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Investigation of the effects of *Lacticaseibacillus rhamnosus GG* administration on metabolic hormones in rats

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The aim of this study was to investigate the effects of *Lacticaseibacillus rhamnosus* GG (LGG), as a probiotic, administration on insulin (INS), insulin-like growth factor-1 (IGF-1), hormone-sensitive lipase (HSL), growth hormone (GH), ghrelin (GHRL), glucagon-like peptide-1 (GLP-1), and glucose-dependent insulinotropic polypeptide (GIP) levels, as well as glucose metabolism in rats. For the experiment of this study, 21 male Wistar rats were categorized into three groups. These groups were the control group (CONT), the group administered LGG for 4 weeks (LGG4), and the group treated with LGG for 10 weeks (LGG10). The LGG groups were administered orally by gavage at a dose of $1x10^{10}$ CFU/mL daily to the rats. Following the completion of the experiments, blood samples were collected to detect the levels of metabolic hormones via ELISA, and glucose levels were determined through standard biochemical analysis. The administration of LGG significantly increased levels of GH, INS, IGF-1, GLP-1, GIP, HSL, and GHRL. Conversely, the LGG decreased glucose levels. However, the increase in GHRL was greater in the LGG4 group. These findings suggest that LGG may act as a potential metabolic regulator in the modulation of glucose homeostasis and metabolic hormone profiles.

Keywords: Probiotics, insulin, IGF-1, GLP-1, ghrelin, glucose metabolism

Introduction

Probiotics, as live microorganisms, have been extensively researched and have been shown to provide health benefits to the host when consumed in sufficient quantities[1]. The intestinal development process, energy metabolism, nutrient absorption, and immune system are regulated by the intestinal microbiota and microbiome, a complex ecological community comprising billions of microorganisms within the gastrointestinal tract[2]. Most probiotics contain Gram-positive, facultative anaerobic, rod-shaped bacterial species. *Lacticaseibacillus rhamnosus* GG (*L. rhamnosus* or *LGG*), previously known as *Lactobacillus rhamnosus* before reclassification, is one of the most studied probiotic strains among researchers, with an extensive research history that instills confidence in its efficacy[3, 4]. Among various probiotic strains, *LGG* has attracted significant attention due to its proven health benefits[5].

Probiotics, especially strains such as *LGG*, have been shown to enhance insulin (INS) sensitivity and improve glucose metabolism through multiple interrelated mechanisms. Experimental studies have shown that *LGG* supplementation not only modulates gut microbiota composition but also enhances the secretion of incretins and promotes β-cell function[6], thereby contributing to improved glycemic control. The primary pathway involves modulating the gut microbiota composition and diversity, which exerts downstream effects on the gut–brain axis and stimulates the secretion of incretin hormones, notably glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP)[7-10]. These incretins enhance glucose-dependent INS secretion from pancreatic β-cells, suppress glucagon release, delay gastric emptying, and improve postprandial glycemic control[11]. Additionally, probiotic-mediated increases in GLP-1 promote β-cell survival and proliferation through activation of cyclic AMP (cAMP)/protein kinase A (PKA) signaling pathways, further contributing to sustained insulinotropic effects[12]. Therefore, increasing GLP-1 levels also helps maintain blood sugar levels within a normal range by stimulating INS secretion in response to glucose. Studies have shown that probiotics may reduce insulin resistance, an important factor in the development of type 2 diabetes[7-10]. Another important mechanism is the production of short-chain fatty acids (SCFAs)—including acetate, propionate, and butyrate—through bacterial fermentation of dietary

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fibers. SCFAs act as signaling molecules by activating G-protein-coupled receptors (GPR41 and GPR43) on enteroendocrine cells, thereby enhancing the secretion of GLP-1 and peptide YY (PYY), which collectively support satiety and glucose regulation[13]. Moreover, probiotics reduce metabolic endotoxemia and low-grade systemic inflammation by strengthening the intestinal epithelial barrier and downregulating lipopolysaccharide (LPS)-induced activation of the Toll-like receptor 4 (TLR4)/NF-κB pathway. This anti-inflammatory effect mitigates insulin resistance, a central pathogenic factor in the development of type 2 diabetes mellitus (T2DM)[14].

Probiotics may affect ghrelin (GHRL) levels, which are related to appetite, by altering the composition of the gut microbiota. A growing body of evidence indicates that the gut microbiota communicates with enteroendocrine cells to shape appetite-regulating hormone profiles, including ghrelin (GHRL), the orexigenic, acylated form acting via GHSR1a. Microbial metabolites, e.g., short-chain fatty acids, bile acids, and microbial–host lipid handling influence both ghrelin synthesis and its O-acylation by ghrelin O-acyltransferase (GOAT), thereby modulating biological activity and downstream hypothalamic signaling [15]. In this regard, some studies indicate that probiotics may lower GHRL levels, leading to reduced hunger and food intake, which may aid in weight management[16, 17]. However, other studies have shown that probiotics, including certain strains of *Lactobacillus*, may raise ghrelin levels[18, 19].

The primary hepatic effector of growth hormone (GH) and a crucial integrator of somatic growth with metabolic homeostasis, insulin-like growth factor-1 (IGF-1) has been linked with contemporary clinical and mechanistic research to insulin sensitivity, lipid handling, and liver health through GH/IGF-1 signaling[20]. Beyond its fundamental role in growth and anabolic processes, an immune–endocrine relay has been mapped, whereby gut-derived IL-13 promotes hepatic IGF-1 production through IL-13R/JAK2/STAT6 signaling, thereby strengthening a causal link from intestinal ecology to the GH/IGF-1 axis[21]. Emerging evidence further suggests that the gut microbiota is closely involved in regulating this pathway, as microbial composition and metabolites influence circulating IGF-1 levels and host growth, indicating that intestinal ecology contributes to endocrine control of metabolism and development[22]. Probiotics can influence IGF-1 levels by enhancing gut health and nutrient absorption, ultimately leading to improved overall growth and development. The exact mechanism still remains unclear, but it is believed that the anti-inflammatory effects of probiotics contribute to the modulation of IGF-1[23].

Hormone-sensitive lipase (HSL) is a catecholamine-responsive neutral lipase that, together with adipose triglyceride lipase (ATGL), governs triacylglycerol mobilization in adipocytes and thereby gates fatty-acid flux to peripheral tissues[24]. Through the gut–adipose axis, microbial metabolites can tune this lipolytic machinery: short-chain fatty acids (SCFAs) acting at FFAR2/FFAR3 dampen lipolysis by reducing HSL phosphorylation, indicating that microbiota composition and fermentation profiles may directly reshape adipose lipid handling[25]. In this context, probiotics—by remodeling the intestinal microbiota, shifting SCFA output, and improving inflammatory tone—may influence fat metabolism in part via HSL. Although the direct effect of probiotics on HSL is not well understood, available studies suggest that probiotic supplementation can support healthier lipid partitioning and modest reductions in adiposity, providing a mechanistic rationale for including HSL as a prespecified readout in probiotic studies[26, 27].

Probiotics, particularly strains like *L. rhamnosus*, modulate the gut microbiome and influence the secretion of metabolic hormones, impacting key physiological processes such as glucose metabolism, appetite control, and lipid storage. Microbiota-derived metabolites such as short-chain fatty acids and bile acids act on intestinal L/K cells (via FFAR2/FFAR3 and TGR5) to tune incretin output (GLP-1/GIP), while parallel microbiome–brain pathways influence orexigenic ghrelin signaling; in addition, commensal cues can raise circulating IGF-1, linking the microbiota to somatotropic tone[28]. These endocrine effects converge with adipose crosstalk, where microbiota–adipokine interactions (leptin, adiponectin) shape insulin sensitivity and lipid handling. In preclinical models, *LGG* improves insulin sensitivity through adiponectin–AMPK signaling and partially prevents diet-induced insulin resistance, providing a strain-specific biological basis for hormone modulation[29]. Taken together, these mechanistic and preclinical data underpin growing efforts to leverage probiotic–host interactions in the prevention and management of metabolic disorders, including obesity and type 2 diabetes.

Therefore, this study aimed to investigate the effects of *Lacticaseibacillus rhamnosus GG* administration on key metabolic hormones, including GH, HSL, IGF-1, GIP, GLP-1, INS, and GHRL, and glucose regulation in rats.

Materials and methods

Animals

In this study, 21 male Wistar rats aged 2-3 months and weighing 230±30 g were used. The rats were obtained from the Laboratory Animal Research and Application Center at Duzce University. The rats were fed *ad libitum* and housed in the laboratory under a 12-hour light/12-hour dark cycle at a room temperature of 23 °C and 60±5% humidity. This study was conducted with ethical approval granted by the Duzce University Local Ethics Committee for Animal Experiments on 18 September 2024, decision number 2024/09/01. The animals were randomly allocated to experimental groups using a computer-generated randomization list. All biochemical measurements were performed by an investigator blinded to group allocation to minimize potential measurement bias. All study methods were conducted in accordance with the Animal Research Regulations.

Groups and experimental procedure

The *LGG* administration periods of 4 and 10 weeks used in this study are commonly used time periods in the literature to evaluate the effects of probiotics on microbiota composition, metabolic hormones, and glucose regulation. Previous research has demonstrated that *LGG* administration for 4-10 weeks drastically alters the composition of gut microbiota significantly and affects metabolic hormones, such as insulin, IGF-1, and GLP-1. Short-term interventions, such as 4 weeks, are typically sufficient to produce early microbiota-related changes, while longer durations, such as 10 weeks, allow for the assessment of more sustained physiological and metabolic effects[7, 10, 16].

In the study, the rats were divided into three groups as control (CONT), *L. rhamnosus* 4 (LGG4), and *L. rhamnosus* 10 (LGG10). The CONT group received at a rate of 1 ml/day of saline orally. The LGG4 group received *LGG* orally at a rate of $1x10^{10}$ CFU/mL/day for 4 weeks. LGG was administered orally at a rate of 1×10^{10} CFU/mL/day for 10 weeks to the LGG10 group.

The rats were anesthetized with 1.25 g/kg urethane twenty-four hours after the last dose. This time point was selected to allow sufficient time for the systemic manifestation of probiotic-related biological effects while minimizing the potential influence of acute gavage-related stress or immediate post-administration fluctuations on the measured biochemical and hormonal parameters [4, 30]. Using the cardiac puncture technique, blood samples were taken after anesthesia. The cervical dislocation method was used to sacrifice the animals following blood collection. The serum was separated from the obtained blood samples by centrifuging them for 15 minutes at 4000 rpm. The serum was then kept at -80°C until analysis.

Determination of Biological Parameters

Serum samples were collected, and the levels of GH, HSL, IGF-1, GIP, GLP-1, INS, and GHRL were measured using the ELISA method. The ELISA kits were provided by SunRed (Shanghai SunRed Biological Technology, China). The catalog numbers were as follows: GH (Cat: 201-11-0552); HSL (Cat: SRB-T-84624); IGF-1 (Cat: 201-11-0710); GIP (Cat: SRB-T-87158); GLP-1 (Cat: 201-11-0720); INS (Cat: 201-11-0708); and GHRL (Cat: 201-11-1650). Furthermore, an OPTIMA brand blood glucose meter and strips (OK Biotech Co., Ltd., Taiwan) were used to measure blood glucose levels.

Statistical Analysis

Normality of data and homogeneity of variances were assessed using the Shapiro–Wilk test and Levene's test, respectively. Since the assumptions for parametric analysis were met, differences in serum glucose and hormonal profiles among experimental groups were analyzed using one-way analysis of variance (ANOVA). When a significant main effect was observed, post hoc pairwise comparisons were conducted using Tukey's honestly significant difference (HSD) test. Statistical significance was defined as $P<0.05$. The analyses were conducted using the Prism 9 software.

Results

Effect of LGG on INS and Glucose Levels

Statistical evaluation demonstrated a distinct difference in blood glucose levels between the groups ($P<0.001$) (Fig 1a). The mean glucose levels recorded in the LGG4 and LGG10 groups were notably reduced compared to the CONT group ($P<0.001$). In addition, glucose levels were further reduced in the LGG10 group compared with the LGG4 group ($P<0.001$).

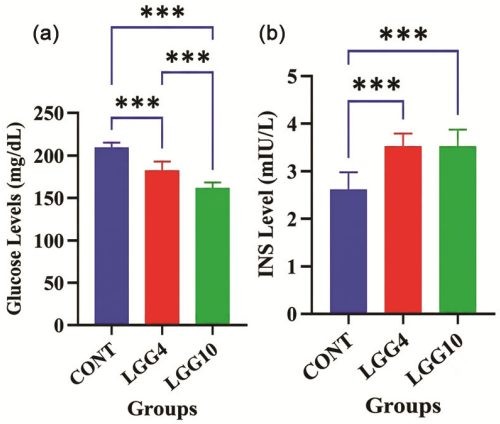

Fig. 1 — The effect of LGG on glucose (a) INS, (b) levels (***P<0.001).

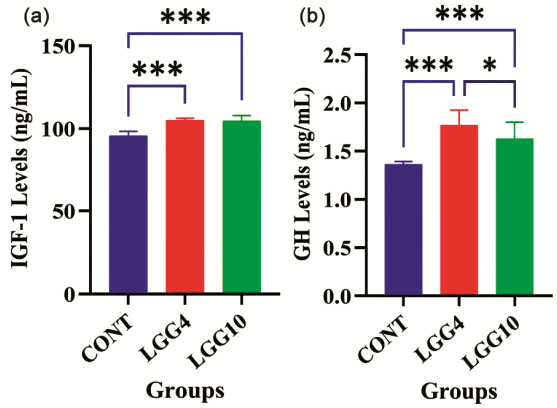

Fig. 2 — The effect of LGG on IGF-1 (a) GH, (b) levels (*P<0.05 and ***P<0.001).

Serum INS levels also varied significantly among the group (P<0.001) (Fig 1b). Both LGG4 and LGG10 exhibited significantly higher INS concentrations compared to the CONT group (P<0.001).

Effects of LGG on IGF-1 and GH Levels

A clear difference in IGF-1 concentrations was identified among the groups based on statistical analysis (P<0.001) (Fig 2a). Closer examination revealed that IGF-1 levels in the LGG4 and LGG10 groups were notably higher than the CONT group (P<0.001).

Similarly, GH levels varied significantly across the groups (P<0.001) (Fig 2b). Both the LGG4 and LGG10 groups exhibited markedly increased GH concentrations compared with the CONT group (P<0.001). However, GH levels in the LGG10 group were slightly but notably lower than those in the LGG4 group (P=0.03).

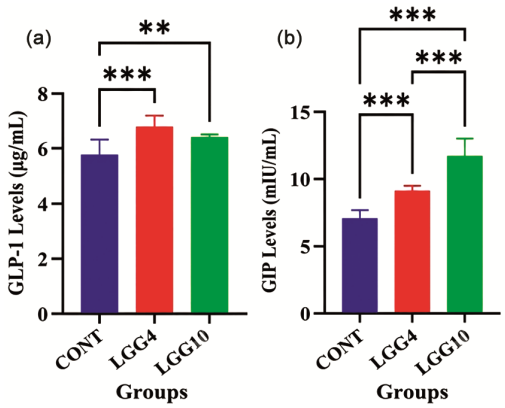

Fig. 3 — The effect of LGG on GLP-1 (a) GIP, (b) levels (**P<0.01 and ***P<0.001).

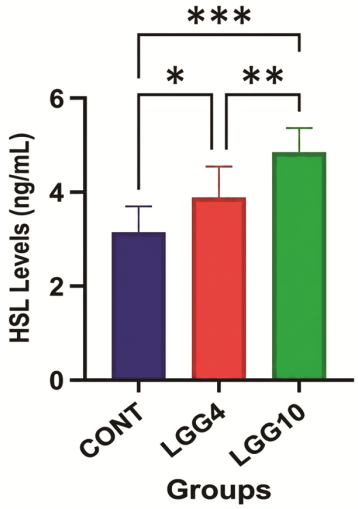

Fig. 4 — The effect of LGG on HSL levels (*P<0.05, **P<0.01, and ***P<0.001).

Effects of LGG on GLP-1 and GIP Levels

A notable variation in GLP-1 levels was observed across the groups (P<0.001) (Fig 3a). Both LGG4 and LGG10 groups displayed elevated GLP-1 concentrations compared with the CONT group (P<0.001 and P=0.003, respectively).

Similarly, a significant difference in GIP concentrations was identified among the groups (p<0.001) (Fig 3b). GIP concentrations in the LGG4 and LGG10 groups were notably higher than those in the CONT group (P<0.001). Furthermore, GIP levels in the LGG10 group exceeded those in the LGG4 group (P<0.001).

Effects of LGG on HSL Level

Between the groups, there was a statistically significant difference was found in HSL levels (P<0.001) (Fig 4). The LGG4 and LGG10 groups had

higher mean HSL concentrations than the CONT group, according to further analysis (P=0.002 and P<0.001). Additionally, HSL levels in the LGG10 group were higher than those in the LGG4 group (P=0.003).

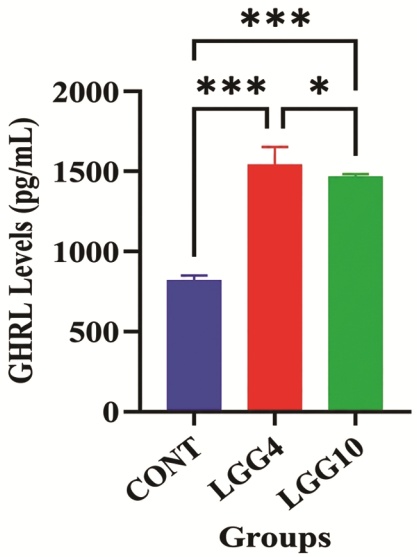

Fig. 5 — The effect of LGG on GHRL levels (*P<0.05 and ***P<0.001).

Effects of LGG on GHRL Level

A statistically significant difference in GHRL levels was observed between the groups (P < 0.001) (Fig 5). Further investigation revealed that GHRL concentrations were higher in both the LGG4 and LGG10 groups compared to the CONT group (P<0.001). Moreover, GHRL levels were significantly higher in the LGG4 group than in the LGG10 group (P=0.040) (Table 1).

Discussion

In the present study, the effects of *LGG* administration on metabolic hormones and glucose levels in rats were investigated. The findings of the present study indicate that *LGG* supplementation for both 4 and 10 weeks caused significant endocrine changes and led to notable improvements in glucose metabolism.

The present study demonstrates that *LGG* treatment considerably increases INS levels while decreasing glucose levels. Furthermore, these results show the insulin-secreting effect of *LGG* and its potential to increase insulin sensitivity. *LGG* regulated glucose metabolism and improved INS sensitivity, as

Table 1 — Effects of LGG on serum biochemical parameters

Parameter	Groups	N	Mean	SD	Min	Max	P
INS (mIU/L)	CONT	7	2,62	0,36	2,18	2,99	
	LGG4	7	3,52*	0,26	3,10	3,85	<0.001
	LGG10	7	3,52*	0,35	3,14	4,05	
IGF-1 (ng/mL)	CONT	7	95	2,88	91	100	
	LGG4	7	105*	0,91	105	107	<0.001
	LGG10	7	105*	3,12	99	107	
GLP-1 (µg/mL)	CONT	7	5,77	0,56	5,15	6,57	
	LGG4	7	6,80*	0,41	6,29	7,47	<0.001
	LGG10	7	6,43*	0,08	6,33	6,55	
GIP (mIU/mL)	CONT	7	7,09	0,59	6,12	7,56	
	LGG4	7	9,13*	0,37	8,53	9,52	<0.001
	LGG10	7	11,70*$^{\#}$	1,31	10,30	13,50	
HSL (ng/mL)	CONT	7	3,14	0,55	2,15	3,94	
	LGG4	7	3,88*	0,66	3,13	4,70	<0.001
	LGG10	7	4,84*$^{\#}$	0,51	4,41	5,73	
GH (ng/mL)	CONT	7	1,36	0,03	1,32	1,38	
	LGG4	7	1,77*	0,16	1,52	1,97	<0.001
	LGG10	7	1,63*$^{\#}$	0,17	1,36	1,85	
GHRL (pg/mL)	CONT	7	822	26,9	801	871	
	LGG4	7	1544*$^{\Delta}$	108,0	1371	1654	<0.001
	LGG10	7	1469*	12,4	1446	1480	
Glucose (mg/dL)	CONT	7	209	5,2	201	214	
	LGG4	7	182*$^{\Delta}$	10,4	170	192	<0.001
	LGG10	7	161*	6,4	152	169	

(*Significant according to the CONT group; $^{\#}$Significant according to the LGG4 group; $^{\Delta}$Significant according to the LGG10 group)

demonstrated in mice with type 2 diabetes, in a study[7]. Similarly, by altering serum metabolites and the microbiome, LGG enhanced INS sensitivity in both the mother and the offspring, according to another study[10]. The gut mucosa produces more SCFA when *LGG* is present[31]. SCFAs stimulate insulin secretion by stimulating GPR41 and GPR43 receptors in pancreatic β-cells, thereby increasing insulin production[29,32,33]. Moreover, *LGG* has been shown to decrease systemic insulin resistance by increasing adiponectin production[34]. These effects facilitate both glucose uptake and the maintenance of metabolic balance.

The study demonstrated that the incretin hormones GLP-1 and GIP were significantly elevated in response to LGG treatment. This result lends credence to LGG's ability to enhance postprandial glycemic responses, especially following meals. GLP-1 and GIP help regulate postprandial glucose levels by stimulating insulin secretion in a glucose-dependent manner[8]. Our results align with the mechanism reported by Liu *et al.* (2024), which states that probiotics induce the release of GLP-1 from enteroendocrine L cells and enhance the production of SCFA through fermentative pathways[35]. Furthermore, the LGG10 group's higher GIP levels compared to those of the LGG4 group suggest an incretin activation that is dependent on both time and dose.

The study noticed significant increases in GH and IGF-1 levels with LGG administration. These results indicate that LGG can be effective on the anabolic axis. Jensen *et al*. (2020) reported that the GH/IGF-1 axis is in a bidirectional interaction with the gut microbiota and that probiotics can regulate this axis[23]. The improvements in gut health, increased nutrient absorption, and suppression of inflammation may trigger the release of IGF-1[27]. Also, it has been suggested that some probiotics increase GABA production, thereby stimulating hypothalamic GHRH secretion and elevating GH levels[36]. The improvement in this axis is important for growth and tissue regeneration.

HSL levels were found to increase significantly in both the LGG4 and LGG10 groups. HSL is a key enzyme in the lipolysis process, facilitating energy mobilization from adipose tissue. The increase in HSL activity by LGG suggests that it plays a regulatory role in lipid metabolism. Plaza-Diaz *et al.* (2019) reported that probiotics may have an effect on energy metabolism and may promote lipolytic activity[27]. The higher HSL levels in the LGG10 group indicate that this effect is enhanced by duration and dose.

The administration of LGG increased ghrelin levels significantly in both LGG groups. This increase was more pronounced in the LGG4 group than in the LGG10 group. GHRL is a hormone that increases feelings of hunger and triggers energy intake. This finding suggests that short-term LGG applications may increase orexigenic activity. However, this effect may diminish over the long term, returning to an adaptive level. John *et al.* (2023) noted that increases in ghrelin levels may regulate appetite and that microbial changes may influence this release[17, 18]. This situation is critical in terms of weight control and energy balance.

The study found that LGG treatment decreased glucose levels, with this effect being more noticeable in the LGG10 group. This finding suggests that probiotic treatment may provide more effective long-term glycemic control. The literature suggests that probiotics contribute to glucose homeostasis through the production of SCFAs, maintenance of mucosal integrity, suppression of inflammation, and stimulation of the enteric endocrine system[5, 9].

Limitations of the Study

This study has some limitations. It was conducted in a small number of healthy male rats, and the molecular mechanisms, gut microbiota composition, and related biomarkers were not evaluated. Therefore, further experimental and clinical studies are needed to confirm and extend these findings.

Conclusion

The *LGG* application has been shown to have significant effects on metabolic hormones in both the short-term and long-term, particularly increasing hormones such as insulin, GLP-1, IGF-1, and GH. It has been concluded that these effects improve glucose metabolism and play a regulatory role in energy balance. However, considering the preclinical nature of this study, any direct clinical implication should be interpreted with caution. Further mechanistic studies and well-designed clinical investigations are needed to clarify the underlying pathways and determine the translational relevance of LGG in metabolic disorders such as obesity and diabetes.

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Ethics approval

Ethical approval for the study was obtained from the Duzce University Animal Experiments Local Ethics Committee on September 18, 2024 (Decision No: 2024/09/01).

Author contribution statement

E.B. and O.B.: Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Resources, Writing - Original Draft, Review & Editing. A.G., M.T., S.D.: Conceptualization, Methodology, Writing - Original Draft, Writing - Review & Editing.

Data availability

All data generated or analyzed during this study are included in this published article. For additional information, please contact the corresponding author (Ersin Beyazcicek).

Competing interest

None of the authors has any conflict of interest to disclose.

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