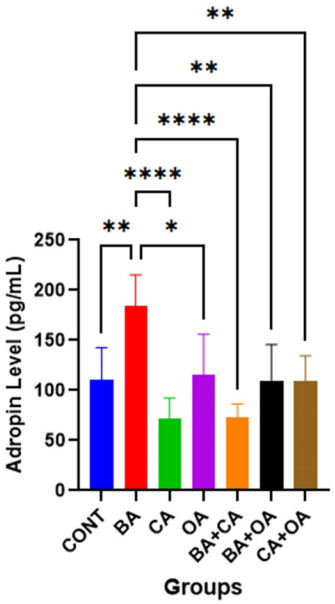

Figure 3. The effect of short, medium, and long-chain fatty acids on adropin levels (*p<0.05, **p<0.01 and ****p<0.0001)

The effects of SCFA, MCFA, and LCFA on leptin levels

A statistically significant difference was detected among the

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groups when comparing leptin levels (p<0.0001) (Figure 4).

Upon further detailed examination of the results, it was determined that the mean leptin level of the BA group was statistically higher than the CONT, KA, OA, BA+CA, BA+OA, and CA+OA groups (p<0.001). Although the mean leptin level of the BA+OA group was higher than the other groups (except the BA group), it was not different (p>0.05).

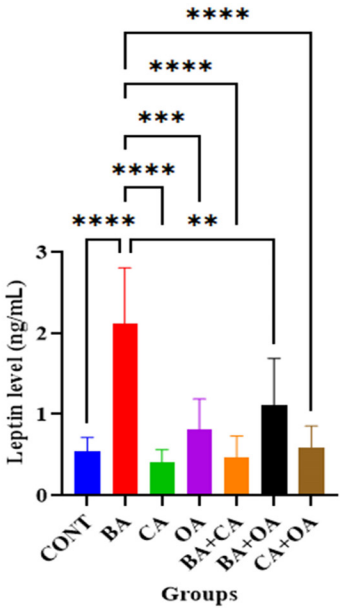

Figure 4. The effect of short, medium, and long-chain fatty acids on leptin levels (**p=0.0089, ***p=0.0001 and ****p<0.0001)

The effects of SCFA, MCFA, and LCFA on ghrelin levels

A statistically significant difference was detected among the groups when comparing ghrelin levels (P=0.0001) (Figure 5).

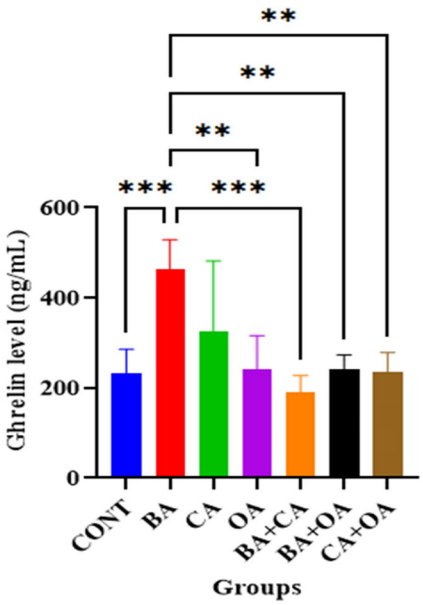

Figure 5. The effect of short, medium, and long-chain fatty acids on leptin levels (**p=0.0089, ***p=0.0001 and ****p<0.0001)

Upon closer examination of the results, it was observed that the mean ghrelin levels of the BA group were statistically higher compared to the CONT, OA, BA+CA, BA+OA, and CA+OA groups (p=0.0010, p=0.0017, p=0.0001, p=0.0015, and p=0.0011, respectively).

Discussion

Nesfatin-1, omentin, adropin, leptin, and ghrelin are molecules known as peptide hormones that possess various biological effects within the body. Additionally, different fatty acids present in foods can impact metabolic functions. SCFA, MCFA, and LCFA are metabolized in distinct ways in the body and possess diverse metabolic effects. Recent studies have indicated the benefits of short and medium-chain fatty acids, particularly dietary supplements like medium-chain triglycerides added to foods, in promoting healthy weight management and metabolic well-being, often due to their appealing taste and aroma. This study examines the relationship between SCFA, MCFA, and LCFA with nesfatin-1, omentin, adropin, leptin, and ghrelin. This research is the first to collectively evaluate the effects of SCFA, MCFA, and LCFA administration on serum levels of nesfatin-1, omentin, adropin, leptin, and ghrelin. Among the groups studied, the group treated solely with butyric acid exhibited higher nesfatin-1 levels compared to all other groups except the CONT group. Similarly, the group treated solely with butyric acid displayed elevated levels of omentin, adropin, leptin, and ghrelin in comparison to all other groups.

These findings suggest that nesfatin-1, alongside its anti-hyperglycemic and anorexigenic effects, could significantly impact metabolic regulation [15]. Recent studies conducted on Siberian sturgeon have provided corroborative results, showing that fasting reduces NUCB2/nesfatin-1 mRNA levels in the brain and liver, while levels increase at 1 and 3 hours after feeding [16]. A high-fat diet significantly elevated serum NUCB2/nesfatin-1 levels in mice. Feeding adult mice a high-fat diet for 17 weeks resulted in obesity, and serum concentrations of NUCB2/nesfatin-1 and NUCB2 mRNA expression in the liver, stomach, and colon were reduced compared to mice on a control diet. [17]. In humans, obesity has been reported to elevate circulating NUCB2/nesfatin-1 levels [18] and decrease NUCB2/nesfatin-1 in the lateral hypothalamic area of the brain [19]. Conversely, a recent case-control study demonstrated that serum levels of NUCB2/nesfatin-1 were lower in obese and diabetic patients compared to healthy controls with normal weight [20]. In line with this finding, several studies have reported a negative relationship between circulating NUCB2/nesfatin-1 levels and body mass index (BMI) in both obese [21] and normal-weight subjects [22]. However, further research is needed to investigate whether these findings are more observable in clinical settings compared to experimental environments and whether factors such as gender, age, and stressors serve as confounding variables. In obese girls aged 6-9 and 12-16, plasma NUCB2/nesfatin-1 levels were lower compared to normal-weight girls, indicating a negative correlation between body weight/BMI and NUCB2/

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nesfatin-1 levels. Similarly, another study demonstrated that serum NUCB2/nesfatin-1 levels were significantly reduced in obese and overweight children and adolescents compared to a normal-weight control group [23]. In contrast, a report has shown a significant increase in serum NUCB2/nesfatin-1 levels in obese children and adolescents. Studies in the literature have indicated that there is no difference in NUCB2/nesfatin-1 plasma levels between fasting and post-meal states in obese children [24]. In the current study, the sole application of butyric acid (SCFA) increases nesfatin-1 levels, whereas combined application with caprylic acid (MCFA) and oleic acid (LCFA) decreases nesfatin-1 levels. When considering the data collectively, it becomes evident that the circulating NUCB2/nesfatin-1 levels under obesity conditions exhibit specific changes related to gender/gender identity and age, which need to be taken into account to explain certain inconsistencies.

Adropin is a novel regulatory protein encoded by a gene associated with energy homeostasis [15]. Research indicates that adropin boosts insulin sensitivity, lessens hepatic steatosis, and retards the onset of obesity in mice consuming a high-fat diet [10]. Consistently, the absence of adropin in mice consistently results in compromised insulin sensitivity, disrupted glucose metabolism, and heightened adiposity. Nevertheless, the precise influences of adropin on mature adipocyte functions, including glucose and lipid metabolism, as well as its effects on endocrine functions, remain significantly unexplored. Moreover, adropin boosts adiponectin mRNA expression while repressing the expression of resistin and visfatin [25]. Adropin has been shown to have a connection with obesity and is suggested to play a role in safeguarding against insulin resistance, dyslipidemia, and compromised glucose tolerance [26]. In the current study, the sole application of butyric acid (SCFA) increases adropin levels, whereas combined application with caprylic acid (MCFA) and oleic acid (LCFA) decreases omentin levels. Due to the absence of similar studies in the literature, these intriguing findings cannot be directly compared.

Leptin is a hormone secreted by fat cells and plays a crucial role in regulating energy balance, appetite control, and metabolism. When leptin levels are high, the brain increases the feeling of fullness, suppressing appetite and increasing energy expenditure. Therefore, individuals with leptin resistance might find weight control more challenging [27]. However, although the data showing that butyric acid increases leptin levels are based on some animal studies, the effects of this fatty acid on humans remain unclear. Additionally, further research is required to comprehensively understand the impact of butyric acid on weight control. In the current study, it was observed that leptin levels were elevated in groups treated solely with butyric acid, as suggested by existing literature. In conclusion, the relationship between butyric acid and leptin is important due to its effects on gut health and weight control. Nevertheless, more research is needed in this area.

Recent studies have indicated that omentin might possess protective properties against impaired glucose tolerance. Reduced omentin-1 expression in adipose tissue has been noted in both overweight and obese individuals, along with patients experiencing insulin resistance, type 2 diabetes, and type 1 diabetes [28]. Kabiri et al. proposed that omentin decreases in the diet and increases in diets rich in olive oil [29]. Another study has reported that LCFA's (long-chain fatty acids) hypothalamic concentration could potentially reduce the levels of orexigenic peptides [30]. Presently, there exist only a few human studies that explore the correlation between dietary fatty acid types and omentin levels in the bloodstream. De Souza Batista et al. revealed a decline in omentin levels and gene expression linked to obesity, highlighting significantly reduced plasma omentin-1 levels in overweight and obese individuals compared to those who are not obese [31]. In the present study, only the group treated with butyric acid showed an increase in average serum levels, whereas the application of other fatty acids either alone or in combination did not elevate omentin serum levels. In contrast to Kabiri et al. [29] groups treated with oleic acid exhibited omentin levels similar to those in the control group. The inconsistencies observed between our results and previous studies may be attributed to various factors, including the fact that our study was conducted on rats, whereas studies on humans considered factors like age groups, gender, physical activity, specific medication usage, and differences in participants' inflammatory conditions.

Circulating ghrelin levels increase between meals, peak during periods of hunger, and decrease within an hour after a meal [32]. Caprylic acid activates ghrelin, affecting hunger perception (and potentially body weight). However, the infusion or oral administration of caprylic acid in different studies has led to conflicting results concerning subsequent food intake [33] and ghrelin activation [34]. Sousa et al. reported that hepatic-portal oleic acid more effectively inhibited feeding in rats compared to hepatic-portal caprylic acid [31]. Studies focusing on mechanisms using the ghrelinoma PG-1 cell line have indicated that ghrelin-producing cells are capable of generating acyl donors by engaging in the β-oxidation of long-chain fatty acids sourced from the bloodstream [35]. In addition, increased intake of medium-chain fatty acids can stimulate AG levels in humans [36] and rodents [37]. Oral administration of oleanolic acid (20 or 40 mg/kg) to C57BL/6J mice for seven days has been reported to reduce ghrelin levels and body weight gain [38]. A study involving 15 hyperlipidemic patients demonstrated that four weeks of oleanolic acid (OA) administration resulted in decreased serum levels of total cholesterol, triglycerides, low-density lipoprotein, glucose, and insulin, as well as an increase in serum levels of leptin [39]. In the current study, only the group treated with butyric acid showed an increase in average serum levels, whereas the application of other fatty acids either alone or in combination did not elevate omentin serum levels. However, although the groups treated with caprylic acid and oleic acid exhibited higher serum ghrelin levels compared to the control group, statistical significance was not determined.

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Conclusion

In conclusion, the relationship between nesfatin-1, omentin, adropin, leptin, and ghrelin is quite complex. Different studies indicate that the consumption of various types of fatty acids, particularly short-chain fatty acids, may contribute to the release of nesfatin-1, omentin, adropin, and ghrelin, thereby potentially enhancing insulin sensitivity and helping in the reduction of leptin resistance.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
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Ethical Approval
Düzce University Animal Experiments Local Ethics Committee, under Decision No: 2021/04/01.

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