https://doi.org/10.46389/rjd-2023-1278
www.rjdnmd.org

Rom J Diabetes Nutr Metab Dis
2023; volume 30, issue 4, pages 440–446

Original Article

Effect of fermented milk *Lactiplantibacillus pentosus* HBUAS53657 on blood glucose, lipid profiles and inflammation in high-fat diet-induced mice

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Received: 2 July 2023 / Accepted: 26 October 2023

Abstract

Lactobacillus pentosus strains with health-promoting properties, such as immunomodulatory and antiproliferative activities, are potential probiotic strains. *L. pentosus* HBUAS53657 is one of the most common strains found in dadih (buffalo fermented milk) originating from Tanjung Bonai Lintau Buo Utara. A previous study found that *L. pentosus* HBUAS53657 had probiotic characteristics. It is necessary to investigate the effect of *L. pentosus* HBUAS53657 fermented milk probiotics on inflammatory markers in experimental animals. This study is a true experimental design with only a post-test control group. The population consisted of Wistar rats (Rattus norvegicus) n=28 divided into four groups: the control group (ND), the High Fat Diet (HFD) group, the High Fat Diet and *L. pentosus* HBUAS53657 group 10^9 CFU/ml (HFDL), and the High Fat Diet and fermented milk with *L. pentosus* strain HBUAS53657 10^9 CFU/ml and 20% oranges group (HFDSF). This feeding was done for six weeks (42 days). The research data was processed and statistically analyzed using the Way ANOVA test, followed by the Post hoc test. The results showed that *L. pentosus* HBUAS53657 fermented milk slowed weight gain in rats given HFDSF by 15.36%, compared to 18.26% in the HFDL group and 24.30% in the HFD group (P<0.01). When compared to the HFD group, the HFDSF and HFDL groups had lower blood glucose, total cholesterol, triglycerides, and LDL (p<0.05, p<0.01, P<0.05). *L. pentosus* HBUAS53657 reduced the level of serum TNF-α on HFD but not significantly. This demonstrates the protective effect of *L. pentosus* HBUAS53657 on lipid metabolism disorders in rats fed high-fat rats. *L. pentosus* HBUAS53657 can reduce HFD-induced proinflammatory cytokines.

Keywords: antidiabetic, antidyslipidemia, probiotic.

Introduction

Probiotics are recommended as complementary therapy agents because they can affect appetite, body weight, and metabolic function via the gastrointestinal pathway and modulate the gut microbiota composition [1]. Dysbiosis, which refers to qualitative and/or functional changes in the gut microbiota, contributes to the etiology of several diseases, particularly those involving autoimmune or inflammatory mechanisms [2]. A high fat intake can disrupt the microbiota balance or dysbiosis. The gut microbiota produces high levels of endotoxin in the bloodstream during dysbiosis, resulting in mild and sustained induction of proinflammatory mediators and mild systemic inflammation. Many human diseases, including obesity, type 2 diabetes, liver and cardiovascular disease, and inflammatory bowel disease, are influenced by this inflammatory pathway. Probiotics prevent or reduce host pathological states, including dysbiosis, obesity, low-grade inflammation and metabolic syndrome [3].

Many articles, reviews, and systematic reviews have been done on the positive effects of probiotics on host health [4, 5]. Probiotics have been shown in the prevention of health problems, including intestinal homeostasis [6, 7], immunomodulatory [8–10], antioxidant and anti-inflammatory [11–13], eczema [14–16] and infectious diseases [17] and metabolic disease or obesity [18–20].

According to a review of the literature, probiotics' antiobesity activity can be mediated by a variety of mechanisms, including changing the composition of the gut microbiota, remodeling energy metabolism, shaping gene expression related to thermogenesis, glucose metabolism, and lipid metabolism, and parasympathetic nerve activity [21]. Intervention research on metabolic disorders has also been conducted. *L. paracasei* HII01 supplementation improves hyperglycemia and inflammatory markers by repairing leaky gut and endotoxemia conditions, making it extremely beneficial in type 2 diabetes patients [22]. Animal studies revealed significant differences between high-fat diets and probiotic groups in the metabolic markers HDL, LDL and the inflammatory markers IL-10, TNF-α, and leptin [23]. Probiotic supplements prevent a variety of inflammatory diseases [24–26]. However, the effect of probiotic supplementation on health improvement remains debatable [27].

Fermented milk is one of the dairy products fermented with lactic acid bacteria. Milk is an extremely important source of nutrition due to the numerous bioactive compounds found in its composition [28]. Buffalo milk contains more nutrients than cow milk in its major components [29]. *Lactobacillus pentosus* strains with health-promoting properties, such as immunomodulatory and antiproliferative activities, are considered potential probiotic strains [30]. *L. pentosus* HBUAS53657 is one of the most common strains found in dadih (buffalo fermented milk) originating from Tanjung Bonai Lintau Buo Utara, Tanah Datar. Fermented milk products with 6% *L. pentosus* HBUAS53657 starter and 20% orange juice produced the best physical and chemical properties, antioxidant tests, the number of lactic acid bacteria, and organoleptic tests [31]. Protein content ranges from 5.81 to 6.33%, fat content ranges from 6.14 to 6.35%, water content ranges from 81.63 to 85.78%, pH 3.57 to 4.23, TTA value 1.30 to 1.85, and the number of LAB colonies ranging from 4.67×10^9 to 9.0×10^9 CFU/mL, antioxidant activity ranging from 25.04 to 37.71 percent, and total phenol 38.32 to 67.20 mgGAE/gr [32]. Based on these findings, this fermented milk product is expected to have anti-inflammatory properties, though more research is needed to determine the extent of its biological properties. It is important to note that different probiotic strains have different properties. As a result, further research is necessary for the effects of one probiotic strain to be generalized to another. This must be taken into account before recommending a probiotic in clinical practice. As a result, preclinical studies on the effect of fermented milk on inflammatory markers are required.

Material and methods

Bacterial strain

L. pentosus HBUAS53657 was isolated from dadih, the traditional fermented buffalo milk collected from local breeders of Tanjung Bonai Lintau Buo Utara, Tanah Datar Regency and then deposited at the Animal Husbandry Product Technology Laboratory, Faculty of Animal Husbandry. Buffalo milk is obtained from Tanjung Bonai Lintau Buo Utara, Tanah Datar Regency. Fermented milk products with the addition of oranges are the results of phase one research (2021) with a predetermined content of water, protein, fat and antioxidant levels.

Experimental animal design

The population of this study was Wistar rats (*Rattus norvegicus*) obtained from the Laboratory of the Faculty of Pharmacy, Andalas University. The sample size was determined using the Federer formula n>6; the minimum number of Wistar rats required was 28. The animals were randomly divided into four groups (n=7 per group), namely the control/Normal Diet group (ND), the High Fat Diet (HFD) group, the High Fat Diet and *L. pentosus* HBUAS53657 CFU/ml (HFDL) group, and the High Fat Diet and fermented milk with the *L. pentosus* HBUAS53657 10^9 CFU/ml addition of 10% orange (HFDSF). The high-fat diet used is commonly used in the University of Andalas Pharmaceutical Laboratory. The sample inclusion criteria were rats aged 8–12 weeks with a body weight of 180–250 grams and no anatomical defects. Inactive mice are characterized by limp movements and do not want to eat, and mice previously used in other studies will be excluded. The Wistar rats were reared under standard laboratory management at 25±2°C, 12 hours in the dark, and 12 hours in the light. Animals were given standard food (water and food ad libitum). The research protocol will be subject to an ethical review by the Ethics Commission of the Faculty of Medicine, Andalas University No 826/UN.16.2/KEP_FK/2022. Body weight and food intake are monitored weekly. This feeding was carried out for 6 weeks. *L. pentosus* HBUAS53657 was administered approx. 1×10^9 CFU/mL once daily for 6 weeks in the HFDL group by oral gavage. Body weight was measured weekly during the trial period with the appropriate scale (model AS-1000; Marte, Santa Rita MG, Brazil). After 6 weeks, the rats were euthanized by decapitation, and biochemical and cytokine parameters were measured in serum. After 6 weeks, the mice were anesthetized with Na thiopental (Ketamine) 50 mg/kg BW intraperitoneally.

Analysis of blood biochemistry

Blood samples were taken from the abdominal aorta and centrifuged at 5000 rpm for 15 minutes. Separated plasma was stored at -20°C to analyze its metabolic and inflammatory profile—determination of inflammatory markers at the Biomedical Laboratory of FK Unand. The method for determining inflammatory markers (TNF-α) is the ELISA method, following the manufacturer's instructions. Measurements of total cholesterol, high-density lipoprotein (HDL-c) cholesterol, triglycerides, and glucose in serum were taken using a commercial kit.

Data analysis

The research data were processed statistically using SPSS. The results are expressed as mean±standard deviation for parametric data or median (maximum-minimum) for non-parametric data. The Kolmogorov-Smirnov test was used to assess the normality of the data. After the data is normally distributed, it is continued using parametric analysis with the one-way ANOVA and the Post-hoc Tukey HSD test. Results expressed as $p\leq0.05$ were considered statistically significant.

Results

The weight gain in each group is shown in Figure 1. The control group (ND) gained 21.45% of their body weight after 6 weeks. The body weight gain in HFD significantly increased compared to the control group (24.30% *vs.* 21.45%, $p<0.05$). However, administration of *L. pentosus* HBUAS53657 significantly decreased the weight gain in HFDL, which was 18.26% and 15.36% in HFDSF.

This present study showed that *L. pentosus* HBUAS53657 can delay the fat accumulation process in rats given HFD.

The HFD group had significantly increased blood glucose compared the control group (ND) compared with the control group (ND) ($P<0.05$). At the same time, administration of *L. pentosus* HBUAS53657 in HFDL and HFDSF significantly lowered blood glucose compared to the HFD group (Figure 2).

Figures 3A, 3B and 3C showed that after 6 weeks of HFD administration, total cholesterol, triglyceride, and LDL levels in rats in the HFD group significantly increased compared with the control group (ND) ($P<0.05$), while in Figure 3D, the HDL levels in the HFD group were not significantly lower than the ND group ($p>0.05$). Total

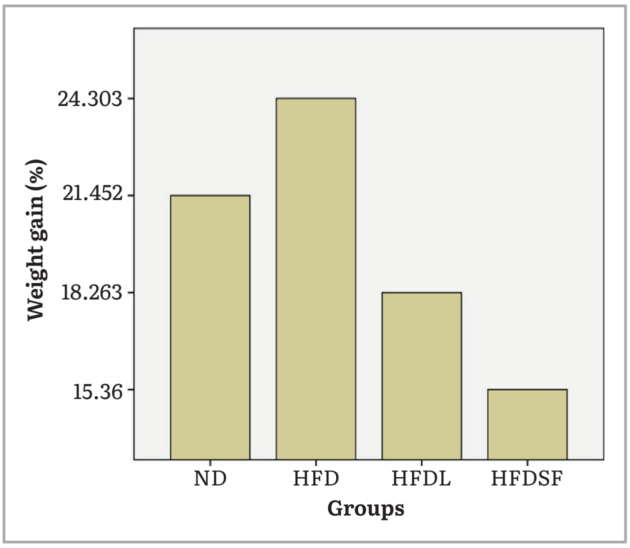

Figure 1: Weight gain over 6 weeks in the Normal Diet (ND), High Fat Diet (HFD) group, HFD + *L. pentosus* HBUAS53657 (HFDL), and HFD + fermented milk (HFDSF).

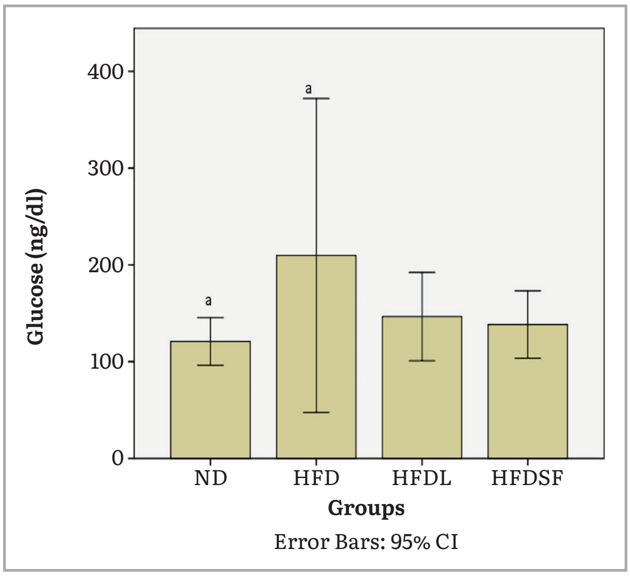

Figure 2: Comparison of blood glucose levels in the Normal Diet (ND), HFD, HFDL and HFDSF. Different letters indicate significant differences ($p<0.05$).

https://doi.org/10.46389/rjd-2023-1278

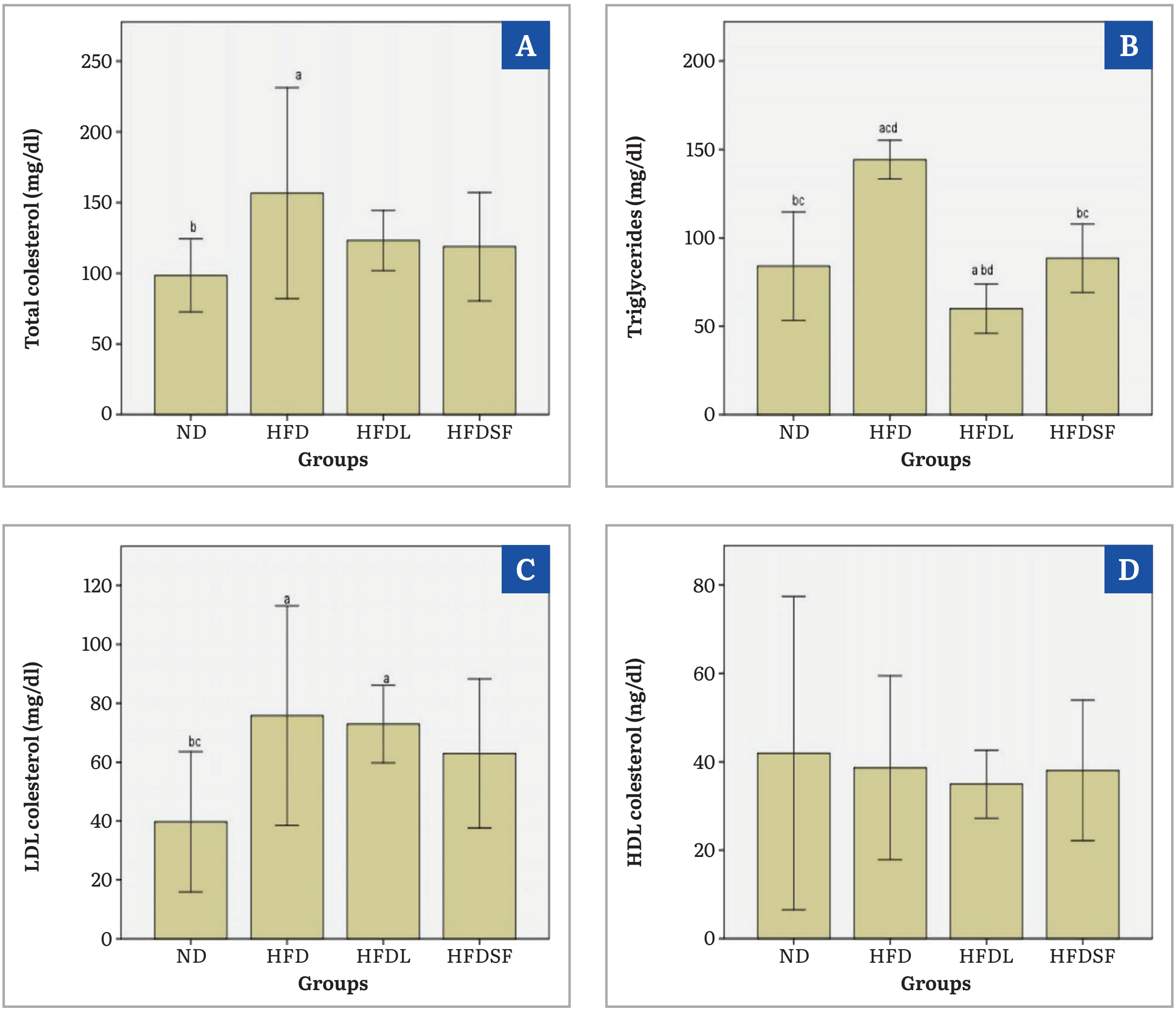

Figure 3: Comparison of lipid profiles in the Normal Diet (ND), HFD, HFDL and HFDSF. A – Rats' serum total cholesterol; B – Rats serum Trigliserida; C – Rats serum LDL colesterol; D – Rats serum HDL colesterol. Different letters indicate significant differences (p<0.05).

cholesterol, triglycerides, and LDL levels were significantly lower in the HFDSF and HFDL groups compared to the HFD (p<0.05, p<0.01, P0<01).

The inflammatory marker TNF alpha did not differ significantly between the HFD and normal groups, nor between the HFDSF and HFDL groups (P>0.05), as shown in Figure 4.

Discussion

The HFD group had significantly increased blood glucose compared to the control group (ND) (P<0.05), while administration of *L. pentosus* HBUAS53657 in HFDL and HFDSF significantly lowered blood glucose compared to the HFD group. This aligns with previous studies on the antidiabetic effect of *Lactobacillus* GG in rats [33]. Probiotic supplementation *Lb. Acidophilus* and *Lb. Casei* with buffalo fermented milk (Dahi) suppresses diabetes rats by inhibiting insulin receptor resistance, maintaining diabetic dyslipidemia, and inhibiting lipid peroxidation and nitrite formation [34]. Changes in blood glucose levels are also linked to glucose uptake and hyperphagia conditions in metabolic diseases. The SGLT1 transporter plays an important role in both physiological and diabetic intestinal glucose absorption. However, regulating glucose uptake and appetite may occur via distinct pathways [35]. Probiotic supplementation of the gut microbiota causes changes in metabolite release, energy metabolism, and appetite [36]. According to this study, *L. pentosus* HBUAS53657 functions as a beta cell antioxidant system that slows down insulin resistance and blood glucose levels, and it also affects appetite and energy metabolism.

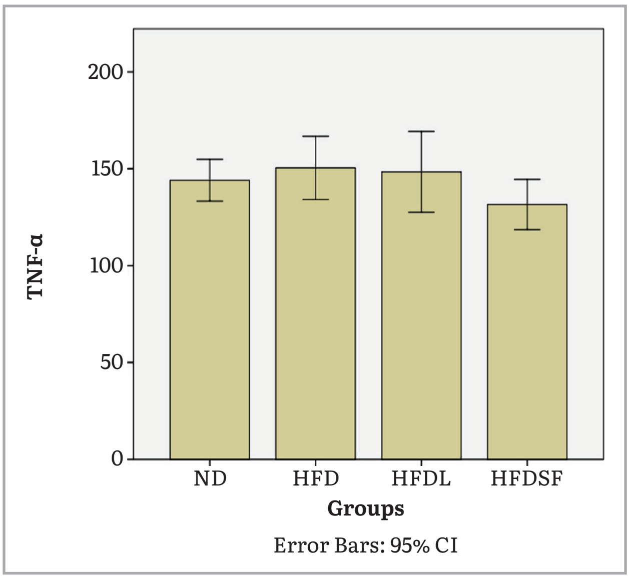

Figure 4: Comparison of inflammatory markers in the ND, HFD, HFDL and HFDSF.

This study also demonstrates the protective effect of L. *pentosus* HBUAS53657, which can improve lipid metabolism disorders in rats given HFD. The HDL was not significantly increased compared to the HFD group. The results follow the earlier studies [37–40], where many strains of *Lactobacillus* administration reduce serum TC, TG, and LDL-C levels in high-fat rats. This study differs from other studies that found that L. *Plantarum* significantly increased HDL in rats [41]. Previous research also discovered that L. *Plantarum S9* administration not only reduced body weight in HFD-treated rats but also decreased serum levels of TC, TG, and LDL-C while significantly increasing serum HDL-C levels [42].

It was observed that the HFDSF group reduced the level of serum TNF-α, followed by the HFDL group, compared with an elevated level of serum TNF-α of the HFD group. It can be concluded that L. *pentosus* strain HBUAS53657 can reduce the level of TNF pathway-associated protein expression in response to HFD. This indicates that the level of inflammatory response is high, whereas there was a decrease in TNF-α in the group that was treated with L. *pentosus* HBUAS53657, indicating that L. *pentosus* strain HBUAS53657 can suppress inflammatory expression by inducing HFD. This study in line with the oral administration of L. *Plantarum*-12, suppresses the proinflammatory factors, including IL-8, IL-1β, and TNF-α in azoxymethane-induced C57BL/6 mice [43, 44]. The anti-inflammatory mechanism of each probiotic strain undoubtedly varies. Previous research discovered that probiotics play a role in maintaining intestinal microbiota balance, restoring tight junction colonies, and regulating inflammatory factors. [44, 45]. Research on intestinal barrier enhancement during chronic inflammatory processes may be a key factor for probiotic therapy [46]. Lactic acid bacteria (LAB) such as Lactobacillus and *Bifidobacterium*, as well as their fermented products, have been shown in numerous studies to improve immunity, prevent the development of gastric mucosal lesions, reduce allergies, and protect against intestinal pathogenic infections. L. *pentosus* HBUAS53657 can reduce inflammation response in HFD-induced mice. L. *pentosus* HBUAS53657 reduces TNF secretion and thus prevents HFD-induced systemic inflammation

Conclusion

In rats given HFD, administration of L. *pentosus* strain HBUAS53657 fermented milk slowed weight gain. This demonstrates that L. *pentosus* strain HBUAS53657 can delay the fat accumulation process in rats given HFD. In the HFD group, administration of fermented milk L. *pentosus* strain HBUAS53657 caused a decrease in blood glucose, total cholesterol, triglycerides, and LDL. This demonstrates the protective effect of L. *pentosus* strain HBUAS53657 on lipid metabolism disorders in high-fat rats. L. *pentosus* strain HBUAS53657 fermented milk can be used as a protector against fat deposition, blood glucose, total cholesterol, triglycerides, and LDL in the HFD-induced group. More research is needed to determine the L. *pentosus* strain HBUAS53657 mechanism or pathway on fat metabolism.

Acknowledgments

We thank our colleague Prof. Drh. Endang Purwati MS, PhD who provided insight and expertise that greatly helped the research. We also thank Dr. Sri Melia STP, MP for assistance with product design.

Conflict of interest

The authors declare no conflict of interest.

Funding

This research was supported by the Nursing Faculty Andalas University's research implementation contract

https://doi.org/10.46389/rjd-2023-1278

for applied research, contract number 41/SPK/PNBP/FKep/Unand-2022.

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