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Papaya Seeds (*Carica papaya* L.) and Lemongrass (*Cymbopogon citratus*) Decoction Ameliorated Mice (*Mus musculus*) with Type II Diabetes Mellitus

Amelia Cantika Darmareta*, Nur Qomariyah
Biology Study Program, Faculty of Mathematics and Natural Sciences, Universitas Negeri Surabaya
*Corresponding Author, e-mail: nurqomariyah@unesa.ac.id

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Abstract
The antioxidant activity of papaya seed and lemongrass can possibly lower blood glucose levels and improve the Langerhans islet in mice with type 2 diabetes mellitus (T2DM) induced by high-fat diet (HFD) and alloxan. This study aimed to evaluate the effect of papaya seed and lemongrass stem decoctions on fasting blood glucose (FBG) levels and diameter of Langerhans islets, as well as to identify the optimal decoction for both parameters. This experimental study used 24 male mice divided into 6 treatment groups: negative control (KN), T2DM-induced positive control (KP), T2DM with metformin (KM), 60% papaya seed decoction (KA), 60% lemongrass decoction (KB), and 60% combined papaya seed and lemongrass decoction (KC). The FBG data were analyzed using Brown-Forsythe test and Games-Howell test. Meanwhile, diameter data of Langerhans islet were analyzed using ANOVA and Duncan test. The results showed that the KB group was the most effective decoction in reducing FBG from 166.5 ± 21.05 mg/dL to 111.25 ± 14.66 mg/dL and improving the diameter of Langerhans islet to 133.29 ± 14.66 µm.

Keywords: non-communicable disease; fasting blood glucose; high fat diet; pancreas

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INTRODUCTION

The most common and most frequently diagnosed form of diabetes mellitus (DM) in humans is type 2 diabetes mellitus (T2DM). Insulin resistance is a primary hallmark of this condition, which accounts for approximately 90% of all diabetes cases (IDF, 2025). This disorder prevents the cells from utilizing glucose optimally, causing glucose to accumulate in the bloodstream and raise blood glucose level significantly. According to the International Diabetes Federation (2021), a fasting blood glucose level of ≥ 126 mg/dL or a random blood glucose level of ≥ 200 mg/dL is diagnostic of diabetes. Factors that can lead to type 2 diabetes mellitus include an unhealthy lifestyle, particularly diet and physical activity (Zulkarnaini *et al*., 2022). Unhealthy dietary habits, such as consuming foods high in fat, sugar, and carbohydrates can lead to excessive fat accumulation in body tissues. In this study, an unhealthy diet was modeled using a high-fat diet (HFD) to increased body fat levels and induce obesity.

Obesity can impair glucose utilization by cells and glucose transporter 4 (GLUT4) translocation (Samuel and Shulman, 2016). The accumulation of visceral fat in obese individuals can reduce insulin sensitivity and lead to insulin resistance (Sari *et al*., 2024). Increased free fatty acids (FFAs) enter the cells via Cluster of Differentiation 36 (CD36) and are converted into long-chain fatty acyl-CoA (LCFA-CoA) (Elkanawati *et al*., 2024). Accumulated LCFA-CoA is broken down into diacylglycerol (DAG) and ceramide. DAG can activate protein kinase C (PKC) and increase serine phosphorylation of IRS-1 (Petersen and Shulman, 2018). This subsequently inhibits PI3K activation, resulting in reduced PI3K activity and Akt activation which play crucial roles in the translocation of glucose transporter 4 (GLUT4), resulting in lower glucose absorbtion in the muscle (Tang *et al*., 2026).

Insulin resistance has negative effects on the body, particularly on the pancreatic beta cells. Persistent high blood glucose causes hyperinsulinemia, leading to pancreas damage (Khin *et al*., 2023). This condition significantly contributes to decreased insulin production and increased blood glucose levels. Damage to pancreatic beta cells includes necrosis and degeneration, which can lead to decreased cell mass, number, and function. Increased beta cell damage is closely associated with a reduction in the diameter of Langerhans islet (Vesall *et al*., 2001; Nubatois *et al*., 2015).

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The management of DM commonly focus on healthy lifestyle, diet, physical exercise, and pharmacological treatment/therapy (Widiasari *et al*., 2021). For people with T2DM, pharmacological therapy can be administered through oral antihyperglycemic medication, such as metformin. Metformin serves as the primary therapy or first line medication for individuals with T2DM (Bailey, 2017). Although effective as a primary therapy for T2DM, metformin can cause side effects such as nausea, diarrhea, and bloating (Rahayu *et al*., 2024). Furthermore, the use of metformin must be closely monitored to minimize negative impacts on both financial and health aspects. Consequently, alternative treatments for diabetes mellitus are needed, for example by using of natural ingredients.

Papaya seeds (*Carica papaya* L.) and lemongrass (*Cymbopogon citratus*) are natural ingredients with potential as antidiabetic agents. The tannins and alkaloids in these two natural ingredients play a role in lowering blood glucose levels and improving the diameter of Langerhans islet. Tannins can neutralize free radicals and reduce oxidative stress caused by increased reactive oxygen species (ROS) (Smeriglio *et al*., 2017), thus reduce damage to pancretic beta cells and subsequently lower blood glucose levels. The tannins in lemongrass can also lower blood glucose levels by increasing glycogenesis activity (Susanti and Bistara, 2023) and delaying glucose absorption in the intestine (Sieniawska, 2015). Wulansari *et al*. (2017) demonstrated that papaya seed extract at doses of 100 mg/kg BW, 200 mg/kg BW, and 300 mg/kg BW was able to lower blood glucose levels and increase the expression of glucose transporter 4 (GLUT4) in diabetic mice. Anungputri *et al*. (2023) also showed that ethanol extract of lemongrass and aqueous extract of lemongrass at doses of 125 mg/kg BW and 250 mg/kg BW respectively showed no significant difference in lowering blood glucose levels and improving the diameter of Langerhans islet in mice.

Based on the above discussion, the novelty of this study lies in the effect of a combination of papaya seeds (*Carica papaya* L.) and lemongrass stems (*Cymbopogon citratus*) decoction to determine their effects on blood glucose levels and diameter of Langerhans islet in T2DM mice, as well as to identify the optimal type of decoction for improving these two parameters.

MATERIALS AND METHODS

This was an experimental study with a completely randomized design (CRD) consisting of six treatment groups; negative control group (KN); positive control induced with HFD and alloxan (KP); metformin-treated T2DM group (KM); as well as T2DM-induced group treated with 60% papaya seed decoction group (KA), 60% lemongrass decoction (KB), and combination of 60% papaya seed and lemongrass decoction (KC). Each treatment group consisted of four replications. This study was conducted from January to June 2026 at Basic Biology Laboratory, Experimental Animal Laboratory, and Microtechnique Laboratory of the Department of Biology, Surabaya State University.

The preparation of the decoctions began with the preparation of powdered natural ingredients. The papaya seeds and lemongrass stems were thoroughly washed, dried in an oven at 45°C for 2 days, then ground into powder. The process for preparing the papaya seed and lemongrass stem decoction followed the method described by Rahman *et al*. (2015). Decoction used was checked for its phytochemical content, including alkaloid, saponin, tanin, and flavonoid using qualitative method. Alkaloid content was tested using Mayer's, Wagner's, and Dragendroff's reagents until orange, brown, and white precipitates formed in each sample respectively. Saponin were tested by shaking a mixture of the decoction and hot water in a test tube until a long lasting foam formed. Tannin were tested by adding a $FeCl_3$ solution which produced a greenish brown or bluish black color. Meanwhile, the flavonoid content was tested by adding Mg powder and concentrated HCl which produced a red color.

This study used 24 male mice of the Deutschland Denken Yoken (DDY) strain, aged 2-3 months, weighing 20-30 g, which were acclimated for 7 days with standard 511 feed and water ad libitum. After accimatization, all groups except the negative control group (KN) were fed a high-fat diet (HFD) consisting of 80% standard 511 feed, 15% beef fat, and 5% duck egg yolk. The HFD was given at 20 g daily for 8 weeks or until the mice were diagnosed with hypercholesterolemic (cholesterol levels ≥130 mg/dL) (Mahmuda *et al*., 2024). Next, all groups except the KN group were induced with alloxan monohydrate at a dose of 110 mg/kg BW via intraperitoneal injection. After six hours of induction, the mice were given a 10% sucrose solution to drink for 48 hours to prevent hypoglycemia (Furman, 2021). Fasting blood glucose levels in mice were measured after 3 days of alloxan induction to confirm that the mice had developed hyperglycemia (≥ 126 mg/dL) (PERKENI, 2019).

Fasting blood glucose (FBG) levels were measured five times: pre-alloxan (after HFD); post-alloxan (day 3 after alloxan induction); and at days 7, 14, and 21 of treatment. Mice scheduled for FBG measurement were fasted for 8-12 hours beforehand. Blood samples were collected from the tail vein of

the mice using a blood lancet, then a drop of blood was placed on a glucose test strip. Fasting blood glucose levels were measured using glucometer (Easy Touch GCU).

Diameter of Islets of Langerhans was examined from pancreas histology slides. Mice were dissected on day 22 of treatment and pancreas were fixed in neutral buffer formalin. Slides were prepared using paraffin method and Hematoxylin-Eosin (HE) staining, as described by Khaleyla *et al*. (2021). The diameter of the Langerhans islet was measured using ImageJ software, using the following formula, as sketched in **Figure 1**.

$$Diameter\ of\ Langerhans\ islet = \frac{dy+dx}{2} \qquad (1)$$

Description:
dy = Diameter on the y-axis
dx = Diameter on the x-axis

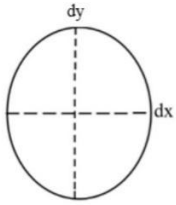


Figure 1. Sketch showing the measurement of the diameter of Langerhans isle. Description: dy = Y-axis diameter, dx = X-axis diameter.

Data of FBG and diameter of Langerhans islet were analyzed using SPSS software. The statistical analysis began with the Shapiro-Wilk test and Levene's test. The fasting blood glucose (FBG) data, which were normally distributed ($p>0.05$) and not homogeneous ($p<0.05$) were followed further analysed using the Brown-Forsythe test to determine the significance of data differences. Then, significant data differences ($p<0.05$) were analyzed using Games-Howell test to identify meaningful differences between the data. Diameters of Langerhans islet data, which were normally distributed ($p>0.05$) and homogeneous ($p>0.05$) were analyzed using One-Way ANOVA ($p<0.05$) and Duncan test ($p<0.05$).

RESULTS

As shown in **Table 1**, the results of the phytochemical test of the 60% combination of papaya seeds (*Carica papaya* L.) and lemongrass stems (*Cymbopogon citratus*) decoction indicated that the decoction contains alkaloids, saponins, and tannins. However, flavonoid was not detected from the decoction tested.

Table 1. Results of the phytochemical analysis of a combination of papaya seeds and lemongrass decoction

Identification	Description
Alkaloids	+
Saponins	+
Tannins	+
Flavonoids	-

Note: (+) contains metabolites, (-) does not contain metabolites

Measurement of FBG from mice models are presented in **Table 2**. FBG on day 21 after the treatments showed that KA (60% papaya seed decoction) had the highest FBG among the other decoctions at 188.25 ± 91.46 mg/dL while KB (60% lemongrass stem decoction) had the lowest FBG compared to other groups at 111.25 ± 14.66 mg/dL, however statistical test showed no significant difference due to large data deviation. Mice given 60% lemongrass decoction group (KB) showed the greatest decrease in FBG at 55.25 ± 18.73 mg/dL, while the smallest decrease in FBG was observed in the positive control group (KP) at -52.25 ± 94.91 mg/dL.

Diameter of Langerhans islets in mice after 21 days of treatments is presented in **Table 3**, while the Langerhans islets from each group are shown in **Figure 2**. The statistical analysis revealed that the diameter of Langerhans islet in mice were normally distributed ($p>0.05$) and homogeneous ($p>0.05$). The results of the One Way ANOVA indicated a significant difference in the data ($p<0.05$). The results of the Duncan test showed that the 60% papaya seed decoction group (KA) was not significantly

different from the positive control (KP) and metformin group (KM) groups. In addition, the negative control group (KN) group was also not significantly different from the KM, KB, and KC groups.

Table 2. FBG of mice at pre-alloxan, post-alloxan, and after decoction treatments on days 7, 14, and 21.

Group*	Fasting Blood Glucose Levels (mg/dL) **				
	Pre-alloksan	Post-alloksan	Treatment on day		
			7	14	21
KN	50.75 ± 0.96[a]	73.25 ± 17.00[a]	95.25 ± 16.68[a]	95.25 ± 12.79[a]	89.5 ± 6.45[a]
KP	111.25 ± 4.29[b]	148.5 ± 16.52[a]	263.25 ± 104.45[a]	320.5 ± 166.08[a]	200.75 ± 109.66[a]
KM	115.25 ± 15.20[b]	189.5 ± 66.41[a]	235.25 ± 120.64[a]	248.75 ± 153.86[a]	169.25 ± 112.46[a]
KA	121 ± 45.33[a]	191 ± 118.09[a]	248.25 ± 205.10[a]	211.5 ± 99.02[a]	188.25 ± 91.46[a]
KB	134.25 ± 34.55[a]	166.5 ± 21.05[a]	139.5 ± 32.11[a]	127.5 ± 39.00[a]	111.25 ± 14.66[a]
KC	127.25 ± 22.56[b]	148.25 ± 22.95[a]	157.75 ± 54.35[a]	139.75 ± 42.93[a]	116.5 ± 30.84[a]

Note: *) KN = Negative control, KP = Positive control (HFD+alloxan induction), KM = T2DM-induced given metformin, KA = T2DM-induced given 60% papaya seed decoction, KB = T2DM-induced given 60% lemongrass decoction, KC = T2DM-induced given 60% combination of papaya seed and lemongrass decotion group. **) Different letters indicate statistical difference at the 0.05 level.

Table 3. Diameter of Langerhans islets in mice models

Group	Diameter of Langerhans (µm) ± SD
KN	118.76 ± 50.13[c]
KP	51.45 ± 13.93[a]
KM	95.11 ± 34.61[bc]
KA	74.15 ± 50.72[ab]
KB	133.29 ± 36.37[c]
KC	116.67 ± 35.88[c]

Note: *) KN = Negative control, KP = Positive control (HFD+alloxan induction), KM = T2DM-induced given metformin, KA = T2DM-induced given 60% papaya seed decoction, KB = T2DM-induced given 60% lemongrass decoction, KC = T2DM-induced given 60% combination of papaya seed and lemongrass decotion group. **) Different letters indicate statistical difference at the 0.05 level.

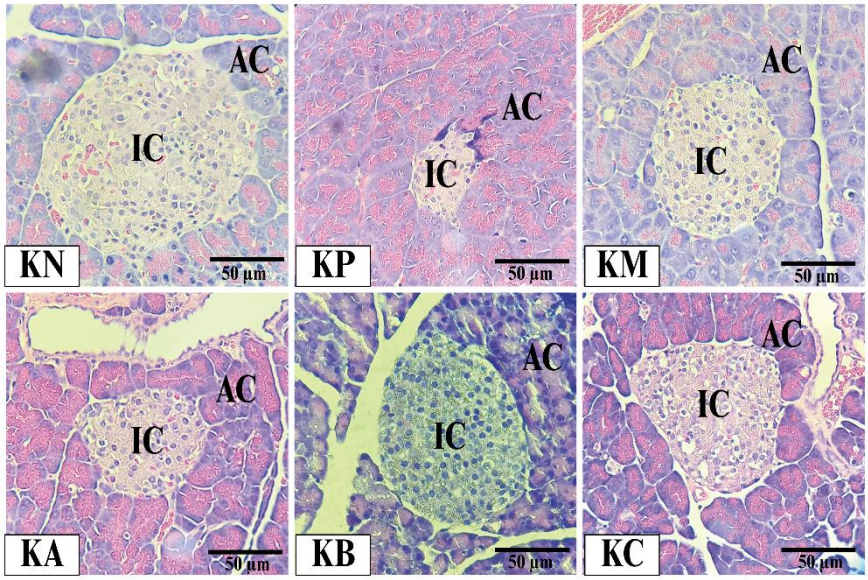


Figure 2. Langerhans islet from each group. IC = Langerhans Islet Cell, AC = Acinar Cell. KN = Negative control, KP = Positive control (HFD+alloxan induction), KM = T2DM-induced given metformin, KA = T2DM-induced given 60% papaya seed decoction, KB = T2DM-induced given 60% lemongrass decoction, KC = T2DM-induced given 60% combination of papaya seed and lemongrass decoction group.

DISCUSSION

Unhealthy lifestyle habits including imbalance of diets and low physical activity can be a risk factor for T2DM. A diet high in fat and sugar, combined with a lack of physical activity will contribute to obesity, consequently disrupts insulin signaling (Choo *et al*., 2026), leading to high blood glucose levels. The beef tallow used in the HFD contained 50.3% saturated fatty acids, dominated by palmitic and stearic acids (Utama *et al*., 2024). These two saturated fatty acids play a role in increasing Low-

Density Lipoprotein (LDL) and insulin resistance through inflammatory and oxidative stress mechanisms. This was demonstrated in a study by Hanna and Qomariyah (2025), which found that HFD containing beef fat over 56 days treatment can increase post-alloxan cholesterol levels to 132.75 ± 4.11 mg/dL. Meanwhile, egg yolk contains 73% cholesterol. Thus, the combination of the two can lead to increase levels of total cholesterol, LDL, and free fatty acids, which can disrupt glucose metabolism. Long-term increases in cholesterol and free fatty acid (FFA) levels can lead to hypercholesterolemia. This condition causes fat accumulation in various tissues, such as muscle, liver, and adipose tissue. Accumulation of FFAs accumulation can trigger increased formation of reactive oxygen species (ROS) (Petersen and Shulman, 2018). This process begins when fat accumulation in muscle tissue is converted into FFAs, which over time leads to further FFA accumulation. These accumulation FFAs are converted into Long Chain Fatty Acid-CoA (LCFA-CoA), which is subsequently broken down into ceramide and diacylglycerol (DAG) (Elkanawati *et al*., 2024). In the ceramide pathway, mitochondrial dysfunction occurs, leading to decreased fatty acid beta-oxidation and electron leakage, resulting in increased ROS levels (Feng *et al*., 2025). An imbalance between free radicals and antioxidants can lead to oxidative stress (Halim and Halim, 2019).

The accumulation of ROS and oxidative stress resulting from HFD and alloxan induction potentially disrupts insulin signalling and damage pancreatic beta cells. Excessive amounts of ROS activates serine-tyrosine kinase pathways, such as JNK (c-Jun N-terminal kinase), which triggers the degradation of IRS-1, thereby inhibiting the translocation of GLUT4 to the cell membrane (Shou *et al*., 2020). Reduced glucose uptake by cells causes high blood glucose level, which subsequently damage pancreatic beta cells due to oxidative stress. This leads to a reduction in the diameter of Langerhans islet and irregular changes in their histological structure.

Papaya seeds and lemongrass are natural ingredients that have potential to improve blood glucose levels and diameter of Langerhans islet in T2DM mice. Water soluble papaya seed extract contains flavonoid, tannin, alkaloid, and saponin (Pokhrel and Karki, 021). Meanwhile, lemongrass is believed to contain tannin, flavonoid, and steroid (Gazwi, 2019). The results of the phytochemical analysis of the 60% combination of papaya seed and lemongrass stem decoction indicated that the decoction tested positive for alkaloid, tannin, and saponin, while flavonoid were not detected in the decoction (**Table 1**). This is due to inappropriate boiling temperature and time as well as the fact that the plant parts used contain only small amounts of flavonoid, so these compound could not be extracted. High temperatures and prolonged boiling times cause the degradation of heat sensitive compounds (Zhang *et al*., 2018).

After treatment, KM experienced a decrease of FBG to 180 ± 109.47 mg/dL (**Table 2**). Metformin works by reducing glucose production in the liver, increasing the sensitivity of body cells to insulin, and reducing glucose absorption in the gastrointestinal tract (Amin *et al*., 2025). Furthermore, FBG on day 21 for KB group was 111.25 ± 14.66 mg/dL while KC was 116.6 ± 30.84 mg/dL, both of which were close to the normal range. Tannin plays a role in neutralizing free radicals and oxidative stress (Smeriglio *et al*., 2017), thereby inhibiting the activation of serine tyrosine kinase pathways such as JNK and activating the insulin signaling pathway. Tannin can increase glycogenesis (Susanti and Bistara, 2023) and delay the absorption of glucose in the intestines (Sieniawska, 2015). According to Ridho (2023), alkaloid can reduce blood glucose levels by stimulating glycogen synthesis, inhibiting gluconeogenesis, and increasing glucose oxidation.

Regarding Islet of Langerhans, KB had the largest diameter compared to the other groups at 133.29 ± 36.37 µm while KC had the second largest diameter at 116.67 ± 35.88 µm (**Table 3**). These two groups did not differ significantly from the KN at 118.76 ± 50.13 µm and the KM group at 95.11 ± 34.61 µm. This suggests that the KB and KC groups were able to repair damage to pancreatic beta cells.

Figure 2 show that the Langerhans islets in KM, KA, KB, and KC mice increased in size after 21 days of treatment, compared to KP. Metformin treatment can increase the sensitivity of body cells to insulin, so that glucose uptake by cells can occur optimally and maintain stable blood glucose levels Amin *et al*. (2025). Meanwhile, the KA, KB, and KC received either papaya seed, lemongrass, or combination of both decoction, which contain tannins, saponins, and alkaloids that can help repair pancreatic beta cells..

The tannin in papaya seeds and lemongrass stems can protect and regenerate beta cells by neutralizing free radicals and reduce oxidative stress (Smeriglio *et al*., 2022). Beta-cell recovery occurs through a free radical scavenging mechanism that decreases the acumulation of ROS within cells and alleviates oxidative stress. Pancreatic beta cells which are highly susceptible to oxidative stress (Maharani *et al*., 2023), such as due to a high-fat diet and alloxan induction, can undergo recovery and

an increase in the diameter of Langerhans islet assissted by antioxidative mechanism of tannins. The antioxidative of tannins occurs through hydrogen atom transfer (HAT), in which tannins donate hydrogen atoms to free radical compounds, thereby producing more stable radicals (Shahidi and Danielski, 2024). Meanwhile, alkaloid regenerate pancreatic beta cells and increase insulin secretion dengan by inhibiting glucose 6-phosphatase and fructose 1,6-biphosphatase which play a role in gluconeogenesis, increase glucose oxidation through glucose 6-phosphate dehydrogenase (Ridho, 2023), and by inhibiting dipeptidyl peptidase-4 (DDP-4) (Röhrborn *et al*., 2015). This mechanism is associated with an increase in the diameter of Langerhans islet due to the recovery of beta cells, which constitute the largest cellular component of these islets.

The results regarding the decrease in fasting blood glucose (FBG) and the improvement in the diameter of Langerhans islet in this study is different from those reported by Wulansari *et al*. (2017), Widaryanti and Tripramatasari (2021), and Anungputri *et al*. (2023). These differences are attributed to variations in extraction methods, decoction concentrations, treatment durations, and secondary metabolite content. The decoction method and concentration used in this study influenced the treatment duration. This is evidenced by the result of the study, which was conducted over 21 days and showed a gradual decrease in FBG levels. Additionally, the decoction method using distilled water as a solvent can also affect the content of secondary metabolites in decoction. High temperatures and long decoction times result in the degradation of heat-sensitive compounds (Zhang *et al*., 2018).

CONCLUSION

The most effective treatment to ameliorate T2DM in mice model was found to be KB group. In which FBG level decreased from 166.5 ± 21.05 mg/dL to 111.25 ± 14.66 mg/dL and resulting diameter of Langerhans Islets of 133.29 ± 36.37 µm.

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CONFLICT OF INTEREST

There is no conflict of interest.

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