

Hepatoprotective Activity of Papaya Seed (*Carica papaya* L.) and Lemongrass Stem (*Cymbopogon citratus*) Decoctions in Mice (*Mus musculus*) with Type II Diabetes Mellitus

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Abstract

Type 2 diabetes mellitus (T2DM) is a condition characterized by insulin resistance that potentially trigger hepatic steatosis through increased de novo lipogenesis and lipolysis in adipose tissue. This condition enhances the formation of reactive oxygen species (ROS), leading to mitochondrial dysfunction due to oxidative stress, which in turn triggers damage to hepatocytes. Papaya seeds and lemongrass stem are known to contain antioxidant compounds such as alkaloids, tannins, and saponins; that have the potential to lower T2DM-associated hepatic damages. This study aimed to determine the effectiveness of decoctions made from papaya seeds, lemongrass stem, and combination of both on the Hepatosomatic Index (HSI) and liver histopathological damage in T2DM mice models. The study used 24 male DDY strain mice divided into six treatment groups: normal control, positive control, metformin, 60% papaya seed decoction, 60% lemongrass stem decoction, and combination of both. Statistic test revealed a significant effect of the treatments on HSI and histopathological scores ($p < 0.05$). Results indicated that decoctions of papaya seed, lemongrass stem, and their combination significantly affected HSI and hepatic histopathological damage scores, with the 60% lemongrass stem decoction proving to be the most optimal treatment.

Keywords: diabetes; NAFLD; hepatosomatic index (HSI); steatosis; inflammation.

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INTRODUCTION

The global prevalence of diabetes mellitus (DM) has risen sharply from 200 million people in 1990 to 830 million in 2022, according to the WHO (2024) with Indonesia recording a prevalence of 11.3%, or approximately 20.4 million cases (IDF, 2024). The majority of cases are Type 2 Diabetes Mellitus (T2DM), characterized by insulin resistance despite normal insulin production.

A high-fat diet (HFD) triggers hyperglycemia and hypercholesterolemia, subsequently leading to insulin resistance in muscle, adipose tissue, and the liver. In T2DM, adipose tissue exhibits reduced insulin sensitivity, which potentially increase lipolysis and the release of free fatty acids to the liver. In turn, insulin resistance in liver can enhance de novo lipogenesis (DNL) (Palma *et al.*, 2022). Triglyceride accumulation in hepatocytes may lead to Non-Alcoholic Fatty Liver Disease (NAFLD), which triggers the formation of reactive oxygen species (ROS), mitochondrial dysfunction, and hepatocyte damage manifesting as steatosis, ballooning, and lobular inflammation (Kaban and Sunarti, 2019). Non-Alcoholic Fatty Liver Disease (NAFLD) correlates with an increased Hepatosomatic Index (HSI), a ratio of liver weight to body weight that serves as an indicator of liver toxicity and health.

Synthetic treatments such as metformin are effective at lowering blood sugar in T2DM, but long-term use carries the risk of gastrointestinal disturbances (Hameed *et al.*, 2017). Therefore, natural-based alternatives are necessary to be studied. Papaya seeds and lemongrass stems have been reported to contain compounds such as alkaloids, tannins, triterpenoids, and saponins (Djahi *et al.*, 2021) which possess possible bioactivity mechanism, such as antidiabetic and hepatoprotective properties. These effects are mediated through various mechanisms, for example free radical scavenging (Huang *et al.*, 2012), inhibition of α -amylase and α -glucosidase enzymes (Behl *et al.*, 2022), and the improvement of insulin sensitivity via the PI3K/Akt pathway in antidiabetic bioactivity (Huang *et al.*, 2018). This study aims to evaluate the effectiveness of papaya seed decoction, lemongrass stem decoction, and a

combination of both on the Hepatosomatic Index (HSI) and liver histopathology in a T2DM mouse model, as well as to determine the most optimal treatment. Decoction by boiling is a processing method commonly practiced by the general public; consequently, the findings of this study can be directly utilized by the community.

MATERIALS AND METHODS

This experimental study employed a Completely Randomized Design (CRD) with six treatment groups and four replicates (totaling 24 male DDY strain mice, aged 2–3 months, weighing 20–30 g). The six groups consisted of normal control (KN) (without HFD, alloxan, and decoction), positive control (KP) (T2DM without decoction), T2DM with metformin group (KM), T2DM with 60% papaya seed decoction group (KA), 60% lemongrass stem decoction group (KB), and 60% combination decoction group (KC).

Preparation of the 60% concentration decoction followed the method of Rahman *et al.* (2015), beginning with the production of simplicia by drying the papaya seeds and lemongrass stems. The material was then pulverized in a blender, and the decoction was prepared by boiling 10 g of simplicia in 100 mL of distilled water at 90°C for 15 minutes. Subsequently, a 60 mL aliquot of the decoction was taken and mixed with 40 mL of distilled water to obtain a decoction with a 60% concentration. Finally, the sample was analyzed for antioxidant compounds using phytochemical tests to detect flavonoids, alkaloids, tannins, and saponins.

The initial step in establishing T2DM model in the experimental animals involved administering a high-fat diet (HFD). Prior to this, the mice underwent a 7 day acclimatization period on a standard diet. Following this period, all groups (except the negative control group) were fed an HFD composed of 80% standard feed, 15% beef fat, and 5% duck egg yolk for 8 weeks; cholesterol levels were monitored periodically to confirm the onset of hypercholesterolemia (≥ 130 mg/dL) (Nugroho *et al.*, 2022). Once hypercholesterolemia was established, the animals were induced hyperglycemia with alloxan (110 mg/kgBW) via intraperitoneal single-dose injection to induce high-level fasting blood glucose levels (≥ 126 mg/dL) (PERKENI, 2019).

Once the test animals had developed T2DM, they were treated with decoction, delivered via gavage needle at a dosage of 1 ml per animal. The decoction was administered for 21 days; subsequently, the animals final body weights were recorded, and they were dissected to weigh their livers for the assessment of the Hepatosomatic Index (HSI). HSI was determined by calculating the ratio of liver weight to mouse body weight using the formula provided below (Putri *et al.*, 2021) :

$$HSI = \frac{\text{Liver Weight (gram)}}{\text{body weight (gram)}} \times 100\%$$

Liver histopathology preparations were produced using paraffin method and stained using Hematoxylin-Eosin as described by Khaleyla *et al.* (2021). Histopathological analysis was performed by counting steatotic and ballooning cells, as well as inflammatory cells in paraffin slide. The total cell counts were then summed, and statistical analysis was conducted.

The Hepatosomatic Index (HSI) and histopathological data obtained in this study were statistically analyzed using the Shapiro-Wilk normality test, Levene's test for homogeneity, and One-Way ANOVA, as the data followed a normal distribution. Duncan's test was employed as a post-hoc analysis to determine whether significant differences existed between the data groups

RESULTS

In this T2DM animal modeling study, fasting blood glucose levels were measured before and after the induction of alloxan to confirm the development of T2DM in each animal. Cholesterol level of T2DM model was recorded at average 149 mg/dL. The results shown in the following **Table 1** indicate that all groups except KN had developed T2DM.

Table 1. Fasting Blood Sugar Levels in Experimental Mice

Group*	Fasting Blood Sugar Levels (mg/dL)	
	Pre-Alloxan	Post-Alloxan
KN	69,5 ± 11,62	82 ± 11,69
KP	111,25 ± 4,29	148,5 ± 16,25
KM	115,25 ± 15,50	189,5 ± 66,41

KA	120 ± 43,42	192,25 ± 117,81
KB	134,25 ± 34,55	166,5 ± 21,05
KC	127,25 ± 22,56	148,25 ± 22,95

Description : *) KN = normal group; KP = positive group; KM = metformin group; KA = papaya seed decoction group; KB = lemongrass stem decoction group; and KC = combination group.

The results of the phytochemical analysis indicate that the combination of the decoction of papaya seeds and lemongrass stem contains antioxidant compounds specifically alkaloids, tannins, and saponins as shown in **Table 2** below. However, flavonoids were absent from the decoctions made in this study.

Table 2. Phytochemical test results for antioxidant compounds in a combined decoction of papaya seeds and lemongrass stem.

Phytochemical Test	Result*
Flavonoid	-
Alkaloid	+
Tanin	+
Saponin	+

Description : (+) : present, (-) : absent

The results showed that the HSI for the positive control group (KP) of $5.08 \pm 0.41\%$ to be higher significantly compared that of the normal control group (KN), at $3.68 \pm 0.37\%$. The three treatment group, KA, KB, and KC, was found to have no significant difference compared to normal control (KN), positive control (KP), and metformin control (KM). The HSI of each treatment group are presented in **Table 3**.

Table 3. Hepatosomatic index of T2DM mice following the administration decoction of papaya seeds and lemongrass stem.

Group	Body Weight (g)*	Liver Weight (g)*	HSI (%)*
KN	31,25 ± 1,26 ^a	1,15 ± 0,13 ^a	3,68 ± 0,37 ^a
KP	41,75 ± 3,30 ^b	2,13 ± 0,30 ^b	5,08 ± 0,41 ^b
KM	38,50 ± 1,73 ^b	1,43 ± 0,19 ^{ab}	3,69 ± 0,32 ^a
KA	38,75 ± 0,96 ^b	1,85 ± 0,34 ^{ab}	4,76 ± 0,78 ^{ab}
KB	39,25 ± 1,71 ^b	1,53 ± 0,13 ^{ab}	3,93 ± 0,19 ^{ab}
KC	38,75 ± 2,75 ^b	1,58 ± 0,62 ^{ab}	4,02 ± 1,33 ^{ab}

Description : *)Different letter notations indicate that the obtained data differed significantly based on the Mann-Whitney test results ($P < 0,05$); KN = normal group; KP = positive group; KM = metformin group; KA = papaya seed decoction group; KB = lemongrass stem decoction group; and KC = combination group.

Histopathological examination of the liver revealed steatosis in hepatocytes within the KP, KA, and KC groups, whereas hepatocyte ballooning was observed in the KP, KM, KA, KB, and KC groups. Lobular inflammation was evident across all treatment groups, including the negative control group (KN). Microscopic views of hepatocytes for each treatment group are presented in **Figure 1**.

Based on the observations made, the results regarding the degree of liver damage measured by the extent of steatosis, inflammation Cell, and ballooning are presented in **Table 4**. Duncan's test showed that KN exhibited the lowest number of inflammatory cells (7 ± 1.71), which was not statistically different from KM (7 ± 0.82) and KB (7 ± 1.29). Conversely, highest inflammation was found in KP (10 ± 1.26), KA (9 ± 0.96), and KC (8 ± 1.26). Regarding steatosis, no cells exhibiting this condition were observed in the KN, KM, or KB. In contrast, steatosis was found in KP, KA, and KC, with the highest level found in KP (5 ± 0.58), followed by KA ($4 \pm 2,65$) and KC ($2 \pm 1,41$). No ballooning cells were observed in the KN or KM groups. However, ballooning cells were present in the KP, KA, KB, and KC groups, with the highest prevalence observed in KP ($4 \pm 1,26$), followed by KA ($3 \pm 2,22$) and KC ($3 \pm 0,50$).

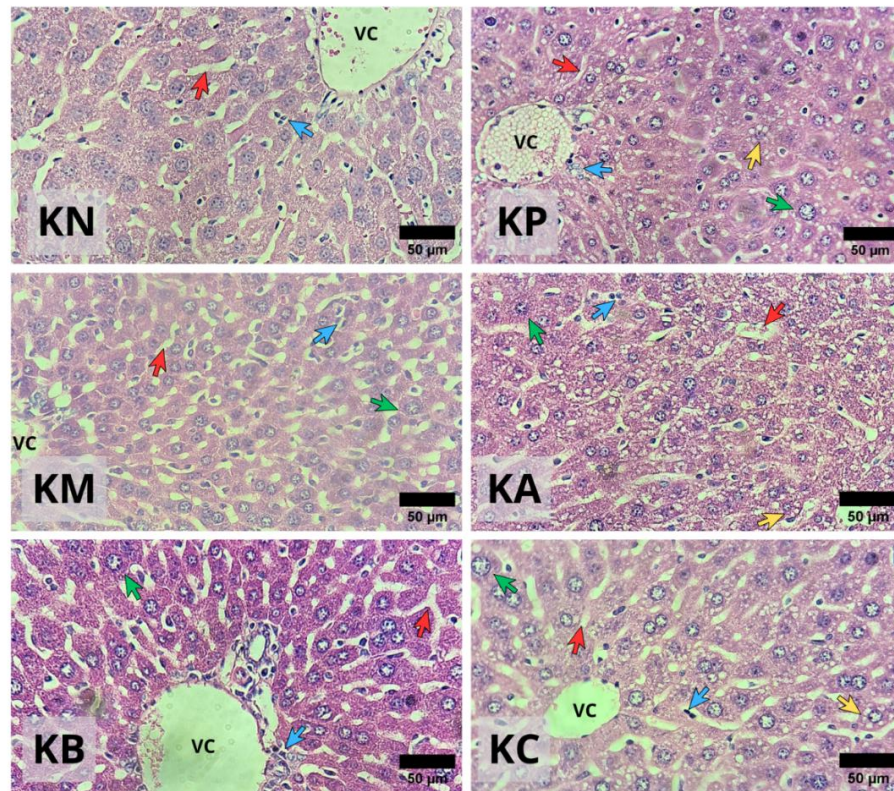


Figure 1. Hepatic histopathology results for each treatment group. KN = normal group; KP = positive control group; KM = metformin group; KA = papaya seed decoction group; KB = lemongrass stem decoction group; and KC = combination group; VC = central vein; red arrow = sinusoid; yellow arrow = steatotic hepatocyte; green arrow = ballooning hepatocyte; and blue arrow = lobular inflammation.

Table 4. Evaluation of abnormal cells in the liver histopathology of experimental mice

Group	Σ Steatosis Cells*	Σ Inflammation Cells*	Σ Balloning Cells*
KN	0 ± 0,00 ^a	7 ± 1,71 ^a	0 ± 0,00 ^a
KP	5 ± 0,58 ^b	10 ± 1,26 ^b	4 ± 1,26 ^b
KM	0 ± 0,00 ^a	7 ± 0,82 ^a	0 ± 0,00 ^a
KA	4 ± 2,65 ^b	9 ± 0,96 ^{ab}	3 ± 2,22 ^b
KB	0 ± 0,00 ^a	7 ± 1,29 ^a	1 ± 1,41 ^b
KC	2 ± 1,41 ^b	8 ± 1,26 ^{ab}	3 ± 0,50 ^b

Description: *)Different letter notations indicate significant differences in the data based on Duncan's post hoc test results ($P < 0,05$); KN = normal group; KP = positive control group; KM = metformin group; KA = papaya seed decoction group; KB = lemongrass stem decoction group; and KC = combination group.

DISCUSSION

A lifestyle involving the high consumption of carbohydrate or fat rich foods triggers fat accumulation in the body. In the liver, high intake of fats or carbohydrates leads to increased glycogen uptake via the de novo lipogenesis (DNL) mechanism (Palma *et al.*, 2022). This condition is exacerbated and induced by insulin resistance in muscle and adipose tissues occurred in T2DM. Insulin resistance in muscle tissue impairs GLUT4 translocation (Huang *et al.*, 2018).

GLUT 4 in muscles is the main agent that helps muscles absorb glucose in the blood as energy in muscles. Additionally, insulin-resistant adipose tissue exhibits increased fat breakdown, or lipolysis (Yang and Mottillo, 2020). The products of lipolysis free fatty acids are released into the bloodstream and eventually reach the liver. Consequently, the liver is subjected to a significant accumulation of fats and sugars. This accumulation stimulates the liver to undergo DNL, a process that normally results in the distribution of triglycerides throughout the body (Palma *et al.*, 2022). However, in the presence of insulin resistance, the products of DNL cannot be distributed throughout the body, resulting in an increase in liver mass that can affect the HSI value, given that the HSI represents the ratio of body weight to liver weight (Putri *et al.*, 2021). Among the treatment groups, the one exhibiting an HSI value most similar to the normal group (3.68%) was the metformin group (3.69%). Regarding the decoction treatment groups, the lemongrass stem decoction group showed an HSI value (3.93%) closest to that of

the normal control group. Meanwhile, the combination group showed a value of 4.02%, and the lemongrass stem decoction group showed a value approaching that of the positive control (4.76%). Therefore, the lemongrass stem decoction group demonstrated a high level of effectiveness. This is supported by Oktaviona *et al.* (2023), who noted that an HSI value closely resembling that of the normal control group indicates a healthy liver condition.

Histopathological evaluation of hepatocytes in the study showed that HFD-fed mice with the exception of the metformin treatment group exhibited hepatic steatosis. This condition arises because the consumption of diets high in carbohydrates or fats promotes fat accumulation in the body, ultimately leading to insulin receptor impairment in peripheral tissues (Zhao *et al.*, 2023). In muscle tissue, insulin receptor dysfunction reduces glucose uptake, thereby stimulating *de novo* lipogenesis in the liver (Smith *et al.*, 2020). This process generates new lipids in the form of VLDL; under conditions of insulin resistance, these lipids are stored within hepatocytes as triglycerides (Palma *et al.*, 2022) a phenomenon identified as steatosis during histopathological examination.

Furthermore, mechanisms within adipose tissue contribute to liver damage. Adipose tissue exhibiting insulin resistance undergoes increased lipolysis, releasing free fatty acids (FFAs) into the bloodstream (Yang and Mottillo, 2020). The liver is a primary destination for these circulating FFAs. Excessive lipolysis in adipose tissue leads to significant hepatic FFA accumulation. High levels of FFA accumulation damage hepatocyte mitochondria (Kaban and Sunarti, 2019), disrupting Na⁺ ion balance and preventing the cell from expelling these ions. Consequently, the cytoplasm undergoes massive swelling, a condition characterized as ballooning degeneration (Andini and Rahman, 2022).

Both ballooning inflammation and steatosis (fatty accumulation) can trigger the infiltration of inflammatory cells. Generally, the recruitment of these cells represents the body's mechanism for addressing damage or responding to foreign particles that threaten hepatocytes (Soliman and Barreda, 2022). However, an excessive presence of inflammatory cells poses a risk to the body. Specifically, massive infiltration of TNF- α and IL-6 into hepatocytes expands the area of inflammation; these inflammatory cells can induce the death of normal hepatocytes surrounding the primary inflammatory site, thereby driving the progression of liver pathology from fibrosis to cirrhosis (Maimunah *et al.*, 2024).

The group treated with the papaya seed decoction (KA) showed similar hepatocyte histopathology compared to positive control (KP); among the treatment groups receiving the decoction, the KA group exhibited the highest incidence of cells undergoing steatosis, balloning, and lobular inflammation. According to Umami *et al.* (2021), papaya seed decoction contains triterpenoids (steroids) and flavonoids; however, the phytochemical analysis conducted by the researchers in this study did not detect flavonoids. Consequently, the antioxidant activity in the papaya seed decoction administered to the subjects was likely attributable solely to triterpenoids (steroids). Research by Randeni *et al.* (2025) indicates that triterpenoids exert beneficial effects by activating the AMPK and PI3K pathways; conversely, steroid content tends to exacerbate insulin resistance in peripheral tissues such as muscle and adipose tissue as well as in the liver (Dewi and Titami, 2024).

The group treated with lemongrass stem decoction (KB) demonstrated good efficacy. This was evidenced by the absence of steatosis in the hepatocytes of KB, similar to those of the normal control (KN) group. This suggests that the antioxidant effects of the lemongrass stem decoction were able to counteract the type 2 diabetes mellitus condition in the experimental animals. The alkaloids present in the decoction are believed to function by enhancing PPAR- α activation, thereby facilitating fatty acid oxidation in the liver (Han *et al.*, 2017). Consequently, lipid droplets within the hepatocytes undergo oxidation, resulting in the absence of observable steatosis. Additionally, tannins play a role in inhibiting the breakdown of carbohydrates into simpler compounds such as sugars by suppressing the expression of α -amylase and α -glucosidase enzymes (Han *et al.*, 2017). Saponins also inhibit lipid peroxidation (Huang *et al.*, 2018); lipid peroxides are reactive oxygen species (ROS) compounds capable of causing excessive oxidative stress. Furthermore, saponins inhibit the expression of pro-inflammatory cytokines such as Tumor Necrosis Factor- α (TNF- α) and interleukin-6 (IL-6), which are the triggers for hepatocellular injury and hyperglycaemia (Jin *et al.*, 2022).

Hepatocyte ballooning ($1 \pm 1,41$) and lobular inflammation ($7 \pm 1,29$) were observed in KB. This may be attributed to the fact that, in this group, the extent of hepatic steatosis was lower relative to the degree of cellular inflammation. This aligns with the "multiple-hit" hypothesis of NAFLD proposed by Tilg and Moschen. (2010), which suggests that ballooning can manifest prior to steatosis. This phenomenon is driven by free fatty acids (FFA) products of adipose lipolysis which trigger mitochondrial dysfunction and oxidative stress that synergistically disrupt the hepatocyte cell

membrane cytoskeleton (Basiglio *et al.*, 2021). Observations revealed that hepatocytes exhibited swelling, a condition resulting from disrupted fluid transport into and out of the cells.

The group treated with the combination of papaya seed and lemongrass stem decoction (KC) showed a lack of efficacy comparable to that of the group treated with papaya seed decoction alone (KA). Nevertheless, compounds tending to exacerbate T2DM conditions continued to exert an effect through the distribution of steatosis cells. Consequently, this study indicates that the lemongrass stem decoction treatment group demonstrated the highest level of efficacy when evaluated based on hepatic histopathology.

CONCLUSION

Based on the Hepatosomatic Index (HSI) and liver histopathology scores, the group treated with the lemongrass stem decoction showed an effectiveness profile most similar to the negative control group; it exhibited an HSI of $3.93 \pm 0.19\%$ and lowest histopathological damage in the hepatocytes.

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CONFLICT OF INTEREST

There is no conflict of interest.

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