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The effects of *Carica papaya* L. juice on plasma aspartate transaminase/alanine transaminase level and liver histopathology in paracetamol-induced mice

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Abstract:

Liver is one of the primary and largest metabolic organs in the body. The function of the liver can be disturbed and damaged by paracetamol and liver damage can be prevented with papaya (*Carica papaya* L.). The purpose of this study was to know the effects of *C. papaya* juice on plasma AST/ALT level and liver histopathology in paracetamol-induced mice. Amount 25 Balb-C mice (*Mus musculus*) were divided into five treatment groups, there were normal, negative control, papaya juice dose (200, 400, 600) mg kg⁻¹ bw⁻¹ groups. The treatment was carried out for 7 d and then all mice (without normal groups) was induced by paracetamol. On the 8th d, blood was collected and all mice were sacrificed. The materials used in this study include *C. papaya* juice, CMC Na, paracetamol, AST and ALT reagents, Hematoxylin-Eosin and used Experimental Laboratory methods. One Way ANOVA and Kruskal Wallis with a confidence level of 95 % and followed by a post hoc test (LSD) to determine differences between groups. Showed that pretreatment with papaya juice could prevent liver damage and inhibit the increase of plasma AST/ALT level and papaya juice dose 600 mg kg⁻¹ bw⁻¹ had significant effects on plasma AST/ALT level and liver histopathology in paracetamol-induced mice. *Carica papaya* L. juice can be used as a hepatoprotective agent.

Keywords: Advantage papaya for health, AST/ALT, hepatoprotective agent, *in vivo*, manja roenigk score.

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Introduction

The liver is one of the major largest metabolic organs, the center of metabolism that occur can be disrupted if liver function is disrupted and damaged⁽¹⁾. Liver damage can caused by toxicity of N-acetyl-p-benzoquinoneimine and can be detected by increasing specific enzymes such as Aspartate Transaminase (AST), Alanine Transaminase (ALT) and detection of liver histology⁽²⁻⁴⁾. Liver damage can be prevented using papaya. The content of papaya juice function as a hepatoprotector. Based on that, this study aims to determine the effects of administration papaya juice on AST, ALT plasma concentration and liver histopathology of mice induced by paracetamol.

Materials and methods

The materials used in this study include papaya (*Carica papaya* L.) juice, CMC Na, paracetamol, AST and ALT reagents, 10 % formalin, xylol, paraffin, and Hematoxylin-Eosin. Amount 25 samples of Balb-C mice (*Mus musculus* [Linnaeus, 1758]) were previously adapted for 7 d at the Laboratory of Pharmacology and Toxicology Faculty of Pharmacy, University of Jember, Indonesia, then 25 samples of mice were divided into five groups, there are normal, negative, papaya juice dose 200 mg kg⁻¹ bw⁻¹, 400 mg kg⁻¹ bw⁻¹, and 600 mg kg⁻¹ bw⁻¹. This treatment was carried out for 7 d, and on the 7th d, all mice without normal group were induced by orally paracetamol dose 300 mg kg⁻¹ bw⁻¹. On the 8th d, blood was collected and followed by measurement of AST and ALT plasma concentration then all mice were sacrificed for taking liver organ and making liver tissue histology preparations with Hematoxylin-Eosin (HE) staining. Observations were carried out under a microscope with 400× magnification and assessed based on Manja Roenigk's histopathology scoring model⁽⁵⁻⁶⁾. And then all data was collected then analysis data using One Way ANOVA and Kruskal Wallis with a confidence level of 95 % and followed by a post hoc test (LSD) to determine differences between groups.

Statistic analysis:

One Way ANOVA and Kruskal Wallis with a confidence level of 95 % and followed by a post hoc test (LSD) to determine differences between groups.

Results

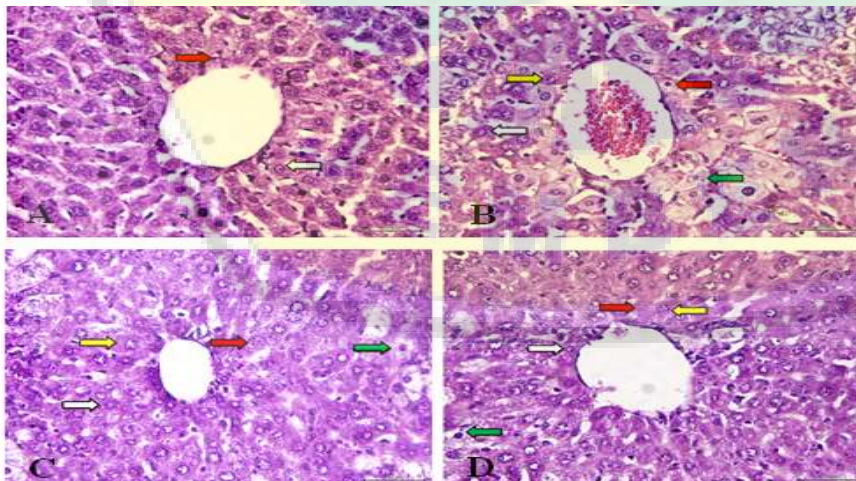
After 7 d of treatment and after being induced by paracetamol, the plasma concentrations of AST and ALT were obtained as follows:

Table 1: Results of the least significant difference (LSD) tests for average AST and ALT levels on plasma

Group	AST (U/L)*	ALT (U/L)*
Normal	18.93 ± 15.17 ^a	4.62 ± 3.23 ^a
Negative	272.79 ± 43.32 ^b	199.08 ± 48.48 ^b
Papaya Juice dose 200 mg kg ⁻¹ bw ⁻¹	127.48 ± 55.59 ^c	113.41 ± 13.56 ^c
Papaya Juice dose 400 mg kg ⁻¹ bw ⁻¹	39.75 ± 21.94 ^a	52.75 ± 32.96 ^d
Papaya Juice dose 600 mg kg ⁻¹ bw ⁻¹	28.39 ± 13.37 ^a	57.81 ± 44.38 ^{c,d}

*Different superscript letters indicate that there are significant differences at $p < 0.05$ between treatments, and the values are expressed as mean ± standard deviation (n=5)

Based on the results in table 1. shows increasing levels of AST and ALT plasma of mice after induced paracetamol dose of 300 mg kg⁻¹ bw⁻¹ compared to the normal group not induced by paracetamol. The administration of papaya juice from three doses showed decrease plasma levels of AST and ALT compared to the negative control group. The results of this study are supported by the research of Rajkapoor *et al.* which showed that water extract and ethanol extract of papaya fruit dose of 250 mg kg⁻¹ bw⁻¹ can reduce the levels of AST and ALT plasma on rat that induced, with water extract of papaya fruit It is better to lower levels of AST/ALT plasma ⁽⁷⁾. The higher dose of papaya juice was given have the greatest ability to inhibit the increase of plasma AST and ALT level. Large doses of papaya juice have more potential hepatoprotector compounds so that they have higher effectiveness in protecting liver cells and inhibiting increases in plasma AST and ALT levels due to induction of paracetamol. In this study, only the treatment group dose of 400 mg kg⁻¹ bw⁻¹ and 600 mg kg⁻¹ bw⁻¹ were able to maintain the normal AST value, but from the three treatment doses, it was not able to keep the normal ALT value. In this study, administration of papaya juice was effective at the optimum dose in preventing liver damage. This is histopathological figure can be seen in figure 1. From the result in figure 1. show that in the negative control group, many cells experienced parenchymatic degeneration, hydropic degeneration, and necrosis when compared to the normal group. The same thing happened in the papaya juice treatment group with a dose of 200 mg kg⁻¹ bw⁻¹ and 400 mg kg⁻¹ bw⁻¹, while the papaya juice treatment group with a dose of 600 mg kg⁻¹ bw⁻¹ and the normal group in general only showed normal cells and necrosis cells.



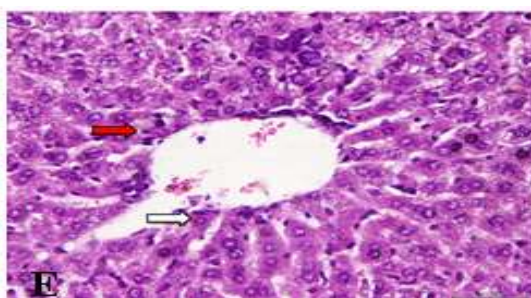


Figure 1: Cross section liver histopathological mice with hematoxylin–eosin staining 400 × magnification; (A) Normal; (B) Negative control; (C) Treatment papaya juice dose 200 mg kg⁻¹ bw⁻¹; (D) Treatment papaya juice dose 400 mg kg⁻¹ bw⁻¹; (E) Treatment papaya juice dose 600 mg kg⁻¹ bw⁻¹; (⇔) Normal hepatocytes; (⇨) Hepatocytes with parenkimatosa degeneration; (⇩) Hepatocytes with hydropic degeneration; (⇨) Necrosis hepatocytes.

Then the calculation of liver histopathology score was performed using the Manja Roenigk's scoring histopathology model presented in table 2.

Table 2: Results of the least significant difference (LSD) tests for average score liver histopathological using manja roenigk score model

Group	Average of score Liver Histopathological ± SD*
Normal	165.0 ± 12.1 ^a
Negative	200.4 ± 6.5 ^b
Papaya Juice dose 200 mg kg ⁻¹ bw ⁻¹	220.6 ± 34.9 ^b
Papaya Juice dose 400 mg kg ⁻¹ bw ⁻¹	183.8 ± 15.5 ^b
Papaya Juice dose 600 mg kg ⁻¹ bw ⁻¹	152.0 ± 2.9 ^a

*Different superscript letters indicate that there are significant differences at $p < 0.05$ between treatments, and the values are expressed as mean ± standard deviation (n = 5)

The data showed that negative control group there was a high increase in a liver histopathological score when compared with the normal group. Whereas in the treatment group, the histopathological score decreased with increasing doses of papaya juice. Liver histopathology score showed that papaya juice 600 mg kg⁻¹ bw⁻¹ had the smallest damage score compared with other treatment groups and the number of scoring for Manja Roenigk was close with the normal group. This results proved that the administration of papaya juice dose 600 mg kg⁻¹ bw⁻¹ was the most effective dose to prevent liver damage in mice due to exposure to reactive metabolites of paracetamol.

Discussion

Induction of paracetamol at a dose of 300 mg kg⁻¹ bw⁻¹ is proven to cause liver damage in mice. The induction of paracetamol causes an increase of plasma AST and ALT levels and increase the degree of liver histopathology. This is supported by previous research that the induction of paracetamol at a dose of 300 mg kg⁻¹ bw⁻¹ can increase plasma AST and ALT levels and cause liver damage to mice in the central region of the liver lobule and even DNA fragmentation^(8, 9). Iwalokun *et al.* show that the induction of paracetamol at a dose of 300 mg kg⁻¹ bw⁻¹ can increase plasma AST and ALT levels compared to the normal group⁽⁸⁾. This condition caused by paracetamol that produces free radicals, namely NAPQI (N–Acetyl–P–Benzoquinone Imine) that can cause damage to liver cells⁽¹⁰⁾. Normally, the body can eliminate NAPQI by conjugating the metabolite mercapturat with the help of GSH (Glutathione) enzymes, but NAPQI which covalently binds to hepatocyte cells can cause damage to hepatocyte cells and in a long time can cause hepatocyte cell necrosis⁽¹¹⁾. This process can increase membrane permeability, then AST and ALT are released into the bloodstream, and there is an increase in plasma AST/ALT concentrations⁽¹²⁾. The administration of papaya juice for 7 d before the induction of paracetamol can reduce plasma AST/ALT levels and be able to reduce the degree of liver histopathology, but not in the whole group. It means that the administration of papaya juice at the optimum dose can reduce the degree of liver histopathology due to the induction of paracetamol. Awodele *et al.* show that the administration of papaya fruit extract dose 300 mg kg⁻¹ bw⁻¹ could protect liver cells from damage in the form of fatty degeneration and necrosis due to the induction of paracetamol⁽¹³⁾. These results showed that administration of papaya juice could reduce levels of

AST/ALT and score liver histopathological. The ability of papaya juice as a hepatoprotective agent is caused by the content of beta-carotene, carotenoids, beta-cryptoxanthin, lycopene, niacin, thiamine, riboflavin, alkaloids, terpenoids, flavonoids (ferulic acid, caffeic acid and rutin), vitamin A, C, and E which can act as antioxidants⁽¹⁴⁻²²⁾. Vitamin C can reduce free radicals by donating hydroxyl atoms to free radicals that are thought to be able to bind NAPQI so that it can prevent bonding with liver cell macromolecules and liver cell damage can be avoided, beta-carotene can reduce free radicals by giving hydrogen atoms from its conjugated double bonds, and vitamin E can prevent lipid peroxidation⁽¹⁵⁾. Besides papaya juice also contains flavonoids (quercetin) which not only act as free radical scavengers by donating electrons but also able to inhibit the work of CYP enzymes in producing free radicals and able to serve as chelating Fe ions by stabilising Fe with do not bind H₂O₂ to form OH- as reactive free radicals^(19, 23). The content of papaya juice is thought to act as a hepatoprotective agent with a mechanism as an antioxidant.

Conclusion

Based on the results can be concluded that the administration of papaya juice was able to decrease plasma AST/ALT levels and score liver histopathological, so papaya juice can act as a hepatoprotective agent. But further research is needed regarding the content of the main compounds of papaya juice which act as hepatoprotective agents.

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