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# Probiotic Fermented Milk *Lactiplantibacillus pentosus* Strain HBUAS53657 and Orange Juice Modulates Body Weight and Blood Glucose of Hyperglycemic Rats

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## ABSTRACT

Increased fasting blood glucose levels, resulting from alloxan-induced pancreatic β-cell damage can significantly alter body weight and increase oxidative stress. This study aimed to evaluate the effects of Probiotic Fermented Milk (PFM) *Lactiplantibacillus pentosus* strain HBUAS53657 and orange juice (OJ) on body weight (BW) and fasting blood glucose (FBG) levels in hyperglycemic rats. This experimental study used 25 male Wistar rats divided into five groups: negative control (K (-)), positive control (K (+)), PFM 1 x $10^8$ cfu/ml (P1), PFM 1 x $10^9$ cfu/ml (P2), and PFM 1 x $10^{10}$ cfu/ml (P3), each combined with 20% OJ for 28 days. Body weight (BW) and Fasting Blood Glucose (FBG) were measured before and after treatment. Data were analyzed using a paired t-test to compare pre- and post-treatment values of BW and FBG. The results showed PFM significantly reduced FBG in all treatment groups, with the lowest post-treatment mean observed in the P3 (105.6 ± 23.23 mg/dl, $p < 0.001$). BW also decreased significantly in P2 ($p = 0.013$) and P3 ($p = 0.018$). The most notable effects were found in P2, which exhibited a significant 17% reduction in BW and 74% decrease in FBG ($p < 0.001$). These findings suggest that probiotic fermented milk of *L. pentosus* HBUAS53657 and orange juice may promote metabolic health by modulating body weight and improving glycemic control in hyperglycemic rats.

***Keywords:*** blood glucose; body weight; hyperglycemia; *Lactiplantibacillus pentosus;* probiotic

## INTRODUCTION

Diabetes Mellitus (DM) is a chronic and complex metabolic disorder marked by sustained high blood glucose levels (hyperglycemia) resulting from a deficiency in insulin production, impaired insulin action, or both[1]. Insulin, a hormone produced by pancreatic β-cells, plays a critical role in facilitating glucose uptake by cells for energy production. When insulin is insufficient or ineffective, glucose accumulates in the bloodstream, disrupting overall glucose homeostasis and leading to widespread metabolic imbalances[2].

One of the systemic consequences of chronic hyperglycemia is involuntary

weight loss, which occurs as the body begins to break down fat and muscle tissue to compensate for its inability to access glucose[3]. This catabolic state is particularly pronounced in insulin-deficient conditions such as Type 1 Diabetes Mellitus (T1DM) where glucose is present in the blood but cannot be utilized effectively by the cells due to the absence of insulin[4]. Additionally, hyperglycemia contributes to increased urinary glucose excretion (glycosuria), leading to osmotic diuresis and further loss of calories and body mass.

The global burden of diabetes is increasing rapidly, posing a major challenge to public health system worldwide. According to The International Diabetes Federation (IDF), the global prevalence of diabetes among adults was estimated at 463 million in 2019 and is expected to rise to 578 million by 2030 and 783 million by 2045[5]. Among its subtypes, T1DM is characterized by an autoimmune attack on pancreatic β-cells, ultimately resulting in absolute insulin deficiency[6]. This destruction is often progressive and irreversible, leading to chronic hyperglycemia from a young age and requiring lifelong insulin therapy for glycemic control[7,8].

In animal studies, this condition is frequently modelled using alloxan, a β-cell-specific cytotoxin that induces T1DM-like hyperglycemia by generating reactive oxygen species (ROS) that selectively damage pancreatic islets[9]. Alloxan enters β-cells via the GLUT2 glucose transporter and undergoes redox cycling to produce superoxide radicals, hydrogen peroxide (H2O2), and hydroxyl radicals. This oxidative burst overwhelms the cells antioxidant defenses, leading to β-cell necrosis and subsequent insulin deficiency. As a result, animals develop persistent hyperglycemia that closely mimics human T1DM[10.]

Experimental studies have also demonstrated that hyperglycemia not only can disrupt metabolic homeostasis but also compromise antioxidant enzyme activities in vital organs, contributing to disease progression.[11,12]

In recent years, the use of probiotics has gained attention as a complementary approach for managing metabolic disorder[12,13]. Probiotic strains, particularly Lactic Acid Bacteria (LAB), are known for their ability to modulate gut microbiota, improve intestinal barrier's function and enhance metabolic profile[14,15]. Among these, *Lactiplantibacillus pentosus* has shown promising probiotic potential. Alzahra[16] successfully isolated *L. pentosus* HBUAS53657 from dadih, a traditional fermented milk product from Lintau, West Sumatera, and identified it as the dominant strain with notable probiotic properties.

Building on this, Susmiati[17] developed a probiotic fermented milk formulation by combining 20% orange juice and 6% of the probiotic L. pentosus HBUAS53657 starter culture[16]. The combination yielded optimal results, showing superior physical and chemical characteristics, high antioxidant capacity, substantial LAB counts, and favorable organoleptic properties. This formulation met the established standards for probiotic beverages, including minimum viable probiotic content of $10^6$-$10^7$ CFU/g[18]. The addition of orange juice not only contributed to the antioxidant capacity of the fermented milk but also improved flavor and enhances overall quality, making it a promising functional drink[19]. Previous studies have shown that oxidative stress in hyperglycemic rats lead to significantly reduce of superoxide dismutase (SOD) enzyme levels in serum, liver, testes, and heart[11]. Furthermore, administration of fermented milk has been associated with improved blood glucose levels in diabetic animal models[13].

Susmiati[20] revealed that 1 x $10^9$ cfu/ml probiotic *L. pentosus* HBUAS53657 ameliorated lipid metabolism disorders in rats fed a high-fat diet, suggesting a broader metabolic benefit. Despite these findings, limited studies have evaluated the dose-dependent effects of this probiotic strain combined with orange juice on

hyperglycemia-induced metabolic disturbances, particularly in relation to body weight and blood glucose regulation. Therefore, this study aimed to investigate the effects of probiotic fermented milk containing three different doses of *L. pentosus* HBUAS53657 combined with orange juice on body weight and fasting blood glucose levels in hyperglycemic rats.

## MATERIALS & METHODS

### *Bacterial strain.*

The strain *Lactiplantibacillus. pentosus* HBUAS53657 was originally isolated from dadih, a traditional fermented buffalo milk, obtained from local breeders in Tanjung Bonai, Lintau, West Sumatera. The isolate was deposited at the Animal Husbandry Product Technology Laboratory, Faculty of Animal Husbandry, Andalas University. Both the buffalo milk and citrus fruits used were sourced from the same district.

### *Probiotic Fermented Milk (PFM) Preparation.*

The starter culture was prepared using 24 ml of *L. pentosus* HBUAS53657, previously enriched in MRS Broth (Merck, Germany) for 24 h at 37°C. The bacterial culture then centrifuged at 14,000 rpm for 10 minutes at 4°C using a Microcentifuge 5417 R (Germany), resulting in pellet. Next, this pellet was inoculated with pasteurized milk and incubated at 37°C for 12 hours.

Probiotic Fermented Milk (PFM) was prepared by inoculating 1500 mL pasteurized fresh buffalo milk with *Lactiplantibacillus pentosus* strain HBUAS53657, at three different concentrations; P1: 1 x $10^8$ cfu/mL, P2: 1 x $10^9$ cfu/mL, P3: 1 x $10^{10}$ cfu/mL. Subsequently, 20% of orange juice was added into each formulation, followed by addition of fresh milk to complete the final volume. Fermentation was carried out at 37°C for 18 hours, and the fermented products were stored at 4°C for 24 hours prior to use.

### *Experimental animal design.*

The experimental animals used in this study were Wistar rats (*Rattus norvegicus*) obtained from the Laboratory of the Faculty of Pharmacy, Andalas University. The sample size was calculated based on the Federer formula $n \geq 5$; with minimum requirement of 25 rats. The animals were randomly divided into five groups (n=5 per group):

- K- (negative control): non-diabetic rats
- K+ (positive control): diabetic rats induced with alloxan (100 mg/kg body weight)
- P1: diabetic rats receiving PFM 1 x $10^8$ cfu/mL
- P2: diabetic rats receiving PFM 1 x $10^9$ cfu/mL
- P3: diabetic rats receiving PFM 1 x $10^{10}$ cfu/mL

Each rat in the treatment groups received 2,5 mL/day of PFM for 28 consecutive days, beginning on day 8 after alloxan induction. All animals (n = 25) remained healthy throughout the experimental period. First, to confirm successful induction of hyperglycemia, we did comparison of blood glucose levels between non-induced control (n = 5; negative control, K-) and the alloxan-induced group (n = 20; hyperglycemic group: K+, P1, P2, P3). Following this, the hyperglycemic rats were randomly assigned into four groups (n = 5 per group), one group was not subjected to PFM treatment (K+) and other three groups were subjected to different doses of PFM treatments for 28 days (P1, P2, P3).

### *Animal Care and Ethical Clearance.*

The Wistar rats were housed under standard laboratory conditions, maintained at 25±2°C with a 12-hour light/dark cycle. They were provided with standard feed and water *ad libitum* and acclimatized for 7 days before the experiment began. Body weight and food intake of the rats were monitored on a weekly basis throughout the study.

### *Body Weight and Fasting Blood Glucose Measurement*

Body weight of each rat was recorded weekly using a digital scale (±0.01 g accuracy) starting from day 1 of the experiment (baseline) until the end of the intervention (day 29). Changes in body weight were used as one of the indicators of metabolic alteration due to hyperglycemia and probiotic treatment. On day 29, rats fasted for 8 hours and blood samples from their tails were collected to measure fasting blood glucose using glucometer (*Accu-check, Roche).* After that, rats were euthanized via ether inhalation and blood samples were collected through the retroorbital sinus for further analysis.

### *Data analysis*

Statistical analysis was performed using SPSS Software. The Kolmogorov-Smirnov test was applied to assess data normality. Results were expressed as mean ± standard deviation (SD) for parametric data. Paired data will be analyzed using the *Paired t-test.* Results expressed as p ≤0.05 were considered statistically significant.

## RESULT

### Body Weight Changes

Body weight was measured at three time periods, as shown in Figure 1. In the negative control group (K-) body weight steadily increased throughout the study period. In contrast, there is a sharp decline of body weight in K+ following hyperglycemia induction, which continues to decrease until the end of the treatment period. In all treatment groups (P1, P2, and P3) body weight decreased after hyperglycemia induction (BW II) compared to initial body weight (BW I). After 28 days of treatment (BW III), group P1 and P2 showed either a slight decrease or stabilization in body weight. Notably, group P3 exhibited a slight increase in final body weight (BW III) compared to BW II in contrast to other treatment groups, suggesting a potential stabilizing effect.

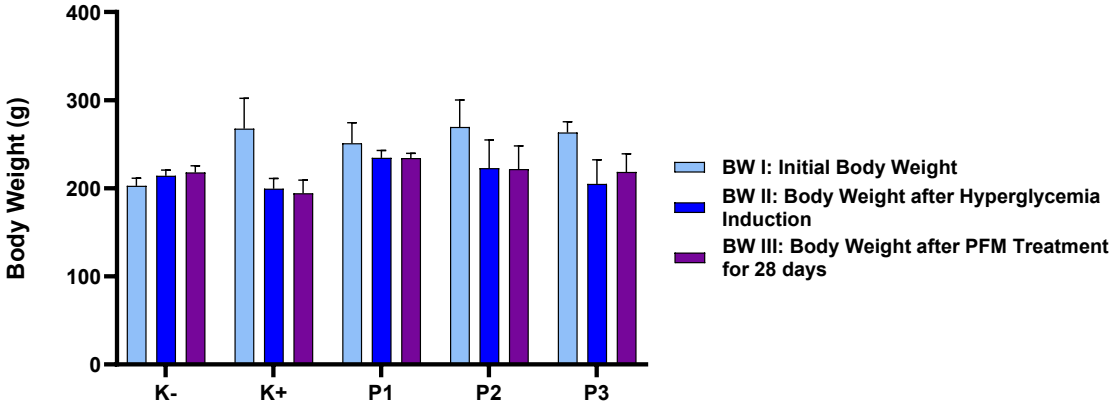


**Figure 1. Body Weight (g) changes in all treatment groups during treatment period. Data are presented as mean ± SD**
**(K-: Negative control group (normal rats), K+: Positive control group (hyperglycemic rats), P1: Hyperglycemic + PFM 1 x $10^8$ cfu/ml, P2: Hyperglycemic + PFM 1 x $10^9$ cfu/ml, P3: Hyperglycemic + PFM 1 x $10^{10}$ cfu/ml).**

The comparison between initial body weight (BW I) and final body weight after 28 days of treatment (BW III) was done to show the overall treatment effect on BW (Table 1). In the negative control group (K-) there is a significantly increase of BW indicating normal growth (7.42%, p<.001). However, a significant weight loss was seen on K+ group (–26.81%, p=0.004), consistent with the effects of untreated hyperglycemia. Among treatment groups, P2 (-17.31%, p=0.013) and P3 (-16.81%, p=0.018) also had significant weight reduction, while P1 showed smaller, non significant weight loss

**Table 1. Changes between Body Weight (g) before (BW I) and after PFM treatment (BW III) for 28 days in all treatment groups**

| Group | n | BW I (Mean ± SD) | BW III (Mean ± SD) | ΔBW (Mean ± SD) | % Change | p-value |
|---|---|---|---|---|---|---|
| K– | 5 | 202.80 ± 8.52 | 217.80 ± 7.69 | +15.00 ± 1.58 | 7.42% | <.001*** |
| K+ | 5 | 267.60 ± 34.59 | 194.2 ± 15.07 | –73.40 ± 27.94 | –26.81% | .004** |
| P1 | 5 | 251.00 ± 23.39 | 234.20 ± 5.35 | –16.80 ± 22.51 | –6.09% | .170 |
| P2 | 5 | 269.40 ± 30.93 | 221.80 ± 26.17 | –47.60 ± 24.96 | –17.31% | .013* |
| P3 | 5 | 263.40 ± 12.05 | 218.60 ± 20.59 | –44.80 ± 25.95 | –16.81% | .018* |

***ΔBW: the mean difference of body weight (BW III – BW I), % Change: the percentage change from BW I. Statistical analysis was performed using Paired t-test. Values are presented as mean ± SD. *p<0.05, **p<0.01, ***p<0.001***

## Fasting Blood Glucose Changes

Fasting Blood Glucose was measured at three time periods, as shown in Figure 2. There is a marked increase in FBG after hyperglycemia induction by alloxan (FBG II) in all groups compared to baseline (FBG I), confirming successful induction. The K- group remained normoglycemic across all time points, while K+ group maintained high glucose levels throughout the experiment. In contrast, groups P1, P2, and P3 demonstrated a significant reduction of FBG after 28 days of treatment (FBG III) with P2 and P3 showing the most notable decreases.

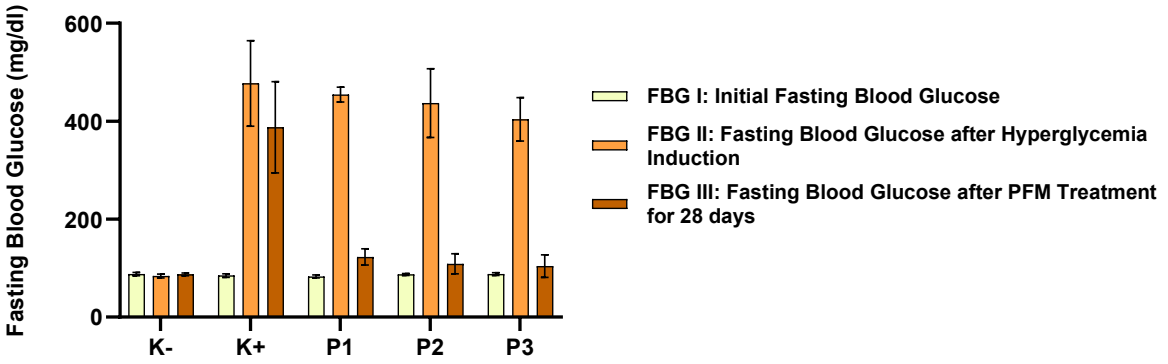


**Figure 2. Fasting Blood Glucose (mg/dl) changes in all treatment groups during treatment period. Data are presented as mean ± SD**
**(K-: Negative control group (normal rats), K+: Positive control group (hyperglycemic rats), P1: Hyperglycemic + PFM 1 x $10^8$ cfu/ml, P2: Hyperglycemic + PFM 1 x $10^9$ cfu/ml, P3: Hyperglycemic + PFM 1 x $10^{10}$ cfu/ml).**

Fasting Blood Glucose (FBG) levels after hyperglycemia induction (FBG II) and after 28 days treatment period (FBG III) is presented in Table 2. Following the 28 days of PFM treatment, FBG levels remained stable in the negative control group (K-), with no significant change, while K+ showed a 26% increase, reflecting uncontrolled hyperglycemia. In contrast, all groups treated with probiotic fermented milk (PFM) demonstrated a significant reduction in FBG levels. Notably, P1, P2, and P3 exhibited substantial decreases of –72.90%, –74.95%, and –73.89% respectively (all p<.001), highlighting the strong antihyperglycemic effect of the intervention.

**Table 2. Changes between Fasting Blood Glucose (mg/dl) after hyperglycemia induction (FBG II) and after PFM treatment period (FBG III) for 28 days in all treatment groups**

| Group | n | FBG II (Mean ± SD) | FBG III (Mean ± SD) | ΔFBG (Mean ± SD) | % Change | p-value |
|---|---|---|---|---|---|---|
| K– | 5 | 83.80 ± 3.83 | 85.00 ± 4.00 | +1.20 ± 4.32 | 1.53% | .569 |
| K+ | 5 | 387.60 ± 93.02 | 477.2 ± 87.36 | +89.60 ± 75.67 | 26.59% | .057 |
| P1 | 5 | 454.40 ± 15.22 | 122.80 ± 16.61 | –331.60 ± 26.97 | –72.90% | <.001*** |
| P2 | 5 | 437.00 ± 70.05 | 108.80 ± 20.53 | –328.20 ± 59.19 | –74.95% | <.001*** |
| P3 | 5 | 404.00 ± 44.35 | 105.60 ± 23.23 | –298.40 ± 37.83 | –73.89% | <.001*** |

***ΔFBG: the mean difference of fasting blood glucose (FBG III – FBG II), % Change: the percentage change from FBG II to FBG III. Statistical analysis was performed using Paired t-test. Values are presented as mean ± SD. ***p<0.001***

## DISCUSSION

In this study, the progression of hyperglycemia and the impact of treatment were assessed by observing changes in body weight (BW) and fasting blood glucose (FBG) levels over 28 days. Initial BW was recorded prior to alloxan induction, while baseline of FBG was measured after hyperglycemia was successfully induced. The negative control group (K-) which received neither alloxan nor PFM treatment, maintained stable BW (Fig 1) and normoglycemic conditions (Fig 2) throughout the study, serving as a healthy physiological reference[21]. In contrast, the untreated hyperglycemic group (K+) showed a marked decline in BW (Table 1; -26.81%, p = 0.004) and sustained hyperglycemia (Table 2; 26.59%, p = 0.057), highlighting the metabolic disturbances caused by alloxan administration.

Weight loss is a well-recognized clinical feature in individuals with type 1 diabetes, primarily due to the breakdown of adipose and muscle tissue, which are major contributors to overall body mass[22]. Consistent with this, previous studies on alloxan-induced diabetic rats have demonstrated that untreated diabetic animals experienced significant weight loss due to enhanced catabolic processes, including muscle and fat breakdown[23,24]. In the present study, BW reduction was also observed across all treatment groups receiving PFM containing *Lactiplantibacillus pentosus* HBUAS53657 and orange juice Group P1 showed a modest decrease of -6.09%, while groups P2 (Table 1; -17.31%, p = 0.013) and P3 (Table 1; -16.81%, p = 0.018) exhibited statistically significant reductions. However, the magnitude of weight loss in these treatment groups was notably less severe than that observed in the untreated hyperglycemia group (K+).

Following administration of alloxan at a dose of 100 mg/kg body weight, a marked increase in fasting blood glucose was observed in groups K+, P1, P2, and P3 (Table 2). This hyperglycemic response reflects alloxan-induced destruction of pancreatic beta cells, which impairs insulin secretion and disrupts glucose regulation[9,23,24]. Alloxan's similarity to glucose allows it to enter beta cells via GLUT2 transporters, where it promotes reactive oxygen species (ROS) and triggers oxidative damage[9]. This toxic effect involves redox cycling, excessive ROS production, and disruption of calcium homeostasis, ultimately leading to reduced insulin production[10,25]. Administration of PFM containing *Lactiplantibacillus pentosus* HBUAS53657 and orange juice reduced fasting blood glucose in groups P1, P2, and P3 (Fig. 2). The decreased in FBG between post-hyperglycemia induction and post-treatment of PFM was also statistically significant in all treatment groups (Table 2; all p = <0.001), highlighting the potent antihyperglycemic potential of PFM in alloxan induced rats.

The beneficial effects of PFM on modulating body weight and fasting blood glucose were because of the probiotic contained in PFM which is *Lactiplantibacillus pentosus* HBUAS53657.

Probiotics have been shown to regulate the intestinal microbiota and enhance the production of metabolites secreted by the microorganism, such as short-chain fatty acids (SCFA) as one of the most important microbiota-derived metabolites[22]. Short Chain Fatty Acids (SCFA) then activate GPR43 and GPR41 receptors on enteroendocrine L cells, stimulating the release of glucagon-like peptide-1 (GLP-1) and peptide YY (PYY)[26]. PYY inhibits intestinal mobility and increase the harvest of energy from the diet, while GLP-1 not only promotes insulin secretion but also slows gastric emptying and suppresses appetite, hence contribute to body weight regulation[27,28]. This mechanism may explain the improved body weight outcomes observed in PFM-treated groups, particularly P2 and P3, where probiotic supplementation appeared to mitigate the typical weight loss associated with hyperglycemia.

Similar findings were reported by Yadav[29] who observed significant reduction of body weight in streptozotocin (STZ)-induced diabetic rats and improved body weight in treated groups rats, suggesting that glycemic control may prevent muscle wasting. Another study using a combination of probiotics and vitamin C also demonstrated significant improvements in body weight and feed intake of diabetic rats, further supporting the role of probiotic in maintaining weight stability under hyperglycemic conditions[23].

The reduction in blood glucose levels observed in the PFM-treated groups may also be attributed to the effects of SCFAs. Beyond their role in regulating intestinal immunity, SCFA enhance insulin sensitivity, modulate glucose metabolism, and reduce systemic inflammation[30,31]. In particular, acetate and propionate, stimulate the secretion of GLP-1, which not only promotes insulin secretion, but also contributes to the differentiation of pancreatic progenitor cells into functional beta cells[32]. Probiotic also have the ability to inhibit α-glucosidase and α-amylase, key enzymes involved in carbohydrate digestion, thereby delaying glucose absorption and improving glycemic control[33,34]. As the *Lactiplantibacillus pentosus* HBUAS53657 is also characterized as lactic acid bacteria, it may also have the ability to produce EPS that exhibit antioxidant properties, which reduce oxidative stress in pancreatic β-cells therefore ameliorating β-cell dysfunction and preserving insulin capacity[35]. Similar findings have been reported in previous studies where probiotic administration lowered fasting blood glucose and improved insulin sensitivity[13,36,37], reinforcing the potential of this new strain as a functional dietary intervention for glycemic control.

The synergistic combination of fresh buffalo milk and orange juice further supports the fermentation process of the treatment product by promoting the growth and activity of the lactic acid bacteria, specifically the probiotic *Lactiplantibacillus pentosus* HBUAS53657, hence improving the antioxidant activity of the fermented milk product[16]. Siam orange juice is rich in phenolic compounds and flavonoids, which are known for their free radical-neutralizing properties. The hydroxyl groups present in these bioactive compounds can donate hydrogen atoms to stabilize ROS. These findings are consistent with the study by Multari[38], which demonstrated that combining orange juice and milk enhances both the antioxidant potential and the viability of lactic acid bacteria.

In line with these mechanisms, our findings demonstrated that FBG levels were significantly reduced in the PFM-treated groups, particularly P2 and P3 when comparing pre- and post-treatment values. This was attributed to the optimal concentration of 1 x $10^9$ cfu/ml of which aligns with FAO recommendations for active probiotic cultures and was found effective in similar studies[31,39,40]. These results underline the hypoglycemic and metabolic potential of the PFM containing *Lactiplantibacillus pentosus* HBUAS53657 and orange juice, suggesting its promise as a

functional dietary intervention in managing hyperglycemia and associated metabolic disturbances.

## CONCLUSION

Probiotic Fermented Milk (PFM) containing *Lactiplantibacillus pentosus* strain HBUAS53657 and orange juice significantly reduced fasting blood glucose, especially at doses 1 x $10^9$ cfu/ml (P2) and 1 x $10^{10}$ cfu/ml (P3), while also modulating body weight in hyperglycemic rats.

### *Declaration by Authors*

**Ethical Approval:** The research protocol was approved by the Ethics Committee of the Faculty of Medicine, Andalas University (Approval No. 89/UN.16.2/KEP-FK/2024).

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**Conflict of Interest:** No conflicts of interest declared.

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