Histopathological and functional liver changes in diabetic rats intervened goat's milk kefir and randu honey

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ABSTRAK

Latar Belakang: *Kejadian diabetes secara global diperkirakan meningkat 19,74% pada tahun 2030, sehingga memerlukan intervensi yang komprehensif. Hiperglikemia kronis berpotensi menyebabkan komplikasi kerusakan jaringan pada organ hati yang bisa dipicu stres oksidatif. Kefir merupakan produk kaya antioksidan yang berpotensi mengurangi stres oksidatif pada penderita DM dengan kerusakan hati yang diindikasi oleh kadar AST dan ALT. Oleh karena itu, konsumsi kefir pada dosis tertentu berkontribusi pada perbaikan kerusakan jaringan hati.*
Tujuan: *Mengamati perbedaan kadar AST, ALT, dan histopatologi hati pada tikus diabetes yang diintervensi kefir susu kambing yang dikombinasikan dengan madu randu.*
Metode: *Studi klinis dengan desain pre-post test menggunakan 42 ekor tikus jantan Sprague dawley (120-150 g) yang diintervensi selama 21 hari. Sampel terdiri dari 6 kelompok yaitu Ks (kontrol sehat), KN (kontrol negatif), K1 (quercetin 15 mg/kg BB), K2 (metformin 62.5 mg/kg BB), P1 (Kefir 1.8 ml/200g BB), dan P2 (preventif). Fungsi hati diukur menggunakan metode spektrofotometri kinetik dan histopatologi menggunakan mikroskop. Kemudian analisis data menggunakan One Way ANOVA dan Kruskal-Wallis.*
Hasil: *Pemberian kefir madu randu selama 21 hari menunjukkan perbedaan signifikan kadar ALT pre dan post test (p=0.001), dan menurunkan rerata ALT menjadi 31.22 ± 2,86 U/L pada kelompok P1, tetapi belum efektif menurunkan kadar AST (P=0.058). Terdapat hasil signifikan perbaikan kerusakan jaringan hati akibat penumpukan lemak pada kelompok P1 dan P2.*
Kesimpulan: *Kefir madu randu menurunkan kadar ALT serta memperbaiki kerusakan jaringan hati akibat penumpukan lemak.*

Kata Kunci: *ALT; AST; diabetes; kefir; histopatologi hati*

ABSTRACT

Background: *The prevalence of diabetes is projected to increase globally by 19.74% by 2030, which necessitates comprehensive interventions. Chronic hyperglycemia-induced oxidative stress contributes to hepatic tissue damage. Kefir is a product rich in antioxidants that has the potential to reduce oxidative stress in diabetic patients with liver damage as indicated by AST and ALT levels. Therefore, consuming kefir at certain doses contributes to the repair of liver tissue damage.*
Objectives: *To observe the differences in AST, ALT levels, and liver histopathology in diabetic rats intervened with goat's milk kefir combined with randu honey.*
Methods: *A clinical study with a pre-post test design using 42 male rats of the Sprague Dawley strain (120-150 g) was conducted for 21 days. The samples consisted of 6 groups: Ks (healthy control), KN (diabetic control), K1 (quercetin 15 mg/kg BW), K2 (metformin 62.5 mg/kg BW), P1 (Kefir 1.8 ml/200g BW), and P2 (preventive). Liver function was measured using the kinetic spectrophotometry method and histopathology using a microscope. Then analyze the data using One-Way ANOVA and Kruskal-Wallis.*

Results: *Administration of randu honey kefir for 21 days showed that there was a significant difference in ALT pre and post test (p=0.001), and reduced ALT levels to 31.22 ± 2.86 U/L in P1 group. There were significant results of improvement in liver tissue damage due to fat accumulation in the P1 and P2 groups.*
Conclusions: *Randu honey kefir reduces ALT levels and repairs liver tissue damage due to fat accumulation.*

Keywords: *ALT; AST; diabetes; liver histopathology; kefir*

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INTRODUCTION

In 2021, the prevalence of diabetes among adults globally reached 537 million, and it is projected to increase by 19.74% by 2030 (1). Around 10.7 million, Indonesia ranks seventh globally and third in Southeast Asia for the highest number of diabetes cases, representing a national prevalence of 11.3% (2). The World Health Organization (WHO) predicts that the number of type 2 diabetes (T2DM) cases in Indonesia will rise to approximately 21.3 million by 2030. Among the total diabetes prevalence, more than 90% are adults with type 2 diabetes mellitus, predominantly associated with overweight and obesity (3). In 2019, 11.3% of global deaths, or 4.2 million, were caused by diabetes (4). Individuals with diabetes are at risk of developing liver disorders such as Non-Alcoholic Fatty Liver Disease (NAFLD), glycogen hepatopathy, cirrhosis, and fibrosis (5). Among patients with DM2, revealed that 23.3% and 21.4% exhibited elevated levels of ALT and AST, respectively (6).

Recent studies in humans and animals indicate that chronic hyperglycemia (T2DM or T1DM) in individuals is associated with morphological changes in the liver and the progression of liver disease (7). According to Schwartz (2016), the liver plays a role in the type 2 diabetes mellitus pathogenesis (8). Type 2 DM is characterized by hyperglycemia, defined as an elevation of blood glucose levels exceeding the normal cut-off. Chronic hyperglycemia can lead to insulin resistance, which triggers gluconeogenesis, resulting in elevated glucose by the liver (8). The liver is also a key mediator of hyperglycemia, contributing to β-cell damage. Persistent glucose production by the liver can lead to inflammation. Oxidative stress is key indicators involved in liver damage under diabetic conditions (9). The impact of oxidative stress induced by hyperglycemia is susceptible to causing damage to the liver, which is an organ sensitive to insulin (10). Complications in diabetes patients involving the liver are associated with elevated AST/ALT levels. These two enzymes catalyze transamination reactions, which are integral to amino acid and carbohydrate metabolism (11). However, both biochemical parameters are elevated in blood circulation, indicating hepatic dysfunction due to leakage from damaged cells. Therefore, ALT/AST levels can be measured to assess liver damage in

diabetic conditions (12). Even in various studies, these two parameters are linked through the De Ritis ratio to show more accurate results (13).

A study proves that diabetes causes changes in liver morphology (14). Liver abnormality conditions, such as excessive fat accumulation, is associated with diabetes mellitus (14). Liver fat accumulation is associated with a decreased ability to suppress hepatic glucose production and a reduction in insulin clearance by the liver, both of which contribute to the onset of T2DM (15). The accumulation of fat triggers oxidative stress, which damages hepatocytes and increases AST and ALT release. The effects of oxidative stress caused by hyperglycemic conditions are prone to inducing liver tissue damage (10). Abnormal inflammatory responses can activate pro-apoptotic genes and damage hepatocytes (16). Liver tissue shows morphological changes as a result of conditions induced by inflammation, swelling, fat accumulation, and cell death (17). These damages can be observed through abnormal structural changes in liver tissue.

Antioxidants are potential compounds for addressing oxidative stress in diabetic patients with liver damage, consequently reducing the progression of complications (9) Kefir is considered a potential functional food with anti-diabetic properties at an affordable price (18). The composition of kefir provides various health effects (19). For individuals who are lactose intolerant, goat milk can serve as an alternative ingredient for kefir production (20). Different combinations of ingredients which consist in goat's milk kefir result in variations in lactose content, reducing sugars, pH values, and titratable acidity (21). Goat milk kefir is more digestible due to its higher content of short-chain fatty acids (22). A study also indicates that goat milk contains smaller protein and fat globules, which are more easily digested compared to cow's milk (23). Research by Ibrahim (2017) also reported that the angiotensin-converting enzyme, which regulates blood pressure, is inhibited by the whey and casein content in goat milk. Furthermore, goat milk kefir can act as an anti-diabetic agent. A study demonstrated that kefir intervention had a positive impact on streptozotocin-induced diabetic rats over a 35-day period (18).

The addition of randu honey can increase the antioxidant content in goat milk kefir (24). Antioxidants are compounds that can serve as an alternative therapy for managing diabetes mellitus. A study demonstrated that the high antioxidant content in honey can improve cardiovascular health, such as atherosclerosis that can lead to coronary disease and stroke in individuals with metabolic syndrome (25,26). Atherosclerosis obstructs blood flow to the heart through arterial stenosis caused by plaque accumulation of LDL and cholesterol (27). A study by Rusmini *et al* (2020) demonstrated that kapok honey administration reduced serum LDL levels in mice fed a high-fat diet (28). Research by Hardiansyah and Kusuma (2022) showed that the addition of 20% honey increased the percentage of inhibition, indicating that 8.29% of the antioxidant content in honey plays a role in scavenging free radicals (24). The greater the

inhibition percentage, the stronger the antioxidant activity. Another study showed the antioxidant activity (IC_{50}) mean of randu honey reaches 0.096 ppm (29). The antioxidant content in randu honey kefir is expected to reduce AST and ALT levels in liver tissue damage caused by inflammation.

Based on the background, observation of liver function and histopathology has the potential as an alternative to determine the condition of cell damage related to insulin and diabetes other than through pancreatic β-cells. Through the intervention of kefir products added with randu honey, it is expected to show the potential of honey kefir in repairing cell damage due to diabetes. Previous studies on goat's milk kefir combined with kapok honey have primarily focused on its production, nutritional content, and organoleptic properties. However, its therapeutic efficacy in a diabetic model has not been investigated, particularly concerning its effects on liver biomarkers such as AST, ALT and on hepatic histopathology. Therefore, this study aimed to observe changes in AST, ALT levels, and liver histopathology in diabetic rats intervened with goat milk kefir added with randu honey.

MATERIALS AND METHODS

Experimental animals

A total of 42 male rats of the Sprague Dawley strain, each weighing 120–150 grams and aged approximately 6–8 weeks, were used in this clinical study with a pre-post test design. The rats were divided into Ks, KN, K1 (quercetin), K2 (metformin), P1 (kefir + honey), and P2 (preventive), with 7 rats in each group (2 animals as reserves) refer to WHO standards (30). An adaptation period of 7 days was provided to acclimate the rats to the new environment and ensure their health (31). The animals were maintained in individually ventilated cages, with the temperature maintained at approximately 22 (±3°C) and humidity at 50±60%. The lighting cycle was set to 12 hours of light and 12 hours of darkness, and food was provided *ad libitum* (32). The standard rodent feed provided to the rats contained 18% crude protein. The rats were observed for 4-5 weeks during the diabetes mellitus modeling phase and 3 weeks during the intervention phase. Body weight measurements were taken every 3 days to monitor changes during the study. The study was approved and received ethical clearance certification from the Ethics Committee of Universitas Prima Indonesia in Medan, with certificate number 041/KEPK/UNPRI/VII/2024.

Formulation of kefir using goat milk and randu honey

The formulation of randu honey kefir was conducted at the iRat.co Laboratory, Bogor. The preparation process began with the pasteurization of 750 mL of goat milk at 72°C for 15 seconds. Then the pasteurized goat milk is cooled at room temperature until it reaches approximately ±27°C. Subsequently, the milk was inoculated with 50 grams (5%) of kefir grains and supplemented with 250 mL of randu honey. The mixture was placed in a sealed container

and incubated for 24 hours at room temperature (±25–27°C) under dark and low-humidity conditions to facilitate fermentation. Following the fermentation period, kefir grains were removed by filtration. The resulting randu honey kefir was then stored at 4°C (24,33,34).

Induction of type 2 diabetes mellitus

There were groups consisting of (Ks) as healthy rats and diabetic rats (KN, K1, K2, P1, P2). Each diabetic group was injected with a combination of streptozotocin (STZ) at a dose of 40 mg/kg body weight (multiple) and a High-Fat Diet (HFD) (35,36). Two groups of mice, designated as P1 and P2, were administered kefir at a dosage of 1.8 ml/200 g body weight.. The treatment protocol differed for group P2, which served as the preventive group. In group P2, kefir administration commenced at the onset of type 2 diabetes mellitus (T2DM) modeling, concurrently with a high-fat diet (HFD) regimen, both at 1.8 mL/200 g BW, then continued with honey kefir intervention for 21 days. The T2DM rats model was established by feeding a HFD for 4–5 weeks, with blood glucose levels monitored and maintained at approximately 200 mg/dL to simulate type 2 diabetes mellitus conditions.

Treatment phase

The treatment phase was divided into two stages: pre-intervention and intervention. Prior to the intervention, blood samples were taken from the rats to measure glucose levels until they reached 200 mg/dL or approached this value. A pre-test was conducted to measure AST and ALT levels before the intervention. The intervention lasted for 21 days, with each group monitored according to the assigned treatment: The Ks group (healthy rats) and KN group (diabetic rats) continued to receive standard feed and aquades. The K1 group (quercetin 15 mg/kg BW + standard feed + aquades) (37), K2 group (metformin 62.5 mg/kg BW + standard feed + aquades)(35), P1 group (kefir 1.8 ml/200g BW + standard feed + aquades) (38), and P2 group (preventive + kefir 1.8 ml/200g BW + standard feed + aquades). The difference in P2 group, honey kefir was administered from the beginning (1.8 mL/200 g BW), concurrently with high-fat diet (HFD), as a preventive intervention to evaluate the potential protective effects of honey kefir.

Evaluation of serum AST and ALT levels and hepatic histopathology examination

The measurement of AST and ALT levels was conducted pre-test and after post-test the treatment, whereas histopathological examination of the liver was performed only at the post-test. Blood samples for the pre-test were collected through the retro-orbital sinus, as this site provides easy access and allows for the collection of an adequate volume of blood (32) Meanwhile, blood samples for the evaluation of AST and ALT concentrations during the post-test were obtained by collecting 0.5 mL of blood directly through cardiac puncture. The cardiac blood collection method was performed at the end of the treatment period, as this terminal procedure results in the euthanasia of the experimental animal (39). Prior to dissection, the rats were anesthetized and then surgically operated to measure AST, ALT levels, and

histopathological changes in the liver. These levels were quantified using the kinetic spectrophotometric method by measuring changes in light absorbance at a wavelength of 340 nm. Liver tissue samples were rinsed, preserved to fixation in 10% neutral buffered formalin, infiltrated, and embedded in paraffin blocks at 56-58°C. Tissue sections (3-5 micrometers) were placed in a water bath, stained with hematoxylin and eosin (H&E), and then examined under a light microscope at 400x magnification (40–42).

Data analysis

The AST/ALT levels data were analyzed using SPSS software 25 version. The initial assumption for statistical analysis was tested for normality (Shapiro-Wilk) and homogeneity of variances across the treatment groups. If these assumptions were satisfied, a one-way ANOVA was performed with a significance level of 5% ($p<0.05$) to assess differences in AST and ALT levels between the groups. Following the one-way ANOVA, post-hoc Duncan's test was conducted to identify which treatment groups were significantly different. However, if the assumptions for one-way ANOVA were not satisfied, an alternative approach using statistical analysis involved the Kruskal-Wallis test, with subsequent post-hoc Mann-Whitney tests. Liver histopathology was described qualitatively to evaluate tissue structural changes

RESULTS AND DISCUSSIONS

One of the potential organs identified as Insulin-positive Cells (IPCs) is the liver (43). The liver organ originates from the same embryology as the pancreas so it can be used as an observation sample in research related to diabetes and insulin hormone conditions. AST and ALT activities in blood plasma can be used as indicators to evaluate hepatocellular dysfunction (12). In contrast to ALT which is only found in the cytoplasm cell, AST is also found in the mitochondria and cytoplasm of hepatocyte cells (44). Therefore, an increase in ALT levels in the blood more specifically indicates liver damage compared to AST, which is also excreted by other organs including the liver, brain, pancreas, heart muscle, lungs, skeletal muscle, kidneys, and blood (13). However, both indicators are often interpreted through the De Ritis ratio. This ratio compares AST/ALT to determine whether liver cell damage is acute or chronic. A De Ritis ratio ≤ 1 indicates acute damage, whereas a ratio > 1 reflects chronic liver conditions (13). This indicates that both parameters are interrelated and can be assessed through the De Ritis ratio to identify the specific nature of cellular damage.

AST and ALT concentration before intervention

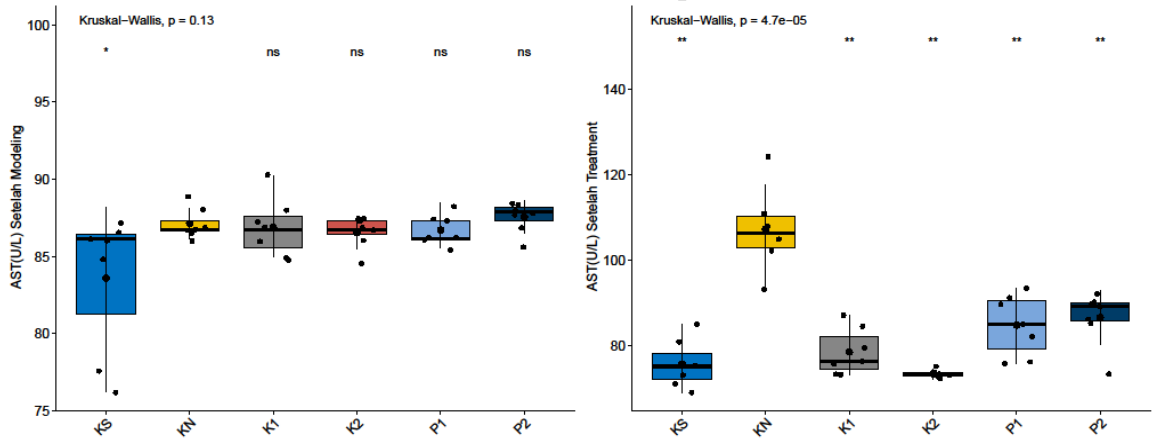
Before the intervention, AST and ALT levels were measured to ensure that the rats were in a normal condition, allowing for comparison with the results following the intervention of randu honey kefir. The following table are the results of the AST and ALT measurements before the intervention:

Table 1. Average Pre-test Results of AST and ALT Levels

Group	ALT (U/L)	AST (U/L)
Ks	25.90 ± 2.59[a]	83.59 ± 4.26[a]
KN	47.68 ± 6.75[d]	87.14 ± 0.99 [a]
K1	42.69 ± 5.88[c,d]	86.88 ± 1.83 [a]
K2	41.65 ± 8.68[b,c,d]	86.55 ± 1.05 [a]
P1	37.08 ± 6.19[b,c]	86.72 ± 1.01 [a]
P2	35.29 ± 4.49[b]	87.55 ± 1.05 [a]

According to Gad (2007) in Yuneldi *et al* (2018), the normal range for ALT levels in rats is between 17,5 - 30,2 U/L, while the normal range for AST levels is between 45,7 - 80,8 U/L (45). **Table 1** above shows the measurement results of ALT and AST levels before the intervention in the Ks, KN, K1, K2, P1, and P2 groups. There was a significant difference (p=0.001) in ALT levels between treatment groups, but in AST measurements there was no significant difference (p=0.125). In this study, the calculation of the De Ritis ratio results showed a score of >1, so, it may be inferred that there is a chronic liver disorder indicated by AST/ALT.

Measurement of AST levels



(a) (b)

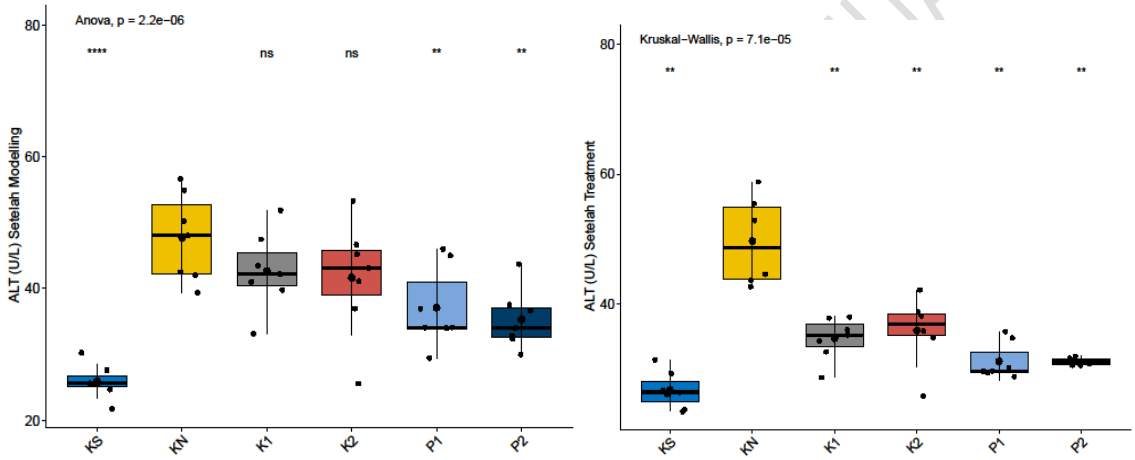
Figure 1. AST levels (a) before and (b) after intervention

Kruskal-Wallis test showed no significant differences (p=0.125) were observed between the treatment groups for pre-test AST levels. All treatment groups showed pre-test results of AST levels that exceeded the normal limit (>80.8 U/L). **Figure 1** shows the highest AST levels were in the P2 group, reaching 87.55 ± 1.05 U/L and the group with the lowest AST levels was group Ks (83.59 ± 4.26 U/L). The increase in AST and AST was caused by cell damage that occurred due to STZ induction (12).

The 21-day kefir honey intervention showed in **Figure 1 (b)** that there are significant differences (p=0.000) in AST levels between the treatment groups. However, the Wilcoxon test

results showed that there was no significant difference (p=0.058) between the pre-post test results of AST levels. Nevertheless, statistical analysis **(Figure 1)** shows that the AST level in the P1, with a mean value 84.72 U/L, showed a greater decrease compared to the P2 group, with a mean of 86.51 U/L. The group with the highest AST levels was KN 107.19 ± 10.34 U/L. When compared to other treatment groups, K1 (quercetin) and K2 (metformin) with average final AST levels of 78.44 U/L and 73.33 U/L were the group that shows the most significant decrease. Therefore, randu honey kefir is still less effective in controlling AST compared to diabetes drugs such as quercetin and metformin. AST is a less specific biomarker for liver injury because it is also abundant in other tissues, such as cardiac and skeletal muscle. Due to this broader distribution, normal AST levels in the blood are typically higher than the more liver-specific ALT (13).

Measurement of ALT levels



(a) (b)

Figure 2. ALT levels (a) before and (b) after intervention

The results of the ANOVA test in **Figure 2 (a)** demonstrated a significant difference (p=0.000) among the rat groups in the pre-test ALT levels. Post hoc analysis revealed that the Ks group significantly differed from the other groups. In the pre-test results of ALT levels, only the Ks group was within the normal limit, which was 25.90 ± 2.59 U/L. Based on the graphic, ALT levels of all treatment groups were higher than Ks and had exceeded the normal limit (>30.2 U/L). However, the ALT level in the P2 group, with a mean of 35.29 U/L, was lower than that in the KN group, which had a mean of 47.68 U/L.

After the 21-day kefir honey intervention, it was found that the P1 and P2 groups had lower ALT levels compared to the KN. There was a significant difference shown in **Figure 2 (b)**, the post-test results of ALT levels between treatment groups (p=0.000). Statistical analysis showed a significant difference in ALT levels (p=0.001). Post-test showed that the mean ALT level in the P1 group was 31.22 U/L and in the P2 group was 31.18 U/L, indicating a reduction

when compared to pre-intervention ALT levels with randu honey kefir. Meanwhile, the K1 (quercetin) group had a mean ALT level of 34.71 U/L and the K2 (metformin) group had a mean of 35.94 U/L. In fact, the reduction in ALT levels in the P1 group was greater by 0.14 compared to the K2 (metformin) group. This indicates the potential of the kefir product to lower ALT levels in the P1 and P2 groups, in alignment with the control groups K1 (quercetin) and K2 (metformin). Align with Sah et al. (2022), this study shows that kefir consumption can protect against liver and kidney injury (46).

Histopathological examination of rat liver

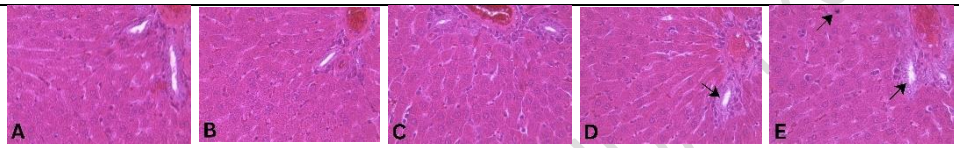
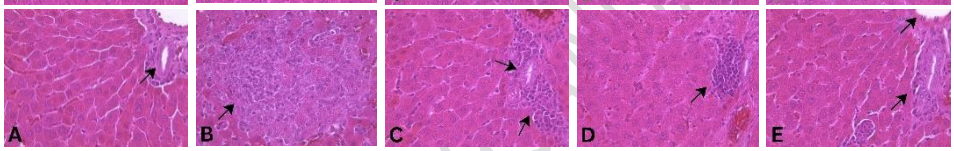
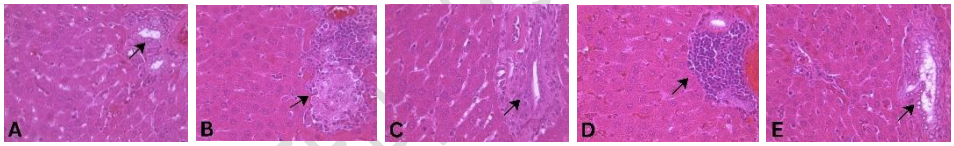
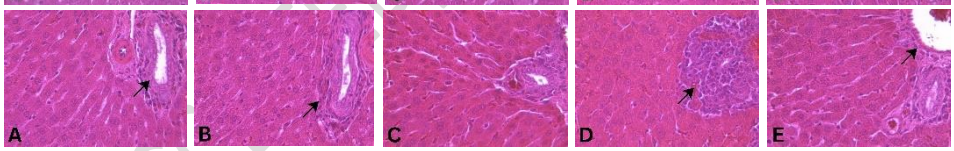
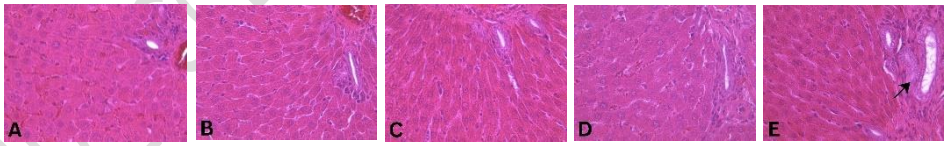
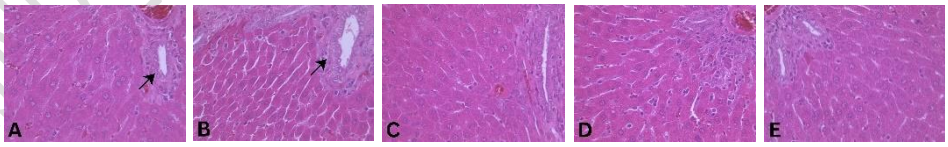
Group	Liver Histopathology
KS (Healthy control)	
KN (Negative Control)	
K1 (Quercetin dose 15 mg/kg BW)	
K2 (Metformin dose 62.5 mg/kg BW)	
P1 (Kefir dose 1,8 ml/200g BW)	
P2 (Preventive)	

Figure 3. Rat Liver Histopathology After Intervention

Research conducted by Zafar et al. (2009) demonstrated that streptozotocin (STZ)-induced diabetic rats exhibited alterations in liver function and hepatocyte structure (12). Furthermore, other studies have reported that STZ administration at certain dosages can lead to more severe dyslipidemia and hepatic dysfunction in rats (47). However, it has also been noted that STZ administered as a single agent does not adequately reproduce the insulin resistance characteristic of the pathophysiology of type 2 DM (48). These discrepancies are likely influenced by several factors, including the STZ dosage, the sex and age of the

experimental animals, as well as the methodologies and experimental conditions employed in the study design (36). To better simulate T2DM, rats were subjected to a combination of a high-fat diet (HFD) and STZ induction at an optimized dose, resulting in partial β-cell destruction and the manifestation of T2DM-like conditions (49,50). This approach is supported by findings from Guo et al. (2018), who recommended the use of HFD in pharmacological studies to achieve more pronounced and reliable outcomes (47).

Rats were treated with 40 mg/kg body weight of STZ to reach a target blood glucose level of 200 mg/dl. Prolonged hyperglycemia can lead to organ damage, including the kidneys, eyes, liver, nerves, heart, and blood vessels (51). A study by Gozali (2020) reported that 70% of diabetes patients develop liver cirrhosis, which leads to liver injury and chronic hepatopathy. Changes in liver structure can be either reversible or irreversible. Liver tissue can shows alterations due to cell death, degeneration, fat accumulation, fibrosis, and cellular swelling caused by fluid retention (52). One cause of this tissue damage is continuous exposure to chemicals or medications. This condition is related to the long-term use of medications in diabetes patients, which can potentially cause fatty degeneration and necrosis, reduce cell regeneration and ultimately lead to cell death (52).

The study findings demonstrate enhanced liver histopathology in rats administered goat milk kefir enriched with randu honey. This finding is consistent with the observed reduction in ALT levels, as ALT is a specific biomarker indicating the repair of liver damage. A normal liver is characterized by a reddish-brown color, and its surface appears smooth and even (53). Under microscopic examination, normal liver tissue exhibits regularly arranged cells, a normal cytoplasm-to-nucleus ratio, and clearly visible central veins and endothelial cells (54). These characteristics were observed in the liver tissue structure of the healthy (Ks) group **(Figure 3)**. The cellular morphology observed in group P1 appeared more organized and closely resembled that of the control group (Ks).

In the descriptive histopathological observation, the KN group exhibited signs of liver degeneration due to fat accumulation. Hepatocytes with fatty degeneration displayed small vacuoles (microvesicular) in the cytoplasm (52). Hepatocyte injury is characterized by cellular swelling and atrophy due to the inhibition of mitotic processes (55). Under the microscope, that fatty degeneration is characterized by the accumulation of lipid vacuoles, increased inflammation, and fibrosis (53). These microscopic features were evident in the KN treatment group. The KN group shows fatty degeneration due to the induction of a combination of STZ and HFD. In some parts **(Figure 3)**, there are dark purple dots which are a sign of inflammation. In contrast to the KN, the other groups (Ks, K1, K2, P1, P2) showed an almost normal microscopic appearance, suggesting that the honey kefir intervention may contribute to the prevention of severe hepatic cellular damage.

Goat milk kefir contains various bioactive components and microorganisms that are

beneficial for health. These include polyunsaturated fatty acids (PUFAs), antioxidants, and lactic acid bacteria (LAB). The lactose content in goat milk kefir is also relatively low, which is around 2.64% (34). This effect is attributed to the presence of lactic acid bacteria (LAB), such as *Streptococcus* and *Lactobacillus*, which participate in the fermentation process by converting lactose into lactic acid through glycolysis (56). Through the Embden-Meyerhof-Parnas (EMP) pathway, lactose is metabolized into pyruvic acid, which is subsequently converted into lactic acid (56). Research reported that fermentation reduces the lactose content in kefir by approximately 30% compared to non-fermented milk (20). Milk lactose is enzymatically hydrolyzed by β-galactosidase to yield glucose and galactose. Therefore, kefir made from goat milk may serve as a viable alternative for individuals with lactose intolerance (20). The concentration of lactic acid bacteria (LAB) in goat milk whey kefir has been reported to range from 1.82 × 10¹⁰ CFU/mL to 5.06 × 10¹⁰ CFU/mL (57). The LAB content in kefir with honey can reach up to 3.50 x 10^{10} CFU/ml. LAB in kefir can modulate gut microbiota, which is associated with weight loss, improvement of liver histopathology, and reduction of inflammation in HFD-induced obese rats (58). Goat milk kefir contains 2.96-3.66% protein, 2.02-5.35% fat, 2.45-5.65% carbohydrates, and 0.42-0.80% ash (59). The proteins in goat milk, including αs1-casein, αs2-casein, and β-casein, contribute to the stability of kefir granules (60). Therefore, goat's milk can be chosen as a basic ingredient for fermentation into kefir.

The addition of honey can enhance the antioxidant content in kefir products (61). Kefir has been shown to significantly reduce oxidative stress in the liver and plays a role in preventing liver damage (62). The saponin and flavonoid content in randu honey has potential antibacterial and antioxidant properties (63). A comparative study showed the Bogor randu honey exhibited the highest inhibitory activity, with 3.12% minimum inhibitory concentration (MIC) against C. albicans and the highest antimicrobial activity based on diffusion and dilution tests and (64). In addition, randu honey contains phenolic compounds (309.12 ± 33.40 mg/GAE kg), flavonoids (47.25 ± 1.49 mg QE/100 g), and vitamin C (25.47 ± 1.62 mg/100 g) (65). The high levels of phenolic compounds found in honey play a significant role in its antimicrobial activity through bacterial membrane disruption and interaction with bacterial DNA (66). The hepatoprotective effect of honey has been demonstrated to repair liver injury in rats by reducing fat degeneration. Increased levels of fatty acids and fat accumulation in liver cells cause damage to the mitochondrial electron transport chain of hepatocytes (67). The impact of this damage increases microsomal pathway fat oxidation. Experimental studies of giving bitter honey at doses of 200 mg/kg and 400 mg/kg for 28 days in diabetic rats have also been shown to reduce AST and ALT levels (68).

One study showed that the antioxidant content in honey can inhibit lipid peroxidation induced by a high-fat diet (HFD) by increasing insulin sensitivity and activating antioxidant pathways mediated by Nrf2 (69). Research by G. Lori et al. (2019) revealed that honey extract

contains bioactive components that inhibit PTP1B, thereby enhancing insulin sensitivity and glucose uptake in HepG2 cells (70). Honey increases glutathione (GSH) levels and glutathione peroxidase (GPx) activity, while reducing malondialdehyde (MDA) levels in the liver. Natural antioxidants in honey, such as chrysin, have been shown to address cognitive decline related to STZ-induced diabetes by modulating oxidative stress indices (SOD, MDA, GSH, and CAT), IL-6, NF-κB, IL-1β, TNF-α, and caspase-3 in the cerebral cortex and hippocampus (71).

The administration of randu honey kefir to diabetic rats represents an alternative option for diabetes management, including the repair of tissue damage in liver cells. A study showed kefir produced from goat milk has potential as an anti-hyperglycemic functional food (72). However, when combined with soy milk, goat milk kefir demonstrated greater potential. Another study by Ozsoy (2016) indicated that kefir has a positive effect on liver fat accumulation in diabetic rats (73). Despite providing positive effects on liver histopathology, recent studies have reported no significant differences in the total levels of AST and ALT (74). Variations in the composition of kefir combinations result in different anti-diabetic effects (18). This demonstrates that the combination of kefir compositions also influences its effectiveness as a therapeutic agent. This study combines kefir grains, goat's milk, and randu honey, which is expected to serve as a viable option for an anti-diabetic product. These findings are supported by a study conducted by Salah et al. (2023), which demonstrated that supplementation with kefir and a high-sucrose high-fat diet (HSFD) exerted therapeutic effects by reducing the degree and stage of hepatic steatosis, inflammation, and fibrosis in a mouse model of non-alcoholic steatohepatitis (NASH). In conjunction with improvements in liver histopathology, a reduction in serum AST and ALT levels was also observed in the kefir-treated group (53).

This study used AST, ALT, and liver histopathology parameters as alternative indicators to insulin-positive cells (IPCs) for assessing abnormalities associated with insulin regulation, complementing conventional observations of pancreatic β-cell integrity. The De Ritis ratio (AST/ALT) was also used to distinguish between acute and chronic hepatic injury. A limitation of this study is the lack of comprehensive investigation to establish the optimal dosage of randu honey kefir. Additionally, potential confounding factors that may reduce the efficacy of the intervention require further analysis to more precisely evaluate the therapeutic potential of honey kefir. Future research is warranted to establish the optimal dosing regimen, identifying factors that affect intervention efficacy, and determine the safety threshold or toxicological limits of honey kefir for potential application in humans.

CONCLUSIONS AND RECOMMENDATIONS

The administration of randu honey kefir 1.8 ml/200g BW in diabetic rats significantly reduced ALT levels (P1 and P2) and alleviated liver tissue damage in diabetic rats. In contrast,

no significant alteration in AST levels. The research findings are consistent with the hypothesis, as the observed reduction in ALT levels indicates an amelioration of liver damage. However, further research is needed to determine the optimal dosage of kefir and to establish its toxicity thresholds in humans.

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