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Study on Healing Effects of Bifidobacterium Infantis 35624 in Inflammatory and Energy Metabolism Parameters in High-Fat-Diet-Induced Obesity in Rat Model

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Abstract Obesity is characterized by increased adipose tissue and low grade inflammation. The gut microbiota is closely associated with the obesity pathophysiology, so the probiotics; living microorganisms are questioned in terms of their effects on obesity related changes. Bifidobacterium infantis 35624 is used as a probiotic supplement in cases of digestive disorders. The aim of this study is to investigate its healing effect on the morphometric and inflammatory-energy metabolism responses in a high-fat diet-induced obese rat model. Three different nutritional groups, each consisting of eight rats, were followed for eight weeks. They received a conventional balanced diet, high-fat diet (HFD), and HFD with the supplementation of Bifidobacterium infantis 35624 respectively. The weight measurements were made weekly. At the end of the study, weight gains and body mass indexes were calculated. Plasma glucose, insulin, interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α) and glucagon-like peptide-1 (GLP-1) levels were evaluated. The weight changes of the HFD group showed a significant difference ($p<0.001$). HFD group with Bifidobacterium infantis 35624 supplementation showed significantly decreased body weight ($p<0,001$) and decreased plasma glucose, insulin, IL-6, TNF- α, GLP-1 levels compared to HFD group without probiotic supplementation ($p<0,05$). Bifidobacterium infantis 35624 may be a candidate probiotic to use in obesity management studies to maintain body weight, host energy metabolism, and inflammatory cytokine levels in high-fat diet nutrition.

Keywords: *High-fat-diet, Bifidobacterium infantis 35624, Interleukin-6, Tumor necrosis factor alpha, Obesity, Glucagon-like peptide-1*

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1. Introduction

Obesity is an increasing health problem affecting 30% of the world's population. It is associated with glucose intolerance, insulin resistance, fatty liver disease, and cardiovascular disease [1]. When there is an imbalance between energy intake and energy expenditure, obesity develops as a result of cellular lipid accumulation and increased adipose tissue with low-grade inflammation [2]. The main indicator of the energy metabolism glucagon-like peptide-1 (GLP-1) is mainly expressed in the gastrointestinal system. The main cytokines involved in inflammatory and immune responses are interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-alpha). These parameters are mentioned as powerful markers in the pathophysiology of obesity [3,4]. Again, recent studies have shown that the gut microbiota has an impact beyond digestion. It has been found to play a prominent role in immune and inflammatory events, and changes in this microbiota have been associated with obesity and metabolic disorders [5]. *Bifidobacteria* species are gram-positive, immobile and anaerobic bacteria. They constitute one of the main groups of bacteria in gut microbiota and they are used by the food industry as probiotic microorganisms in recent years, as some strains have been shown to have some beneficial effects [6]. Probiotics are described as living microorganisms that can influence and protect the natural composition of gut microbiota and

contribute to human health. Their benefits, such as facilitating digestion, weight change and supporting immunity, have been reported [7]. *Bifidobacterium infantis 35624* is in clinical use as a probiotic formula for dyspepsia and irritable bowel syndrome [8]. But, no study has yet been observed about its effect on obesity in the literature, and this study has been planned with the aim of addressing this deficiency. We evaluated the morphometric, biochemical, and inflammatory-energy metabolism responses in high-fat-diet-induced obesity. Additionally, we examined IL-6, TNF-α, and GLP-1 levels with high-fat diet and the probiotic *Bifidobacterium Infantis 35624* supplementation.

2. Materials and Methods

2.1. Ethical Considerations

This study was carried out in accordance with the recommendations of the guide "Regulation on Experimental Animals" (Republic of Turkey). The protocol of the study was approved by the Animal Experiments Local Ethics Committee of Ordu University (16/02/2021, no: 82678388)

2.2. Animal Model and Dietary Interventions

Twenty-week-old male Sprague Dawley (SD) rats weighing 250-300 g (n =24) were obtained from the Experimental Animals Application and Research Center of Ondokuz Mayıs University, Samsun, Turkey. All rats were kept in an air-conditioned room with a 12-hour light and dark cycle at constant temperature and humidity (23 ±1 °C and 55-65%, respectively). Free access to food and water has been provided. After one week of adaptation, rats were randomly divided into three groups (n =8) which fed a normal-fat diet (NFD), a high-fat diet (HFD), and a HFD with probiotic supplementation (HPFD). NFD was a standard feed diet containing 10% kcal fat, and HFD was a cafeteria diet containing 60% kcal fat, were obtained from Arden Research and Experiment Company, Ankara, Turkey.

Probiotic capsule as *Bifidobacterium infantis 35624* (Symbiosys Alflorex; Biocodex, France) was obtained from the local pharmacy in Ordu, Turkey. Each capsule contained 10^9 *Bifidobacterium infantis 35624* in powder form. The probiotic content was drawn into the syringe with 0.5 ml of water, diluted, and mixed for the supplementation therapy. Each rat in the HPFD group was fed daily with this probiotic supplementation by oral gavage.

The rat weights were recorded weekly. In the evaluation of obesity, the Body Mass Index (BMI = Body weight (g)/height (cm^2)) value calculated by measuring the body weight and naso-anal length of the rats was used. BMI 0.48-0.68 g/cm^2 was determined as the normal range, and BMI > 0.68 g/cm^2 was evaluated as obese [9].

At the end of the 8-week treatment period, all rats were sacrificed by cervical dislocation under deep anesthesia. Intraperitoneal ketamine 90 mg/kg (Ketalar; Eczacıbaşı, Istanbul, Turkey) and xylazine hydrochloride 3 mg/kg (Rompun; Bayer, Leverkusen, Germany) were used for the anesthesia. All efforts were made to minimize suffering.

2.3. Biochemical Analysis

Blood samples were collected by entering the bifurcation aorta with a ten cc injector, and 4-5 ccs of blood was taken and transferred to appropriate laboratory parameter tubes with an empty glass. Glucose measurements were made using the colorimetric method. IL-6, TNF-α, GLP-1, and insulin levels were studied by ELISA (Sunred; Shanghai, China). All measurements were made in Ordu University Biochemistry Research Laboratory.

2.4. Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences software program, version 26.0 for windows. Power analysis was performed to determine the sample size using the G*Power 3.1.9.6 statistical program. The effect size was calculated with the help of the study conducted by Çelik and Söğüt [10] and found to be f = 0.6836. The total sample size calculated to reach 80% power value at a 95% confidence level was found to be 24. For this reason, the total sample size in the study was determined to be 24, with 8 rats in each group. All parametric data were described as the mean ± standard deviation. The significance of the differences in mean values among the two groups was evaluated by two-tailed unpaired Student's t tests. More than two groups were evaluated by a one-way ANOVA followed by Tukey's test. p value of <0.05 was considered significant.

3. Results

3.1. Body Weight, Glucose, and Insulin Levels

At the beginning of the study, the mean body weights of the groups were similar and BMI was 0.56 g/cm^2 for each group. After eight weeks of the study, NFD group did not become obese (BMI: 0.60 g/cm^2) while the HFD group was diagnosed with obesity (BMI:0.72 g/cm^2). A significant difference in final body weight between the ND and HFD groups was observed (p<0.001). Moreover, the HPFD group showed a significantly lower mean body weight than the HFD group (p< 0.001). The weight and BMI values of HPFD group were similar to those of the NFD group. Plasma glucose and insulin levels were increased in the HFD group compared to the NFD group (p<0,004 and p<0.001 respectively). These metabolic parameters were significantly lower in the HPFD group than in the HFD group (p<0.005 and p<0.001 respectively). The comparison of the glucose and insulin levels was shown in Figures 1A and 1B.

3.2. Inflammatory Cytokines and Energy Metabolism Parameters

TNF-α and IL-6 levels increased in the HFD group compared to the NFD group (p<0.039 and p<0.017, respectively). However, these cytokines were significantly lower in the HPFD group than in the HFD group (p<0.031 and p<0.038, respectively). The TNF-α and IL-6 levels of the NFD group and HPFD group were found to be similar.

The TNF-α and IL-6 levels of the groups were shown in Figure 2 and Figure 3.

GLP-1 levels increased in the HFD group compared to the NFD group (p<0,001). The GLP-1 levels were significantly lower in the HPFD group than in the HFD group (p<0.005). The GLP-1 levels in the NFD group and HPFD group were found to be similar. GLP-1 levels of the groups were shown in Figure 4. The morphometric and laboratory parameters evaluated in the study were shown in Table 1.

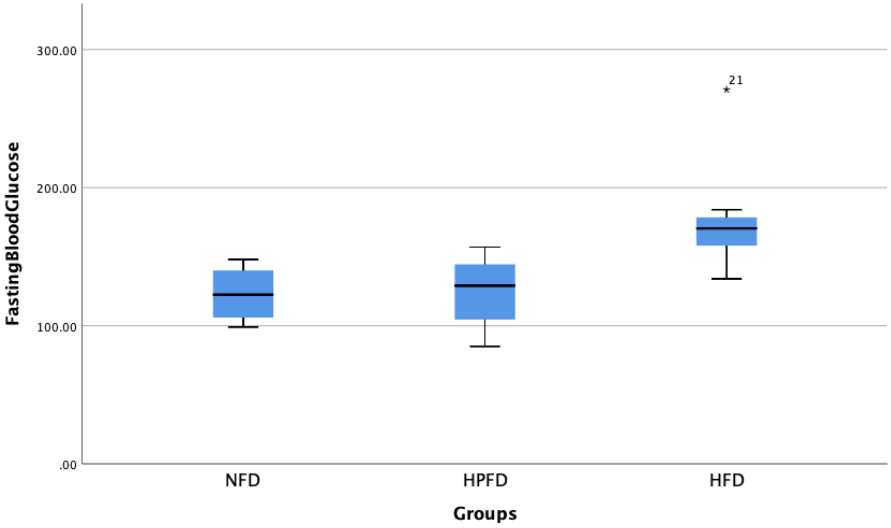

Figure 1A. The comparison of the glucose levels. NFD = Normal fat diet, HFD = High-fat diet, HPFD = High-fat diet with probiotic supplementation

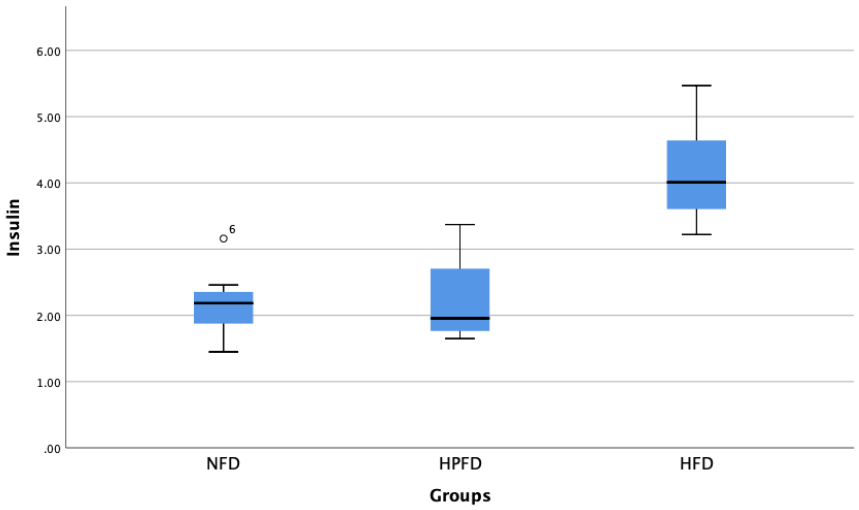

Figure 1B. The comparison of the insulin levels. NFD = Normal fat diet, HFD = High-fat diet, HPFD = High-fat diet with probiotic supplementation

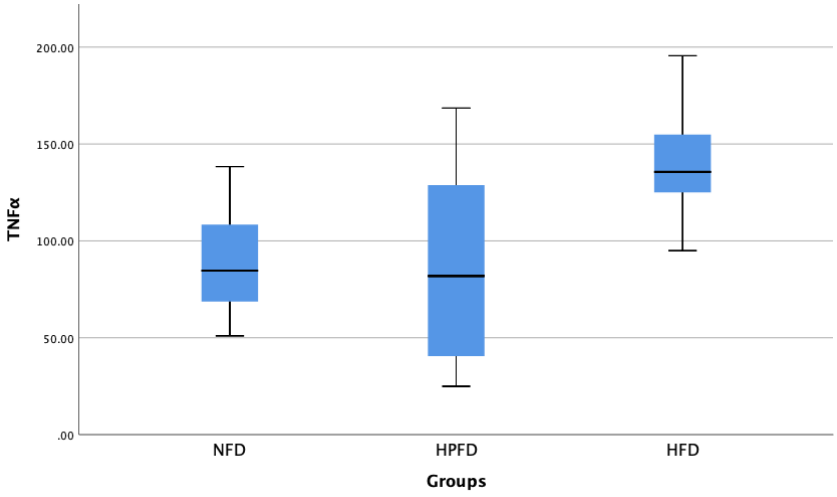

Figure 2. The comparison of the TNF- α levels. NFD = Normal fat diet, HFD = High-fat diet, HPFD = High-fat diet with probiotic supplementation

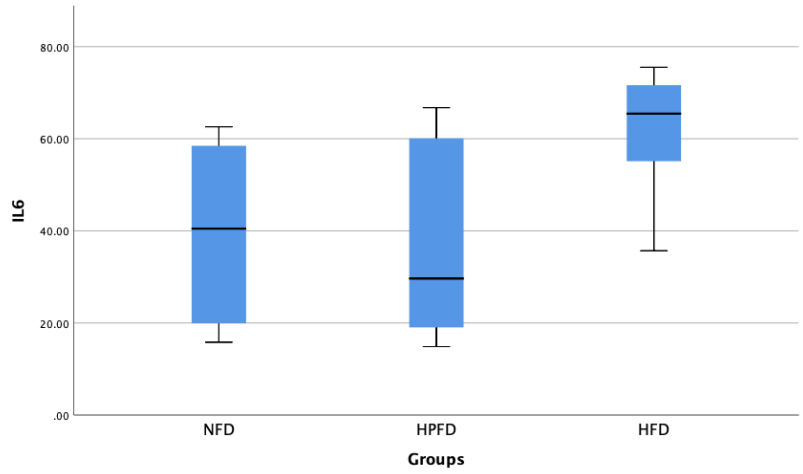

Figure 3. The comparison of the IL-6 levels. NFD = Normal fat diet, HFD = High-fat diet, HPFD = High-fat diet with probiotic supplementation

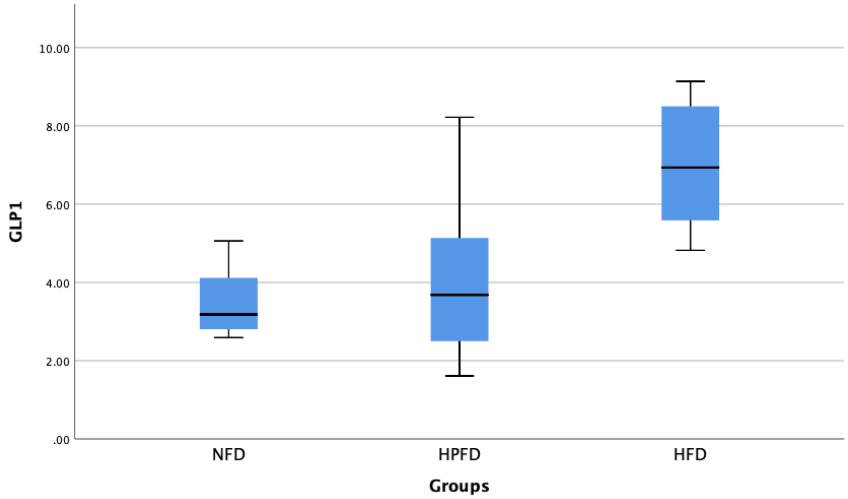

Figure 4. The comparison of the GLP-1 levels. NFD = Normal fat diet, HFD = High-fat diet, HPFD = High-fat diet with probiotic supplementation

Table 1. Morphometric and laboratory parameters of the study

	NFD (n=8) group Mean±SD	HFD (n=8) group Mean±SD	HPFD (n=8) group Mean±SD	P-value			
				NFD/ HFD	NFD/HPFD	HFD/ HPFD	All groups
Initial Body weight (gr)	273±9	273.75±10.34	274.5±8.31				
Final Body weight (gr)	292.5±8.23	333.8±18.26	295.1±7.66	0.0001		0.0001	
Glucose (mg/dL)	123±18.91	177.38±40.64	124.75±25.5	0.004	0.992	0.005	0.002
Insulin (IU/L)	2.18±0.50	4.15±0.74	2.23±0.65	0.001	0.984	0.001	0.001
TNF-alfa (ng/L)	89.11±29.25	140.18±30.58	86.98±51.93	0.039	0.993	0.031	0.019
IL-6 (pg/ml)	39.51±19.46	61.94±13.09	37.39±21.79	0.017	0.971	0.038	0.027
GLP-1 (ug/ml)	3.48±0.86	7.00±1.64	4.06±2.14	0.001	0.763	0.005	0.001

One way ANOVA test was used. A value of $p< 0.05$ was considered significant.

4. Discussion

The alteration and function of the gut microbiota may lead to a pro-inflammatory state as the onset of some diseases and obesity [11]. Turnbaugh et al. compared gut microbiota composition in obese and lean individuals, and they reported that gut microbiota was different in both cases, suggesting that the alteration of the gut microbiota may be associated with an increased or reduced body weight [12]. The most commonly involved bacteria are *Lactobacillus* and *Bifidobacterium* in gut microbiota. Studies have shown that an imbalance between these species is the most common cause of the disorders in the human body [13]. Zuo et al. demonstrated that the major *Bacteroidetes* genus *Bacteroides* quantity was significantly lower in the obese group than in the normal-weight group as a result of the examination of the gut

microbiota in obese and normal-weight individuals [14]. The changes in gut microbiota especially with the reduction of *Bacteroidetes* have been found to be associated with the obesity development in many studies [15]. In the present study, the weight gain in the HPFD group was significantly lower than that in the HFD group. *Bifidobacterium infantis 35624* supplementation kept the weights similar to those of the normal diet feeding despite the high fat feeding. Likewise, plasma glucose and insulin levels were found to be significantly lower in the HPFD group than in the HFD group. Both energy metabolism imbalance and low-grade inflammation have been implicated in the pathophysiology of obesity and obesity-related diseases [16]. The main source of IL-6 and TNF-α is a macrophage infiltration of white adipose tissue (WAT) which induces insulin resistance in adipocytes [17]. Adipose tissue mass is largely formed by WAT which is mostly responsible for the triglycerides storage, and it is critical for energy storage, endocrine communication, and insulin sensitivity [18]. Increased adipose tissue in obesity causes an increase in the inflammatory cytokines IL-6 and TNF-α and a decrease in insulin sensitivity [19]. Adipose tissue contains the immune cells such as lymphocytes, monocytes, and macrophages. Increased adipose tissue and low grade inflammation are responsible for the release of the inflammatory cytokines IL-6 and TNF-α which were found to be related to the several disorders such as obesity, insulin resistance, and cardiovascular diseases**.** [20]. In the present study, obesity caused an increase in IL-6 and TNF-α levels. Similarly, in a recent study, the levels of pro-inflammatory cytokine IL-6 were found significantly higher in obese than non-obese participants [21]. Again in another study, the secretion of inflammatory cytokines and adipokines started while the secretion of anti-inflammatory and protective cytokines declined with the development of obesity [22]. It was stated that two main inflammatory processes work together to drive disease in the obesity status; the systemic low-grade inflammation that damages the vascular endothelium and causes organ dysfunction1, and a more aggressive adipose tissue inflammation that result to the release of cytokines such as IL-6 and TNF-α and adipokines and contributes to peripheral insulin resistance [23].

Food intake and energy balance are controlled via the gut microbiota, hormonal effects, and the nervous system. The gut influences the immune system with inflammatory responses to conditions such as infections, antibiotic treatments, vitamin deficiencies and some diseases throughout life. The gut microbiota plays an important role in these responses [24]. The end products of nutrients activate enteroendocrine cells (EECs) of the gut through the influence of gut bacteria. Nutrients are thus sensed by the paracrine effects of enterocytes [25]. Inflammation disrupts the control mechanism of the gut by damaging the intestinal epithelium, increasing the permeability of enterocytes and allowing some bacterial particles called lipopolysaccharide (LPS) to diffuse through the gut into the blood. Elevated levels of bacterial plasma LPS are known as "metabolic endotoxaemia" [26]. This status was found to be associated with obesity. LPS infusion was observed to increase total body weight, cause inflammation in adipose tissue, and induce fasting hyperglycaemia and hyperinsulinaemia [27]. In one study, a high-fat or high-carbohydrate meal was observed to induce this state [28]. In another study, experimental endotoxemia reduced systemic insulin sensitivity by 35% [29]. Metabolic endotoxemia was observed to be typically associated with a reduction in intestinal *Bifidobacterium*, which is known to maintain mucosal barrier function against bacterial antigens [30]. The gut plays an important role in maintaining energy balance and preventing obesity. Energy intake in the human body is controlled by GLP-1, a peptide hormone secreted by enteroendocrine cells [31]. After ingestion of a meal, the presence of nutrients in the intestinal lumen, and in particular ingested glucose and carbohydrates, stimulate GLP-1 secretion. The main function of GLP-1 is to stimulate pancreatic B-cells for insulin secretion and glucose uptake into peripheral tissue cells [32]. GLP-1, primarily produced by EECs following nutrient ingestion, is typically secreted within 10–15 min postprandially, peaking at 60–90 min. This effect is due to the release with the following oral glucose ingestion whereas intravenous glucose does not create this effect**.** This result shows that the intestinal mucosal cells and gut microbiota play an essential role in GLP-1 release [33]. The overweight and obese individuals had physiologically high levels of GLP-1, which has been shown to provide energy balance by increasing insulin activity [34]. Similarly, the present study found that insulin and GLP-1 levels were increased with a high-fat diet. This may be a response to increased food and calorie intake, as seen in other studies.

The gut microbiota has been found to be associated with GLP-1 secretion, and in the case of inflammation, the changes in the gut microbiota and impaired GLP-1 levels lead to insulin resistance and even diabetes mellitus [35]. Many studies have been indicated the beneficial effects of the probiotics in protecting the natural composition of the gut microbiota, preventing the metabolic endotoxemia and inflammation, reducing the inflammatory cytokines, and improving the GLP-1 secretion [36,37].

Some species of gut microbiota have been found to be more effective in improving obesity-related disorders. In particular, the knowledge that *Bifidobacteria* species decrease in obesity has led to a trend in research using these bacterial species as probiotics in this area [38]. In one study, *Bifidobacterium* spp probiotics improved glucose tolerance and insulin secretion. Moreover, the proinflammatory cytokines both in plasma and in adipose tissue changed in parallel with glucose and insulin levels [39]. In another study, the probiotic supplement used as an immunoregulator and containing *Bifidobacterium pseudocatenulatum SPM 1204, Bifidobacterium longum SPM 1205* and *Bifidobacterium longum SPM 1207* provided a reduction in adipose tissue and body weight with the lipid-lowering effect in obese rats induced by a high-fat diet [40]. Similarly, probiotic supplementation with *Bifidobacterium spp*. (including *B. longum, B. bifidum, B. infantis* and *B. animalis*) improved insulin resistance and reduced inflammatory adipocytokine expression in obese mice [41]. *Bifidobacterium infantis strain 35624* is a naturally occurring microorganism in the gut. Its probiotic formula is well established in patients with functional gastrointestinal disorders and irritable bowel syndrome (IBS). TNF-α and IL-6 levels have been reduced in some intestinal and extra-intestinal

inflammatory diseases by the use of *Bifidobacterium infantis 35624*, and it has been suggested that it modulates host inflammatory processes beyond the gut [42]. Similarly, in the present study, levels of the inflammatory cytokines IL-6 and TNF-α were found to be increased with high-fat feeding and decreased with *Bifidobacterium infantis 35624* supplementation to levels close to those seen with normal-fat feeding.

5. Conclusions

The findings of this study are consistent with the view that pro-inflammatory cytokines TNF-α and IL-6 and indicator of energy metabolism GLP-1 increase with high-fat nutrition. As it is known that *Bifidobacteria* genus is a major part of the gut microbiota and some of its species have been found to have healing effects in obesity-related studies, *Bifidobacterium infantis 35624* as probiotic may be also a candidate to be part of the therapeutic approach for the obesity prevention and treatment studies.

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Author Contributions

All authors contributed to the study's conception and design. Ö.Ö. was responsible for the conducting the search, screening potentially eligible studies and writing the reports. Ö.Ö. and Ç.A performed the experiments. Ç.A. and O.B. performed the sacrification and blood collection. In addition, Ç.A. was responsible for analyzing data, providing statistical analysis. F.E. contributed to design, review, and editing the study. T.B. performed laboratory analyzes and biochemical assessments.

Competing Interest

The authors declare that they have no competing interests.

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Data availability

Data is provided within the manuscript.

Consent for publication

Not applicable

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