



## Research Paper

# White tea causes less change in Apelin levels in high fat diet fed Rats

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### ABSTRACT

Obesity is characterized by an abnormal increase in the number and volume of adipocytes. Adipose tissue is an endocrine organ that stores energy and synthesizes bioactive molecules called adipokines. Discovered in bovine stomach extracts, apelin has been found to be an adipokine with its secretion from adipose tissue and has been reported to play a role in various physiological functions in obesity and its comorbidities. In this study, the effect of white tea, which is obtained from *Camellia sinensis* plant and has positive effects on health such as antiobesitic and antidiabetic, on apelin levels in rats fed a high-fat diet was investigated. For this purpose, 32 *Sprague Dawley* 6-8 weeks old male rats were divided into four groups as control, high-fat diet, high-fat diet+orlistat, high-fat diet+white tea. The rats were fed ad libitum, orlistat 30 mg/kg and white tea 5 mg/kg every day by oral gavage for 13 weeks. At the end of the experiment, serum apelin-13, apelin-36, insulin levels ELISA; Serum glucose, triglyceride, cholesterol, HDL-C, LDL-C levels were determined by autoanalyzer technique. In addition, HOMA-IR was calculated. There was a statistically significant difference in last body weight, apelin-13, glucose and cholesterol levels between the groups ( $p<0.05$ ). A significant and positive correlation was found between apelin-13, apelin-36, insulin and HOMA-IR levels, only between insulin and HOMA-IR ( $p<0.05$ ). It was concluded that obesity and/or metabolic disorders affect apelin levels, white tea has antiobesitic, hypoglycemic, insulin tolerance and hypocholesterolemia effects, and the physiological effects of white tea may indirectly cause less change in apelin levels.

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## INTRODUCTION

Obesity is a chronic pathological condition caused by many factors, in which the number and volume of fat cells increase with the accumulation of energy in the adipose tissue, if the energy intake is higher than the energy spent. Obesity negatively affects the individual, economy and quality of life by bringing along many health problems, especially cardiovascular diseases (CVD), diabetes, various cancers, and sleep apnea (De Lorenzo et al., 2019). This situation has led to an increase in the interest in adipose tissue (AT) and studies in this field and new targets for alternative treatment methods have been sought (Atakan et al., 2021). AT, a special type of connective tissue, consists largely of lipid-filled cells called adipocytes. AT shows

continuous lifetime variability in adipocyte number and size, depending on energy intake and expenditure. Besides energy storage, it is an active endocrine organ capable of synthesizing many biologically active substances (adipokines) that affect metabolic balance (Longo et al., 2019). Discovered in bovine stomach extracts in 1998, apelin is an adipokine member of AT. Apart from AT, apelin has been detected in many tissues and organs such as lung, mammary gland, testis, muscle, and brain (Fève et al., 2016).

Apelin plays a role in the regulation of various physiological functions, including energy metabolism, and is seen as a therapeutic target for different pathological

conditions (Antushevich and Wójcik, 2018). There are various isoforms of apelin such as apelin-36, apelin-17, apelin-13, apelin-12, and their effects vary according to the form. Many studies have focused on apelin-13 due to its high biological activity (Kakizawa, 2016). Tea, which is an important life culture in Turkey and in the world, is the most consumed beverage after water due to its non-alcoholic and beneficial effects on health. It is a genus of flowering plants in the family Theaceae, botanically called *Camellia sinensis*. White, green, oolong and black teas obtained from this species are obtained by processing in different ways (Eröz and Bozok, 2018). Due to the minimal processing of white tea, its medicinal effects are also quite high. Due to the strong antioxidant activities of the phenolic substances it contains, it has been reported to be associated with CVD, diabetes, cancer, skin diseases, bone and tooth development, antimicrobial effect, and metabolism (Hinojosa-Nogueira et al., 2021). In this study, it was aimed to determine the effect of white tea preparations obtained from the *Camellia Sinensis* plant, which is the main agricultural product of Rize and its region, on the level of apelin protein, which is known to be associated with obesity, in rats fed a high-fat diet (HFD) and to determine one of the possible ways of the antiobesitic effect of white tea.

## MATERIALS AND METHODS

### Animals and procedures

A total of 32 6-8 weeks old Sprague Dawley male rats were obtained from RTEU Experimental Animals Application and Research Center. The care of the rats was adjusted as 23(±2)°C, 55% (±5%) humidity and 12 h day/night cycle. The cages were cleaned every week and sawdust was used as litter. Rats fed *ad libitum* with a normal diet (Bayramoğlu Yem ve Un San. Tic. A.Ş., Whole Pellet Rat Feed) for one week and adapted to the laboratory were randomly selected and divided into 4 groups in transparent polyethylene cages with 8 rats (n=8) in each group. In order to create an obesity model, HFD (Arden Research & Experiment, 22% kcal from fat) was given *ad libitum* as 15-20 g/day per rat. The water given to the animals was given as tap water in special bottles.

### Study groups and preparation

Animal groups: 1) Control (C) group fed a normal diet, 2) HFD group fed a high-fat diet, 3) The group fed a high-fat diet and given antiobesity drug [orlistat (OL)], and 4) A high-fat diet fed group and white tea (WT) given group. During the 13-week period, one rat was lost in each of the C and HFD+OL groups, studies and statistics were based on these numbers. Orlistat (Xenical) is used as a pharmacotherapy agent in obesity. Orlistat, an inhibitor of pancreatic lipase, prevents the digestion of triglycerides and stops the intake of dietary fat into the body (Moini et al., 2020). Orlistat was prepared by dissolving 30 mg/kg in

distilled water. The white tea plant was obtained from the General Directorate of Tea Enterprises (ÇAYKUR). White tea was weighed at 5 mg/kg, brewed in boiled and slightly rested (90-95°C) drinking water for 10 min and brought to room temperature. The dose of the given substance was calculated to correspond to 1 mL (1 mL of gavage applied to all rats). Weekly weights were weighed. The substances to be given to the rats were calculated per kg and updated every week. All of them were prepared fresh daily and applied. Diets and other practices were continued until the weight of the rats in the HFD group was more than 20% of the weight of the rats in the C group (Buettner et al., 2007).

### Biochemical analyzes

At the end of the experimental period, blood samples were taken into serum biochemistry tubes by intervention from the intracardiac left ventricle under anesthesia. For biochemical analysis, sera were stored at -80°C until the study day. Serum apelin-13 (Bt Lab, Cat No. E1427Ra, Lot: 202103014), apelin-36 (Bt Lab, Cat No. E1331Ra, Lot: 202103014) and insulin (Bt Lab, Cat No. E0707Ra, Lot: 202103014) levels determined using ELISA kits. Serum glucose, triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) levels were measured with the help of an autoanalyzer (Beckman Coulter AU5800). Fasting blood glucose (FBG) and fasting insulin (FI) values and insulin resistance were detected by applying the HOMA-IR test (Ufat, 2015). Insulin Resistance formula:

$$\text{HOMA-IR} = \frac{\text{FBG (mg/dL)} \times \text{FI } (\mu\text{U/mL})}{405}$$

### Statistics

The data obtained from the study were transferred to the computer environment and analyzed. The data, which were determined not to fit the normal distribution, were first analyzed with Kruskal-Wallis analysis of variance and then with the post-hoc corrected Benferroni test to find the group that made a difference. Results were expressed as median and 25-75% quartiles [Interquartile range (IQR)]. Spearman's correlation analysis was applied to test the correlation between parameters.  $p < 0.05$  was considered statistically significant.

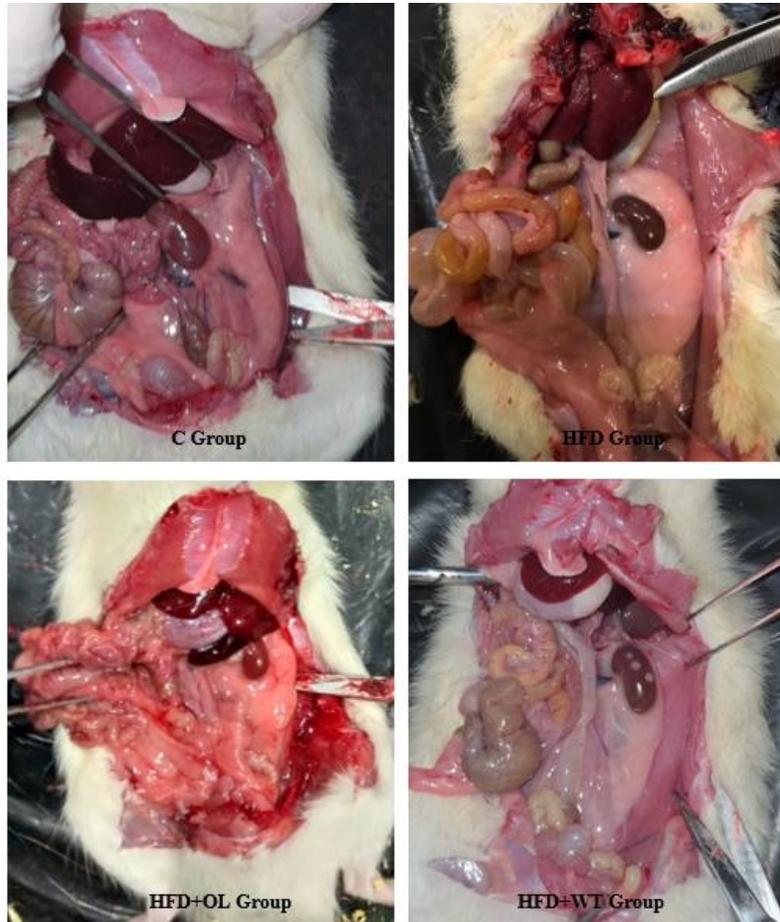
## RESULTS

### Macroscopic views of rats

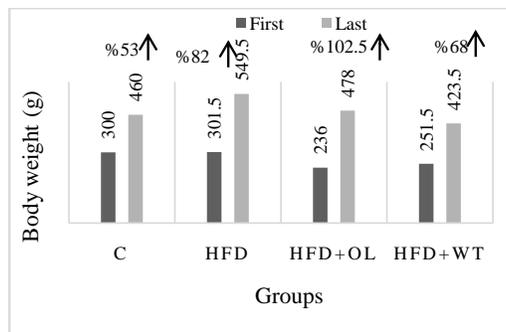
The AT differences of the rats belonging to the groups at the end of the experimental period are shown in [Figure 1](#).

### Body weight of rats

According to the initial body weight (BW) of the rats at 13



**Figure 1.**Adipose tissue views of rats

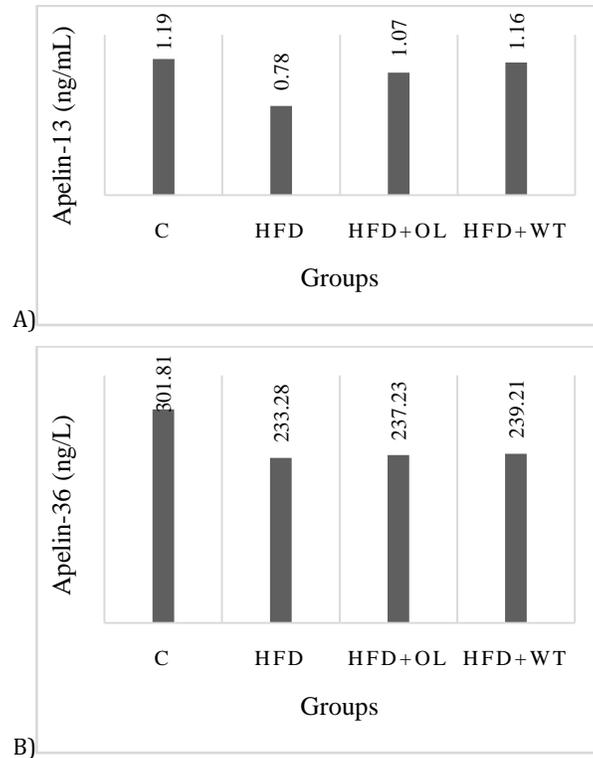


**Figure 2:** First and last body weights of rats

weeks, a weight gain of 53% in the C group, 82% in the HFD group, 102.5% in the HFD+OL group, and 68% in the HFD+WT group was observed. In addition, the final BW of the rats was 20% higher in the HFD group than in the C group. When the final BW of the rats was examined, there was a statistically significant difference and it was seen that it was higher in the HFD group than in the C and HFD+WT groups ( $X^2=18.340$ ,  $p=0.000$ ) (Figure 2).

### Biochemical results

There was a statistically significant difference between the apelin-13 levels of the rats, and it was found to be lower in the HFD group than in the C group ( $X^2=9.965$ ,  $p=0.019$ ). On the other hand, no statistically significant difference was found between the apelin-36 levels of the rats ( $p>0.05$ ) (Figure 3A and B). While there was no statistically



**Figure 3**A) Apelin-13 and B) apelin-36 levels of the groups

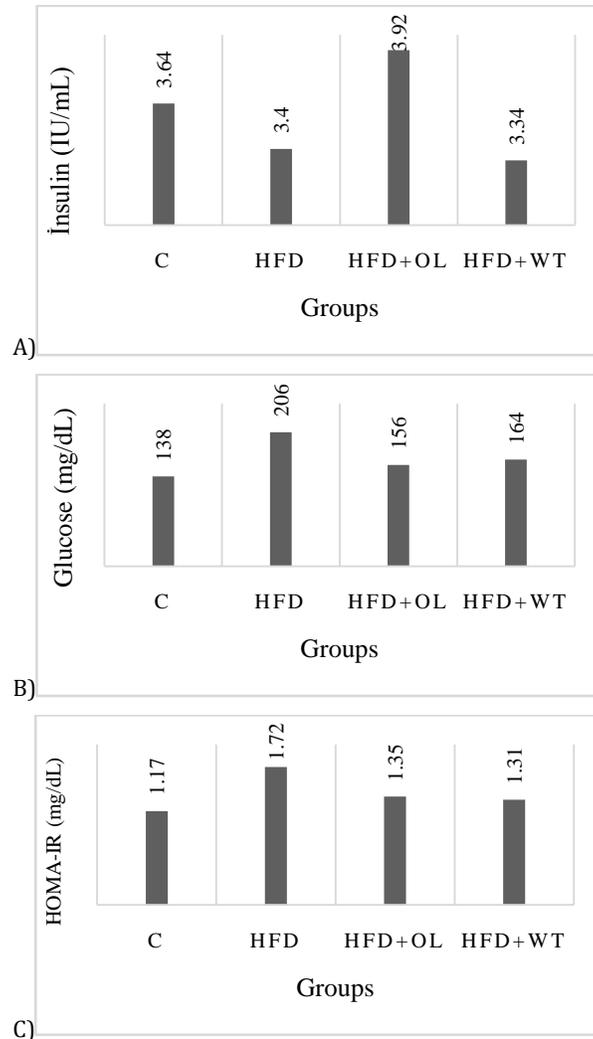
significant difference between the insulin and HOMA-IR levels of the rats ( $p > 0.05$ ), there was a statistically significant difference between the glucose levels of the rats and it was seen that the C group was lower than the HFD group ( $X^2 = 8.824$ ,  $p = 0.32$ ) (Figure 4A, B and C). There was a statistically significant difference between the TC levels of the rats, and it was observed that the C group was lower than the HFD group ( $X^2 = 9.435$ ,  $p = 0.024$ ). On the other hand, no statistically significant difference was found between the TG, HDL-C and LDL-C levels of the rats ( $p > 0.05$ ) (Figure 5). In addition, when the relationship between apelin-13, apelin-36, insulin and HOMA-IR levels was examined, there was a statistically significant and positive relationship between insulin and HOMA-IR ( $r = 0.455$ ,  $p < 0.05$ ), but no statistically significant relationship was found between other parameters ( $p > 0.05$ ).

## DISCUSSION

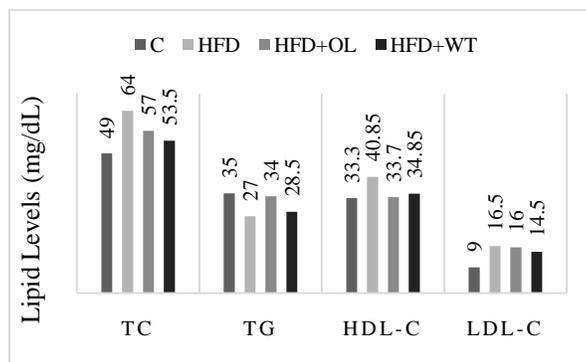
Obesity is characterized by an excessive and abnormal increase in AT. It is a multifactorial disease caused by various reasons such as genetic predisposition, incorrect regulation of energy balance, environmental and social factors. However, insulin resistance is an important public health problem that affects morbidity and mortality by causing many chronic diseases, especially diabetes,

hypertension, atherosclerosis, and CVD (Rayalam et al., 2008; Leal and Mafra, 2013). AT is a highly specialized tissue that plays an important endocrine role (autocrine and paracrine effect) and affects other tissues and organs (standard endocrine effect) through the synthesis and secretion of many bioactive molecules such as adipokines (Kojta et al., 2020). Adipokines; It is involved in the physiological regulation of fat storage and development, metabolism and eating behavior, and also plays an important role in obesity and its comorbidities (Boucher et al., 2005). The diversity of adipokines and their interactions affect many different metabolic processes of AT. With the increasing interest in AT in recent years, attention has been drawn to adipokines and their relationship to obesity and its comorbidities (Kojta et al., 2020).

Apelin, an adipokine is a peptide encoded by the APLN gene and widely expressed in various organs and tissues such as heart, lung, kidney, liver, AT, gastrointestinal tract, and brain. Various isoforms of apelin (apelin-36, apelin-17, apelin-13, apelin-12) exist. These isoform levels vary and show effects according to the tissue in which they are found. These bioactive peptides act via the G protein-coupled receptor APJ and show differential physiological effects mainly on the cardiovascular system and regulation of fluid homeostasis. It has been reported that apelin, one of the adipokines, is effective in the regulation of glucose metabolism, lipolysis, food intake, cell proliferation and angiogenesis (Kakizawa et al., 2016; Kojta et al., 2020).



**Figure 4.** A) Insulin, B) glucose and C) HOMA-IR levels of the groups



**Figure 5:** Lipid levels of the groups

There are diet, physical activity, lifestyle change, behavior change, pharmacotherapy, bariatric surgery methods in the treatment of obesity. As an alternative to these treatment

methods, herbal preparations and plant compounds have gained worldwide popularity in recent years due to their easy accessibility, cost-effectiveness, natural origins, rich

molecular diversity, less side effects, rich traditional knowledge base and use (Shende et al., 2020, Borah et al., 2021). Many epidemiological, clinical, in vivo and in vitro studies have shown that tea obtained from the *Camellia sinensis* plant and its phytochemicals have certain preventive and therapeutic effects on various biological activities and obesity and its comorbidities (Shang et al., 2021).

In this study, the effects of white tea, which is a type of tea and reported to have an antiobesitic effect on increased AT and apelin-13 and apelin-36 secreted from AT in rats fed with HFD were investigated. In addition, serum insulin, glucose, HOMA-IR, TC, TG, HDL-C and LDL-C levels, which are metabolic parameters associated with obesity, were examined. In this study, orlistat was suspended at 30 mg/kg/day, white tea was infused at 90-95°C for 10 min at 5 mg/kg/day and given orally to the rats for 13 weeks. In a study, orlistat was suspended in distilled water at 10 mg/kg/day and given orally to rats fed HFD for 12 weeks (Suleiman et al., 2020). In another study, 40 mg/kg orlistat was suspended in distilled water with 1% dimethyl sulfoxide and 0.1% Tween 20 and given orally twice a day for 12 weeks to rats fed with HFD (Lim et al., 2012). While the infusion doses of white tea vary in the literature, it has been reported in a study that white tea brewed at 98°C for 7 minutes has high antioxidant capacity and phenol content (Pérez-Burillo et al., 2018). Studies on the effects of white tea on BW and AT are limited in the literature. In a study, it was observed that when white tea was administered at 1 g/kg for 9 weeks in HFD-induced obese mice, it decreased BW and white adipose tissue (WAT) by increasing energy expenditure and fatty acid oxidation. Among the different types of tea, white tea has been reported to be the most effective (Liu et al., 2019). In another study, it was observed that 2% white tea infusion was applied for 28 days in female rats and was very effective in slowing down weight gain (Sun et al., 2019).

On the other hand, in another study, it was observed that 0.5% white tea extract did not reduce BW and visceral adiposity when administered for 8 weeks in HFD-induced obese mice (Teixeira et al., 2012). Antiobesitic effect of white tea has been shown in a study in vitro that white tea extract (polyphenols and methylxanthines) effectively inhibits adipogenesis and stimulates lipolysis activity (Söhle et al., 2009). In addition, in vitro studies have shown that white tea infusion inhibits lipase activity, especially pancreatic lipase. Thus, white tea stops the intake of dietary fat into the body by preventing the digestion of triglycerides (Gondoin et al., 2010; Tenore et al., 2013). In this study, when the weight gain status of the rats is examined, it is seen that it is mostly in the HFD+OL group, followed by the HFD, HFD+WT, and C groups, respectively. When the final BW and AT growth of the rats is examined at the macroscopic level, it is seen that it is the highest in the HFD group, followed by the HFD+OL, C, HFD+WT groups, respectively. Although the weight gain was the highest in

the HFD+OL group, the fact that the last BW was the highest in the HFD group caused AT to grow more. Likewise, although there was the least weight gain in the C group, the lowest final BW in the HFD+WT group is associated with the highest first BW in the C group. On the other hand, the fact that AT growth was the least in the HFD+WT group and the final BW was significantly lower than the HFD group shows that white tea has an antiobesitic effect, in line with the literature. This effect by reducing WAT shows that white tea mainly inhibits adipogenesis and induces lipolysis. In addition, the fact that the weight gain and AT growth of the HFD+WT group was less than that of the HFD+OL group suggests that the pancreatic lipase inhibiting feature of white tea may be more effective than orlistat. It has been shown in some studies that white tea has antidiabetic effects in insulin resistance, prediabetes and type 2 diabetes mellitus (type 2 DM). Since these metabolic disorders are closely related to obesity, the antidiabetic effects of white tea are important. Studies in prediabetic rats have shown that 1% white tea improves glucose and insulin tolerance when administered for 2 months (Alves et al., 2015; Nunes et al., 2015; Dias et al., 2016). In addition, white tea increased mRNA and protein expression levels and cardiac antioxidant capacity of glucose transporter (GLUT)-1 and GLUT-3 in the heart tissue of prediabetic rats. It has been shown that protein expression levels of GLUT-1 and GLUT-3 decrease in the cerebral cortex of prediabetic rats and suppress lipid peroxidation and protein oxidation (Alves et al., 2015; Nunes et al., 2015). In another study, it was shown that when 0.5% white tea extract was applied for 4 weeks in prediabetic rats, blood glucose decreased significantly and glucose tolerance improved compared to the control and prediabetic control groups. On the other hand, it has been shown that white tea consumption does not affect serum insulin and fructosamine levels (Islam, 2011). In a study conducted in diabetic rats, it was shown that when the ethanolic extract of white tea was applied at 100 mg/kg for 14 days, FBG was significantly reduced compared to the diabetic control group (Ardiana et al., 2018). In another study, it was shown that when 5.1% white tea was applied for 1 month in diabetic and non-diabetic rats, blood glucose decreased compared to the control and diabetic control groups (Amanzadeh et al., 2020).

In a study conducted in obese and diabetic mice, it was shown that when 2% white tea was administered for 6 weeks, blood glucose was significantly reduced and glucose tolerance improved compared to the obese and diabetic control group. However, white tea has been shown to have a protective activity of  $\beta$  cells in the pancreatic islets of Langerhans against oxidative and inflammatory damage (Xia et al., 2022). It has been shown in vitro that 2.5% white tea extract in human liver cancer cell line (HepG2) is highly effective in reducing glucose uptake (Tenore et al., 2013). In a study on white tea catechins, it was shown that it can control postprandial hyperglycemia by inhibiting the

activity of  $\alpha$ -amylase and  $\alpha$ -glucosidase enzymes (Yilmazer et al., 2012). In this study, when the blood glucose levels of the rats were examined, it was seen that there was a statistically significant difference between the groups, and it was the highest in the HFD group, followed by the HDD+WT, HFD+OL, and C groups, respectively ( $p < 0.05$ ). On the other hand, when the insulin levels of the rats were examined, it was seen that there was no statistically significant difference between the groups and it was the lowest in the HFD+WT group, followed by the HFD, C, HFD+OL groups, and there was no increase in parallel with blood glucose levels ( $p > 0.05$ ). When the HOMA-IR levels of the rats were examined, it was seen that there was no statistically significant difference between the groups, and it was the highest in the HFD group, followed by the HFD+OL, HFD+WT, and C groups, respectively. These findings in line with the literature, show that white tea may have a hypoglycemic effect by lowering blood glucose and improving glucose tolerance. It also suggests that white tea may reduce insulin resistance and/or increase insulin sensitivity instead of increasing insulin secretion.

Although some studies have shown that white tea is effective in obesity and its comorbidities by attenuating lipid metabolism disorders, the mechanisms underlying its therapeutic effects are not clear. In a study, when various tea extracts, including white tea, were applied for 9 weeks in obese mice induced by HFD, blood and liver TG levels were significantly reduced, blood and liver TC levels were lower, but not significantly, compared to the untreated group. It has been shown that there is no difference (Liu et al., 2019). In another study, it was shown that when 0.5% white tea extract was applied for 8 weeks in HFD-induced obese mice, blood TG levels were reduced and there was no significant difference in the cholesterol-rich lipoprotein profile. It has also been shown to reduce oxidative stress in the liver and AT (Teixeira et al., 2012). In a study conducted in prediabetic rats, it was shown that when 0.5% white tea extract was applied for 4 weeks, liver weight and liver glycogen increased significantly, and blood TC and LDL-C decreased significantly compared to the prediabetic control group (Islam, 2011). In another study, it was shown that when 5.1% white tea was administered to diabetic and non-diabetic rats for 1 month, TG, TC and LDL-C levels were significantly decreased, and HDL-C levels increased compared to the control and diabetic control groups (Longo et al., 2019). (-)-Epigallocatechin-3-gallate and (-)-epicatechin-3-gallate from white tea extracts reduce TC by inhibiting genes involved in very low-density lipoprotein cholesterol (VLDL-C) production in HepG2 cells and inducing LDL receptor (LDLR) expression. has been shown in vitro (Luo et al, 2020). In another study, it was shown in vitro that 2.5% white tea extract decreased cholesterol uptake, increased LDLR binding activity and HDL-C levels in HepG2 cell lines (Tenore et al., 2013).

In this study, when the blood TC levels of the rats were examined, it was seen that there was a statistically

significant difference between the groups and it was the highest in the HFD group, followed by the HFD+OL, HFD+WT, and C groups, respectively ( $p < 0.05$ ). The same sequence is seen in the LDL-C levels of the rats and there is no statistically significant difference between the groups ( $p > 0.05$ ). These findings show that white tea has a hypocholesterolemia effect in parallel with the literature. On the other hand, when the TG and HDL-C levels of the rats were examined, there was no statistically significant difference between the groups ( $p > 0.05$ ). Contrary to the literature, it is seen that the TG level is highest in the C group, followed by the HFD+OL, HFD+WT, and HFD groups, respectively. Considering the roles of apelin secreted from AT in glucose and lipid metabolism, it is of great importance to understand the contribution of this adipokine to regulation/irregularities in obesity and complications of obesity such as insulin resistance, type 2 DM, and CVD (Castan-Laurell et al., 2005). Various studies in animals and humans have reported different results with apelin in physiological and pathological conditions. This may be associated with ethnicity, gender, age groups, body fat distribution, different isoforms of apelin, and differences in the methods applied (Kiyak et al., 2016). In a study, it was shown that apelin and insulin levels were not significantly different in HFD-induced obese mice compared to the control group, but there was a strong correlation between apelin and insulin in the obese and control mouse groups. This indicates that obesity-independent apelin and insulin interact with each other (Tarin, 2015). In another study, it was shown that apelin and insulin levels in overweight individuals were not significantly different compared to the control group and apelin was not significantly correlated with any parameter. However, it has been shown that glucose, TG, hemoglobin A1c (HbA1c) and HOMA-IR levels are significantly higher in overweight individuals (Daşgın, 2016). In contrast to these studies, it was shown that apelin, insulin, HOMA-IR, TG, TC and LDL-C levels were significantly higher in corn obese women compared to the control group, and apelin was positively correlated with abnormal metabolic parameters and obesity indices ( Zaki et al., 2017).

In parallel, it has been shown that apelin levels are significantly higher in morbidly obese individuals compared to the control group and apelin has a positive correlation with body mass index (BMI) (Heinonen et al., 2015). Similarly, apelin levels were shown to be significantly higher in obese children with corn compared to the control group, and apelin was positively correlated with insulin, HOMA-IR, glucose, TC, TG levels and obesity indices (El Wakeel et al., 2018). Similarly, apelin-12 levels in obese girls in China have been shown to be significantly higher than in the control group. In addition, apelin-12 has been shown to have a positive correlation with insulin and HOMA-IR in all obese children, and with glucose in all boys, after adjusting for age and BMI in obese girls (Ba et al., 2014). These studies support that insulin directly regulates

apelin expression in adipocytes in relation to obesity-related hyperinsulinemia (Alipour et al., 2017). Contrary to the literature, it has been shown that apelin-12 levels are significantly lower in obese children compared to the control group, and apelin has a negative correlation with insulin, HOMA-IR levels, and BMI (Tapan et al., 2010). However, the current hypothesis is that the increase in AT with obesity causes tissue hypoxia, which increases the apelin gene expression to stimulate angiogenesis and provide adequate oxygen (Rayalam et al., 2008). In a study conducted in obese and non-obese individuals with Polycystic Ovary Syndrome (PCOS), it was shown that apelin levels were significantly higher than the control group, and apelin was positively correlated with insulin and HOMA-IR levels (Ünal, 2014). In parallel, it has been shown that apelin-36 levels are significantly higher in PCOS individuals with insulin resistance compared to the control group, but there is no significant correlation with BMI (Kiyak et al., 2016). In another study, it was shown that apelin levels were significantly higher in obese individuals with type 2 DM compared to the control group and decreased after treatment with hypoglycemic agents. In addition, it has been shown that apelin is positively correlated with HOMA-IR levels and not significantly correlated with BMI (Yu et al., 2018). Similarly, it has been shown that apelin levels and visceral adiposity index are significantly higher in individuals with type 2 DM.

In another study, it was shown that apelin and insulin levels were higher in diabetic rats compared to the control group, but there was no significant difference (Ufat, 2015). These studies support that increased apelin levels, independent of BMI, are an intrinsic compensatory mechanism for insulin resistance. It has been reported that low apelin levels in healthy lean individuals may be a consequence of insulin sensitivity rather than a cause (Krist et al., 2013). In a study, it was shown that the apelin levels of three different groups, individuals with glucose intolerance, metabolic syndrome, and type 2 DM, were significantly lower than the control group, and there was no significant difference in the apelin levels of the prediabetes group compared to the control group (Barim, 2013). In another study, it was shown that apelin levels were significantly lower in obese youth, especially in prediabetic patients, compared to the control group (Kotaniidou et al., 2014). In a study conducted in China, it was shown that apelin-17 level was significantly lower in individuals with newly diagnosed and untreated type 2 DM compared to the control group, and apelin-17 was negatively correlated with HOMA-IR, glucose and HbA1c. It has been reported that apelin can indirectly affect glucose metabolism independently as well as the direct effect of insulin on glucose uptake (Zhang et al., 2009). However, it has been reported that apelin expression decreases due to hyperinsulinemia in the early stages of metabolic disorders such as prediabetes or newly diagnosed type 2 DM and obesity, and apelin expression increases in various

metabolic disorders such as deterioration of insulin resistance and insulin secretion due to damage of  $\beta$  cells with the prolongation of hyperglycemia time (Cavallo et al., 2012).

Different results have been reported regarding the effects of interventions to reduce BW, such as bariatric surgery, hypocaloric diet, and exercise, on apelin levels in various obesity models. In a systematic review, it was reported that a hypocaloric diet may reduce apelin levels with weight loss and decreased insulin levels (Yuzbashian et al., 2017). In another study, it was shown that BMI, insulin, apelin, and mRNAs of apelin and APJ in AT, which are high in obese individuals, decrease significantly with hypocaloric diet (Castan-Laurell et al., 208). Similarly, calorie restriction and exercise have been shown to significantly decrease BW, BMI, body fat percentage and apelin-36 levels in overweight male individuals, and insulin resistance has been shown to improve significantly (Galedari et al., 2017). In another study, it was shown that exercise BW, BMI, body fat percentage, waist circumference and apelin-12 levels were significantly decreased in middle-aged obese women, and there was no significant difference in apelin-36 levels (Jang et al., 2019). Similarly, apelin-12 levels, which are high in morbidly obese individuals, have been shown to decrease significantly after bariatric surgery (Arica et al., 2017). In contrast to these studies, it has been shown that apelin-13 is lower and insulin is higher in obese and insulin resistant individuals, and there is a significant difference between HOMA-IR and insulin levels after 10% weight loss with diet, but there is no significant difference between apelin-13 levels (Can, 2018). Similarly, despite the significant improvement in visceral adiposity, BW, BMI, and glucose metabolism after diet and weight loss in individuals with metabolic syndrome, it has been shown that there is no significant change in apelin levels. Therefore, it has been reported that apelin is not as strongly associated with AT as other adipokines (Heinonen, 2009). In another study, it was shown that weight loss with lifestyle change was not associated with a decrease in apelin levels in obese children and there was no significant relationship between weight status, insulin resistance, and cardiovascular risk factors (Reinehr et al., 2017).

In the literature, it has been reported that 6-week-old Sprague-Dawley male rats fed with HFD (45% from fat) may develop an obesity and insulin resistance model in 8-12 weeks (Zhang et al., 2020). However, it has been reported that the Sprague-Dawley breed is more prone to obesity and related complications related to feeding with HFD compared to the Charles River breed (Devan et al., 2017). In this study, when the apelin-13 levels of the rats were examined, it was seen that there was a statistically significant difference between the groups, and it was the lowest in the HFD group, followed by the HFD+OL, HFD+WT, and C groups, respectively ( $p < 0.05$ ). The same sequence was observed in the apelin-36 levels of the rats, and there was no statistically significant difference between

the groups ( $p>0.05$ ). In addition, when the relationship between apelin-13, apelin-36, insulin and HOMA-IR levels was examined, there was a significant and positive relationship only between insulin and HOMA-IR levels ( $p<0.05$ ). These findings suggest that the increase in AT due to obesity and the onset of metabolic disorders such as hyperglycemia, hypercholesterolemia, and insulin resistance in rats in the HFD group decrease the expression of apelin, but the increased obesity and related metabolic disorders due to the induction of HFD may increase the expression of apelin with an internal compensatory mechanism. In other words, the fact that higher apelin levels were not observed in the HFD group, as expected, indicates that the rats did not sufficiently form a model of obesity and insulin resistance due to a high-fat diet. However, the effect of white tea on improving metabolic disorders suggests that it may cause less change in apelin expression in rats in the HFD+WT group.

## CONCLUSION

In conclusion, it can be said that obesity and/or metabolic disorders affect apelin levels, white tea has antiobesitic, hypoglycemic, improving insulin tolerance and hypocholesterolemia effects, and the physiological effects of white tea may indirectly cause less change in apelin levels. However, more extensive and advanced studies are needed to elucidate the mechanism of action of white tea on apelin, which is a potential biomarker in the evaluation of metabolic risk factors in obesity.

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