RESEARCH ARTICLE

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The Hepatoprotective Effects of Ethanolic Extract Noni Fruits (*Morinda citrifolia* L.) on Rats (*Rattus norvegicus*) Liver with SGPT and Histopathological Evaluations

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ABSTRACT

The liver is an important organ that plays a role in metabolism in the human body. However, the use of certain types of chemical compounds tends to damage these organs. This study aims to determine the hepatoprotective effectiveness of noni fruit (*Morinda citrifolia* L.) against exposure to hepatotoxic compounds. This research was conducted by experimental method with Groups I to III treated with noni extract with concentrations of 10, 15, and 20%, respectively. Group IV was treated with acetaminophen, a hepatotoxic substance, as a positive control and group V was treated with Na.CMC as a negative control. Data *serum glutamate pyruvate transaminase* (SGPT) levels and histopathological examination of the liver of the test animals were then analyzed by *One-Way Anova*. Histopathological examination results showed hepatotoxicity caused by high doses of acetaminophen 10 g/70 KgBW in the positive control group achieved a score of +4 (severe damage), groups I and II showed a score of +3 (moderate damage), and in group III only showed a score of +3 (moderate damage). +2 (light damage). The results of SGPT examination and histopathology showed that the ethanol extract of noni fruit at a concentration of 20% had a hepatoprotective effect.

Keywords: Hepatoprotective, histopathology, liver, noni, SGPT.

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I. Introduction

Drugs that induce liver disorders that are used continuously have a significant risk of liver disease that can trigger *acute liver failure* [1]. The liver is an organ that works to metabolize every compound that enters the body. The liver has various functions, one of which is the portal venous circulation which channels 75% of the acini which play an important role in the physiological processes of the liver, not only in terms of carbohydrate metabolism, but also protein and fatty acids [2]. An increase in the enzyme *Serum Glutamate Pyruvate Transaminase* (SGPT) can be a marker that there is damage to the liver [3].

The liver is the main organ that functions to balance metabolism and detoxify metabolites from the use of drugs that enter the body. Severe disturbances due to chemical compounds, free radicals, or cell death can interfere with its function [4]. The liver can often experience disorders that are usually caused by viruses or bacteria even by drugs and various foods consumed [5]. Damage to the liver due to oxidative stress that affects the mitochondrial cells of hepartocytes becomes pathological which is closely related to nuclear *factor erythroid 2-related factor 2* (Nrf2). Because it is directly related to hepatic disorders [6]. Liver disorders that most often occur are due to the use of acetaminophen [7]. Therefore, to avoid major side effects on the body, a search for medicinal ingredients from natural ingredients is carried out which is known to have a good protective effect on the body.

Noni (*Morinda citrifolia* L.) is a plant that is widely grown in tropical countries, and historically its juice has been widely used in medicine and maintaining health [8]. Noni is one of the plants that is usually used in the treatment of hypertension, skin diseases, respiratory disorders, and liver function disorders [9].

The purpose of this study was to determine the hepatoprotective effect of noni ethanol extract using SGPT and histopathological parameters. SGPT is one of the parameters of liver condition, where if SGPT is increased then the liver is damaged, besides that, observations are also seen from the histology of the liver, namely fat, hemorrhage, necrosis, and fibrin. In previous studies on noni hepatoprotectors only used a protective effect based on SGPT and SGOT values. In this study, parameters other than SGPT were used, namely by direct examination of cells by histopathology. This study uses SGPT because it is specific for liver cell damage with SGPT, while SGOT can also be active on other cell damage such as the heart, so that it will bias the data later. Another difference was also seen in the use of CCl_4 in previous studies while this study used acetaminophen as an inducer [10]. Acetaminophen was

chosen because it is a very consumptive product in the community and is almost consumed by all groups as an antipyretic and painkiller.

Research on noni fruit in 1950, showed the activity of antibacterial substances against *Escherichia coli*, *Pseudomonas aeruginosa*, and *M. pyrogenesis*. In 1972, compounds xeronine and proxeronine which are precursors were found in large quantities in noni fruit by Heinicke. This substance functions as a substance to regulate the specific function and shape of body cells [11]. Based on the description above, the researchers thought that there might be a hepatoprotective effect from the ethanolic extract of the noni fruit that could be seen in the cells in the liver.

II. Research Method

Design used in this study is an experimental design carried out in the pharmacology laboratory of the Faculty of Pharmacy, Universitas Muslim Indonesia. The study was conducted ± 4 weeks starting from animal adaptation, treatment, to serum and histopathological examination.

The tools used are a set of maceration tools, a set of histopathological examination tools, a photometer (Microlap), a micropipette (Huawei), a rotavapor, an analytical balance (Ohaus), a centrifuge (PLC Series), and a syringe. The tool used to measure SGPT levels in this study is a photometer, by measuring the absorbance based on the results of measurements using ultraviolet light at a wavelength of 340 nm.

The materials used were aquadest, EDTA (*Ethylene Diamine Tetra Acid*) 5%, ethanol extract of noni fruit, ethanol, Na.CMC (*Sodium Carboxy Methyl Cellulose*) 1%, acetaminophen preparation, and serum reagent SGPT (ELITech).

A. The Course of Research

1) Sampling

The sample used was noni fruit (*Morinda citrifolia* L.) from Makassar and harvested by picking the ripe fruit in the morning.

2) Processing of Samples

Noni fruit that has been collected is then cleaned and cut into thin slices then dried in the sun for 3x24 hours and made in the form of dry simplicia for easy extraction.

3) Making Colloidal Na.CMC

Prepared tools and materials to be used. Then 1 gram of Na.CMC was weighed. Na.CMC was then dissolved with 50 ml of warm water while using a magnetic stirrer until mixed. Then*add*up to 100 ml and mix until homogeneous. After that, it was transferred to a closed container at storage temperature. To maintain stability, it can be stored at a temperature of 2-8 °C, but must be reheated if you want to use it.

4) Extraction of Noni

Fruit Simplicia dried noni fruit was weighed 300 g then soaked with 900 ml of 96% alcohol, then allowed to stand for approximately 5x24 hours. Next, the sample was filtered using filter paper and the dregs were soaked again with 96% alcohol and stirred again and allowed to stand for 3 x 24 hours. The filter results (filtrate) produced from the first and second extraction processes were then evaporated using a rotary evaporator to obtain a thick extract.

5) Preparation of suspension of noni fruit ethanol extract

For suspension of 10% concentration of noni fruit extract, 10 g of ethanol extract of noni fruit were weighed first using paraffin paper which was then put into a mortar with the help of a spatula and added little by little 1% Na.CMC suspension while stirring until homogeneous. After being homogeneous, it was put into a 100 ml volumetric flask and the volume was made up to 100 ml. The same was done for the manufacture of extract concentrations of 15% and 20%.

6) Preparation of acetaminophen suspension

After the acetaminophen was crushed and then weighed as much as 8721,864 mg. Then suspended with 1% Na.CMC until homogeneous. Then it is made up to a volume of 100 ml and then later given orally. If the suspension has not been used, it can be stored at a temperature of 2-8^{o}C to maintain its stability.

B. Preparation and Treatment of Test Animals

The method in this study was experimental testing by examining the blood specimens of the test animals. In this study, 25 white rats (*Rattus norvegicus)* were used which were divided into 5 groups. For groups I, II, and III as the test group, each of which received noni ethanol extract with concentrations of 10%, 15%, and 20%, while groups IV and V as the positive and negative control groups were given Na.CMC 1%, respectively for approximately 7 days.

The first step is to measure the initial SGPT levels for all treatment groups using the Human Analyzer and SGPT reagent kit. ± 1 ml of blood was taken which was then added with EDTA and separated between serum and plasma using a centrifuge at 3000 rpm. Serum was taken and then added to the SGPT reagent kit and measured using the Human Analyzer. All test animals were given the same food before and after treatment. Measurement of initial SGPT levels as a reference for initial levels before treatment. After obtaining initial data, then the test animals were given treatment from group I to group V for 7 consecutive days with a volume of 5ml/200gBW. On the 8th day, SGPT measurements were taken again before acetaminophen induction. After that, all groups were induced with acetaminophen 10g/kgBW orally, except for group V as a negative control, they were still given 1% Na.CMC. After that, the final SGPT measurement was carried out on the 8th day in the same way as the initial measurement. After 24 hours, the final SGPT levels were measured, and histopathological examination was performed.

C. Histopathological Observation

Testing the effect of noni fruit extract was carried out microscopically on the liver of rats from groups I, II, III, IV, and V which were treated for 8 days, and histopathological examination was carried out on day 9. Histopathological procedures were carried out in a veterinary laboratory starting from the fixation process, specimen cutting, embedding, staining, and microscopic examination for sample reading.

Histopathological examination was carried out by examining the liver cells of rats that were included in the research group. The procedure was carried out by means of fixation, specimen cutting, *Processing* and *Embedding*,

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cutting, staining, and microscopic examination. The rats were taken from the liver and the cell slices were preserved in film preparations which would later be observed directly under a microscope. Changes in tissue or cell morphology were observed by staining *Hematoxylin and Eosin* from infected tissue preparations. The data obtained from the SGPT examination and histopathological results were processed using the *One-Way Anova* with a confidence level of 95%.

III. Research Result

From the laboratory examinations that have been carried out, the results of the initial SGPT examination, SGPT after treatment, final SGPT after induction, and histopathological features in the sample (n=25) white rats were obtained. The data can be seen in Table I as follows:

TABLE I: RESULTS OF ANOVA ONE-WAY EXAMINATION IN RATS SGPT TEST

Activity	Result		
	First SGPT (mean±S.D)	SGPT after use extract (mean±S.D)	SGPT after induced acetaminophen (mean±S.D)
Ethanol extract of noni fruit 10%	18,6±4,73	54,4±31,26	33,8±26,47
Ethanol extract of noni fruit 15%	21,28±5,44	45,02±10,14	27,78±14,69
Ethanol extract of noni fruit 20%	32,4±15,16	46,58±7,09	15,46±3,71
Induction Control Na.CMC 1% + acetaminophen	15,92±6,15	60,37±12,35	108,2±15,72
Negative control Na.CMC 1%	4,06±9,07	4,48±10,01	5,84±13,05

Data presented in One-Way ANOVA test (n=5) per group, Repeated ANOVA analysis with confidence level 95%
P<0.001 for the noni ethanol extract group 20%
Na.CMC (Sodium Carboxymethyl Cellulose), SGP*T (Serum Glutamic Pyruvic Transaminase)*

From the results of statistical tests using the *One-Way Anova*, clinically there was a difference in the increase in SGPT values in during initial measurements, after administration of noni extract, and after induction acetaminophen. From the statistics, the SGPT value showed that the use of extracts could be hepatoprotective, as seen in the 15% and 20% extracts which showed a minimal increase in SGPT when exposed to the hepatotoxic compound, namely acetaminophen.

The statistical results of the One-Way Anova test in the 20% noni extract group showed p value = 0.009 which means that a significant protective effect was caused by the 20% noni extract. In the control group, acetaminophen induction showed a p value = 0.029 which means that the administration of acetaminophen significantly increased the SGPT value, while the Na.CMC control group showed a p value = 0.374 which means that there was no increase in the SGPT value in the rat liver.

From the changes in the data, the changes that occurred in the positive control group were much larger than the other groups. This indicates the possibility of damage to the liver of rats induced by Na.CMC 1% + acetaminophen so that the increase in serum SGPT is quite high which can be clearly seen in positive controls while for negative controls who were only given 1% Na.CMC alone did not experience an increase in serum SGPT the same. once because 1% Na.CMC is not hepatotoxic like acetaminophen. In the other treatment group, it was slightly higher than the negative control group but was still in the normal level, probably due to the influence of the ethanol extract. However, the SGPT value of the treatment group was still considered normal.

In this study acetaminophen was chosen as an inducer because acetaminophen is a chemical compound that can cause liver necrosis. Acetaminophen or acetaminophen itself is used as an antipyretic and analgesic used in several countries.reports of *acute liver injury* due to acetaminophen [12]. Acetaminophen, which is metabolized in the liver via sulfatation, glucuronidation, and oxidation of cytochrome P450 pathways into a toxic metabolite, namely N-acetyl-p-benzoquinoneimine (NAPQI), a toxic metabolite will be bound by glutathione to form mercaptopuric acid which is easily excreted. Toxic causes are toxic metabolites that cannot be bound by glutathione, due to excessive amounts of metabolites caused by overdose [13], [14]. The presence of NAPQI is very influential on glutathione S-Transferase which will increase oxidative stress in liver cells. In addition, NFE2-related factor 2 (Nrf2) also regulates the occurrence of acetaminophen overdose [15].

Normal SGPT values in rats ranged from 17.5 – 30.2 U/L [16]. Toxicity to the liver will cause an increase in the enzymes SGPT, SGOT, albumin, until the bilirubin increases from normal conditions. This was evident from the increase in the SGPT enzyme which was carried out as a parameter that was also identified in addition to histopathology. High levels of SGPT in rats given acetaminophen indicate an activity of liver disorders that occur [17].

IV. Result the Anatomy Liver of Rats

Apart from the SGPT examination, histopathological examination of the liver of rats was also carried out which showed differences in the severity of the rats which were analyzed using the *One-Way Anova*. The results showed that there was a very significant difference between the moderate level of liver damage and severe liver damage in normal mice (negative control) with p <0.05. Meanwhile, the ratio of liver with mild and moderate damage was significantly different with a p value of 0.003. Significant differences were also seen in moderately damaged and severely damaged livers with p < 0.001.

Histopathology was also carried out to prove in real terms the similarity of the increase in SGPT in mice with the condition of the liver cells of mice directly. An increase in SGPT indicates damage to liver cells, therefore histopathology was carried out to see directly whether the increase in SGPT, it was the result of damage to rat liver cells.

Damage to the liver of rats was seen with several types of damage, including the presence *congestion,* formation of *fibrin,* to *necrotic* liver cells. Interesting things can be seen in the differences in the liver of rats given the extract and positive and negative control rats. A significant difference in

the level of damage was clearly seen in mice that were not given the extract, especially those given only high doses of acetaminophen. This result is also clearly seen in the results of statistical tests carried out by *post hoc One-Way Anova*.

The results of the ANOVA test using histopathological examination data with $p<0.001$ showed that there was a significant difference in the level of liver damage in each group. The liver damage of rats was quite severe with the use of acetaminophen for the positive control group, whereas in groups I and II there was moderate damage and treatment in group III showed mild damage after being induced by acetaminophen. The results of histopathological examination of liver cells of white rats found several types of damage such as *haemorrhage* (bleeding), *congestion* (blood dams), *bile duct proliferation* gallbladder), *necrotic* (cell damage), and *fibrin* (blood threads).

The histopathological scores performed showed that for extracts 10% and 15% showed moderate damage with a score of +3 or moderate damage. The 20% extract showed that the liver was in a slightly damaged condition with a score of +2. The acetaminophen group showed severe damage, namely a score of +4 which indicated that there was quite severe damage. As for the negative control, the liver did not change or was in normal condition. If it is adjusted with the SGPT examination, the extract at a higher concentration had a better protective effect because the damage was only mild damage, while the liver that was not given the extract suffered severe damage. It is possible that a slightly higher concentration can provide maximum protection effectiveness so that there is no damage to the liver. The mild damage to rat liver cells in group III indicated that there was a protective mechanism of noni fruit extract against rat liver. This shows that the compounds in the noni fruit extract are antioxidants.

The content in the noni fruit which is thought to act as a hepatoprotection from antioxidant compounds and minerals contained therein, there is proxeronine which is a precursor to xeronine which functions to maintain cell function. Along with the increase in the amount of xeronine in the body, even though the body is exposed to stress or toxins, the cells will be more active and healthier because the amount of xeronine increases, including liver cells [18].

Antioxidants have the function of neutralizing free radicals formed from the body's metabolic processes. In addition, the nutritional compounds in noni fruit that are needed by the body such as carbohydrates, proteins, vitamins, and essential minerals are also abundant in it [9].

Antioxidants and anti-inflammatory which play an important role in protecting the liver from free radicals [19], [20]. Previously, it was reported that noni fruit has a high antioxidant content and has been tested in vitro [21]. Because of this, several flavonoid-derived compounds have been identified as having hepatoprotective activity [22]. Although the hepatoprotective properties of noni fruit are still a matter of speculation. [23], [24]. *Morinda citrifolia* is reported to contain a lot of flavonoids [25]. Flavonoids have anti-inflammatory, antiallergic, antihaemorhagic, antimutagenic, antineoplastic, and hepatoprotective effects [26]. The possibility of noni can be anti-inflammatory, anti-cancer, and has a protective effect on liver cells. Exposure to exogenous toxins causes hepatocyte cells to occur resulting in increased release of SGPT and SGOT enzymes [21]. As an anti-cancer compound, Nordamnacanthal (NDAM) has links with NK cells, T-*helper*, and cytokines in the body [27]. In addition, the incidence of atherosclerosis associated with TNF- and IL-1B cytokines can also be lowered and affect blood lipid profiles [28].

However, the protection provided does not mean there is no risk at all, but the noni fruit extract can minimize the risk of damage to the liver from toxic compounds. The level of damage that can be seen histopathologically between group III and the positive control group is shown in the following Fig. 1.

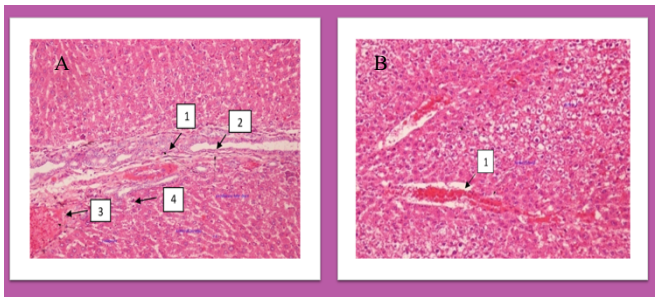

Fig. 1A. In the liver of rats given acetaminophen (positive control) there were (1) proliferation of bile ducts (multiple gallbladder), (2) congestion (blood dams), (3) fibrin (blood threads), and (4) necrotic (cell damage).
Fig. 1B. In rat liver with an extract concentration of 20% there is congestion (blood dam).

V. Conclusion

Above results show that the administration of the extract can reduce the level of damage that occurs in the liver of rats, so this indicates that the administration of the extract can protect the liver from damage caused by compounds that are hepatotoxic. The best results were shown by giving the extract with a concentration of 20% with a mild level of damage.

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Conflict of Interest

Authors declare that they do not have any conflict of interest for this research.

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