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Effect of nephroprotectors of javanese bark extract (Lannea coromandelica) on aspirin-induced rat serum creatinine levels

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ABSTRACT

Kidney disease is a global health problem based on the increase of incidence, prevalence, and morbidity rate. According to RISKESDAS 2018, the prevalence of chronic kidney disease (CKD) was increased significantly. Lannea coromandelica stem bark contains flavonoid was exhibited antioxidant that could be potential as nephroprotector. This study aimed to find out the nephroprotector effect of ethanolic extract of Lannea coromandelica stem bark by measurement serum creatinine levels at rats (Rattus novergicus). This study was used experimental laboratory method. In this study used 25 rats were divided into 5 groups. Group 1 was administered Na CMC 1 % as negative control group. Group 2 was administered aspirin 600 mg/kg body weight as induced control group. Group 3, 4, and 5 were administered Lannea coromandelica stem bark ethanolic extract with the doses 400 mg/kg body weight, 800 mg/kg body weight, and 1200 mg/kg body weight, respectively. The extract of lannea coromandelica stem bark groups were given for 4 days orally. Blood of rats were collected from the orbital sinus eye to be measured creatinine serum level at 5th day. The data was analyzed statistically with one way ANOVA and Paired samples test. The result of this study exhibited that there was a differences of creatinine levels between pre and post treatment with p-value=0.033< 0.05. In conclusion, this study presented that ethanolic extract of Lannea coromandelica stem bark was decreased serum creatinine levels at doses 800 and 1200 mg/kg body weight against the aspirin induced on rats.

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1. Introduction

Kidney failure is a global health problem seen by increasing incidence, prevalence, and morbidity rates. Based on data from the World Health Organization (WHO), it shows that up to 50% of people with acute or chronic kidney failure are known and only 25% receive treatment and 12.5% are well treated. The 2018 report on basic health research (Riskesdas) showed that the prevalence of chronic kidney disease (CKD) increased sharply in the 45-54 age group (5.6%), followed by that of 55-64 years (7.2%) and that of those aged ≥75 years (7.48%), highest in the age group 65-74 years (8.2%).

The protective effect of prostaglandins on the kidneys can be counteracted by the administration of NSAIDs such as aspirin, which block the production of these hormones. Therefore, the administration of NSAIDs in renal hypoperfusion with prerenal causes is best known as a trigger for ischemia-induced renal injury in acute renal failure (AKI).

One of the traditional herbal medicines widely used by Indonesians, people of Southeast Sulawesi in particular, is Javawood (Lannea coromandelica) or known as "aju Jawa" in Bugis society. This plant is one of the traditional herbal medicines that is still frequently used by the Bugis today due to its powerful properties. Usually used to treat internal and external wounds. The Bugis also often use this Javanese aju plant to treat diarrhea, nausea and vomiting. Java bark has pharmacological activities including anti-inflammatory, toothache medicine and gastroprotective activity [1], [2]. Java wood from Sulawesi has antioxidant and antibacterial activity [3]–[5].

Based on phytochemical studies, the stem bark of the Javanese woody plant (Lannea coromandelica) has been reported to contain compounds belonging to the class of carbohydrates, steroids, cardiac glycosides, terpenoids, tannins and flavonoids [6]. In addition, the n-hexane, dichloromethane and ethyl acetate fractions of the bark. The stems and leaves of the Java wood plant have antioxidant, antimicrobial and thrombolytic activities [6]. The results of the antioxidant activity tests performed showed that the AAI (Antioxidant Activity Index) values of 70% ethanol extract, water extract and vitamin C were 5.5679 (very strong) ; 0.0667 (low); and 9.6254 (very strong) [4].

Much research has been done on Javanese bark (Lannea coromandelica). However, there has been no research on the activity of Java bark (Lannea coromandelica) as a nephroprotector. Also, many kidney failure patients in Indonesia have not undergone treatment for kidney failure due to its high cost. Based on this, there is a need for research to prove the nephroprotective ability of Javanese bark (Lannea coromandelica) in acetosal-induced rats, so that it can be used as an alternative therapy for kidney failure. given the content of Javanese bark (Lannea coromandelica), one of which is an effective flavonoid as an antioxidant.

2. Method

2.1.Tools and materials

The tools used in this study were oral probes, rat scales, analytical balances, glassware (EDTA vacutainers, beakers, test tubes), rotary evaporators, hot plates, and a Mindray BA-88A emi-autochemical analyzer.

The materials used in this study were distilled water, 70% ethanol, Java bark (Lannea coromandelica), Na CMC and aspirin.

Java bark (Lannea coromandelica) used in this study is from Lepo-Lepo village, Baruga district, Kendari city, Southeast Sulawesi province.

2.2.Sample Extraction

In this study, the extraction of the bark of Java (Lannea coromandelica) was carried out by the maceration method at room temperature with 6 L of 70% ethanol for 5 days. After filtration on filter paper, the filtrate obtained is evaporated on a rotary evaporator until a thick extract is obtained for weighing, and the yield is calculated.

$$\text{Extract Yield Calculation::} \frac{\text{Extract weight obtained}}{\text{Additional sample weight}} \text{ x } 100\% \quad (1)$$

2.3.Induction of Aspirin

The dose of aspirin known to impair renal function in rats is 600 mg/kg BW. Aspirin was given orally after 1 hour of administration of CMC Na and Java bark extract daily for 4 days.

2.4.Grouping and Treatment of Test Animals

Rats (Rattus norvegicus) were adapted for 10 days, then blood was taken from the test animals to test serum creatinine before treatment (pre-test). The test animals were randomly divided into 5 groups each consisting of 5 test animals. The negative control group received 1% Na CMC. The induction control group received aspirin 600 mg/kgbb. Groups 3, 4 and 5 were the treatment groups which received the ethanolic extract of Java bark (Lannea coromandelica) at the respective doses of 400 mg/kg, 800 mg/kg and 1200 mg/kg. The treatment was given for 4 consecutive days orally and on the 5th day blood was taken from the test animals from the orbital sinus of the eye and then a serum creatinine test (post-test) was performed using the Mindray BA-88A Semi-Autochemistry Analyzer.

2.5.Processing and data analysis

The data obtained were statistically analyzed using the ANOVA (Analysis of Variant) test. If there is a significant difference, it is continued with the Post Hoc test and the Pierced Sample test. The degree of significance used is $\alpha = 0.05$.

3. Results and Discussion

Nephrotoxicity is defined as kidney disease or dysfunction resulting directly or indirectly from exposure to drugs, industrial or environmental chemicals. Thus, drug nephrotoxicity is drug-induced renal dysfunction.

Tests such as serum creatinine, gromelular filtration rate (GFR), blood urea nitrogen (BUN), urine protein, microalbuminuria, and others can be used as indicators of kidney damage. Creatinine is the product of creatine phosphate in muscle and is usually produced at a constant level (based on muscle mass). Most creatinine is eliminated from the blood by

the kidneys, mainly by glomerular filtration as well as by proximal tubular secretion. Creatinine can be measured from plasma, serum or urine. Lipemic probe materials may interfere with the color changes that occur during the reaction. Fasting is not required for the creatinine test as it is not affected by a protein diet [7].

The aim of this study was to determine the effect of administration of Java bark extract (Lannea coromandelica) on increasing serum creatinine levels in rats (Rattus norvergicus). To determine the dose of java bark (Lannea coromandelica) that can increase the renal protective effect by reducing serum creatinine levels of aspirin-induced rats (Rattus norvergicus).

The results of chemical analysis of the blood of rats (Rattus norvegicus) to test creatinine levels were performed at the end of the 5th day of treatment can be seen in Table 1.

Table 1. Creatinine measurement results

No	Group	Average blood creatinine level (mg/dL) *(mean ± SE)*	
		Before	**After**
1.	Normal Control	0,6667 ± 0,81445	1.3333 ± 0,57735
2.	Negative Control	0,8333 ± 1.01160	1.3333 ± 0,75056
3.	Group I	1,1667 ± 0,55076	0,6667 ± 0,28868
4.	Group II	0,8333 ± 0,77675	0,4333 ± 0,35119
5.	Group III	0,4667 ± 0,30551	0,3667 ± 0,3055

Information:
1. Normal Control (Giving Na CMC 1%)
2. Negative Control (Giving aspirin 600 mg/kgbb Rats)
3. Group 3 (Giving extract 400 mg/kgbb Rat)
4. Group 4 (Providing 800 mg/kgbb of rats)
5. Group 5 (Providing 1200 mg/kgbb of rats)

Based on phytochemical studies, the stem bark of Java wood plant (Lannea coromandelica) has been reported to contain compounds of primary metabolites such as carbohydrates and secondary metabolites including steroids, cardiac glycosides, terpenoids, tannins and flavonoids [6] The results of the antioxidant activity test on the bark of the woody Javanese plant (Lannea coromandelica) conducted by [4] showed the AAI value (antioxidant activity index) of the 70% ethanol extract , which is very strong. One of the secondary metabolites that can function as antioxidants are flavonoids.

The maserate obtained is then evaporated on a rotary evaporator to obtain a thick extract to be weighed, then the yield is calculated. The results of the extraction process show that up to 1510.45 grams. Dried Java bark (Lannea coromandelica) yielded 37.9 grams of thick extract with a yield value of 2.5%.

Based on the research data in Table 4, the mean creatinine levels of test animals in the pretreatment and posttreatment groups showed significant differences. The creatinine level with the highest value after treatment was obtained by the negative control group with administration of aspirin with a value of 1.3333 ± 0.75056 and the normal control group with administration of 1% Na CMC, namely with an average value of the creatinine level of 1.3333 ± 0.57735. Meanwhile, the decrease in creatinine levels was the smallest in

treatment group 6 when administering a dose of Java bark (Lannea coromandelica) ethanol extract of 1200 mg/kg body weight with a serum creatinine mean of 0.3667 ± 0.3055. Then followed by treatment group 5 with the administration of ethanolic extract of Java bark (Lannea coromandelica) at a dose of 800 mg/kgbb with a value of 0.4333±0.35119. Treatment group 3 received a dose of Java (Lannea coromandelica) bark ethanol extract of 400 mg/kg body weight with a mean serum creatinine level of 0.6667 ± 0.28868. Creatinine levels in groups 5 and 6 decreased relative to the normal value of creatinine levels in male white rats between 0.20 and 0.50 mg/dL [8].

According to Wientarsih [9], creatinine is a metabolite of keratin which is entirely excreted in the urine by glomerular filtration. The increase in blood creatinine levels and the amount of creatinine in urine can be used to estimate glomerular filtration rate. Blood creatinine levels better reflect kidney function and are more stable than blood urea levels.

Data on serum creatinine levels before and after each treatment were processed using the Kolmogorov-Smirnov method to determine the distribution of the data. Data processing results showed that the data were normally distributed and had homogeneous variances, so data processing continued using one-way analysis of variance (One Way ANOVA) to determine differences between groups. treatment. Analysis using one-way variance showed a significant value of 0.006 ($p<0.05$) which indicated a significant difference in rat serum creatinine levels.

Because there was a significant difference in serum creatinine levels of white rats (Rattus norvergicus), the statistical test was continued with the Post Hoc test to find out between groups which had significant differences in serum creatinine levels . Based on Post Hoc test results after treatment, it showed that there was a significant difference ($p<0.05$) between the negative control group and the extracted group at a dose of 800mg/kg of BW rats ($p=0.048$) and the extract 1200 mg/kgBW rats ($p=0.036$). There was no significant difference between the negative control group with the extract dose of 400 mg/kgbb of rats ($p=0.126$) and the normal group ($p=0.1$). This shows that the higher the administration of Java bark extract (Lannea coromandelica), the better it improves rat serum creatinine levels due to exposure to medicinal chemicals. This may be due to the content of antioxidant compounds, namely flavonoids in the bark of Java bark (Lannea coromandelica) which are able to protect the kidneys against the toxic effects of acetosal.

In the normal control group there was an increase in serum creatinine levels, this group received only 1% Na CMC treatment. In this group, there should be no increase in serum creatinine levels because 1% CMC Na is not an irritant that can damage kidney cells, causing increased serum creatinine levels. Kidney cell damage thus increasing serum creatinine levels may be influenced by external factors that cannot be controlled, such as the psychological conditions and the initial state of the rat kidneys before receiving the treatment.

The negative control group experienced the greatest increase in serum creatinine levels. According to Susilowati, the use of aspirin can cause kidney damage, such as tubular necrosis. Damage to the proximal tubules of the kidney is caused by toxic acetosal. According to Zulfiani, the drug excretion process that occurs in the kidneys can have adverse effects on the kidneys. This is due to high blood flow to the kidneys, which can

cause large amounts of drugs and chemicals to be sent into the systemic circulation to the kidneys.

To see the difference in the increase in serum creatinine levels of white rats (Rattus norvergicus) before and after treatment, the paired samples test was used, and the results obtained showed a significance of p = 0.033 (p < 0.05) indicating a significant difference in the serum creatinine level of the white rats. (Rattus norvergicus) before and after treatment.

The One Way ANOVA i.e. 0.006 (p<0.05) and Paired Samples Test i.e. p=0.033 (p<0.05) data obtained showed that H0 was rejected, meaning that it There was a significant difference in serum creatinine levels in white rats (Rattus norvergicus). Post hoc test results showed that there was a significant difference in the negative control group with the 800 mg/kg extract dose of BW rats (p=0.048) and the 1200 mg/kg extract of BW rats (p=0.036). This shows that the 70% ethanolic extract of Java bark (Lannea coromandelica) has a nephroprotective effect on increasing creatinine levels in white rats (Rattus norvergicus) at doses of 800 mg/kgbb rats and 1200 mg /kgbb rats.

The highest dose of 70% ethanol extract of Java bark (Lannea coromandelica) in the oral treatment of rats was 1200 mg/kgbb of rats. The dose of 70% ethanolic extract of Java bark (Lannea coromandelica) 1200 mg/kg BW rats is a non-toxic dose.

The kidney is an important organ in the elimination of toxic xenobiotics compared to other organs. Administration of aspirin may cause a significant increase in serum creatinine levels indicating that this drug may affect kidney function. Aspirin inhibits the Krebs cycle and alters lipid and amino acid metabolism and produces lactic acid and ketones from metabolic acidosis. Aspirin also interferes with hemostasis by damaging hepatocytes and interfering with prostaglandin synthesis.

The protective ability of Java bark (Lannea coromandelica) on the kidneys may be due to the presence of antioxidants which may act as exogenous antioxidants so administration of 70% ethanolic extract of Java bark (Lannea coromandelica) at a dose of 800 mg/kgbb 1200 mg/kgbb rats showed that there is a protective capacity which can be seen by a decrease in serum creatinine levels which is possible due to the presence of a antioxidant mechanism.

4. Conclusion

The conclusion of this study was that the 70% ethanol extract of java bark (Lannea coromandelica) had a nephroprotective effect in increasing creatinine levels of rats and java bark (the dose of Lannea of 800 mg/kgbb of rats and 1200 mg/kgbb of rats had a nephroprotective effect marked by the reduction of serum creatinine levels of rats.

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