



(MUDIMA)



Study of Antioxidant Activity and Hepatoprotector Potential of Ethanol Extracts of Bark *Mezzettia Parviflora* Becc. On Liver Function of Wistar Strain Rats (*Rattus Novergicus* L.)

Masykur¹, Nurdin^{2*}, Lukman Hakim³, Rosnizar⁴, Widya Sari⁵, Asmaul Husna⁶, Ria Ceriana⁷

^{1,2,3,4,5,6}University of Syiah Kuala Banda Aceh

⁷Academy of Mandiri YPPM Pharmacy Banda Aceh

Corresponding Author: Nurdin nurdin@usk.ac.id

ARTICLE INFO

Keywords: *Mezzettia Parviflora* Becc, Stem Bark, SGOT, SGPT, Hepatoprotector, Antioxidant

Received : 4 March

Revised : 19 April

Accepted : 24 May

©2024 Maskur, Nurdin, Hakim, Rozniar, Sari, Husna, Ceriana: This is an open-access article distributed under the terms of the [Creative Commons Atribusi 4.0 Internasional](https://creativecommons.org/licenses/by/4.0/).



ABSTRACT

This study aims to analyze the hepatoprotective potential of ethanol extract of *Mezzettia parviflora* Becc. stem bark. (EEKBM) on serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) levels in rats induced by toxic doses of paracetamol, as well as measuring the antioxidant concentration of EEKBM. The method used in this research was a Completely Randomized Design (CRD) consisting of 6 treatment groups and 4 replications. The test animals used were 24 individual male rats that were induced by hepatotoxicity with 1350 mg/kgBW of paracetamol on day 7, except for the normal control (K0) which was given distilled water. Test animals received treatment with distilled water in the negative control (K-), Hepa-Q as much as 11.34 mg/kgBW in the positive control (K+), EEKBM dose of 150 mg/kgBW (P1), dose of 300 mg/kgBW (P2), and a dose of 600 mg/kgBB (P3) for 14 days. Data on SGOT and SGPT levels were analyzed using Analysis of Variance (ANOVA) with a significance level of 5% with the Tukey test as a further test. The results of the study showed that there was a significant difference ($P < 0.05$) in the effect of giving EEKBM on SGOT and SGPT levels. Based on the research results, it was concluded that a dose of 150 mg/kgBB EEKBM has hepatoprotective potential. Spectrophotometric measurement results show that EEKBM has an IC₅₀ value of 96.308 $\mu\text{g/mL}$, categorized as strong antioxidant activity

INTRODUCTION

The liver is the largest and most important organ in the body which is located in the upper right quadrant of the abdominal cavity, precisely under the diaphragm (Sudoyo, 2014). The liver has an important role because it functions as an organ of synthesis, detoxification, formation and excretion of bile (Ozougwu, 2017). This organ detoxifies xenobiotic compounds in the blood. Xenobiotic compounds are foreign compounds to the body and must be metabolized so they can be excreted from the body (Rahmawati *et al.*, 2018).

One of the xenobiotic compounds is a drug (Rahmawati *et al.*, 2018). Medicines can cause liver damage. Another term for liver damage caused by drugs is Drug Induced Liver Injury (DILI), namely drugs that are categorized as hepatotoxic so they can induce liver damage such as paracetamol (Yoon *et al.*, 2016 and (Rafita *et al.*, 2016). Paracetamol toxicity occurs due to the buildup of paracetamol metabolites by cytochrome P450 enzymes in the form of N-acetyl-p-benzoquinone (NAPQI) which are toxic and free radicals (Oktavia *et al.*, 2017 and (Ikawati, 2010). Paracetamol poisoning is the main cause of drug-induced liver failure which is most common in the United States and England (Graham *et al.*, 2013).

Liver damage can be detected by increasing levels of serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) enzymes in the blood. The potential for liver damage can be prevented by administering liver-protecting substances called hepatoprotectors. Hepatoprotector is a compound that can provide protection to the liver from liver damage (Yusuf *et al.*, 2018). Many hepatoprotective compounds are obtained from plants, one of which is plants from the Annonaceae family (Husna & Husni, 2018 and (Zakiah *et al.*, 2017).

Annonaceae family plants contain flavonoid compounds which function as antioxidants so they can be used as hepatoprotectors (Parapaga *et al.*, 2018), for example bark of soursop (*Annona muricata* L.) (Masykur *et al.*, 2023b)a and bark of sugar apple (*Annona squamosa* L.) (Masykur *et al.*, 2023a). The ongkea plant (*Mezzettia parviflora* Becc.) is also a member of the Annonaceae family which contains flavonoid, tannin and phenolic chemical compounds and has antioxidant activity (Mufidah *et al.*, 2012). Members of the Annonaceae

family which also contain flavonoids are the *Mezzettia parviflora* Becc. (goat weed), so it is thought to have antioxidant levels and has the potential to be a hepatoprotector. Information regarding the potential of plants from the *Mezzettia* genus as hepatoprotectors is still very limited. Therefore, this research was carried out to determine the hepatoprotective potential of the goat gompol plant (*Mezzettia parviflora* Becc.) on the liver function of rats (*Rattus norvegicus* L.) through analysis of SGOT and SGPT levels.

METHODS

Place and Time of Research

The study was conducted in September and December of 2020. The Syiah Kuala University (USK) Faculty of Veterinary Medicine's Experimental Animal Laboratory handled the preparation and care of the test animals. Preparation of *Mezzettia parviflora* extract. carried out at the Organic Chemistry Laboratory, Faculty of Mathematics and Natural Sciences, USK. Antioxidant tests were carried out at the Analysis and Instrumental Laboratory, Chemical Engineering, USK. The Research Clinical Laboratory in Kuta Alam District, Banda Aceh, examined the levels of serum glutamic pyruvic transaminase (SGPT) and glutamic oxaloacetic transaminase (SGOT).

Tools and Materials

The tools used in this research were the Orion AquaMate 8000 uv-vis spectrophotometer, gastric sonde, mortar and pestle, maceration container, dropper pipette, beaker, measuring flask, test tube, test tube rack, spatula, analytical balance, economical rotary evaporator RE 100-S, spoon, measuring cup, 1 mL syringe, blood tube, capillary tube, rat rearing cage measuring 50 cm x 40 cm x 30 cm with the top covered with wire mesh and a drinking bottle.

The components utilized in this research were 2 kg of *Mezzettia parviflora* bark. (goat weeds). Other ingredients include distilled water, 96% ethanol, plastic funnel, cuvette, DPPH crystals, aluminum foil, SGOT reagent, SGPT reagent, Whatmann filter paper, feed, physiological NaCl, 24 aged three-month-old male rats weighing an average amount of 268.458 ± 12.53 g, tissue, label paper, mask, gloves,

rice husks, ad libitum feeding and drinking water (twice a day at 11.00 WIB and 17.00 WIB).

Research Methods

This study employed an experimental strategy using a completely randomized design (CRD) that included four replications and six treatments, specifically:

K0, or normal control: Rats received 14 days of distilled water.

Negative control (K-): Rats induced by paracetamol 1350 mg/kgBW on day 7.

Positive control (K+): Rats given Hepa-Q 11.34 mg/kgBW for 14 days + paracetamol 1350 mg/kgBW on day 7.

Treatment 1 (P1): Rats were given ethanol extract of *Mezzettia parviflora* bark. 150 mg/kgBW for 14 days + paracetamol 1350 mg/kgBW on day 7.

Treatment 2 (P2): Rats were given ethanol extract of *Mezzettia parviflora* bark. 300 mg/kgBW for 14 days + paracetamol 1350 mg/kgBW on day 7.

Treatment 3 (P3): Rats were given ethanol extract of *Mezzettia parviflora* bark. 600 mg/kgBW for 14 days + paracetamol 1350 mg/kgBW on day 7.

Determination of the treatment dose of *Mezzettia parviflora* bark. ethanol extract. based on the dose range in previous research (Zakiah *et al.*, 2017). The procedure for testing hepatoprotective activity which includes a period of administering paracetamol and plant extracts to experimental animals is based on research by (Indahsari, 2017). Preparation of doses of ethanol extract of *Mezzettia parviflora* bark. stem bark, calculation of doses of paracetamol and Hepa-Q. Determination of the minimum number of test animals is based on the formula as follows:

$$(t - 1) (n - 1) \geq 15 \quad t = \text{number of treatments}$$

$$(6 - 1) (n - 1) \geq 15 \quad n = \text{number of repetitions}$$

$$5n - 5 \geq 15$$

$$5n \geq 20$$

$$n \geq 4$$

Four test animals were found to be in each category based on the computation results. As a result, a total of 24 test animals were used in this investigation.

How it Works

1. Sample Collection and Processing

Samples of goat gompol (*Mezzettia parviflora* bark) were obtained from the Sultan Daulat District, Subulussaalam City, Aceh Province's Soraya

Research Station, Leuser Ecosystem Area. With the help of a guide, collection is done in areas where these plants are believed to be found. The samples that have been collected are then air-dried at room temperature. The bark is cut into small pieces and finely ground into a homogeneous powder and the sample is ready to be extracted.

2. Sample Extraction

Bark samples of *Mezzettia parviflora* bark. 1 kg of dried (simplicia) is used, put into a container for maceration. The extraction process was carried out by maceration as carried out by (Ramdaniah, 2014), namely by using 96% ethanol solvent and simplicia soaked for 3x24 hours. The maceration process is carried out repeatedly until a yellowish colored solution is obtained. After that, the filtrate was concentrated and filtered at 35 °C using a rotary evaporator. After that, the extracted material was put in a covered bottle and refrigerated at 15 °C. To make it easier to provide to experimental animals, the extract is prepared as a liquid suspension that is dissolved in distilled water.

3. Antioxidant Test

To test for antioxidant content, the DPPH (1,1-Diphenyl-2-picrylhydrazyl) technique was used, as described by (Ridho, 2013). A total of 0.005 g of extract was diluted with 96% alcohol in a 50 mL volumetric flask so that the concentration became 100 ppm. DPPH crystals were weighed as much as 0.002 g and then dissolved with 96% alcohol in a 10 mL volumetric flask so that the concentration was 0.002% (w/v). A total of 1 mL of sample with a concentration of 50 µg/mL, 75 µg/mL, 100 µg/mL, 125 µg/mL and 150 µg/mL was added to 2 mL of 0.002% DPPH solution, mixed and shaken until homogeneous, then left for 30 minutes. The sample is then poured into a cuvette and then put into a spectrophotometer for measurements with a wavelength of 516 nm. The percentage of antioxidants is calculated using the following equation (Pujiarti *et al.*, 2015):

$$\% \text{ Antioxidant} = [(Ac - As)] / Ac \times 100$$

Information:

Ac: Absorbance control

As: Sample absorbance

The antioxidant activity data obtained was then entered into Microsoft Excel to obtain the percentage of antioxidant values. The concentration values of the 5 extract samples and their percent inhibition

were plotted respectively on the x and y axes in the linear regression equation. The linear regression equation obtained in the form $y = ax + b$, is used to find the IC50 (Inhibitor Concentration 50%) value of each sample, the y coefficient states the y value of 50 and the x value that will be obtained is IC50. The IC50 value states the sample concentration required to reduce free radicals by 50% (Ridho, 2013).

4. Care of Experimental Animals

In this investigation, 24 male Wistar rats, weighing an average of 268.458 ± 12.53 g at three months of age, were employed. The mice utilized were acquired from Syiah Kuala University's Faculty of Veterinary Medicine's Experimental Animal Laboratory. For seven days, mice were housed in cages that were 50 cm by 40 cm by 30 cm and had a wire mesh cover to help with acclimatization. Every three days, the cage is cleaned and coated in husk up to a height of 3 cm. Natural lighting was used for 21 days of cage maintenance at the Experimental Animal Laboratory, Faculty of Veterinary Medicine, Unsyiah. Standard pellets were used as food, and mice were given unlimited access to drink (as needed).

5. Treatment of Experimental Animals

a. Administration of plant ethanol extract and paracetamol

The Experimental Animal Laboratory provided seven days for the acclimatization of test animals. After acclimation, mice designated as negative control (K-) and normal control (K0) were treated with distilled water for a period of 14 days. Hepa-Q, a pharmaceutical medication, was given to positive control (K+) mice at a dose of up to 11.34 mg/kgBW in 1 mL of distilled water.

Test animals in three groups were each given a dose of ethanol extract of *Mezzettia* sp stem bark. for 14 days after acclimatization with three dose levels, namely a dose of 150 mg/kgBW in treatment group 1, a dose of 300 mg/kg/BW in treatment group 2 and a dose of 600 mg/kgBW in treatment group 3. The extract was given orally using a probe. stomach. Rats in each group except K0 were given paracetamol on day 7 with a toxic dose of 1350 mg/kgBW with an administration volume of 1 mL and after 2 hours they were given ethanol extract of *Mezzettia parviflora* bark. stem bark. according to the dose level of each treatment group.

b. SGOT and SGPT Measurements

Rat blood was taken from the heart on the 15th day after EEKBM treatment. The blood collection method was carried out as in the research of (Fahrimal *et al.*, 2014). The mice were anesthetized with chloroform then a needle was inserted directly into the heart, the blood was sucked out slowly and collected in a clean, dry blood tube. 3 mL of blood was taken from each mouse. Blood samples were sent to the Research Clinical Laboratory for SGOT and SGPT measurements.

Research Parameters

The parameters used in this research were the antioxidant concentration of *Mezzettia parviflora*. as well as rat blood SGOT and SGPT levels.

Data Analysis

The data obtained in this research is quantitative and descriptive data. Quantitative data in the form of SGOT and SGPT levels were analyzed using One Way ANOVA (Analysis of Variant) and further tested with Tukey at the 5% level (Gomez & Gomez, 2006). The software used to process quantitative data is SPSS statistics 18. Antioxidant levels will be explained descriptively. The software used to process antioxidant levels is Microsoft Office Excel 2007.

RESULTS AND DISCUSSION

Antioxidant Test

The human body is naturally able to produce antioxidants and can conjugate free radicals with the help of the enzyme glutathione-SH (GSH). However, if the free radicals formed from toxic doses of paracetamol are very high, GSH will no longer be able to bind optimally so liver function disorders will occur. As a result, extra antioxidants from outside the body are required as treatment for paracetamol toxicity. An added antioxidant in this study was *Mezzettia parviflora* bark stem bark ethanol extract (EEKBM). The presence of secondary metabolites in EEKBM, which may have antioxidant properties, is assumed to be the reason for the variation in mean levels of SGOT and SGPT in the treatment regimen. It is believed that the chemicals in EEKBM have the ability to bind NAPQI, which is a type of free radical created by paracetamol.

Determination of antioxidant activity values in DPPH (2,2-diphenyl-1-picrylhydrazyl) was the method employed in this investigation. (Robinson, 1963) clarified that the objective of this technique is to quantify antioxidant activity, namely by measuring the capture of stable free radicals, such as DPPH combined with chemicals that act as hydrogen donors and act as antioxidants. DPPH free radicals

can be reduced, and measurements are carried out using UV-Vis spectrophotometry. The IC50 (Inhibitory Concentration) value, which expresses the value of free radical reduction activity, is shown in the resultant value. Based on measuring the antioxidant activity of EEKBM spectrophotometrically, the IC50 value is 96.3081 $\mu\text{g/mL}$ (Table 1).

Table 1. Antioxidant Activity of EEKBM

Concentration (PPM)	Control Absorbance	Sample Absorbance	% Antioxidant	IC50
50	0,7058	0,697	1,289	96,308
75	0,7058	0,679	3,840	
100	0,7058	0,549	22,287	
125	0,7058	0,503	28,691	
150	0,7058	0,480	31,978	

The EEKBM IC50 value is obtained from the results of calculating the linear regression equation in Figure 4.2, the regression equation used is $y = 0.344x - 16.874$ and $R^2 = 0.921$. Based on this equation, it can be assumed that the y coefficient is IC50, while the x coefficient is the coefficient of the extract whose value will be sought. The value of x obtained is the concentration required to reduce 50%

of DPPH radical activity. The value of $R^2 = 0.921$ which is close to +1 or a positive value indicates that as the concentration of the extract increases, the antioxidant activity becomes greater. This can be seen from the curve of the relationship between EEKBM concentration and percent inhibition in Figure 1.

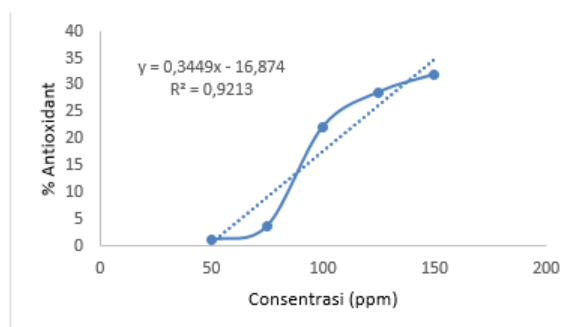


Figure 1. EEKBM Linear Regression Curve

Based on the obtained calculation findings, the IC50 EEKBM value is 96.3081 $\mu\text{g/mL}$. According to Molyneux (2004), the concentration of the test substance that may reduce free radicals by 50% is known as the IC50 value. The amount of free radical scavenging activity increases with decreasing IC50 value. According to Blois (1958), a compound has a very strong antioxidant if the IC50 value is less

than 50 ppm, a strong antioxidant if the IC50 value is between 50 - 100 ppm, a medium antioxidant if the IC50 value is between 100-150 ppm and a weak antioxidant if the IC50 is between 150 -200 ppm and if the IC50 value is above 200 ppm then it is considered a very weak antioxidant.

Table 1 indicates that EEKBM has a strong antioxidant activity and the potential to be a

hepatoprotector. The highest concentration (150 ppm) of EEKBM is able to block 31.978% of DPPH radicals. Based on the results of phytochemical screening in preliminary tests that have been carried out, the groups of compounds that are thought to have potential as antioxidants in EEKBM include flavonoids, terpenoids, phenols, tannins, saponins, steroids and alkaloids. Several compounds have the potential to act as antioxidants, namely flavonoids, terpenoids, phenols and tannins (Rabeta & Lin, 2015; Ridho, 2013; Ismeri, 2011), saponins and nitrogen group compounds, namely alkaloids and xanthines, which act as hepatoprotectors (Ismeri, 2011). (Ridho, 2013) explains that flavonoid and terpenoid compounds in their structure contain hydroxyl groups (-OH) which can donate hydrogen atoms to free radicals, so these compounds have the potential to act as antioxidants. (Grace-Lynn *et al.*, 2012, Marzouk, 2009) added that the hydroxyl group can capture free radicals such as NAPQI and convert them into non-active metabolites so that they do not cause damage to body cells.

The secondary metabolite content of EEKBM in the form of phenolic compounds is also antioxidant, so it has the potential to bind free radicals produced by paracetamol in the form of NAPQI. According to (Dwijayanti, 2011), Because they give free radicals hydrogen, phenol chemicals stabilize free radicals, making them antioxidants. According to (Fahrudin *et al.*, 2015) and (Rousdy *et al.*, 2023) phenol compounds have the potential to function as hepatoprotectors since they can lower blood levels of liver enzymes, raise GSH levels, and enhance the appearance of hepatocyte injury.

The secondary metabolite tannin contained in EEKBM is also an antioxidant compound which has an OH group and can be donated to free radicals. (Zakaria, 2007); (Seyoum *et al.*, 2006); and (Sulandi, 2013), reported that the OH group in tannin and alkaloid compounds will replace GSH which has decreased due to the presence of free radicals from administering toxic doses of paracetamol. Apart from that, tannins can also help conjugate paracetamol to mercapturic acid and convert NAPQI into an inactive and hydrophilic compound so that it can be excreted in the urine.

RAT SGOT and SGPT Levels

Measurement of serum glutamate oxaloacetate transaminase (SGOT) and serum glutamate pyruvate transaminase (SGPT) levels was carried out after administering ethanol extract of *Mezzettia parviflora* bark. stem bark. (EEKBM). SGOT and SGPT level data were tested statistically, including normality test, homogeneity test, ANOVA test and Tukey's advanced test. Based on the normality test, the data is normally distributed with a significant value ($p > 0.05$). The data is declared homogeneous, with a sig value ($p > 0.05$) and has no differences in variation because it comes from the same population. The data from the SGOT and SGPT levels were then subjected to an Analysis of Variance (ANOVA) test to determine whether or not there was a real effect in each treatment group and tested further using the Tukey test. Based on statistical tests, administration of various doses of EEKBM had a significant effect ($p < 0.05$) on SGOT and SGPT levels in mice after being induced by paracetamol (Table 2 and Table 3).

Table 2. The Average SGOT Levels of Rats After Administering Paracetamol and Followed by Administering Various Doses of *Mezzettia Parviflora* Becc. Bark Extract (EEKBM)

Treatment	Parasetamol (mg/kgBw)	Hepatoprotector (mg/kgBw)	Average level of SGOT $\bar{x} \pm sd$ (IU/L)
K0	-	-	52,5 ^a \pm 6,403
K-	1350	-	373,75 ^c \pm 6,449
K+	1350	Hepa-Q 11,34	170,5 ^{ab} \pm 50,342
P1	1350	EEKBM 150	140,75 ^{ab} \pm 79,16
P2	1350	EEKBM 300	177 ^b \pm 40,158
P3	1350	EEKBM 600	121,75 ^{ab} \pm 84,2

Note: Different Superscript Letters (a, b and c) Indicate There is a Significant Difference ($P < 0.05$)

Normal control test animals (K0) had an average SGOT level of $52.5 \pm 6,403$ IU/L. The

results obtained are in accordance with research by Wibowo *et al.* (2008) and Gad (2006), namely

normal SGOT values in mice range from 45.7 – 80.8 IU/L. SGOT levels in mice treated with K- (373.75 ± 6,449 IU/L) were significantly different ($p < 0.05$) compared to those treated with K0. The accumulation of the reactive toxic metabolite from paracetamol, N-acetyl-p-benzoquinone imine (NAPQI), which is not best neutralized by glutathione (GSH), is assumed to be the reason of the elevated levels of SGOT K-. According to (Clark *et al.*, 2012), consuming a single dose of paracetamol of 15 g or more can cause liver damage through the toxic metabolite of paracetamol, namely N-acetyl-p-benzoquinone imine (NAPQI). (Anugerah *et al.*, 2018) stated that if there is damage to the tissue, the cells will break so that the enzymes will break down out of the hepatocytes and then enter the circulatory system. Therefore, the levels of these enzymes increase in the blood.

The mean SGOT levels of mice treated with K+ (170.5 ± 50,342 IU/L) were not significantly different ($p > 0.05$) from those treated with K0. SGOT K+ levels which are still high compared to normal levels indicate that Hepa-Q is considered unable to optimally repair the damage that has occurred. Based on the results obtained, SGOT levels in the K0 treatment were not significantly different ($p > 0.05$) from the P1 (150 mg/kgBW) and P3 (600 mg/kgBW) treatment groups, but were significantly different ($p < 0.05$) from the P2 treatment (300 mg/kgBW). The mean SGOT values for treatments P1, P2 and P3 were 140.75±79.16 IU/L, 177±40.158

IU/L and 121.75±84.2 IU/L.

SGOT levels showed a significant difference ($p < 0.05$) between the P1, P2 and P3 treatment groups and the K- treatment group, but were not significantly different ($p > 0.05$) when compared with the K+ treatment. This proves that EEKBM has the same ability as the treatment given by Hepa-Q (K+) even though it is not optimal. This is thought to be because the EEKBM dose used was a single dose. This dose is a dose without mixtures of various other plant ingredients. Meanwhile, Hepa-Q is a synergistic extract supplement that contains various plant extracts. The content of the Hepa-Q supplement is thought to be able to neutralize and protect liver damage caused by the buildup of paracetamol metabolites. The composition of Hepa-Q consists of extracts of *Silybum marianum*, *Curcuma xanthorrhizae*, *Oleum xanthorrhizae* and fructus *Schisandrae*. Curcumin is one of the active compounds of Hepa-Q, based on the research results of (Stoner & Mukhtar, 1995), curcumin is able to increase the GSH content of the liver so that its need to conjugate with NAPQI will be fulfilled.

SGOT levels obtained in test animals (K-, K+, P1 and P2) are generally higher than SGPT levels. This condition is caused because the SGOT enzyme is not only produced by the liver, according to (Yusuf *et al.*, 2018), (Qodriyati *et al.*, 2016), and (Harrison, 1999), the SGOT enzyme is also produced by muscles, heart muscle, spleen, lungs, brain and kidneys.

Table 3. Average SGPT levels in Rats After Administration of Paracetamol and Followed by Administration of Various Doses of *Mezzettia Parviflora* Becc. Bark Extract (EEKBM)

Treatment	Parasetamol (mg/kgBw)	Hepatoprotector (mg/kgBw)	Average level of SGPT $\bar{x} \pm sd$ IU/L
K0	-	-	52,75 ^a ± 3,096
K-	1350	-	259,75 ^c ± 20,205
K+	1350	Hepa-Q 11,34	64,25 ^{ab} ± 6,85
P1	1350	EEKBM 150	80,00 ^{ab} ± 24,496
P2	1350	EEKBM 300	88,5 ^{ab} ± 17,597
P3	1350	EEKBM 600	155,50 ^b ± 99,484

Note: Different Superscript Letters (a, b and c) Indicate There is a Significant Difference ($P < 0.05$)

The average SGPT level of K0 treatment obtained in this study was $52.75 \pm 3,096$ IU/L, this level is in accordance with the normal level of SGPT in mice according to Sujono *et al.* (2015) which ranges from 42.9 – 67.4 IU/L. SGPT levels in mice treated with K- were significantly different ($p < 0.05$) compared to those treated with K0. High levels of SGPT treated with K- (259.75 ± 20.205 IU/L) indicate impaired liver function. Harrison, (1999) explains that the SGPT enzyme is a specific marker of liver damage because it is produced in large quantities in the liver cytosol. The SGPT enzyme is produced in the liver and released into the blood where the levels are directly proportional to the condition of the liver itself.

SGPT levels in mice treated with K+ were not significantly different ($p > 0.05$) from those treated with K0. The mean SGPT level in the K+ treatment was 64.25 ± 6.85 IU/L. Even though the SGPT levels of K+ treatment were higher than K0, K+ treatment was still considered capable of improving liver function disorders even though it did not return to normal. This shows that treated animals given Hepa-Q supplement pharmacological therapy were able to improve liver function disorders. The Hepa-Q content used contains *Silybum marianum* plant extract or also known as Milk thistle which contains silymarin as its active compound. Based on data from research conducted by (Trappoliere *et al.*, 2009) reported that silymarin has biological activity as an antioxidant so that silymarin is able to maintain hepatocyte membrane integrity and inhibit the entry of toxic substances. Based on the results of several studies that have been conducted, it is reported that silymarin has hepatoprotective activity against paracetamol-induced injury so that it can reduce SGOT and SGPT levels (Panjaitan *et al.*, 2011).

Based on the results, treatment K0 was not significantly different ($p > 0.05$) from treatments P1 and P2, and significantly different ($p < 0.05$) from treatment group P3. The mean SGPT levels in

treatments P1, P2 and P3 were $80.00 \pm 24,496$ IU/L, $88.5 \pm 17,597$ IU/L and $155.50 \pm 99,484$ IU/L. Based on these results, EEKBM at a dose of 150 mg/kgBB and a dose of 300 mg/kgBB is thought to be able to improve disorders that occur in the liver. SGPT levels showed a significant difference ($p < 0.05$) between the P1, P2 and P3 treatment groups and the K- treatment group, but were not significantly different ($p > 0.05$) when compared with the K+ treatment. This shows that EEKBM has the same ability as Hepa-Q in improving paracetamol-induced liver function disorders.

SGPT levels were higher than SGOT levels in the P3 treatment group (600 mg/kgBW), thought to be caused by acute liver function damage that occurred due to paracetamol toxicity and overdose of ingredients in EEKBM. According to (Saraswati, 2015); (Hidayat *et al.*, 2013) and (Sudoyo *et al.*, 2009), the increase in SGPT is greater than SGOT when acute damage occurs, but does not reach the cell mitochondria. SGPT levels in test animals in the P1, P2 and P3 treatment groups were lower than in the K- treatment, indicating that the extract dose used had the potential to be a hepatoprotector, although not as high as K+.

The high standard deviation values for the SGOT levels in the K+, P1 and P3 treatments as well as the SGPT levels in the P1 and P3 treatments were due to outlier data which was thought to occur due to individual sensitivity to toxic substances. The high levels of SGOT and SGPT are influenced by the sensitivity of the rat's body's response to paracetamol administration. According to (Nurmawati, 2017), individuals' adaptive responses to changes in their bodies vary. Apart from sensitivity, large increases in SGOT levels in the serum can be caused by extensive tissue necrosis. (Qodriyati *et al.*, 2016) explained that SGOT levels can be immediately detected in the blood circulation if trauma or necrosis occurs in a tissue.

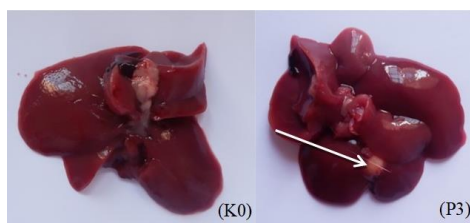


Figure 2. Macroscopic View of Rat Liver

Based on the macroscopic characteristics of the rat liver (Figure 2), treatment P3 is different from treatment K0, there is a liver that has a cloudy white swelling in one of the liver lobes. The test animals that experienced swelling were P3U2 and P3U3. This swelling is thought to indicate the formation of liver cysts due to the accumulation of toxic materials from the metabolism of the toxic substance paracetamol. The swelling in one of the liver lobes is thought to be due to degenerative changes in the hepatocyte cells and cell vacuoles. According to (Dewi & Saraswati, 2009), hepatocyte cell damage is characterized by changes in cell structure in the form of cell swelling which is called degenerative changes.

Administration of EEKBM at doses of 300 mg/kgBW (P2) and 600 mg/kgBW (P3) is considered not to have potential as a hepatoprotector because there are indications of increasing liver function disorders. The higher dose of EEKBM given is thought to cause an overdose of plant secondary metabolites in test animals. Overdose of secondary metabolites causes the buildup of free radicals. This is supported by (Decker, 1997), where several secondary metabolites in the phenolic group can be prooxidants. Excessive levels of flavonoids in the body can be oxidized by peroxidase enzymes to form free radical compounds which can oxidize glutathione in hepatocytes.

Based on data analysis, it can be concluded that EEKBM at a dose of 150 mg/kgBW is the most effective dose for preventing liver function disorders due to induction of toxic doses of paracetamol. The decreased mean levels of SGOT and SGPT in the P1 treatment group compared to the K-, P2-, and P3 treatments suggested that the dose utilized in this group may have hepatoprotective properties. This

shows that NAPQI reactive metabolites can be maximally neutralized so that the process of repairing liver function disorders occurs.

CONCLUSION

According to the research findings, with an effective dose of 150 mg/kgBW, the ethanol extract of *Mezzettia parviflora* Becc. stem bark has the potential to be a hepatoprotector. With an IC50 value of 96.308 $\mu\text{g/mL}$, the stem bark of *Mezzettia parviflora* Becc. exhibits significant antioxidant activity in an ethanol extract.

REFERENCES

- Anugerah, A., Pratiwi, W. R., & Wahyuningsih, M. S. H. (2018). Pengaruh Kombinasi Ekstrak *Tithonia diversifolia* (Hemsley) A.Gray dan *Curcuma domestica* Val. pada Fungsi Hati dan Ginjal Tikus Model Kanker. *Majalah Farmasetik*, 14(1), 1. <https://doi.org/10.22146/farmasetik.v14i1.41923>
- Clark, R., Fisher, J. E., Sketris, I. S., & Johnston, G. M. (2012). Population prevalence of high dose paracetamol in dispensed paracetamol/opioid prescription combinations: An observational study. *BMC Clinical Pharmacology*, 12(11), 1–8. ???
- Decker, E. A. (1997). Phenolics: Prooxidants or Antioxidants? *American Journal of Human Biology*, 55(11), 396–407.
- Dewi, U. K., & Saraswati, T. R. (2009). Efek Rebusan Daun Tapak Dara pada Dosis dan Frekuensi yang Berbeda terhadap Kerusakan dan Akumulasi Glikogen pada Hepar Mencit (*Mus musculus*). *Bioma*, 11(1), 1–5.
- Dwijayanti, K. R. (2011). Daya Antibakteri Minyak Atsiri Kulit Batang Kayu Manis

- (*Cinnamomum burmannii* Bl.) terhadap *Streptococcus mutans* Penyebab Karies Gigi. In Skiripsi. Universitas Sanata Dharma.
- Fahrimal, Y., Eliawardani, Rafina, A., Azhar, A., & Asmilia, N. (2014). Profil Darah Tikus Putih (*Rattus norvegicus*) yang Diinfeksi Trypanosoma evansi dan Diberikan Ekstrak Kulit Batang Jaloh (*Salix tetrasperma* Roxb.). *Jurnal Kedokteran Hewan*, 8(2), 164–168.
- Fahrudin, F., Duryadi Solihin, D., Kusumorini, N., & Ningsih, S. (2015). Isolasi Efektifitas Ekstrak Gambir (*Uncaria gambir* (Hunter) Roxb.) sebagai Hepatoprotektor pada Tikus (*Rattus norvegicus* L.) yang Diinduksi CCl₄. *Jurnal Ilmu Kefarmasian Indonesia*, 13(2), 115–122.
- Gomez, E. A., & Gomez, A. A. (2006). Prosedur Statistik untuk Penelitian Pertanian.
- Grace-Lynn, C., Darah, I., Chen, Y., Latha, L. Y., Jothy, S. L., & Sasidharan, S. (2012). In Vitro antioxidant activity potential of Lantadene A, a pentacyclic triterpenoid of Lantana plants. *Molecules*, 17(9), 11185–11198.
- Graham, G. G., Davies, M. J., Day, R. O., Mohamudally, A., & Scott, K. F. (2013). The modern pharmacology of paracetamol: Therapeutic actions, mechanism of action, metabolism, toxicity and recent pharmacological findings. *Inflammopharmacology*, 21(3), 201–232. <https://doi.org/10.1007/s10787-013-0172-x>
- Harrison. (1999). Prinsip-Prinsip Ilmu Penyakit Dalam. EGC.
- Hidayat, A., Christijanti, W., & Marianti, A. (2013). Pengaruh Vitamin E Terhadap Kadar SGPT dan SGOT Tikus Putih Galur Wistar yang Dipapar Timbal. 3(1), 1–6.
- Husna, F., & Husni, P. (2018). Review Artikel: Aktivitas Hepatoprotektor Trengguli (*Cassia fistula* L.). *Farmaka*, 16(3), 91–99.
- Ikawati, Z. (2010). Cerdas Mengenali Obat. Kanisius.
- Indahsari, N. K. (2017). Gambaran Histopatologi Hepar Tikus Putih (*Rattus Norvegicus*) yang Diinduksi dengan Parasetamol dosis Toksik Pasca Pemberian Ekstrak Etanol Daun Kelor (*Moringa Oleifera*). *Jurnal Kimia Riset*, 2(2), 123–230.
- Ismeri. (2011). Aktivitas Ekstrak Etanol Air Daun Kari (*Murraya kuenigii*) sebagai Hepatoprotektor pada Tikus Putih Galur Sparague Dawley. Institut Pertanian Bogor.
- Marzouk, A. M. (2009). Hepatoprotective triterpenes from hairy root cultures of *Ocimum basilicum* L. *Zeitschrift Fur Naturforschung - Section C Journal of Biosciences*, 64(3–4), 201–209. <https://doi.org/10.1515/znc-2009-3-409>
- Masykur, M., Nurdin, Hakim, L., Rosnizar, Sari, W., Ulfa, M., Sari, N. Y., & Ceriana, R. (2023a). Effect of Ethanol Extract of Sugar Apple (*Annona squamosa* L.) Stem Bark on Rat SGPT and SGOT. *Jurnal Penelitian Pendidikan IPA*, 9(10), 8695–8706. <https://doi.org/10.29303/jppipa.v9i10.4773>
- Masykur, Nurdin, Hakim, L., Rosnizar, Sari, W., Ulfa, M., Sari, N. Y., & Ceriana, R. (2023b). Effect of Ethanol Extract of Soursop (*Annona muricata* L.) Stem Bark on Rat Liver Function. *Pakistan Journal of Biological Sciences*, 26(10), 516–528. <https://doi.org/10.3923/pjbs.2023.516.528>
- Mufidah, Manggau, M. A., Alam, G., Bahar, M. A., Kasim, S., & Rusdi, M. (2012). Efek Antiagregasi Platelet Fraksi Klika Ongkea (*Mezzetia parviflora* Becc.). *Majalah Farmasi Dan Farmakologi*, 16(1), 51–54.
- Nurmawati, T. (2017). Studi Respon Fisiologis dan Kadar Gula Darah pada Tikus Putih (*Rattus Norvegicus*) yang Terpapar Streptozotocin (STZ). *Jurnal Ners Dan Kebidanan (Journal of Ners and Midwifery)*, 4(3), 244–247. <https://doi.org/10.26699/jnk.v4i3.art.p244-247>
- Oktavia, S., Ifora, I., Suhatri, S., & Susanti, M. (2017). Uji Aktivitas Hepatoprotektor Ekstrak Daun Sirih Hijau (*Piper betle* Linn.) Terhadap Kerusakan Hati Yang Diinduksi Parasetamol. *Jurnal Farmasi Higea*, 9(2), 109–117.
- Ozougwu, J. C. (2017). Physiology of the liver. *International Journal of Research in Pharmacy and Biosciences*, 4(8), 13–24.

- Panjaitan, R. G. P., Manalu, W., Handharyani, E., & Chairul. (2011). Aktivitas Hepatoprotektor Ekstrak Metanol Akar Pasak Bumi dan Fraksi-Fraksi Turunannya. *Jurnal Veteriner*, 12(4), 319–325.
- Parapaga, V. F. S., Durry, M. F., & Lintong, P. M. (2018). Efek Pemberian Ekstrak Daun Sirsak (*Annona muricata* L.) terhadap Gambaran Histopatologi Hati Tikus Wistar (*Rattus norvegicus*) yang Diinduksi Rifampisin. *Jurnal E-Biomedik*, 6(2), 195–199. <https://doi.org/10.35790/ebm.6.2.2018.22173>
- Pujiarti, R., Widowati, T. B., Kasmudjo, & Sunarta, S. (2015). Kualitas, Komposisi Kimia, dan Aktivitas Antioksidan Minyak Kenanga (*Cananga odorata*). *Jurnal Ilmu Kehutanan*, 9(1), 3–11.
- Qodriyati, N. L., Sulistyani, E., & Yuwono, B. (2016). Kadar Serum Glutamic Oxaloacetic Transaminase (SGOT) pada Tikus Wistar (*Rattus norvegicus*) Jantan yang Dipapar Stresor Rasa Sakit Electrical Foot Shock selama 28 Hari. *E-Jurnal Pustaka Kesehatan*, 4(1), 73–77.
- Rabeta, M. S., & Lin, S. P. (2015). Effects of different drying methods on the antioxidant activities of leaves and berries of *Cayratia trifolia*. *Sains Malaysiana*, 44(2), 275–280. <https://doi.org/10.17576/jsm-2015-4402-16>
- Rafita, ita dwi, Lisdiana, & Marianti, A. (2016). Pengaruh Ekstrak Kayu Manis Terhadap Gambaran Histopatologi Dan Kadar Sgot-Sgpt Hepar Tikus Yang Diinduksi Parasetamol. *Life Science*, 4(1), 29–37.
- Rahmawati, N., Sugiyanta, & Sakinah, E. N. (2018). Pengaruh Pemberian Cuka Apel “A” terhadap Kadar MDA Hepar Tikus Wistar Jantan yang Diinduksi Parasetamol Dosis Toksik. *Pustaka Kesehatan*, 6(2), 272. <https://doi.org/10.19184/pk.v6i2.7667>
- Ramdaniah, P. (2014). Uji Efek Hepatoprotektor Ekstrak Etanol Daun Kembang Merak (*Caesalpinia pulcherrima* L.) dengan Parameter Enzim SGPT dan SGOT pada Tikus Jantan (*Rattus norvegicus*) yang Diinduksi Parasetamol. Universitas Islam Negeri Alauddin Makassar.
- Ridho, E. Al. (2013). Uji Aktivitas Antioksidan Ekstrak Metanol Buah Lakum (*Caryatia trifolia*) dengan Metode DPPH (2,2-Difenil-1-Pikrilhidrazil). In Skripsi. Universitas Tanjungpura.
- Robinson, T. (1963). *The Organic Constituents of Higher Plants*. Burgess Publishing Company.
- Rousdy, D. W., Wardoyo, E. R. P., & Wulandari, C. (2023). Pengaruh Ekstrak Metanol Buah Lakum (*Cayratia trifolia* L. Domin) Terhadap Nilai SGOT dan SGPT Tikus Putih Diinduksi Parasetamol. *Bioscientist: Jurnal Ilmiah Biologi*, 11(2), 1123–1134.
- Saraswati, T. R. (2015). Efek Pemberian Serbuk Kunyit dalam Pakan Terhadap Hepar Puyuh Jepang (*Coturnix japonica*). *Buletin Anatomi Dan Fisiologi*, 23(2), 94–100.
- Seyoum, A., Asres, K., & El-Fiky, F. K. (2006). Structure-radical scavenging activity relationships of flavonoids. *Phytochemistry*, 67(18), 2058–2070. <https://doi.org/10.1016/j.phytochem.2006.07.002>
- Stoner, G. D., & Mukhtar, H. (1995). Polyphenols as cancer chemopreventive agents. *Journal of Cellular Biochemistry*, 59(22 S), 169–180. <https://doi.org/10.1002/jcb.240590822>
- Sudoyo, A. W. S. S. A. I. (2014). *Buku Ajar Ilmu Penyakit Dalam*. Internal Publishing.
- Sudoyo, A. W., Setiyohadi, B., Alwi, I., Marcellus, Simadibrata, & Setiati, S. (2009). *Buku ajar ilmu penyakit dalam edisi V*. Interna Publishing.
- Sulandi, A. (2013). Aktivitas Antioksidan Ekstrak Kloroform Buah Lakum (*Cayratia trifolia*) dengan Metode DPPH (2,2-Difenil-1-Pikrilhidrazil). In Skripsi. Universitas Tanjungpura.
- Trappoliere, M., Caligiuri, A., Schmid, M., Bertolani, C., Failli, P., Vizzutti, F., Novo, E., Manzano, C. di, Marra, F., Loguercio, C., & Pinzani, M. (2009). Silybin, a component of silymarin, exerts anti-inflammatory and anti-

- fibrogenic effects on human hepatic stellate cells. *Journal of Hepatology*, 50(6), 1102–1111.
<https://doi.org/10.1016/j.jhep.2009.02.023>
- Yoon, E., Babar, A., Choudhary, M., Kutner, M., & Prysopoulos, N. (2016). Acetaminophen-induced hepatotoxicity: A comprehensive update. *Journal of Clinical and Translational Hepatology*, 4(2), 131–142.
<https://doi.org/10.14218/JCTH.2015.00052>
- Yusuf, M. I., Tee, S. A., Karmila, K., & Jabbar, A. (2018). Efek Hepatoprotektor Ekstrak Terpurifikasi Batang Galing (*Cayratia trifolia* L.Domin) Pada Tikus Putih Wistar Jantan (*Rattus noervegicus*). *Jurnal Mandala Pharmacon Indonesia*, 4(1), 13–19.
<https://doi.org/10.35311/jmpi.v4i1.18>
- Zakaria, Z. A. (2007). Free radical scavenging activity of some plants available in Malaysia. *Iranian Journal of Pharmacology and Therapeutics*, 6(1), 87–91.
- Zakiah, N., Yanuarman, Y., Frengki, F., & Munazar, M. (2017). Aktifitas Hepatoprotektif Ekstrak Etanol Daun Sirsak (*Annona Muricata* L.) Terhadap Kerusakan Hati Tikus yang Diinduksi dengan Parasetamol. *AcTion: Aceh Nutrition Journal*, 2(1), 25–31.