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Effect of Graviola Oil Extract on Anti-obesity Effect and Adipokine (Apelin and Adiponectin) Response in High Fat Diet-induced Obese Rats

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ABSTRACT

Background: This study aims to investigate the anti-obesity effect of GOE with adipokine (apelin and adiponectin) response at different doses (100 and 200 mg/kg) of GOE in normal healthy and obese rats with High-fat diet (HF).

Methods: In this study, 36 adult male Wistar albino rats, aged between 8-10 weeks, were used. 6 groups were created, with 6 rats in each group: Control (C), Rat group without GOE and HF application, G100 (GOE 100 mg/kg group given with oral gavage route of administration (OGRA), G200 (GOE 200 mg/kg group given with OGRA), HFC (HF control group): no HF and no GOE group), HF100 (rats receiving HF were 100 mg/kg graviola oil extract added to their diet), HF200 (rats receiving HF were 200 mg/kg graviola oil extract added to their diet). Blood samples were taken from the tail vein (*vena caudalis*) of all on days 0 and 60 of the study. Apelin and adiponectin levels in the serum samples were measured by ELISA method.

Result: In the present study, a significant increase ($p<0.01$) was observed in the mean serum apelin level in the HF groups at the end of the 60 day after HF induction, while a significant decrease ($p<0.01$) was also detected in the adiponectin level. On the other hand, when examined in terms of BW, the most significant decrease due to GOE addition in the HF groups, *i.e.* the anti-obesity effect, was determined in the HFG200 mg/kg group ($p<0.01$). As a result, it was concluded that GOE may be safe and beneficial when administered at a dose of 200 mg/kg in obesity-induced rats.

Key words: Adiponectin, Antiobesity effect, Apelin, Graviola, Obesity, Rat.

INTRODUCTION

The prevalence of overweight and obesity is increasing worldwide, reaching epidemic proportions. Obesity is abnormal or excessive fat accumulation that poses a health risk. It is a chronic health problem that is increasing in prevalence worldwide and can increase the risk of developing diabetes, high blood pressure, insulin resistance, stroke, cardiovascular diseases and other problems (Haslam and James, 2005; Di Ciaula and Portincasa, 2024; Fassler *et al*., 2024; Kaur *et al*., 2018; Galindo *et al.,* 2019). Obesity results from the interaction of many genetic, epigenetic, physiological, behavioral, sociocultural and environmental factors, leading to an imbalance between energy intake and expenditure (Frühbeck *et al*., 2018). Excess fat accumulation is usually measured by body mass index (BMI), which is calculated by the ratio of height to weight (weight per square of height-w/h^2). BMI, a widely used indicator of obesity, is classified as follows (kg/m^2): <18.5 for underweight, 18.5-24.9 for normal weight, 25-29.9 for overweight and ≥30 for obese (Croghan *et al*., 2018).

Adipokines play a central role in the development of obesity-associated metabolic disorders (Bayraktar, 2020). Adipokines play an important role in the development of a group of obesity-related diseases such as insulin resistance, inflammation, hypertension, cardiovascular and metabolic disorders (de Oliveira Leal and Mafra, 2013). Apelin is a hormone secreted from adipose tissue, the endogenous ligand of the G protein-coupled orphan apelin receptor (APJ) (Tatemoto *et al*., 2001). Apelin has been associated with health problems such as obesity (Boucher *et al*., 2005), diabetes (Li *et al*., 2006), heart failure (Földes *et al*., 2003) and cancer (Wang *et al*., 2008). Adiponectin (GBP28, adipoQ, ACRP30 collagen VIII and complement C1) is an adipokine hormone secreted from adipose tissue with a molecular weight of 30 kDa and consisting of 247 amino acids (Kadowaki and Yamauchi, 2005). Adiponectin is an antidiabetic and antiatherogenic protein and its concentrations are reduced in obesity-associated metabolic and vascular diseases. Insulin resistance in obesity is associated with leptin resistance and reduced adiponectin levels (Balsan *et al*., 2015).

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Medicinal and aromatic plants are used in traditional and complementary medicine to help treat and control obesity. Therefore, researching the properties of plants and fruits with anti-obesity effects and their effects on the endocrine system is important for both the pharmaceutical and food industries. Graviola (*Annona muricata*) is the fruit of a broadleaf, flowering, evergreen tree called Annona muricata, also known as guyabano. Graviola contains valuable phytochemical compounds such as bulatacin, asimicin and squamosin, which contain acetogenins (Anuragi *et al*., 2016). Graviola has anti-obesity (Elekofehinti *et al*., 2020), antidiabetic and hypolipidemic (Aderibigbe *et al*., 2009), anti-inflammatory (Moghadamtousi *et al*., 2015), anticancer (Ezirim *et al*., 2013) hepatoprotective (Riza Arthur *et al*., 2012) effects. It is reported that high-fat diet-ınduced feeding in rats reflects human obesity (Buettner *et al*., 2007). In the literature search, no study examines GOE's effect on adipokine (apelin and adiponectin) response in HF-induced obesity rats. In this study, the adipokine (apelin and adiponectin) response and anti-obesity effect of GOE were investigated at different doses (100 and 200 mg/kg) in normal healthy and HF-induced obesity rats.

MATERIALS AND METHODS

The study used 36 male Wistar rats, 8-10 weeks old, as animal material. Before starting the study, the Ethics Committee's approval was obtained from the Research Center Ethics Committee (Decision No: 2024-86/3). The composition of the experimental diet used in the study is shown in Table 1 and the chemical composition of Graviola (*Annona muricata* L.) extract oil is shown in Table 2.

The experimental protocol was formed as follows:

Control group (C) (n=6): Rat group without GOE and HF application for 60 days.

G100 mg/kg group (M100): Rats were given OGRA and MOE 100 mg/kg daily for 60 days.

G200 mg/kg group (M200): Rats were given OGRA and MOE 200 mg/kg daily for 60 days.

HF Control group (HFC): Rats treated with HF and no GOE for 60 days.

HF+G100 mg/kg group (HFG100): In rats induced obesity by HF administered OGRA with GOE extract 100 mg/kg (n=6).

HF+G200 mg/kg group (HFG200): In rats induced obesity by HF administered OGRA with GOE extract 200 mg/kg (n=6).

Collection of serum samples

Blood samples were taken from the tail vein of rats on day 0 of the study and tail vein (*vena caudalis*) on 60 days. Blood samples were collected in tubes without anticoagulant and centrifuged in a refrigerated centrifuge (NF 1200R, NÜVE, Türkiye) for 10 minutes at 3000 rpm in the laboratory and the resulting sera were separated.

Measurement of serum apelin and adiponectin level

In measuring serum apelin and adiponectin levels obtained in the study, ELISA kit type-specific for rat apelin ELISA kit (BT LAB, Cat. No E1026Ra, CHINA) and adiponectin ELISA kit (BT LAB, Cat. No E0758Ra, CHINA) an intra-assay coefficient of 8.0% and an inter-assay coefficient of 10.0% was utilized under the manufacturer's protocol.

Measuring body weight levels

The live weights of rats in all study groups were weighed every weekend using a precision scale (Shimadzu UX 620 Digital Precision Scale - Precision: 0.001 gr. Max: 620 gr.).

Statistical analysis

Statistical data analyses were performed with SPSS version 15 (IBM, USA). Normality and homogeneity tests of the data were performed with Kolmogorov-Smirnov, Shapiro-Wilk and Levene's tests. Differences between groups were analyzed with the nonparametric Kruskal Wallis Test. The interaction between groups and time for repeated measurements (0 and 21 days) was analyzed with the general linear model (GLM). The significance level in the analysis results was accepted as $p<0.05$.

RESULTS AND DISCUSSION

Obesity is a worldwide concern because it carries an increased risk of multiple serious conditions, including

Table 1: Composition of High fat diet and Normal rat diet.

High fat diet		Normal rat diet	
Nutrients	%/100 g	Nutrients	%/100 g
Carbohydrate	41	Carbohydrate	49.8
Protein	18	Protein	22
Fat	41	Fat	3
Ingredients	%/100 g	Calcium	0.8
Powdered rat feed	69.0	Phosphorus	0.4
Maize oil	5.0	Fiber	4
Ghee	7.0	Moisture	12
Milk powder	19.0	Ash	8
Total energy (kcal/100 g)	415.0	Total energy (kcal/100 g)	308.5

type 2 diabetes, cardiovascular disease, nonalcoholic fatty liver disease and cancer. Overweight and obesity are abnormal or excessive fat accumulation, posing a health risk. On day 0 of the study, the mean BW levels in the C, G100, G200, HFC, HFG100 and HFG200 groups were found to be 191.28, 193.40, 192.17, 242.93, 243.38, 242.33 g. Similarly, at the end of the 60 day, the mean BW levels in the groups were determined to be 301.42, 316.20, 345.28, 369.87, 347.20 and 321.18 g BW, respectively ($p<0.01$) (Table 3). In groups C and G, the lowest BW level was determined in group C due to GOE addition, while the highest level was determined in group G200 ($p<0.01$). In HF-induced groups, the highest BW level was determined in HFC groups, while the most significant decrease due to GOE addition was determined in HF200 groups ($p<0.01$). Our current results are consistent with research results reporting that GOE supplementation reduces body weight levels in HF-induced obesity rats (Son *et al*., 2016; Sasso *et al*., 2019). We speculate that this is due to the anti-obesity effect of GOE.

Obesity is a metabolic and phenotypic change with increased production of proinflammatory mediators resulting from increased accumulation of white adipose tissue. Apelin crosses the blood-brain barrier by satiety transport or simple diffusion and acts in hypothalamic regions that regulate appetite (Reaux *et al*., 2022). The presence of apelin receptors and apelin in the hypothalamus, gastric mucosa and fat cells demonstrates its role in appetite, digestion and metabolism. Apelin levels increase in serum due to hyperinsulinemia and insulin resistance in obesity. Therefore, serum apelin levels are reported to be higher in obese individuals than in lean individuals (Fournel *et al*., 2017). On day 0 of the study, the mean serum apelin levels in the C, G100, G200, HFC, HFG100 and HFG200 groups were found to be 0.72, 0.73, 0.73, 0.86, 0.86 and 0.85 ng/ml. Similarly, at the end of the 60 day, the mean serum apelin levels in the groups were determined to be 0.74, 0.75, 0.86, 1.03 and 0.95, 0.89 ng/ml, respectively (Table 3). The highest mean serum apelin level was determined in the HF groups due to obesity-related hyperinsulinemia and an increase in insulin resistance ($p<0.01$). In HF-induced obesity groups, the most significant reduction due to GOE supplementation was determined in the HFG200 groups ($p<0.01$). Sümer *et al.* (2024) found that rats treated with white tea in HFD groups had a decrease in weight gain and serum apelin 13 and apelin 36 levels in their research, in which they

Table 2: Composition of Graviola (*Annona muricata* L.) leaf oil extract.

Ingredients	Value
Moisture (%)	95.18
Protein (%)	0.80
Ash (%)	0.77
Fat (%)	0.12
Total carbohydrate (%)	3.25
Dietary fiber (%)	0.80

Table 3: Mean serum apelin, adiponectin and values (ng/ml) and statistical comparisons (Mean±SD) of the study groups.

Groups	Apelin (ng/ml)				Adiponectin (ng/ml)				Body weight (BW) (g)			
	0 day		60 day		0 day		60 day		0 day		60 day	
	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation
C	0.72	0.02	0.74	0.02	7.10	0.36	6.60	0.15	191.28	0.81	301.42	2.03
G100	0.73	0.03	0.75	0.03	7.20	0.18	6.47	0.30	193.40	4.41	316.20	0.85
G200	0.73	0.03	0.86	0.08	7.17	0.34	6.18	0.34	192.17	0.56	345.28	4.80
HFC	0.86	0.04	1.03	0.04	5.42	0.65	4.53	0.37	242.93	1.68	369.87	5.60
HFG100	0.86	0.05	0.95	0.07	5.68	0.39	4.58	0.28	243.38	1.25	347.20	3.75
HFG200	0.85	0.04	0.89	0.06	5.75	0.25	4.68	0.34	242.33	2.00	321.18	1.47
Diet	<0.01		<0.01		<0.01		<0.01		<0.01		<0.01	
Time	<0.01				<0.01				<0.01			
Diet×Time	<0.01				0.241				<0.01			

*Means within a column showing different superscripts are significantly different ($p<0.05$).

examined the effects of white tea on weight gain, glucose metabolism and lipid metabolism, as well as apelin-13, apelin-36 and insulin levels in a high-fat diet (HFD)-induced obesity model in rats. As a result of the study, they stated that white tea can be an effective antiobesity agent and offer a safer, natural alternative to traditional treatments. Our study's results are consistent with studies reporting that serum apelin levels decrease in obesity (Taheri *et al*., 2002; Clarke *et al*., 2009; Fournel *et al*., 2017; Sümer *et al*., 2024).

Adiponectin is positively associated with insulin sensitivity and its serum level decreases in obesity (Arita *et al*., 1999). On day 0 of the study, the mean serum apelin levels in the C, G100, G200, HFC, HFG100 and HFG200 groups were found to be 7.10, 7.20, 7.17, 5.42, 5.68 and 5.75 ng/ml. Similarly, at the end of the 60 day, the mean serum apelin levels in the groups were determined to be 6.60, 6.47, 6.18, 4.53, 4.58 and 4.68 ng/ml, respectively ($p<0.01$) (Table 3). In groups G and C, the lowest mean serum adiponectin level was determined in C, while the highest level was determined in group G200 ($p<0.01$). The highest mean serum adiponectin level was determined in the HFC groups ($p<0.01$). In HF-induced obesity groups, the most significant reduction due to GOE supplementation was determined in the HFG200 groups ($p<0.01$). Our current results are consistent with the research results reported in the literature reporting that it reduces body weight levels in obese rats (Sasso *et al*., 2019). Although the current results of our study are limited in terms of studies examining the effect of GOE on serum adiponectin levels, they are consistent with similar research results in the literature reporting that it decreases in HF-induced obesity groups (Padmanabhan and Arumugam, 2014; Xiang *et al*., 2019; Orabi *et al*., 2020). We think that the reason for this is due to the difference in the method reported in the studies (dose difference, animal species, *etc*.) together with the anti-obesity effect of GOE.

Conclusion

Apelin, which shows its effect by binding to the angiotensin II protein J receptor (APJ), has a regulatory role in glucose and lipid metabolism and is associated with obesity, adiponectin, with its anti-inflammatory effects and a protective role against insulin resistance and excessive hepatic lipid accumulation, is an adipokine associated with obesity. It is thought that examining apelin and adiponectin levels will be useful in obesity management. As a result, it was concluded that GOE, which is reported to have an anti-obesity effect, may be safe and beneficial in HF groups when the most pronounced effect is applied with HFG at a dose of 200 mg/kg.

Disclaimers

The views and conclusions expressed in this article are solely those of the authors and do not necessarily represent the views of their affiliated institutions. The authors are responsible for the accuracy and completeness of the information provided, but do not accept any liability for any direct or indirect losses resulting from the use of this content.

Informed consent

All animal procedures for experiments Central Research were approved by the Committee of Experimental Animal Care and handling techniques were approved by the University of Animal Care Committee.

Conflict of interest

The authors declare that there are no conflicts of interest regarding the publication of this article. No funding or sponsorship influenced the design of the study, data collection, analysis, decision to publish, or preparation of the manuscript.

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