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Effects of Lactobacillus rhamnosus GG on some adipokine levels in rats fed Western diet

Efectos de Lactobacillus rhamnosus GG sobre algunos niveles de adipocinas en ratas alimentadas con dieta occidental

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ABSTRACT

Adipokines regulate energy homeostasis. High-fat Western diet leads to obesity and disrupts adipocyte metabolism. Probiotics such as *Lactobacillus rhamnosus* GG are effective in obesity management. This study investigates the effect of *Lactobacillus rhamnosus* GG on serum adipokine levels in rats fed a High-fat Western diet. Thirty 5-6 week old male Wistar albino rats (*Rattus norvegicus domestica*) were randomly selected and divided into three groups: control (standard chow), W (45% fat), and a WLgroup supplemented orally with *Lactobacillus rhamnosus* GG in vegetable oil for 16 weeks. At the end of the study, blood samples were collected from rats via cardiac puncture, and serum adipokine levels were measured using ELISA kits. Body weight, naso-anal length, and BMI (body mass index) exhibited statistically significant increases in the W group. In the *Lactobacillus rhamnosus* GG-supplemented group (WL), body weight and BMI decreased, while naso-anal length increased. SFRP5 and CT1 levels were low, and asprosin and vaspin levels were high in the Wgroup. CT1, vaspin, and asprosin levels increased in the *Lactobacillus rhamnosus* GG-supplemented group. In conclusion, *Lactobacillus rhamnosus* GG alleviates obesity, increases naso-anal length, and reduces BMI in rats fed a High-fat Western diet. These results suggest that *L. rhamnosus* may regulate serum CT1, vaspin, and asprosin levels, but not omentin or SFRP5 in the High-fat Western diet model.

Key words: Adipokine; high fat western diet; probiotic; Lactobacillus rhamnosus

RESUMEN

Las adipocinas regulan la homeostasis energética. La dieta occidental alta en grasas conduce a la obesidad y altera el metabolismo de los adipocitos. Los probióticos como *Lactobacillus rhamnosus* GG son eficaces en el manejo de la obesidad.Este estudio investiga el efecto de *Lactobacillus rhamnosus* GG en los niveles séricos de adipocinas en ratas alimentadas con una dieta occidental alta en grasas. Un total de 30 ratas macho Wistar albino (*Rattus norvegicus domestica*) de 5-6 semanas de edad fueron seleccionadas y divididas aleatoriamente en tres grupos: control (pienso estándar), W(45% de grasa) y un WL grupo suplementado oralmente con *Lactobacillus rhamnosus* GG en aceite vegetal durante 16 semanas. Al final del estudio, se recolectaron muestras de sangre de las ratas mediante punción cardíaca y se midieron los niveles séricos de adipocinas utilizando kits ELISA. El peso corporal, la longitud naso-anal y el IMC (índice de masa corporal) mostraron aumentos estadísticamente significativos en el grupo W. En el grupo suplementado con LGG (WL), el peso corporal y el IMC disminuyeron, mientras que la longitud naso-anal aumentó. Los niveles de SFRP5 y CT-1 fueron bajos, y los niveles de asprosina y vaspina fueron altos en el grupo W. Los niveles de CT-1, vaspina y asprosina aumentaron en el grupo suplementado con *Lactobacillus rhamnosus* GG. En conclusión, *Lactobacillus rhamnosus* GG alivia la obesidad, aumenta la longitud naso-anal y reduce el IMC en ratas alimentadas con una dieta occidental alta en grasas. Estos resultados sugieren que *L. rhamnosus* puede regular los niveles séricos de CT-1, vaspina y asprosina, pero no los de omentina o SFRP5 en el modelo de dieta occidental alta en grasas.

Palabras clave: Adipocina;dieta occidental alta en grasas; probiótico, Lactobacillus rhamnosus

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INTRODUCTION

Obesity is a significant public health problem. This condition affects a large portion of the population worldwide. Obesity plays an important role in the development of many metabolic diseases such as diabetes, hypertension and heart diseases. Therefore, high-fat diets, cafeteria diets and high-calorie diets are models of obesity that have been used for experimental studies in animals [1].

It has been suggested that, among these models, High-fat Western diet (HFWD) are more similar to the human diet [1]. Evidence from long-term studies indicates that diets with a substantial caloric content prepared with high levels of fat and/or sugar expand adipose tissue and cause obesity [2].

Adipose tissue accumulates surplus calories in the form of triacylglycerol and has been considered an endocrine organ, secreting adipokines [3 ,4]. Adipokines, structurally similar to cytokines, are responsive to fluctuations within adipocytes for triacylglycerol storage, exerting both local and systemic effects inflammatory processes [5],[6].

Gut microbiota modulate body weight, adipose tissue and low-grade inflammation [7]. In addition to family genes, environment, drug use and nutrition play a major role in the change of microbiota types in the digestive system [8].

Dietary patterns cause changes in intestinal microbiotaand its metabolic functions [9]. They may also affect the circulating adipokine levels [10]. Changes in intestinal structure or microbiota composition may affect adipokine levels [11].

There is increasing interest in modifying the composition or function of the gut microbiota to prevent obesity and related metabolic syndromes [12]. Administration of probiotic strains, including *Bifidobacterium longum* [13], *Lactobacillus plantarum* [14] and *Lactobacillus casei* [15 ,16], improves gut microbiota dysbiosis and consequently prevents obesity-related metabolic disorders. *Lactobacillus rhamnosus* (*L. rhamnosus*) is a representative strain of *Lactobacillus*. *L. rhamnosus*, which is a common probiotic, has been shown to be effective in combating obesity [17]. While the anti-obesity effects of *L. rhamnosus* have been explored [18], the impact of *L. rhamnosus* on adipokine levels requires further in-depth investigation.

Therefore, the aim of this study was to investigate the effects of *L. rhamnosus* GG (LGG) on some adipokine levels (omentin, secreted frizzled-related protein 5 (SFRP-5), cardiotrophin-1 (CT-1), vaspin, asprosin) in rats (*Rattus norvegicus*) fed a HFWD.

MATERIALS AND METHODS

Experimental protocols were performed in accordance with the regulations regarding the use of laboratory animals. Ethical approval was obtained from the Animal Experimentation Committee (2019/8-14), Hatay Mustafa Kemal University Experimental Research Center, Hatay, Turkey.

Experimental design and animals

Thirty male Wistar albino rats (*Rattus norvegicus*), ages 5–6 weeks, weighing an average of 123.33 ± 20.14 g, were used in this investigation. Three to four rats per cage were kept in stainless steel cages with standardized lighting (12 h of light and 12 h of darkness), a constant temperature (22 ± 2 °C), and a humidity level of 55% ± 10%.

After one week of adaptation, the rats were randomly divided into three groups. Each group consisted of ten rats. All animals survived until the end of the experiment. The experiment lasted 16 weeks. During the experiment, food and water were provided *ad libitum.*

Baseline and final measurements of body weight (OHAUS NVT 6201,Switzerland) and naso-anal length were obtained for all animals. The body mass index (BMI) of each animal was calculated as the ratio of body weight (g) to the square of the naso-anal length (cm^2).

The control group (C) of rats was fed a commercial normocaloric standard rat chow (Bil-yem®,Turkey), which consisted of 2.70 kcal/g including 12% fat, 60% carbohydrate and 28% protein.

The first experimental group (W) of rats was fed only a HFWD consisting of 5.00 kcal/g including 45% fat, 35% carbohydrate and 20% protein created based on open data principles (D12451, Research Diets) [19]. The second experimental group served as the probiotic (WL) group and received a HFWD supplemented with LGG.

LGG (ATCC 53103) was purchased from the Menarini Group (Florance, Italy) (trade name Kaleidon). The probiotic supplement was in liquid form and one probiotic drop contained $1x10^9$ CFU of LGG, sunflower oil and an emulsifier. One drop of LGG was mixed with 0.1 mL of vegetable oil and administered by gavage to the WL group, while rats in both the C and W groups received only 0.1 mL of vegetable oil daily (d) as a placebo for 16 weeks.

Biochemical analysis

After the study was concluded, animals were euthanazied by cardiac puncture under anaesthesia (Xylazine 10 mg/kg (Rompun 2%, Bayer, Germany) and Ketamine HCl 75 mg/kg (Ketasol 10%, interhas, Turkey)). Blood samples were collected and allowed to clot at room temperature for 30 min. Subsequently, they were centrifuged at 1790 G units (NF800R Desktop Centrifuge, Nuve, Turkey) for 15 min at 4°C. Serum supernatants were separated and stored at -80°C (DF290 Deep Freezer, Nuve, Turkey) until further analysis of serum adipokines.

Serum omentin, SFRP-5, CT-1, vaspin, asprosin were determined by enzyme-linked immunosorbent assay (ELISA) kits. ELISA kits (Fine Test) for Omentin (Rat Intelectin1/Omentin/ER1117), SFRP-5 (Rat SFRP-5/ER1945), CT-1 (Rat CT-1/ER0868), adipocyte/ER0249, Vaspin (Rat Vaspin/(Visceral Adipose Specific Serine Protease Inhibitor/ER1420), Asprosin (Rat Asprosin/ER1944) were purchased from Fine Biological, Wuhan, China. All procedures were performed according to the manufacturer's instructions. Analyses were performed using a microplate reader at 450 nm (Spectrostar Nano, BMG Labtech, Germany).

Statistical analysis

For statistical evaluations, the Windows SPSS 22.0 package program was used. One-way analysis of variance (ANOVA) followed by Duncan's post-hoc test was used for multiple comparisons in parametric data sets. For non-parametric data, multiple comparisons were performed using the Kruskal-Wallis test followed by Tamhane's test. Analysed data are presented as mean ± standard error of the mean. A significance level of P<0.05 was used for statistical analysis.

RESULTS AND DISCUSSION

The increasing prevalence of obesity worldwide is attracted the adminstration of probiotics for the prevention and treatment of obesity attention [20]. The most obvious finding in HFWD studies is weight gain. Previous studies have shown that probiotic supplementation reduces weight gain [21 , 22]. At the beginning of the study, there were no differences in body weight among the groups (P>0.05). At the end of the study, the body weight of the W group was significantly higher than that of the C group (P<0.05). Conversely, the body weight of the WL group was found to be notably lower compared to the W group at the end of the study (P<0.05). No significant difference was observed between the WL and C groups at the end of the study (P>0.05) (TABLE I). In addition, these effects are occured by regulating adipogenesis and glucose metabolism, and reducing proinflammatory cytokines in adipose tissue [20].

TABLE I
Baseline and final body weight changes of all animal groups

	Groups			
Parameter	**C**	**W**	**WL**	**p**
Baseline Weight(g)	122.02±21.10[a]	125.83±27.69[a]	123.00±11,64[a]	0.719
Final Weight(g)	488.06±36.77[b]	550.88±61.95[a]	502.28±23.14[b]	0.001

Values are presented as mean ± SE (standard error) C: Control, W: fed a high-fat western diet (HFWD) and WL: fed a HFWD supplemented with L.rhamnosus GG. Superscripts (a, b, c) indicate significant differences across groups in the same row (p<0.05).

Probiotic supplements cause decreases in the (BMI as well as body weight by the same mechanism [23]. A statistically significant decrease in BMI was evident in the WL group relative to the other two groups within this study. BMI fluctuations mirrored the changes seen in body weight (TABLE I) and naso-anal length (TABLE II). No significant differences in initial naso-anal lengths were observed among the groups (P>0.05). However, the naso-anal length of the WL group was significantly greater than that of both the W and C groups at the end of the study (both P<0.05) (TABLE II). This shows that probiotic supplements also contribute to height increase. The study of a systematic meta-analysis showed that probiotics supported the development of weight and height gain in children with growth retardation [24]. In addition, the relationship between growth hormone and the gut microbiome may have a positive impact on gut and metabolic health [25]. In this study showed that the naso-anal lenghtsof the rats in the WL group was longer, consistent with the literature, and the difference was statistically significant contrast to other two groups. LGG supplementation, butyrate production in the intestine increased and trabecular bone volume increased [26]. In addition, the increase in height may be related to LGG count and duration colonization and function in the animal's gastrointestinal tract [27]. The current study findings are consistent with the studies conducted, and height and weight changes can be explained by the positive effects of *L.rhamnosus* GG supplemention to the diet on the intestinal microbiota.

TABLE II
Baseline and final naso-anal lengths changes of all animal groups

	Groups			
Parameter	**C**	**W**	**WL**	**p**
Baseline naso-anal length (mm)	**153.10±10.343[a]**	**152.40±14.14[a]**	**147.1±6.00[a]**	**0.115**
Final naso-anal length (mm)	**248.40±4.718[c]**	**253.50±4.58[b]**	**266.9±4.61[a]**	**0.000**

Values are presented as mean ± SE (standard error) C: Control, W: fed a high-fat western diet (HFWD) and WL: fed a HFWD supplemented with L.rhamnosus GG. Superscripts (a, b, c) indicate significant differences across groups in the same row (p<0.05).

By the end of the study, the W group, maintained on a HFWD, exhibited the highest BMI levels (P<0.05) (TABLE III). Both the probiotic-supplemented WL group and the control group (C) displayed BMI values that were markedly lower than the W group (P<0.001). Additionally, a notable distinction was observed between the C group and the WL group (P<0.001). The finding that the WL group, which received probiotic supplementation, presented the lowest BMI value strongly suggests that probiotics can significantly contribute to lowering BMI.

TABLE III
Baseline and final Body mass index (BMI) changes of all animal groups

	Groups			
Parameter	**C**	**W**	**WL**	**P**
Baseline BMI (gr/ cm²)	**0.52±0.06[a]**	**0.55±0.14[a]**	**0.57±0.06[a]**	**0.507**
Final BMI (g/ cm²)	**0.79±0.04[b]**	**0.86±0.07[a]**	**0.70±0.02[c]**	**0.000**

Values are presented as mean ± SE (standard error). Body mass index (BMI).C: Control, W: fed a high-fat western diet (HFWD) and WL: fed a HFWD supplemented with L.rhamnosus GG. Superscripts (a, b, c) indicate significant differences across groups in the same row (p<0.05).

Lactobacillus probiotics have been reported to attenuate adiposity, improve lipid profiles, and prevent adverse alterations in adipokine levels in animal models fed obesogenic diets [28]. Moreover, it increases the levels of anti-inflammatory adipokines while simultaneously decreasing the levels of pro-inflammatory adipokines. Anti-inflammatory adipokines, such as adiponectin, omentin-1, SFRP5, and CT-1, play a crucial role in regulating energy metabolism. They contribute to improved energy utilization in key tissues, including the liver, skeletal muscle, pancreas, and adipose tissue itself [29]. Omentin-1 is highly expressed in visceral adipose tissue, while circulating levels of omentin are decreased in obese individuals [30].

In addition, especially exercise training result in a significant increase in the serum omentin-1 concentrations and insulin-sensitization. In this study, no significant difference between three groups was seen in omentin levels. This result may indicate that *L. rhamnosus* supplementation may not affect omentin-1 levels without exercise effect. Secreted frizzled-related protein 5 SFRP5 has beneficial effects on insulin sensitivity and is a new marker of chronic inflammation associated with adipose tissue. Serum SFRP5 levels are low in subjects with obesity and type 2 diabetes mellitus [31].

In the present study, SFRP-5 levels were decreased in the W and WL groups compared to the C group (TABLE IV). This finding may suggest that *L. rhamnosus* alone is not sufficient to correct this significant decrease. Serum concentrations of SFRP-5 have been increased in obese patients undergoing calorie restriction [32 , 33 , 34 , 35]. The relationship between CT-1 levels and obesity/metabolic diseases in humans remains elusive. While CT-1 gene expression levels are downregulated in white adipose tissue in diet-induced obese mice (*Rattus norvegicus*) [36], plasma levels have been shown to be increased in individuals with obesity and metabolic syndrome [37].

TABLE IV
Presents the adipokine levels in all groups at the end of the experimental period

	Groups			
Parameters	**C**	**W**	**WL**	**P**
Omentin (ng/mL)	**4.08±0.65**	**4.04±0.71**	**4.26±0.43**	**0.701**
SFRP-5 (pg/mL)	**9.16±1.65[a]**	**5.55±0.43[b]**	**5.86±2.05[b]**	**0.000**
CT-1 (pg/mL)	**24.05±3.37[a]**	**15.27±3.50[b]**	**21.78±3.70[a]**	**0.000**
Vaspin (pg/mL)	**155.77±11.48[c]**	**281.93±100.32[b]**	**536.64±99.25[a]**	**0.000**
Asprosin (pg/mL)	**93.09±15.58[c]**	**168.34±38.63[b]**	**222.17±39.67[a]**	**0.000**

Values are presented as mean ± SE (standard error) . C: Control, W: fed a high-fat western diet (HFWD) and WL: fed a HFWD supplemented with L.rhamnosus GG.Superscripts (a, b, c) indicate significant differences across groups in the same row (P<0.05).

On the contrary, some studies are showed that CT-1 levels are lower in overweight and obese individuals compared to normal weight individuals [38]. In the present study, CT-1 levels decreased in the W group. On the other hand, increased CT-1 levels in the C and WL groups were also consistent with decreased weight gain and BMI (TABLE IV). CT-1 is a protein that belongs to theinterleukin-6 (IL-6) cytokine family [39]. While initially identified for its role in cardiac hypertrophy, emerging evidence suggests potential involvement of CT-1 in regulating glucose and lipid metabolism [40]. The increased CT-1 levels in the WL group (TABLE IV), which was fed the same diet as the W group but supplemented with LGG, may indicate the beneficial effect of LGG on these pathway.

The other two adipokines evaluated in the current study are vaspin and aspirosin. Although they are linked to obesity and insulin resistance and are considered inflammatory adipokines, it has been stated that increases in these two parameters may be a protective mechanism against metabolic syndrome [41 , 42].

Vaspin is elevated in obese and streptozotocin-induced diabetes mellitus fed a high-fat diet [43]. On the contrary, it has been shown to enhance glucose tolerance and insulin sensitivity and inhibit the expression of genes associated with insulin resistance [44]. Similarly, asprosin levels are increased in obesity with insulin resistance [45]. The results of the current study were similar to these and vaspin and aspirosin levels increased and were statistically significant in the two experimental groups fed HFWD compared to the control group. However, this increase was statistically significant and higher in the WL group compared to the W group (Table IV).

Vaspin administration reduces food intake [46]. Asprosin, which stimulates food intake, is a centrally acting oroxygenic hormone. [47 , 48]. Asprosin levels exhibit a positive correlation with body mass index [49]. Despite all these negative data, asprosin is thought to play a role in the regulation of glucose homeostasis [45]. The change in vaspin concentrations with nutrition indicates that it may be a contributing factor in the regulation of body weight homeostasis [50].

In this study, both adipokine levels were significantly higher in the WL group compared to the other two groups (TABLE IV). The lower BMI and body weight in this group despite higher adipokine levels suggest that LGG contributes to the maintenance of homeostasis despite HFWD feeding.

CONCLUSIONS

In the current study, it was shown that the strain-specific probiotic (*L. rhamnosus*) was effective in improving obesity-related adipokines. On the other hand, the effectiveness of a high-fat western diet and *L. rhamnosus* application on omentin, Secreted frizzled-related protein 5, cardiotrophin-1 and vaspin, aspirosin was investigated for the first time. *L. rhamnosus* was determined to have beneficial effects on a high-fat western protein feeding by preventing the decrease in serum cardiotrophin-1 levels. It also supports the effects of two adipokines on hunger and feed intake by causing a significant increase in vaspin and asprosin levels. *L. rhamnosus* supplementation together with a high-fat western protein provides the preservation of body mass index and body weight by acting on certain adipokines. However, further studies are needed to understand the physiological pathways of this effect.

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Authors contributions

AO, MB and CT designed the experiments. AO performed the tests and collected the samples. MB and CT were present at all stages of the studies. AO prepared Elisa's analyses and statistics. BD contributed to the preparation of the article for publication. AO was the author of the article. All authors contributed to the study and approved the final version of the manuscript for publication.

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Conflict of interest

The authors declared no conflict of interest.

Ethical approval

This study was approved by the Hatay Mustafa Kemal University Local Ethics Committee (2019/8-14) and the experimental methods were carried out in accordance with ethical rules.

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