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Effect of probiotic-fermented milk containing *Lactiplantibacillus pentoses* strain HBUAS 53657 on serum glutathione peroxidase activity and pancreatic histopathology in hyperglycemic rats

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ABSTRACT

Background: Hyperglycemia is characterized by elevated blood glucose levels caused by impaired insulin production or function, leading to oxidative stress. Probiotic-fermented milk containing *Lactiplantibacillus pentosus* strain HBUAS 53657 (PFM) has antioxidant and antimicrobial properties that may reduce oxidative stress.

Objective: This study aimed to investigate the effects of PFM *L. pentosus* strain HBUAS 53657 on serum glutathione peroxidase (GPx) activity and pancreatic histopathology in hyperglycemic rats.

Method: A post-test-only experimental design was conducted using 25 adult male Wistar rats divided into five groups (n = 5 per group): normal control (K–), hyperglycemic control (K+), and hyperglycemic rats treated with PFM at doses of 1×10^8 CFU/day (P1), 1×10^9 CFU/day (P2), and 1×10^{10} CFU/day (P3) for 28 days. Serum GPx activity was assessed via spectrophotometry, Langerhans islet area was measured using ImageJ, and islet damage was evaluated using the Ningrum Score. Statistical analysis was performed using One-Way ANOVA and Kruskal-Wallis tests.

Results: PFM administration at all doses significantly increased serum GPx activity ($p = 0.002$), with an optimal dose of 1×10^9 CFU/day. PFM also increased the Langerhans islet area ($p = 0.001$) and reduced islet damage scores ($p < 0.001$) in a dose-dependent manner.

Conclusion: Probiotic-fermented milk containing *Lactiplantibacillus pentosus* strain HBUAS 53657 increases serum GPx activity, expands Langerhans islet area, and reduces islet damage in hyperglycemic rats.

Keywords: antioxidant, glutathione peroxidase, hyperglycemia, pancreatic histopathology, probiotics

Introduction

Hyperglycemia is characterized by blood glucose levels that exceed normal thresholds, with fasting plasma glucose levels ≥ 126 mg/dL or random plasma glucose levels ≥ 200 mg/dL [1]. Glutathione peroxidase (GPx), an enzyme within the endogenous antioxidant defense system, plays a critical role in scavenging reactive oxygen species (ROS). Along with superoxide dismutase (SOD), catalase (CAT), and glutathione S-transferase (GST), GPx activity decreases in hyperglycemia, accompanied by a reduction in the catalysis of reduced glutathione (GSH) to oxidized glutathione (GSSH) [2].

In type 2 diabetes mellitus (T2DM), the pancreatic histopathology frequently reveals a decline in beta-cell numbers and structural alterations in these cells [3,4]. Dysfunction of pancreatic alpha cells has also been observed in individuals with diabetes [5]. Insufficient insulin levels result in the dysregulated hypersecretion of glucagon, which exacerbates hyperglycemia and amplifies insulin resistance [6].

Probiotics, as defined by the World Health Organization (WHO), are live microorganisms that confer health benefits to the host when administered in adequate amounts [7]. The hypoglycemic effects of probiotics are increasingly being explored in animal models and clinical trials, demonstrating potential benefits such as lowering blood glucose levels, improving insulin sensitivity, modulating gut microbiota, and alleviating diabetes-related symptoms [8].

Lactiplantibacillus pentosus strain HBUAS 53657, a dominant lactic acid bacterium isolated from *dadih*—a fermented milk product derived from buffalo milk in Lintau, Tanah Datar, West Sumatra—has been identified as a probiotic [9]. Research by Susmiati et al. (2023) demonstrated that fermented milk containing *L. pentosus* strain HBUAS 53657 exerted protective effects against lipid metabolism disorders, slowed weight gain and blood sugar increases, and reduced total cholesterol, triglycerides, and LDL levels in rats compared to untreated groups [10]. Moreover, increased GPx activity was observed in diabetic rats treated with probiotics such as *L. casei* compared to untreated diabetic rats [11].

Based on these findings, this study aims to evaluate the effects of probiotic-fermented milk (PFM) containing *L. pentosus* strain HBUAS 53657 on serum glutathione peroxidase activity and pancreatic histopathology in hyperglycemic rats.

Methods

Isolation of *Lactiplantibacillus pentosus* HBUAS 53657

L. pentosus HBUAS 53657 was isolated from *dadih*, a traditional fermented buffalo milk collected from local breeders in Tanjung Bonai Lintau Buo Utara, Tanah Datar Regency, Indonesia. The strain was deposited at the Animal Husbandry Product Technology Laboratory, Faculty of Animal Husbandry. Fermented milk products with orange supplementation were developed based on previous research by Azzahra (2021).

Animals and hyperglycemic rat model

This study was approved by the Ethics Committee of the Faculty of Medicine, Andalas University, Padang (approval No. 33/UN.16.2/KEP-FK/2024). Adult male Wistar rats were used and divided into five groups, with five rats per group. Rats that failed to achieve fasting blood sugar levels > 126 mg/dL following induction, died during the study or became sick were excluded. The rats were acclimatized to laboratory conditions for seven days before the experiment and housed under standard conditions: temperature of 25 ± 2°C, a 12-hour light/dark cycle, and ad libitum access to food and water.

Treatment groups

The rats were randomly divided into five groups as follows: (i) normal group: rats without alloxan induction no treatment, (ii) hyperglycemia group: rats with alloxan-induced hyperglycemia and no treatment, (iii) treatment group P1: rats with alloxan-induced hyperglycemia, treated with probiotic-fermented milk (PFM) at a dose of 1×10^8 CFU/2.5 mL/day, (iv) rats with alloxan-induced hyperglycemia, treated with probiotic-fermented milk (PFM) at a dose of 1×10^9 CFU/2.5 mL/day, (v) rats with alloxan-induced hyperglycemia, treated with probiotic-fermented milk (PFM) at a dose of 1×10^{10} CFU/2.5 mL/day. PFM was administered orally once daily for 28 days.

On the first day, rats in the hyperglycemia and treatment groups (P1, P2, P3) received a single dose of alloxan at 100 mg/kg body weight to induce hyperglycemia. Fasting blood glucose levels were measured 14 hours after fasting using blood samples obtained with a glucometer. On day 29, GPx levels and pancreatic histopathology were assessed.

Sample collection

Blood samples were collected from the retro-orbital sinus under anasthesia with chloroform. The pancreas was harvested post-mortem and fixed in formalin for histopathological analysis.

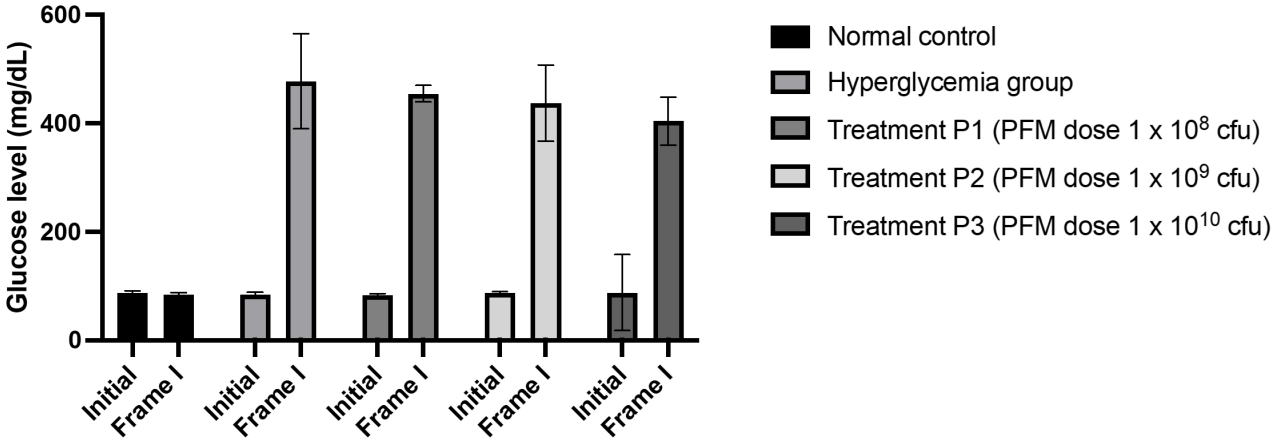

Figure 1. Average fasting blood glucose levels before and after alloxan administration

Glutathione peroxidase (GPx) activity assay

GPx activity was measured using a GSH-Px assay kit and spectrophotometry. Enzymatic and chromogenic reactions were used to quantify GPx activity. The assay involved the reaction of reduced glutathione (GSH) with hydrogen peroxide (H_2O_2) in the presence of GPx, with non-enzymatic reactions subtracted. GSH reacted with dinitrobenzoic acid to form a stable yellow 5-thio-dinitrobenzoic acid anion. Absorbance was measured at 412 nm to calculate GSH consumption.

Histopathological analysis of the pancreas

Pancreatic tissues were sectioned and stained with hematoxylin-eosin (H&E) for microscopic examination. Damage to the endocrine components of the islets of Langerhans was evaluated in five random fields of view using the Ningrum scoring system [12]. Cellular damage was graded on a scale of four levels. Microscopic analysis was performed at 40× and 100× magnifications.

Statistical analysis

Data were analyzed using statistical software and expressed as mean ± standard deviation. Normality tests were conducted to determine whether data were distributed normally. Parametric tests were applied to normally distributed data, while nonparametric tests were used for non-normal data. Post hoc analysis was performed to identify significant relationships between variables

Results

Blood glucose levels after alloxan induction

The fasting blood glucose levels before and after alloxan administration are summarized in Figure 1. Before alloxan administration, the average fasting blood glucose levels across all groups were within the normal range. Following alloxan administration, a significant increase in fasting blood glucose levels was observed in the hyperglycemia, P1, P2, and P3 groups, indicating successful induction of hyperglycemia.

Effect of probiotic-fermented milk (*L. pentosus* HBUAS 53657) on glutathione peroxidase activity

The effects of probiotic-fermented milk (PFM) on glutathione peroxidase (GPx) activity in hyperglycemic rats are shown in Figure 2. PFM administration significantly increased GPx activity in all treatment groups compared to the hyperglycemia group ($p = 0.002$, $p < 0.05$). The highest increase in GPx activity was observed in the P2 group (1×10^9 CFU/day).

Post-hoc Bonferroni analysis revealed a significant difference in GPx activity between the P2 group and the hyperglycemia group ($p = 0.0008$, $p < 0.05$). Additionally, significant differences were noted between treatment groups (P1, P2, and P3), with P2 identified as the optimal dose for enhancing GPx activity.

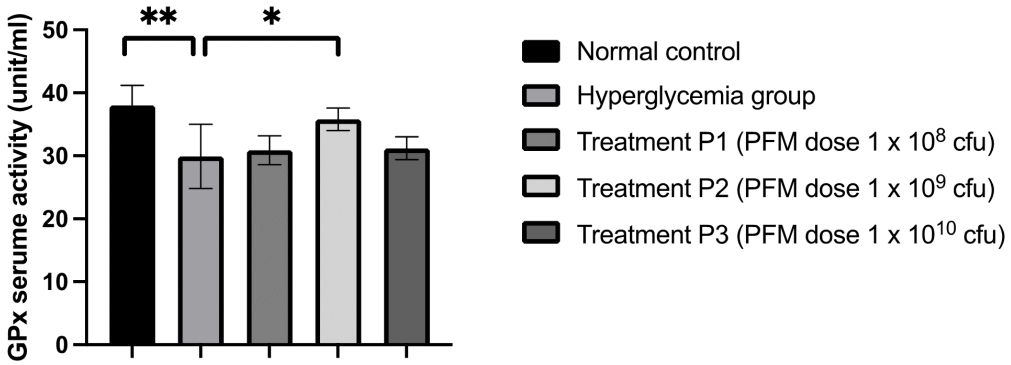

Figure 2. Effect of PFM (*L. pentosus* HBUAS 53657) on serum GPx activity in hyperglycemic rats ($p < 0.05$, One-Way ANOVA with Post Hoc Bonferroni test)

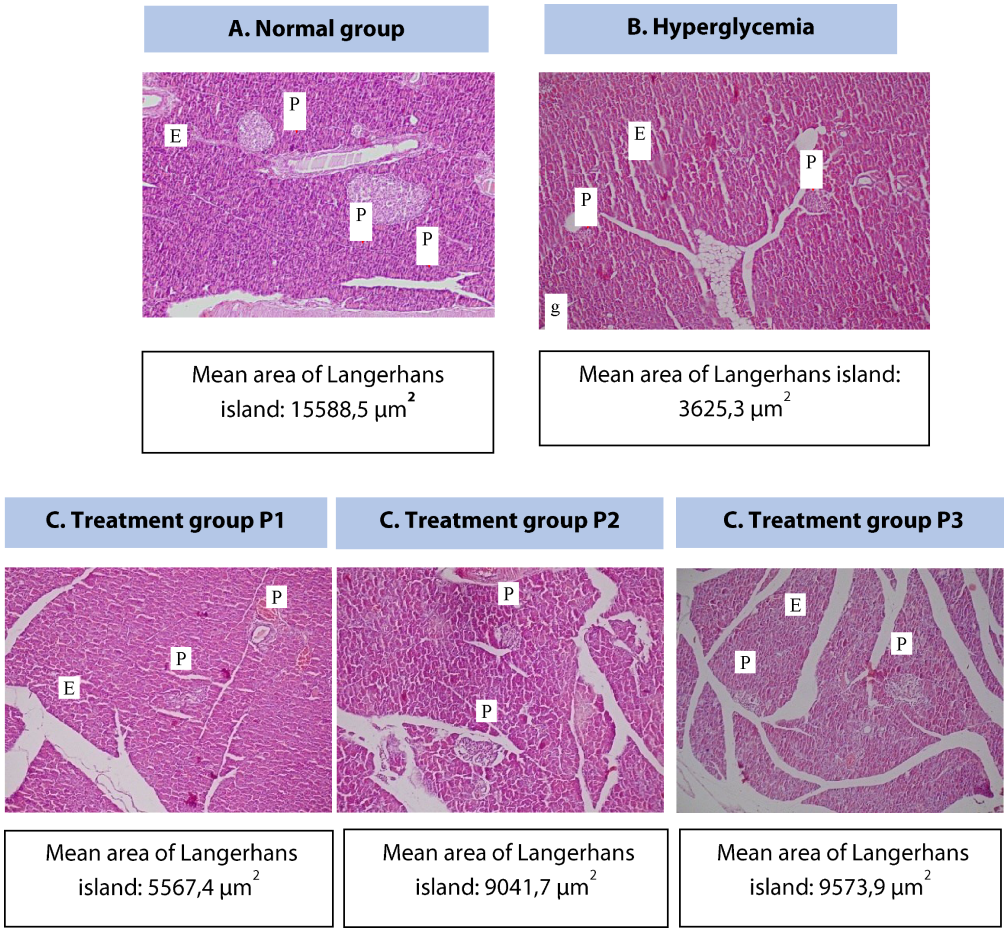

Figure 3. Pancreatic histological features, including Langerhans islets (P) and exocrine components (E). Hematoxylin-eosin staining, original magnification 10×. Scale bar: 200 µm, 100 µm, 50 µm

Histopathological examination of the pancreas

Microscopic analysis revealed differences in the histopathology of the pancreas among the groups (Figure 3). The hyperglycemia group exhibited marked atrophy and a reduction in Langerhans islet size. In contrast, administration of PFM improved the islet size, particularly in the P2 and P3 groups. The P3 group demonstrated the largest islet area, averaging 9573.9 µm^2.

Statistical analysis showed significant differences in the average islet area between the P2 and P3 groups and the hyperglycemia group ($p < 0.05$). Post-hoc Bonferroni analysis confirmed significant increases in islet size in the P2 group ($p = 0.007$)

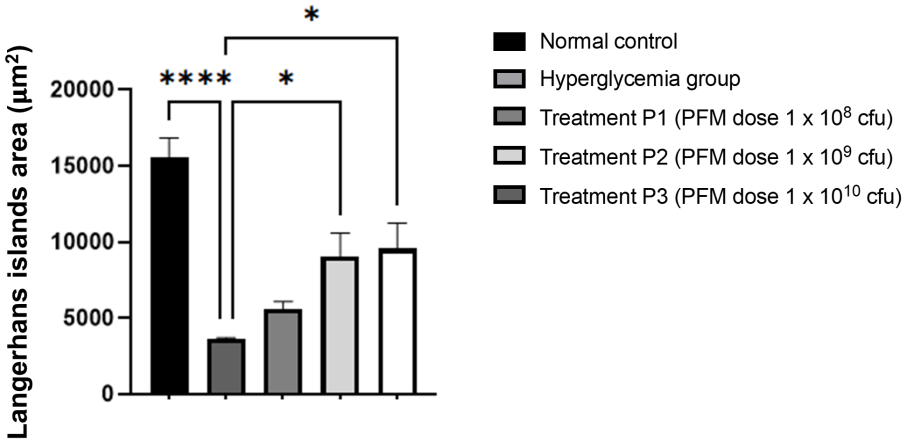

Figure 4. Langerhans islet area measurements (ImageJ application) ($p < 0.05$, Kruskal-Wallis with Post Hoc Bonferroni test)

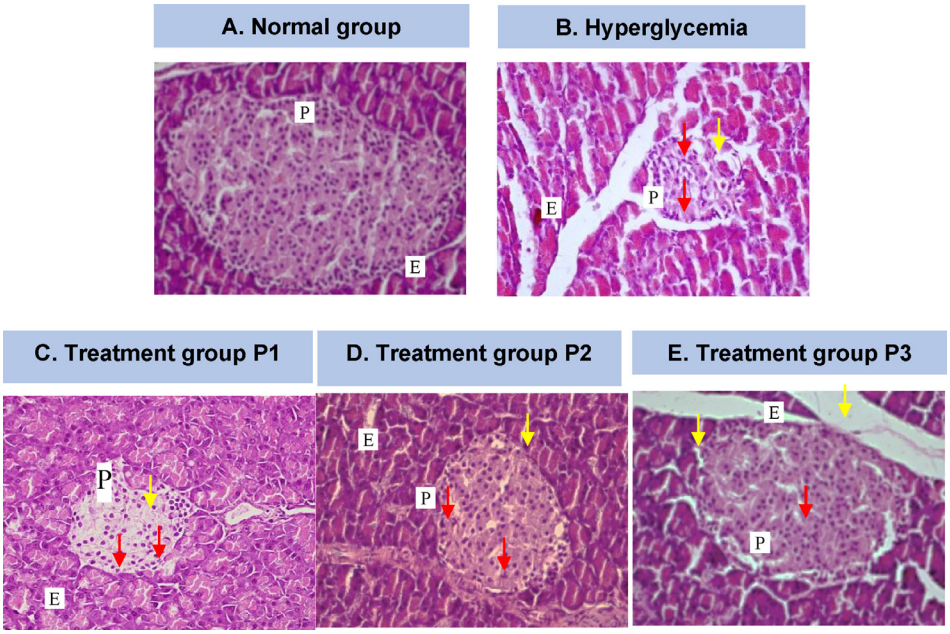

Figure 5. Histological features of Langerhans islets showing reduced damage with PFM treatment. Hyperglycemia group showed a decrease in the number of cells (atrophy), the boundaries of the islands were very unclear (↓), and the cells were necrotic almost completely (↓). Hematoxylin-eosin staining, original magnification 40×. Scale bar: 200 µm, 100 µm, 50 µm.

and the P3 group ($p = 0.008$) compared to the hyperglycemia group. However, no significant differences were found among the treatment groups (P1, P2, and P3) (Figure 4).

Histopathological assessment of Langerhans islet damage

Histopathological assessment (Figure 5) showed that the hyperglycemia group exhibited severe damage to the Langerhans islets, characterized by cell atrophy and poorly defined islet boundaries. Treatment with PFM reduced these damages, with P2 and P3 groups showing mild damage (average damage score = 2).

Kruskal-Wallis analysis revealed a significant reduction in Langerhans islet damage scores across all treatment groups compared to the hyperglycemia group ($p < 0.001$, $p < 0.05$). The lowest damage score was observed in the P3 group (1×10^{10} CFU/day). Post-hoc Bonferroni analysis confirmed significant differences in damage scores between the P2 group ($p = 0.026$) and the hyperglycemia group, as well as the P3 group ($p = 0.009$).

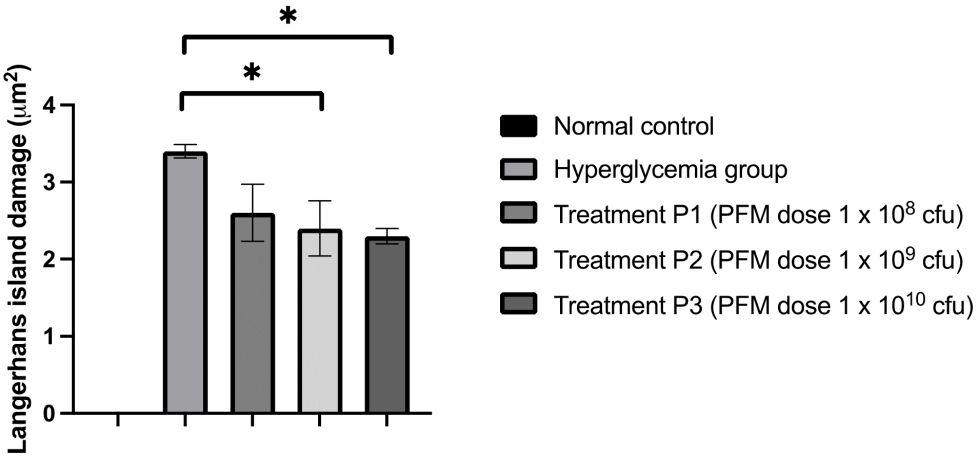

Figure 6. Damage scores of Langerhans islets (ImageJ application) ($p < 0.05$, Kruskal-Wallis with Post Hoc Bonferroni test)

Discussion

Hyperglycemic rats exhibited significantly reduced glutathione peroxidase (GPx) activity compared to the control group ($p = 0.002$). This reduction is attributed to alloxan-induced pancreatic beta-cell damage, which disrupts insulin production and leads to hyperglycemia. Hyperglycemia triggers the generation of reactive oxygen species (ROS), including superoxides and hydroxyl radicals, along with an increase in malondialdehyde (MDA), resulting in oxidative stress and decreased GPx activity. GPx is a critical antioxidant enzyme that maintains cellular redox balance by detoxifying free radicals and peroxides. It utilizes reduced glutathione (GSH) to neutralize these toxic species, with oxidized glutathione disulfide (GSSG) formed as a byproduct [13–15].

In this study, the administration of *Lactiplantibacillus pentosus* strain HBUAS 53657 in fermented milk (PFM) increased GPx activity, particularly in treatment groups P2 (1×10^9 CFU/day) and P3 (1×10^{10} CFU/day). The antioxidant effect of PFM is linked to the production of exopolysaccharides by probiotics, which bind to hydroxyl radicals and peroxides, reducing free radical levels [16]. Additionally, probiotics enhance glutathione production by promoting short-chain fatty acid (SCFA) synthesis, particularly butyrate, which stimulates GSH biosynthesis. Maintaining intracellular GSH levels is essential for protecting GPx-1 activity from peroxide-mediated inhibition, as demonstrated in previous studies [13–15].

Meta-analyses, such as the study by Roshan et al. (2019), have shown that probiotics significantly increase serum GSH levels in diabetic patients [17]. Similarly, Zheng et al. (2019) reported that probiotics and synbiotics improve antioxidant indicators such as total antioxidant capacity and GSH while reducing MDA levels in diabetes mellitus patients [18]. Studies on animal models, including Zhao et al. (2017), found that probiotics enhance oxidative stress biomarkers like superoxide dismutase (SOD), GPx, and GSH while lowering MDA levels [19]. Probiotic strains such as *Lactobacillus paracasei* have been specifically noted to increase CAT, GPx, and SOD activity while reducing MDA to near-normal levels [20]. Fermented milk is an effective carrier for delivering probiotics to improve antioxidant status [21].

This study also observed the beneficial effects of PFM *L. pentosus* strain HBUAS 53657 on pancreatic histopathology in hyperglycemic rats, particularly in preserving the area and reducing damage to the islets of Langerhans. Morphological changes in the pancreas, such as reduced islet size, beta-cell damage, and cell death, were prominent in the positive control group due to alloxan-induced oxidative stress. Alloxan selectively damages pancreatic beta cells by mimicking glucose and binding to insulin receptors [22].

PFM administration mitigated these effects, with treatment groups 2 and 3 exhibiting a marked reduction in Langerhans islet damage. A dose-dependent protective effect was observed, with

the highest dose (1×10^{10} CFU/day) resulting in minimal damage. This aligns with previous research indicating that probiotic-fermented milk exerts antioxidant effects via bioactive peptides produced during fermentation, influenced by milk nutrients and *Lactobacillus* strains [23].

The addition of Siamese orange juice to fermented buffalo milk in this study likely enhanced its antioxidant quality, as oranges are rich in flavonoids, tannins, phenols, terpenoids, vitamin C, and steroids [24]. Probiotics also possess antidiabetic properties by regulating gut hormones such as GLP-1, which stimulates pancreatic beta-cell proliferation, prevents apoptosis, and improves insulin synthesis. Several *Lactobacillus* species (*L. paracasei, L. casei, L. plantarum, L. rhamnosus*, and *L. brevis*) have demonstrated protective effects on islet cells, promoting islet regeneration, improving cellular morphology, and reducing damage [25–29].

Interestingly, the study found that the highest probiotic dose (1×10^{10} CFU/day) did not yield better results than the intermediate dose (1×10^{9} CFU/day) for GPx activity or pancreatic histopathology. This may be due to the existence of an optimal probiotic dose. According to the International Scientific Association for Probiotics and Prebiotics (2014), the functional dose of probiotics for food or supplements is typically 1×10^{9} CFU/day. Higher doses may lead to hyperstimulation of the immune system or dysbiosis, depending on the type and duration of administration [30].

Conclusion

This study concludes that probiotic-fermented milk containing *Lactiplantibacillus pentosus* strain HBUAS 53657 effectively enhances serum glutathione peroxidase (GPx) activity in hyperglycemic rats. Additionally, the probiotic demonstrated a significant protective effect on pancreatic histopathology, improving the islets of Langerhans and reducing cellular damage.

Further research is recommended to explore the effects of *L. pentosus* strain HBUAS 53657 on other antioxidant enzymes, such as catalase, and to employ advanced immunohistochemical techniques for a more detailed evaluation of pancreatic histopathology. Investigation of the histopathological effects on liver tissue is also suggested to provide a more comprehensive understanding of the systemic benefits of this probiotic.

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Author contributions

YR: original draft preparation, resource acquisition, visualization, and manuscript writing. YE and YN: supervision and manuscript review. CI: final manuscript preparation and editing.

Declaration of interest

The authors declare no conflicts of interest with any private, public, or academic entities related to the content of this manuscript.

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