Research Article

Antidiabetic Potential of Goat's Milk Kefir from Different Regions of Indonesia: Biochemical and Histopathological Evidence in Streptozotocin-Induced Wistar Rats

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Abstract | This study aimed to evaluate the effectiveness of goat's milk kefir as a functional antidiabetic food through an in vivo experiment using male Wistar rats (*Rattus norvegicus*). A completely randomized design with nine treatment groups and ten replications was used. Treatments included normal healthy rats (T1), untreated diabetic rats (T2), diabetic rats treated with glibenclamide (T3), and diabetic rats administered kefir from different regions of Indonesia: West Java (T4), Kalimantan (T5), Central Java (T6), East Java (T7), North Sumatra (T8), and West Sumatra (T9). Kefir was given orally at a dose of 2 mL per rat per day for 36 days. The results showed a significant reduction (p<0.05) in fasting blood glucose levels in kefir-treated groups compared to untreated diabetic rats. Body weight decreased in all groups except normal controls, while pancreatic weight was lowest in untreated diabetic rats and highest in normal rats, with no significant differences among kefir-treated groups. Histopathological analysis revealed that the number of Langerhans islets in T4 and T6 was comparable to that of normal rats, and the islet area did not differ significantly across kefir treatments. The lowest pancreatic islet cell damage was observed in T4. On day 36, T4 exhibited an average fasting blood glucose level of 97.00±28.54 mg/dL, body weight of 202.40±25.73 g, pancreatic weight of 0.686±0.98 g, and a Langerhans islet area of 13,198.74 μm^2. In conclusion, kefir from West Java (T4) showed the most significant potential as a functional food for diabetes management.

Keywords | Antidiabetic, Blood glucose, Histopathology, Kefir, Pancreas, Wistar rats

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INTRODUCTION

Diabetes mellitus is recognized as one of the most significant global health challenges, with its prevalence steadily increasing each year, including in Indonesia. This metabolic disorder is characterized by impaired glucose metabolism resulting from insulin deficiency or resistance, which can lead to serious complications affecting multiple organ systems (Seo *et al.*, 2022). The management of diabetes extends beyond pharmacological interventions and increasingly incorporates functional food-based strategies, which are considered safer and associated with minimal side effects. Among the various functional foods currently under investigation, kefir a fermented milk

product containing diverse probiotic microorganisms and bioactive compounds has attracted considerable scientific interest. Recent studies suggest that kefir may exert beneficial effects on glycemic control and metabolic health, positioning it as a promising candidate for complementary diabetes management (Azizi *et al*., 2021).

Kefir, an acidic probiotic fermented beverage originating from the Caucasus, Eastern Europe, and the Balkans, consists predominantly of an exopolysaccharide matrix hosting a symbiotic community of lactic acid bacteria, acetic acid bacteria, and yeasts (Garofalo *et al*., 2020). Kefir is produced through the fermentation of milk using kefir grains, which are complex symbiotic consortia of microorganisms. The primary microbial groups present in kefir grains include lactic acid bacteria such as *Lactobacillus kefiri*, *L. kefiranofaciens*, *L. plantarum*, *L. casei*, *L. brevis*, *Lactococcus lactis*, *Leuconostoc mesenteroides*, and *Streptococcus thermophilus* as well as acetic acid bacteria like *Acetobacter aceti* and *Acetobacter pasteurianus*, and non-pathogenic yeasts including *Saccharomyces cerevisiae*, *Kluyveromyces marxianus*, *Candida kefyr*, and *Kazachstania unispora* (Alraddadi *et al*., 2022). The metabolic activity of these microorganisms results in the production of lactic acid, which lowers the pH, preserves the milk, and imparts a characteristic sour taste. Ethanol and carbon dioxide are also generated, contributing to the refreshing and slightly effervescent quality of kefir, while acetic acid provides a sharp aroma and exhibits antimicrobial properties. Additionally, kefir contains kefiran, a polysaccharide produced by *Lactobacillus kefiranofaciens*, which functions as a probiotic and prebiotic, and enhances the viscosity of the beverage. Kefir is also rich in vitamins and bioactive compounds, including B vitamins (such as B1 and B12), folate, bioactive peptides, and components with antioxidant and immunomodulatory activities (Sankhla *et al*., 2022).

The microbial composition of kefir grains is strongly influenced by their geographical origin, resulting in kefir from different regions exhibiting distinct characteristics and bioactive potential. Studies have demonstrated that the diversity of bacteria and yeasts within kefir grains can vary significantly depending on the local environment, which in turn affects the functional properties of the resulting kefir. This microbial diversity is crucial, as it contributes to the production of various bioactive compounds with potential health benefits (Azizi *et al*., 2021). Several investigations have reported that kefir consumption can lower blood glucose levels, improve lipid profiles, and provide protective effects on pancreatic beta cells through antioxidant and anti-inflammatory mechanisms (Abdul Hakim *et al*., 2023). These effects are believed to be mediated by the synergistic action of probiotic microorganisms and their metabolites, which help reduce oxidative stress and inflammation associated with diabetes. Additionally, kefir has been shown to enhance insulin sensitivity and restore gut microbiota balance, both of which play crucial roles in regulating glucose metabolism. The ability of kefir to modulate the gut microbiome is particularly significant, as a healthy gut microbiota is increasingly recognized as a key factor in maintaining metabolic health and preventing chronic diseases, such as diabetes (Seo *et al*., 2022).

Although the antidiabetic properties of kefir have been extensively documented, comparative studies on kefir derived from diverse local sources in Indonesia remain limited. Given Indonesia's vast biodiversity and the regional variation in kefir grain microbiota across areas such as West Sumatra, West Java, North Sumatra, Kalimantan, Central Java, and East Java, the resulting kefir products may exhibit distinct biological activities. This study investigates the antidiabetic efficacy of kefir produced from grains collected from six Indonesian regions using male Wistar rats (*Rattus norvegicus*) as an experimental model. Parameters evaluated include random and fasting blood glucose levels, body and pancreatic weights, Langerhans islet morphology, and pancreatic histopathology. The findings aim to elucidate the potential of regionally sourced kefir in reducing blood glucose and mitigating pancreatic damage, providing a scientific basis for developing antidiabetic functional foods rooted in Indonesia's local resources.

MATERIALS AND METHODS

Preparation of kefir

The kefir production procedure, using a kefir grain starter modified from Ferawati *et al*. (2024), was performed as follows: goat milk was pasteurized at 65°C for 30 minutes and subsequently cooled to 40°C. The milk was then dispensed into glass jars and inoculated with 10% (w/v) kefir grain starter, as per the experimental design, followed by homogenization. Incubation was carried out for 24 hours at 37 °C under anaerobic conditions. After fermentation, the kefir was separated from the grains and homogenized. Maturation was continued for 12 hours at refrigeration temperature. The kefir was then ready for use.

Experimental animals and design

Ninety healthy male Wistar rats (250–300 g, 10 weeks old) were obtained from UD. Wistar Experimental Animal Farm, Muaropalam (Padang, Indonesia). Prior to the experiment, the animals were acclimatized for one week under standard laboratory conditions. The rats were housed individually in stainless-steel cages under controlled environmental conditions (temperature, 22±2 °C; relative humidity, 60 ± 5%; and a 12/12 h light–dark cycle), with free access to standard feed (Ratbio) and water.

The rats were randomly divided into nine groups (n = 10 per group) as follows:
(1) normal control (non-diabetic, untreated);
(2) diabetic control;
(3) diabetic + glibenclamide (10 mg/kg BW/day);
(4) diabetic + kefir from West Java;
(5) diabetic + kefir from Kalimantan;
(6) diabetic + kefir from Central Java;
(7) diabetic + kefir from East Java;
(8) diabetic + kefir from North Sumatra; and
(9) diabetic + kefir from West Sumatra.

Induction of diabetes

Experimental diabetes was induced by a single intraperitoneal injection of streptozotocin (STZ; 40 mg/kg BW) freshly dissolved in cold 0.1 M citrate buffer (pH 4.5). Following STZ administration, the rats were provided with 5% glucose solution for 24 hours to prevent initial hypoglycemia. Blood glucose levels were measured 72 hours post-STZ injection, and rats with fasting blood glucose levels ≥ 126 mg/dL were considered diabetic and included in the study (Pazra *et al*., 2023).

Kefir samples were orally administered at a dose of 2 mL per rat per day (Nurliyani *et al*., 2015). Body weight and blood glucose levels (Random Blood Glucose) were measured every three days in the morning until day 36 of the experimental period. If the random blood glucose (RBG) level of the experimental rats was ≥ 250 mg/dL, the animals were classified as diabetic (positive for diabetes mellitus) (Ghasemi and Jeddi, 2023).

Blood glucose measurement and pancreatic histopathological examination

Blood samples were collected from the tail vein by cutting the distal tip of the tail. Blood glucose concentration was determined immediately using a portable glucometer (Accu-Chek®, Roche Diagnostics, Germany). On day 36, fasting blood glucose levels were determined. Fasting was induced by withholding food while allowing free access to water (*ad libitum*). After the fasting period, blood glucose concentration was measured using a glucometer (Mutalub *et al*., 2025). Subsequently, surgical procedures were performed to collect pancreatic tissues for histopathological examination.

The excised pancreatic tissues were carefully rinsed with physiological saline to remove. The samples were then fixed in 10% neutral-buffered formalin, dehydrated through a graded series of ethanol, cleared in xylene, and embedded in paraffin wax. Sections of approximately 5 µm thickness were prepared using a rotary microtome and stained with hematoxylin and eosin (H and E). Histological evaluation was conducted under a light microscope to assess the number of Langerhans islet fields, the degree of cellular damage, and the area of the islets. Morphometric measurements were performed using ImageJ software (NIH, USA). The histopathological changes were compared among the experimental groups to evaluate the effect of kefir administration on pancreatic tissue structure and integrity (Akwu *et al*., 2024). Cellular damage was assessed semi-quantitatively using a four-point scoring system as follows: Score 0: normal histological architecture, with no evidence of cellular damage or abnormalities, or involvement of < 25% of cells; Score 1: mild cellular damage, involving > 25% to < 50% of cells; Score 2: moderate cellular damage, involving > 50% to < 75% of cells; Score 3: severe cellular damage, involving > 75% of cells (El-Esawy *et al*., 2016).

This study was conducted by following the National Research Council: Guide for the Care and Use of Laboratory Animals (National Research Council, 2011). All experimental procedures were conducted in compliance with the ethical standards approved by the Ethics Committee of the Faculty of Pharmacy, Andalas University (Ethical Code: 21/UN16.10.D.KEPK-FF/2025).

Statistical analysis

One-way analysis of variance (ANOVA) was used to evaluate the study's data, and the Duncan multiple range grouping test was used to compare the means of the study's various groups. Means and standard errors of the data were shown. At $p < 0.05$, differences were determined to be significant.

RESULTS AND DISCUSSION

Body weight measurement

Body weight measurements of the experimental rats showed a progressive increase in the diabetic groups receiving kefir treatment. In contrast, the untreated diabetic group exhibited a gradual decrease at each three-day measurement interval. A significant difference in body weight was observed between the kefir-treated diabetic groups (T4, T5, T6, T7, T8, and T9) and the normal control (T1), the untreated diabetic group (T2), and the diabetic group treated with the commercial drug glibenclamide (T3), particularly on day 36 after treatment. However, no significant differences were detected among the kefir-treated groups receiving kefir produced from different grain sources. The detailed results of body weight measurements in the experimental rats are presented in Table 1.

The increase in body weight observed in diabetic rats treated with kefir indicates a potential improvement in metabolic function and glucose utilization. Under diabetic conditions, chronic hyperglycemia and insulin deficiency often lead to enhanced proteolysis and lipolysis, resulting in

Table 1: Changes in body weight (g) of experimental rats following treatment (mean ± S.D., n = 10).

Body weight (g)	Rat groups								
	T1	T2	T3	T4	T5	T6	T7	T8	T9
Before Acclimatization	192.60±5.12^{a}	177.80±13.95^{a}	183.60±11.86^{a}	187.20±19.17^{a}	178.60±12.99^{a}	182.60±11.84^{a}	184.40±11.43^{a}	205.20±16.91^{a}	189.60±4.39^{a}
After acclimatization	206.00±9.41^{a}	201.00±17.03^{a}	199.60±15.16^{a}	204.40±15.68^{a}	201.60±14.99^{a}	204.80±14.68^{a}	209.00±5.15^{a}	222.80±27.16^{a}	206.40±6.31^{a}
Day-0	215.00±14.42^{b}	178.20±18.59^{a}	180.00±23.99^{a}	185.60±20.02^{a}	174.80±21.68^{a}	178.60±17.16^{a}	179.20±14.31^{a}	198.20±18.05^{ab}	186.60±8.68^{a}
Day-3	225.40±14.84^{d}	163.80±21.69^{a}	170.80±4.09^{ab}	178.80±16.24^{abc}	180.40±9.24^{abc}	180.00±13.98^{abc}	178.40±14.77^{abc}	194.00±12.88^{c}	184.00±7.75^{bc}
Day-6	224.40±14.81^{c}	168.80±20.17^{a}	174.40±8.08^{a}	174.60±16.62^{a}	186.60±4.34^{ab}	185.40±16.95^{ab}	180.60±13.63^{ab}	200.20±15.17^{b}	186.40±9.07^{ab}
Day-9	229.80±15.67^{c}	170.60±16.56^{a}	177.00±7.31^{a}	187.60±21.75^{ab}	189.80±15.45^{ab}	185.20±15.83^{ab}	188.00±12.04^{ab}	200.20±13.63^{b}	182.20±9.44^{ab}
Day 12	236.20±18.21^{c}	163.20±21.39^{a}	183.40±11.59^{b}	190.60±22.50^{b}	191.60±7.60^{b}	191.00±9.69^{b}	195.00±15.46^{b}	200.20±18.09^{b}	187.20±5.85^{b}
Day 15	236.00±18.68^{c}	164.20±20.12^{a}	184.20±11.58^{ab}	198.00±29.28^{b}	199.20±8.67^{b}	187.00±10.56^{ab}	195.20±15.59^{b}	203.40±21.17^{b}	185.80±9.47^{ab}
Day 18	240.20±20.33^{d}	165.40±20.65^{a}	181.00±9.77^{ab}	208.40±27.21^{c}	201.40±11.69^{bc}	189.40±11.55^{bc}	197.80±15.27^{bc}	204.40±15.77^{bc}	186.20±12.29^{abc}
Day 21	238.80±16.72^{c}	158.40±25.76^{a}	180.60±11.72^{b}	204.60±24.13^{b}	202.00±9.67^{b}	187.00±11.87^{b}	199.40±17.97^{b}	203.40±16.10^{b}	186.40±13.24^{b}
Day 24	243.80±19.51^{c}	164.00±26.28^{a}	181.20±11.73^{ab}	205.60±27.04^{b}	198.60±14.36^{b}	193.20±11.90^{b}	202.20±21.78^{b}	201.40±18.73^{b}	180.60±9.24^{ab}
Day 27	246.40±21.03^{c}	164.20±28.25^{a}	181.60±14.64^{ab}	202.40±26.91^{b}	203.40±8.99^{b}	199.60±19.67^{b}	200.40±19.37^{b}	205.00±18.15^{b}	184.00±7.31^{ab}
Day 30	247.80±21.79^{d}	165.20±30.56^{a}	177.00±12.85^{ab}	203.20±26.38^{bc}	205.80±10.28^{bc}	202.80±23.86^{bc}	204.60±18.98^{bc}	207.20±16.63^{c}	187.40±6.23^{abc}
Day 33	249.00±23.49^{c}	163.80±29.66^{a}	173.20±12.97^{a}	212.60±24.89^{b}	205.00±10.42^{b}	207.00±21.21^{b}	206.80±19.75^{b}	208.60±15.73^{b}	190.00±4.30^{ab}
*FBW Day 36	233.60±22.0^{e}	147.60±21.67^{a}	161.60±16.13^{ab}	202.40±25.73^{d}	189.60±17.43^{cd}	192.60±18.37^{cd}	193.80±21.60^{cd}	194.40±13.13^{cd}	174.00±4.06^{bc}

Note: ^{a,b,c,d,e}Means with different superscript letters within a row indicate a significant difference ($p < 0.05$). Negative control (T1), positive diabetic control (T2), glibenclamide treatment (T3), and kefir treatments (T4–T9). *Fasting Body Weight (FBW).

Table 2: Random and fasting blood glucose levels (mg/dL) of experimental rats before and during treatment (mean ± S.D., n= 10).

Blood glucose level on day (mg/dL)	Rat groups								
	T1	T2	T3	T4	T5	T6	T7	T8	T9
End of acclimatization period	93.60±7.41^{a}	104.40±6.96^{a}	111.00±7.38^{a}	109.00±3.11^{a}	104.20±3.34^{a}	101.80±1.23^{a}	106.40±3.56^{a}	105.20±8.92^{a}	107.80±3.56^{a}
RBG Day-0	91.00±11.49^{a}	459.40±11.88^{b}	449.80±12.54^{b}	407.40±10.65^{b}	409.20±11.23^{b}	409.40±12.44^{b}	392.60±17.83^{b}	400.60±18.24^{b}	370.20±16.12^{b}
RBG Day-3	103.60±8.90^{a}	616.20±11.20^{e}	481.60±18.29^{d}	252.00±12.71^{b}	431.80±20.34^{d}	392.20±15.21^{cd}	278.00±14.66^{bc}	341.40±11.90^{bcd}	463.00±21.67^{d}
RBG Day-6	97.80±8.49^{a}	466.00±28.45^{d}	361.20±19.33^{cd}	176.40±12.54^{ab}	310.20±17.47^{bc}	440.40±18.57^{cd}	296.00±15.65^{bc}	385.40±19.57^{cd}	434.80±18.55^{cd}
RBG Day-9	114.60±14.17^{a}	497.80±18.22^{c}	358.20±20.11^{bc}	299.00±16.27^{b}	360.80±19.34^{bc}	439.00±17.33^{bc}	360.00±19.11^{bc}	339.80±24.10^{bc}	484.00±12.51^{c}
RBG Day 12	109.40±7.42^{a}	490.40±24.58^{de}	407.60±18.62^{bcde}	249.80±21.77^{ab}	362.80±22.42^{bcde}	465.80±18.99^{cde}	327.20±16.88^{bcd}	321.40±19.72^{bc}	504.80±13.84^{e}
RBG Day 15	114.40±8.79^{a}	490.20±21.10^{c}	380.00±28.31^{bc}	222.40±22.62^{ab}	393.80±20.82^{c}	378.80±13.75^{bc}	329.60±14.44^{bc}	341.40±11.92^{bc}	481.00±17.99^{c}
RBG Day 18	111.20±12.33^{a}	531.60±54.52^{d}	346.80±30.51^{bc}	244.60±33.71^{ab}	379.00±30.04^{bcd}	363.20±25.08^{bcd}	301.60±17.30^{bc}	357.20±23.44^{bcd}	449.20±22.41^{cd}
RBG Day 21	109.40±11.60^{a}	501.00±43.66^{d}	379.40±28.62^{bcd}	213.00±32.64^{ab}	419.20±29.08^{bcd}	297.60±34.77^{abcd}	265.60±32.06^{abc}	290.20±18.72^{abc}	456.80±21.28^{cd}
RBG Day 24	107.60±14.04^{a}	480.60±77.21^{c}	296.20±31.56^{bc}	255.00±25.87^{ab}	418.00±23.60^{bc}	353.00±28.01^{bc}	267.80±18.22^{ab}	318.60±22.44^{bc}	418.80±34.09^{bc}
RBG Day 27	103.60±17.88^{a}	433.80±42.12^{d}	311.00±21.44^{bcd}	176.80±18.26^{ab}	373.20±14.21^{cd}	381.00±22.05^{cd}	245.00±31.64^{abc}	251.60±18.20^{abc}	451.80±19.10^{d}
RBG Day 30	104.40±5.32^{a}	464.40±21.92^{e}	315.80±26.33^{bcd}	169.40±19.99^{ab}	432.80±29.70^{de}	343.80±26.18^{cde}	248.60±20.71^{abc}	189.00±19.36^{ab}	296.60±22.31^{bcd}
RBG Day 33	97.00±16.77^{a}	430.00±55.37^{e}	250.40±20.12^{bcd}	130.00±31.23^{ab}	366.80±24.18^{de}	292.20±24.17^{cd}	155.80±12.55^{ab}	165.60±17.91^{abc}	292.20±20.52^{cd}
*FBG Day 36	83.60±12.60^{a}	210.40±84.52^{b}	99.60±15.64^{a}	97.00±28.54^{a}	101.80±23.04^{a}	81.60±12.03^{a}	99.20±13.44^{a}	104.20±6.97^{a}	110.20±24.18^{a}

Note: ^{a,b,c,d,e}Means with different superscript letters within a row indicate a significant difference ($p < 0.05$). Negative control (T1), positive diabetic control (T2), glibenclamide treatment (T3), and kefir treatments (T4–T9). *Random Blood Glucose (RBG) and Fasting Blood Glucose (FBG).

body weight loss. The administration of kefir appeared to attenuate this catabolic state, suggesting its role in enhancing insulin sensitivity and promoting nutrient absorption. Kefir is a fermented milk product derived from a complex microbial consortium known as kefir grains. These grains consist of proteins, exopolysaccharides (primarily kefiran), and an interactive microbial ecosystem comprising bacterial species such as *Lactobacillus kefiranofaciens*, *Lacticaseibacillus paracasei* (basonym *Lactobacillus paracasei*), *Lactiplantibacillus plantarum* (basonym *Lactobacillus plantarum*), *Lactobacillus acidophilus*, and *Lactobacillus delbrueckii* subsp. bulgaricus, as well as yeasts including S*accharomyces cerevisiae*, *S. unisporus*, *Candida kefyr*, and *Kluyveromyces marxianus* ssp. marxianus (Hamsho *et al*., 2025).

Furthermore, the unique composition of kefir has been extensively investigated in anti-inflammatory studies, which have demonstrated its potential as a potent immunomodulatory agent. The bioactive components of kefir, including peptides, organic acids, and probiotic microorganisms, are believed to contribute to its beneficial effects. These findings are consistent with previous reports, which show that fermented milk products exert antidiabetic effects by modulating gut microbiota composition, reducing oxidative stress, and enhancing pancreatic β-cell function (Matejčeková and Valík, 2025). Therefore, the observed improvement in body weight among kefir-treated groups may reflect the combined effects of microbial metabolites, antioxidant capacity, and enzymatic activity that collectively help restore metabolic balance in diabetic rats.

Interestingly, no significant differences in body weight were observed among the diabetic groups treated with kefir originating from different grain sources. This finding suggests that, despite regional variations in kefir grains, their fundamental probiotic and bioactive properties remain relatively similar in modulating metabolic responses. The dominant microbial species commonly found in kefir grains, such as *Lactobacillus kefiri*, *Lactobacillus kefiranofaciens*, *Leuconostoc mesenteroides*, and *Saccharomyces kefir*, play central roles in producing metabolites that contribute to glycemic control and nutrient metabolism. Although previous studies have reported that microbial composition and fermentation performance may differ depending on the geographical origin of kefir grains (Gentry *et al*., 2023), these variations may not be sufficient to cause significant differences in physiological parameters such as body weight. It is likely that all kefir preparations provided comparable levels of bioactive compounds (Yegin *et al*., 2022), such as kefiran, organic acids, and antioxidant metabolites, which collectively contributed to maintaining body weight stability in diabetic rats.

Blood glucose changes

The blood glucose levels of the experimental rats showed a marked increase on day 0 (72 hours after STZ injection) (Table 2). A gradual reduction in blood glucose levels was subsequently observed from day 15 to day 36 following treatment. The random blood glucose (RBG) values measured on day 33 indicated that only the rats in groups T4, T7, and T8 exhibited RBG levels below 250 mg/dL. Furthermore, the fasting blood glucose (FBG) levels measured on day 36 showed significant differences ($p < 0.05$) between the untreated diabetic group (T2) and the normal control (T1), as well as all kefir-treated groups (T3, T4, T5, T6, T7, T8, and T9). Meanwhile, no significant differences ($p > 0.05$) were observed in FBG values among all kefir-treated groups compared with both the normal control and the diabetic group treated with the commercial drug glibenclamide.

The reduction in blood glucose levels observed in kefir-treated diabetic rats indicates that kefir possesses hypoglycemic potential comparable to that of the commercial antidiabetic drug glibenclamide. The gradual decline in glucose concentration from day 15 to day 33 suggests that continuous kefir administration may contribute to improved insulin sensitivity. Furthermore, Alsayadi *et al*. (2014) reported that regular kefir administration can significantly reduce blood glucose levels, primarily due to its exopolysaccharide content, the presence of bacteria and yeast, and their established hypoglycemic activities. The probiotics present in kefir, particularly *Lactobacillus kefiranofaciens*, *Lactobacillus kefiri*, and *Saccharomyces kefir*, are known to modulate the gut microbiota, leading to increased production of short-chain fatty acids (SCFAs) that enhance glucose metabolism and regulate insulin secretion. In agreement with the findings of Arda *et al*. (2025), short-chain fatty acid (SCFA)-producing microorganisms in kefir have been reported to enhance the secretion of glucagon-like peptide-1 (GLP-1) by upregulating intestinal receptors (GPR43 and GPR41) activated by SCFAs. This mechanism not only elevates GLP-1 levels but also increases plasma insulin concentrations, thereby playing a crucial role in blood glucose regulation.

Kefir is recognized as a rich source of bioactive peptides, organic acids, and antioxidant compounds that may attenuate oxidative stress and protect pancreatic β-cells from streptozotocin-induced damage (Amorim *et al*., 2019). Its strong antioxidant profile comprising phenolic acids, flavonoids, and diverse organic acids facilitates efficient scavenging of reactive oxygen species (Kumar *et al*., 2021). These bioactive constituents are believed to promote insulin biosynthesis and aid in the restoration of pancreatic function. The normalization of fasting blood glucose levels observed in kefir-treated diabetic rats, comparable to that

in glibenclamide-treated groups, further supports the hypothesis that kefir exerts its antihyperglycemic effects through multiple pathways (Teruya *et al*., 2002), including modulation of gut microbiota, stimulation of endogenous insulin secretion, and protection of pancreatic tissue from oxidative injury. This multifactorial mechanism aligns with previous findings indicating that fermented milk products can significantly reduce blood glucose levels and improve metabolic homeostasis in diabetic models. Furthermore, subsequent research on genetically diabetic mice supplemented with kefiran for 30 days demonstrated a marked reduction in blood glucose levels compared with the control group (Maeda *et al*., 2004). Likewise, Ağagündüz *et al*. (2024) reported that inhibition of α-glucosidase and pancreatic α-amylase key hydrolytic enzymes responsible for carbohydrate digestion effectively suppressed postprandial hyperglycemia, highlighting a potential therapeutic strategy for managing type II diabetes.

A decrease in blood glucose levels observed in diabetic rats treated with kefir derived from grains of West Java (T4), East Java (T7), and North Sumatra (T8) suggests that the microbial composition of kefir grains from these regions may possess greater biological activity in lowering blood glucose compared to grains from other regions. According to Mansour *et al*. (2024), this variation is likely attributed to differences in the dominant microbiota, particularly lactic acid bacteria (*Lactobacillus* spp.) and yeasts (*Saccharomyces* spp., *Kluyveromyces* spp.), which play essential roles in the synthesis of bioactive compounds during fermentation. Moreover, differences in enzymatic activity and antioxidant capacity among kefir samples may further contribute to this effect. Kefir produced from these three regions has been reported to exhibit higher free radical scavenging activity and more substantial α-glucosidase inhibitory potential, both of which play important roles in reducing intestinal glucose absorption. Therefore, the synergistic interaction between probiotic microorganisms and secondary metabolites formed during fermentation is believed to be a key factor underlying the pronounced glucose-lowering effects observed in the T4, T7, and T8 groups.

In the present study, alterations in body weight were found to have a strong association with blood glucose regulation in diabetic rats. Diabetes is commonly characterized by a progressive loss of body weight resulting from impaired carbohydrate metabolism, which consequently enhances proteolysis and lipolysis. The administration of kefir resulted in both an improvement in body weight and a reduction in fasting blood glucose levels, suggesting enhanced insulin responsiveness and increased glucose uptake in peripheral tissues (Guzel-Seydim *et al*., 2021). The recovery of body weight observed in kefir-treated groups may be attributed to improved energy metabolism and the attenuation of oxidative stress. Supporting evidence by Tiss *et al*. (2020) demonstrated that kefir-fermented soy milk (FSM) exhibited vigorous α-amylase inhibitory activity, with an IC_{50} value of 52.71 µg/mL. In hypercaloric high-fat-high-fructose diet (HFFD) rats, FSM administration reduced intestinal and pancreatic α-amylase activity by 26% and 31%, respectively, leading to a 36% reduction in blood glucose compared with untreated HFFD rats. Similarly, Hadisaputro *et al*. (2012) found that oral supplementation with plain kefir for 30 days significantly lowered plasma glucose concentrations in streptozotocin-induced hyperglycemic Wistar rats relative to the control group. Collectively, these findings reinforce the hypothesis that kefir and its fermented derivatives exert hypoglycemic effects through multiple mechanisms, including inhibition of carbohydrate-hydrolyzing enzymes, enhancement of insulin sensitivity, and mitigation of oxidative damage.

Table 3: Mean pancreatic weight (g) of rats in different experimental groups after treatment (mean ± S.D., n = 10).

Treatment	Pancreatic weight (g)
T1	0.786±0.98^{c}
T2	0.516±0.43^{a}
T3	0.632±0.40^{ab}
T4	0.686±0.98^{bc}
T5	0.594±0.75^{ab}
T6	0.598±0.11^{ab}
T7	0.572±0.41^{ab}
T8	0.642±0.47^{b}
T9	0.670±0.15^{bc}

Note: ^{a,b,c,d,e}Means with different superscript letters within a column indicate a significant difference ($p < 0.05$). Negative control (T1), positive diabetic control (T2), glibenclamide treatment (T3), and kefir treatments (T4–T9).

Pancreatic weight

In this study, the pancreatic weight of untreated diabetic rats was significantly lower than that of all other experimental groups ($p < 0.05$) (Table 3). In addition to the normal control group (T1), rats in groups T4, T8, and T9 exhibited significantly higher pancreatic weights ($p < 0.05$) compared with the untreated diabetic group (T2). These findings suggest that kefir administration in these treatment groups effectively mitigated diabetes-associated pancreatic atrophy, contributing to the preservation or restoration of pancreatic tissue mass. The marked reduction in pancreatic weight observed in untreated diabetic rats reflects progressive pancreatic atrophy resulting from β-cell destruction induced by streptozotocin (STZ). STZ is known to selectively damage insulin-producing β-cells within the islets of Langerhans through mechanisms

involving DNA alkylation and excessive generation of reactive oxygen species (ROS), ultimately leading to apoptosis and diminished insulin secretion (Pazra *et al*., 2023). The subsequent loss of β-cell mass and function contributes to structural deterioration and a measurable decline in pancreatic tissue weight.

Conversely, diabetic rats treated with kefir exhibited significantly higher pancreatic weights, suggesting that kefir administration exerted protective or regenerative effects on pancreatic tissue. These effects are likely attributed to the potent antioxidant and anti-inflammatory activities of kefir, which alleviate oxidative stress and prevent further β-cell damage (Tanure *et al*., 2025). The bioactive components and probiotic microorganisms present in kefir particularly *Lactobacillus kefiranofaciens*, *Lactobacillus plantarum*, and *Saccharomyces cerevisiae* have been reported to enhance pancreatic antioxidant enzyme activity, inhibit lipid peroxidation, and promote insulin synthesis (Lv *et al*., 2025). Collectively, the preservation of pancreatic weight in kefir-treated groups indicates that kefir supplementation may contribute to maintaining pancreatic structural integrity through synergistic antioxidant, anti-inflammatory, and insulinotropic mechanisms.

Table 4: Histopathological evaluation of the Langerhans islet area (μm^2) and islet number in different treatment groups (mean ± S.D., n = 10).

Treatment	Langerhans islet area (μm^2)	Islet number
T1	26164.54^{c}	2.80±0.20^{d}
T2	5680.26^{a}	1.80±0.47^{a}
T3	15052.10^{b}	2.36±0.23^{b}
T4	13198.74^{b}	2.60±0.14^{bcd}
T5	7917.80^{ab}	2.48±0.11^{bc}
T6	11028.62^{ab}	2.68±0.11^{cd}
T7	9251.44^{ab}	2.40±0.14^{bc}
T8	14335.81^{b}	2.32±0.18^{b}
T9	10719.27^{ab}	2.40±0.14^{bc}

Note: ^{a,b,c,d,e} Means with different superscript letters within a column indicate a significant difference ($p < 0.05$). Negative control (T1), positive diabetic control (T2), glibenclamide treatment (T3), and kefir treatments (T4–T9).

Pancreatic histopathology and islet morphometry

Histopathological observations (Table 4) demonstrated that the number of pancreatic islets per microscopic field in diabetic rats treated with kefir (T4–T9) showed no significant difference compared with the T3 (glibenclamide) and T1 (normal control) groups. The lowest number of islets per field was recorded in the untreated diabetic group (T2). Administration of streptozotocin (STZ) induced marked atrophy of the islets of Langerhans, characterized by a reduction in islet size and number per unit area, which were substantially lower than those observed in the normal control group.

Microscopic evaluation also revealed cellular damage manifested as cytoplasmic shrinkage, pyknotic nuclei, and lytic cells with indistinct nuclear boundaries, indicating degenerative and necrotic changes in the endocrine cells. Under hematoxylin and eosin (H and E) staining, it was difficult to clearly distinguish degeneration from necrosis, as these regressive changes represent a morphological continuum (Akwu *et al*., 2024). Therefore, for the sake of objectivity, degeneration and necrosis were not evaluated separately in this study. For future investigations, more sensitive staining methods such as immunohistochemistry with specific cellular markers could be used to differentiate these processes more accurately.

Histopathological examination revealed that kefir administration markedly improved the structural integrity of the islets of Langerhans in diabetic rats. This improvement was evidenced by lower histopathological damage scores and increased islet number and area compared with the diabetic control group (T2). Notably, the islet size in the kefir-treated groups (T4 and T8) appeared larger than that observed in other kefir-treated groups, accompanied by a reduced degree of endocrine cell degeneration within the islets. These findings suggest that kefir supplementation may not significantly impact the total islet count; instead, its beneficial effects are likely associated with the restoration of islet morphology and enhancement of β-cell function, contributing to improved pancreatic recovery. Furthermore, variations in islet size and histological damage among groups receiving different types of kefir milk suggest that differences may influence the therapeutic potential of kefir in microbial composition and regional origin. Each kefir variant may possess unique bioactive compounds and enzymatic profiles that modulate oxidative stress and inflammatory responses, thereby affecting pancreatic regeneration (Pereira *et al*., 2021). In contrast, treatment with the standard antidiabetic drug glibenclamide failed to restore pancreatic morphology to a condition comparable to that of the normal control group (T1).

In line with the pancreatic weight findings, histopathological observations further supported the protective role of kefir against STZ-induced pancreatic damage. Consistent with the findings of Gülbahçe Mutlu *et al*. (2021), the pancreatic tissues of untreated diabetic rats exhibited extensive degenerative alterations, including cellular necrosis, vacuolization, and disorganization of the islets of Langerhans, which are indicative of β-cell destruction. These morphological changes corresponded to the reduced pancreatic mass observed in this group.

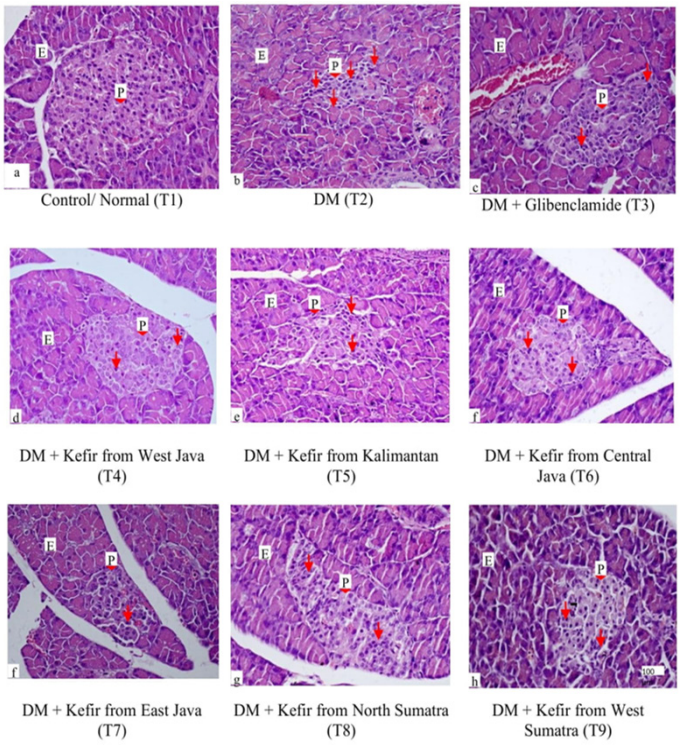

Figure 1: Pancreatic histology of experimental animals under high magnification, showing the exocrine component (E) and the endocrine component, the islets of Langerhans (P). Negative control (T1), positive diabetic control (T2), glibenclamide treatment (T3), and kefir treatments (T4–T9). Hematoxylin–eosin staining, original magnification 400×, scale bar = 100 µm.

As shown in Figure 1, the positive control group (DM) induced with STZ exhibited pronounced atrophy of the islets of Langerhans. The endocrine cells displayed clear signs of cellular damage (↓), including degeneration and necrosis, characterized by cytoplasmic shrinkage, pyknotic nuclei, and cell lysis. In contrast, the kefir-treated groups demonstrated variable islet sizes, with the T4 and T8 groups showing relatively larger islets compared to the T5 and T7 groups. A noticeable reduction in the proportion of damaged endocrine cells within the islets of Langerhans accompanied these morphological improvements. Furthermore, pancreatic sections from diabetic rats treated with kefir exhibited marked improvements in tissue organization, characterized by partially restored islet morphology, reduced necrotic areas, and increased cellular density within the islets of Langerhans. These findings indicate that kefir administration effectively attenuated β-cell loss and promoted the recovery of pancreatic tissue structure. This result is consistent with the findings of Yilmaz *et al.* (2022), who reported that the observed protective effects are likely attributed to the antioxidant and anti-inflammatory compounds produced during kefir fermentation, such as peptides, phenolic metabolites, and exopolysaccharides, which synergistically act to neutralize free radicals and alleviate oxidative stress.

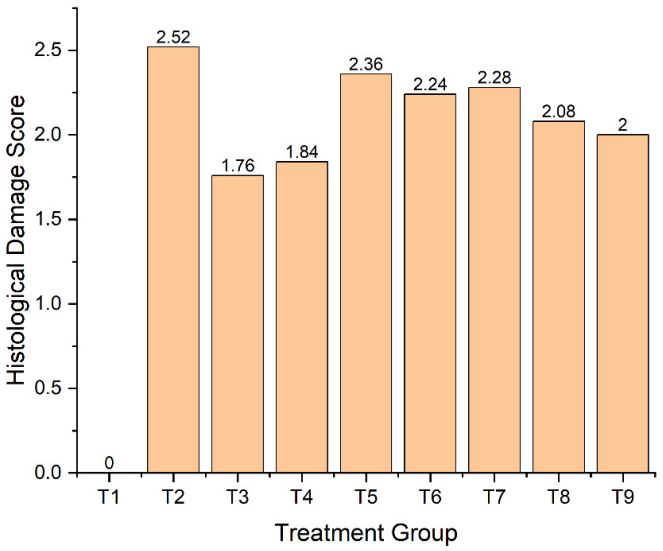

Figure 2: Histological damage scores of langerhans islets in different treatment groups.

As shown in Figure 2, kefir administration markedly improved the histological structure of the pancreas in STZ-induced diabetic rats, as indicated by reduced histological damage scores. Variations in the degree of histological recovery were observed among the kefir-treated groups, with pancreatic tissue from group T4 exhibiting superior structural restoration compared with other kefir-treated groups and comparable to that of glibenclamide-treated rats. STZ-induced pancreatic β-cell damage occurs when the compound enters cells via the glucose transporter-2 (GLUT-2) on the β-cell membrane, triggering the release of free radicals and an increase in intracellular oxidative stress. Reactive oxygen species (ROS), such as superoxide (O_2^-), can damage cellular components, leading to cell death and acute pancreatic inflammation (Mondal *et al.*, 2025). These findings are consistent with those of Nurliyani *et al.* (2015), who reported that healthy pancreatic β-cells exhibit dense islets of Langerhans with an abundance of β-cells. In contrast, diabetic conditions are characterized by reduced islet density and significant β-cell loss. Notably, in the kefir-treated group (T4), diabetic rats administered goat milk kefir for 36 days showed an increased average number of Langerhans islets and β-cells.

Furthermore, probiotic strains present in kefir, particularly *Lactobacillus kefiranofaciens* and *Saccharomyces cerevisiae*, have been reported to enhance pancreatic antioxidant defense mechanisms by upregulating catalase and superoxide dismutase (SOD) activities while decreasing malondialdehyde (MDA) levels (Wang *et al.*, 2022). These biochemical effects contribute to maintaining β-cell viability and insulin secretory function. Collectively, the observed increase in pancreatic weight and histological restoration in kefir-treated diabetic rats suggests that kefir exerts a dual protective role in the pancreas preventing

oxidative damage and promoting β-cell regeneration. This finding supports the hypothesis that kefir may serve as a functional dietary supplement capable of ameliorating pancreatic dysfunction associated with diabetes mellitus.

CONCLUSION

Administration of kefir for 36 days significantly improved glycemic control, body weight, and pancreatic weight in rats with streptozotocin-induced diabetes. Histological analysis revealed enhanced pancreatic structure and reduced damage scores in all kefir-treated groups, with kefir from West Java (T4) exhibiting the most pronounced effects. These findings indicate that T4 kefir effectively preserves β-cell integrity, mitigates oxidative stress, and promotes pancreatic regeneration, highlighting its potential as a functional dietary intervention for diabetes management.

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NOVELTY STATEMENT

This study is the first to comparatively evaluate goat's milk kefir from six distinct Indonesian regions in a streptozotocin-induced diabetic rat model, demonstrating region-specific differences in antidiabetic efficacy. By integrating glycemic parameters with pancreatic morphometry and histopathological assessment, this research provides comprehensive evidence of β-cell preservation and pancreatic regeneration. The findings reveal that kefir from West Java exhibits superior functional potential, highlighting the critical role of geographical microbial diversity in determining the therapeutic efficacy of fermented functional foods.

AUTHOR'S CONTRIBUTION

F conceptualized the research, conducted the experiments, and analyzed the data. YM and SM drafted and wrote the manuscript. A and ELSS carried out the laboratory work and performed data visualization.

Generative AI and AI-assisted technology statement

The authors confirm that no generative artificial intelligence (AI) tools or AI-assisted technologies were used in the writing, analysis, or preparation of this manuscript.

Conflict of interest

The authors have declared no conflict of interest.

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