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Research Article

Nephroprotective Activity Test of Ethyl Acetate Fraction of Breadfruit Leaves (*Artocarpus altilis*) Against Male White Rats of Wistar Strain

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ABSTRACT

Breadfruit leaves (*Artocarpus altilis*) contain a variety of compounds, one of which is flavonoids that have the potential to be nefroprotective. The purpose of this study was to test the nephroprotective activity of ethyl acetate fraction of breadfruit leaves (*Artocarpus altilis*) in male white rats. This study is experimental with a pre-test and post-test control group design. The subjects were male white rats who were grouped into 6 groups, namely the normal group, the negative group, the comparator drug group, the ethyl acetate fraction group at a dose of 100 mg/kg BB, the ethyl acetate fraction group at a dose of 200 mg/kg BB, and the ethyl acetate fraction group at a dose of 400 mg/kg BB. The average results of each group for the parameters for measuring serum creatinine levels were 0.5 mg/dl, 2.3 mg/dl, 0.9 mg/dl, 2.2 mg/dl, 1.8 mg/dl, and 1.4 mg/dl. The conclusion of this study is that the ethyl acetate fraction of breadfruit leaves has a nephroprotective activity that can prevent an increase in creatinine levels in mice that have been induced with sodium oxalate. The dose of ethyl acetate fraction of 400 mg/kg BB showed the most effective dose in preventing increased creatinine levels.

Keywords: Breadfruit Leaves, Kidneys, Nephroprotective.

INTRODUCTION

The kidneys function to maintain the acid-base balance, blood fluid and electrolytes, as well as excrete waste materials and excess salts. The kidney excretion mechanism involves three stages: filtration, tubular reabsorption, and tubular secretion. Blood containing salts, glucose, and other fine substances passes through the glomerulus to be filtered. Cells and plasma proteins are too large to pass through the filter pores and remain in the bloodstream. The filtered fluid then flows through the renal tubules, where the cells absorb all substances needed by the body and leave behind what is not required. By adjusting the amount of substances absorbed or left in the tubules, the cells can regulate the composition of urine on one side and the composition of blood on the other. Under normal conditions, all glucose is reabsorbed, most water is reabsorbed, and most waste products are excreted (Laura, R.P. *et al*., 2011).

The idneys are a very important organ to maintain the overall hemostasis of our body. This vital organ participates in the balance of several important physiological functions such as in the balance of acids, bases and hydro-minerals, the regulation and synthesis of several hormones, specifically erythropietin which is necessary for the synthesis of hemamtit, controlling blood pressure and making red blood cells. Kidney failure is a condition in which kidney function decreases (Bencheikh. *et al*., 2021).

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Kidney failure occurs when the kidneys are unable to remove the body's metabolic wastes or perform their regular functions. A substance that is normally eliminated in urine accumulates in body fluids due to impaired renal excretion, causing disturbances in metabolic, fluid, electrolyte, and acid-base functions. Kidney failure is a condition in which kidney function declines, making it unable to filter the body's metabolic waste and maintain the balance of electrolytes such as sodium and potassium in the blood or urine. This disease progressively worsens slowly until kidney function deteriorates and eventually the kidneys lose their function (Hutagaol, 2017).

The prevalence of kidney failure disease in Indonesia is increasing every year. In 2018, the prevalence of kidney failure was 3.8%, and in West Sumatra province, kidney failure patients accounted for 3.5% (Riskesdas, 2018). According to WHO (2019), the prevalence of chronic kidney disease worldwide is 15% of the population, causing 1.2 million deaths. Data from 2020 shows that there were 254,028 deaths due to chronic kidney failure. In 2021, the data amounted to more than 843.6 million, and it is estimated that deaths due to chronic kidney failure will increase by 41.5% by 2040. These high numbers indicate that chronic kidney failure ranks 12th among all causes of death (Aditama, Kusumajaya, 2023).

Nephroprotective is a protective activity for the kidneys that can be found in compounds derived from natural materials. Compounds that are nefroprotective are compounds that have the ability to protect the kidneys from various kidney disorders caused by free radicals, one of which is flavonoid compounds. One of the compounds that can be nephropotent is antioxidants (Padmalochana, 2017). Breadfruit leaves contain various chemical compounds such as flavonoids, phenols, tannins, aceticolin, quercetin, alkaloids, camphorols, and potassium. These compounds can be used to treat kidney dysfunction. Flavonoids as antioxidants can lower oxidative stress. The compound in breadfruit leaves that can shed kidney stones is a potassium compound. Potassium compounds work by blocking calcium which can combine with oxalate, carbonate or urate compounds which are compounds that form kidney stones (Muktiwi et al., 2020).

Breadfruit leaves contain various chemical compounds such as flavonoids, phenols, tannins, acetylcholine, quercetin, alkaloids, kaempferol, and potassium. These compounds can be used to address kidney dysfunction. People use breadfruit leaves to treat kidney function disorders by drinking a decoction of old breadfruit leaves with a dose of 15 g daily (Muktiwi et al., 2020). In previous studies, breadfruit leaf extract at a dose of 200 mg/kg BB could prevent an increase in serum creatinine levels (I'syatulhasanah et al., 2017. According to Siviani, Y., Nirwana, A.P. (2020), breadfruit leaves can be utilized as an antibacterial, and ethyl acetate extract of breadfruit leaves is able to inhibit the growth of Pseudomonas aeruginosa at an optimal concentration of 100%.

In previous research, breadfruit leaf extract at a dose of 200 mg/kg body weight was able to prevent an increase in serum creatinine levels (I'syatulhasanah et al., 2017). Based on the description above, the researcher is interested in conducting a study on the activity of the ethyl acetate fraction of breadfruit leaves in inhibiting kidney stone formation at doses of 100 mg/kg, 200 mg/kg, and 400 mg/kg body weight, with the parameter used in this study being the analysis of serum creatinine levels.

METHODS

Tools and Materials

The tools used in this study were a rat cage, a photometer (Dumolabs DC20), a set of centrifuges, a hotplate (IKA C-MAG HS 7), an analytical digital scale (OHAUS CP214), a water bath, a micro pipette (Socorex), a porcelain cup (IWAKI), a measuring flask (Pyrex), a stirrer, an erlenmeyer (Pyrex), a test tube (Pyrex), a test tube rack, a measuring cup (Iwaki), a water bath, an erlenmeyer (Pyrex), a glass beaker, a measuring flask, a separation funnel (Iwaki), stirring rod, drip pipette, measuring pipette, spatel, spoon, syringe (One Med), mortar and pestle (Iwaki), steam cup (Iwaki), drip plate (Iwaki), oven (Memmert), sieve, filter paper, blender (Andika,M., et al., 2024).

The materials used in the study were male white rats of the wistar strain, breadfruit plant (*Artocarpus altilis*.) the part studied was fresh and dark green leaves, 70% ethanol (Brataco), sodium

oxalate (Merck), aquadest, ethyl acetate (Merck), elliclid toxin, magnesium powder (Merck), concentrated hydrochloric acid (Merck), mayer reagent (Merck), wagner reagent (Merck), dragendrof reagent (Merck), anhydrous acetic acid (Merck), Concentrated sulfuric acid (Merck), Chloroform (Merck), Na-CMC (Andika,M., et al., 2024).

Making Breadfruit Leaf Extract

Three hundred grams of simplicia powder were put into a maceration vessel and macerified using 3 L of 70% ethanol solvent. The extraction process lasts for approximately 3 days. Maserat (maceration results) is filtered using filter paper and accommodated in containers. The maserat is then concentrated using a rotary evaporator until a viscous ethanol extract is obtained (Andika,M., et al., 2024).

Making Ethyl Acetate Fraction of Breadfruit Leaves

The fraction was carried out by the liquid-liquid extraction (ECC) method using ethyl acetate solvent. The ethanol extract of breadfruit leaves previously obtained was dissolved with 100 mL of aquadest, put into a separation funnel plus 100 mL of n-hexane, shaken. The n-hexane fraction is separated. The water fraction is added to 100 mL of ethyl acetate, beaten to add ethyl acetate and then shaken, then let stand until two layers are formed, namely the upper layer (ethyl acetate) and the lower layer (water). The two layers are separated taken ethyl acetate fraction and set aside. The water fraction is fractionated again with ethyl acetate and repeated until a clear ethyl acetate fraction is obtained. The ethyl acetate fraction obtained is collected and steamed using a waterbath until the concentration of solvent in the fraction decreases (Rahimah et al., 2022).

Preparation of Test Animals

The test animals to be used in this study are 30 male white Wistar rats weighing 140-200 grams and aged 3-4 months. Before treatment, the rats were acclimated to the new environment for 7 days and provided with adequate food and water. The animals are considered healthy if the difference in body weight before and after acclimatization does not exceed 10% and they visually display normal behavior. The rats are randomly divided into 6 groups, with each group consisting of 5 rats.

Testing Parameters

Procedure for collecting test animal blood samples, Blood samples are taken through the vein in the eye area. Thirty blood samples are taken, each in the amount of 1-2 mL, and placed in Eppendorf tubes. After that, the blood samples are centrifuged at a speed of 3000 rpm for 15 minutes and then the serum is collected (Andika, et al., 2024). Measurement of Test Animal Blood Creatinine The creatinine measurement is done by adding 1000 µL of Reagent I and 50 µL of serum. After that, it is homogenized and incubated for 5 minutes, then 250 µL of Reagent II is added. Then it is homogenized and incubated for 2 minutes. After that, creatinine is measured using a photometer. The normal creatinine level in Wistar rats is 0.2-0.8 mg/dL (Sukmawati & Asmaliani, 2019). Data Analysis The obtained data are analyzed using nonparametric statistical tests with the Kruskal-Wallis analysis method, followed by Duncan's test.

RESULTS AND DISCUSSION

Sample Identification

In this study, the samples used were breadfruit leaves (*Artocarpus altilis*) taken from Koto Tangah, Tilatang Kamang District, Agam Regency, West Sumatra Province. The samples were identified at the Herbarium of Andalas University, Department of Biology, Faculty of Mathematics and Natural Sciences, Andalas University, with the aim of determining the identification of the samples to be used. Based on the identification results, the breadfruit leaf samples belong to the species *Artocarpus altilis* (Parkinson) Fosberg of the Moraceae family.

Sample in the form of breadfruit leaves was prepared weighing 5 kg, which was first washed. The washing was done to remove other impurities attached to the crude drug. The washing was carried out using running clean water until the leaves were completely free from dirt or foreign objects. After that, the leaves were cut using scissors and placed on a surface before being chopped, then dried at room temperature. The drying process aims to reduce the water

content so that the material or sample is not easily affected by bacteria and to facilitate the processing. Next, the sample was powdered using a blender, and after blending, it was sieved. The sieving process aims to standardize the powder particle size from the sample so that the particles obtained do not affect the results of subsequent steps (Ismiranty et al., 2023).

After obtaining the thick extract, an organoleptic test was conducted visually by observing the shape, color, and smell. The results of the organoleptic examination of the extract showed that the breadfruit leaf extract (*Artocarpus altilis*) was a thick extract, green in color, and had a characteristic smell. (Fardi & Raharjo, 2022) The organoleptic test is also called a sensory test, which is an examination carried out using human senses as the main tool, such as the sense of sight/eyes, sense of smell/nose, sense of taste/tongue, and sense of touch/hands (Wahyuningtias, 2010).

The next process is fractionation. Fractionation is a technique for separating extract obtained from maceration that has been evaporated. This fraction uses various solvents with different polarities, so each solvent contains compounds with different polarities as well. The solvent used for fractionation in this study is ethyl acetate. In the preparation of fractions, liquid-liquid fractionation is carried out using a 1:1 ratio. The thick extract before fractionation is first dissolved in 100 ml of water, then placed into a separating funnel and 100 ml of n-hexane is added. The separating funnel is shaken vigorously and then left for a while until two clearly separated liquid layers form. The n-hexane fraction is separated from the water fraction and then collected in a different container. The aqueous fraction was then further subjected to liquid-liquid fractionation with 100 ml of ethyl acetate three times using a separatory funnel to form two distinct layers. The ethyl acetate fraction and the aqueous fraction were separated into different containers. The obtained ethyl acetate fraction was then concentrated using a rotary evaporator and a water bath at 40 ºC. The yield of the ethyl acetate fractionation was 3.0917 grams. The difference between an extract and a fraction is that extraction is the process of obtaining active compounds from a plant, whereas a fraction is a method of separating mixture components derived from the extract obtained. Fractionation is carried out to separate major groups of contents from one another based on differences in polarity (Andika, M. *et al.,* 2024).

Production of *E.bulbosa* Extraction & Fraction

Maceration produced a thick extract weighing 21.8717 g with a yield of 14.87%. Fractionation produced 3.0917 g with a yield of 23%. The obtained yield meets the minimum yield standard of 7.2% (Magfirah et al., 2020). The yield test is designed to assess the efficiency of extraction and fractionation based on the percentage of extract and fraction obtained from the initial sample. Based on Table 1, the tested compounds were found to be positive for containing flavonoids, alkaloids, saponins and tannins in the phytochemical screening test.

Table 1. Phytochemical test results of the ethyl acetate fraction from *Artocarpus altilis*

No.	Test	Reagent	Result	Note
1.	Flavonoid	HCl Concentrated + Mg Powder	+	Brick red precipitate
2.	Alkaloid	Dragendorff	+	Orange to brick red precipitate
		Mayer	+	White precipitate
		Boucardat	+	Brown to black precipitate
3.	Terpenoid	Lieberman- Bouchard	+	Purplish red
4.	Tanin	FeCl3	+	Blackish green

Creatinine Level Test

The obtained serum was reacted with reagent 1 in a test tube, then the tube was shaken using a vortex mixer to ensure a homogeneous mixture of serum and reagent. It was then left to stand for 5 minutes, after which reagent 2 was added to the test tube containing the mixture of reagent 1 and serum.

The creatinine level was then tested using a photometer at a wavelength of 505 nm. After obtaining the initial serum creatinine levels, each group of rats was given treatment. The treatment for each group was carried out for 7 days. Afterwards, blood was taken again from the rats to re-test the creatinine levels in each group.

Table 2. Creatinine level test results

No	Treatment	After Induction	After Treatment	Difference
1	Negative	0,5 mg/dL	0,5 mg/dL	0 mg/dL
2	Positive	0,4 mg/dL	2,3 mg/dL	1,9 mg/dL
3	Comparator (Batugin)	0,6 mg/dL	0,9 mg/dL	0,3 mg/dL
4	Dose 100 mg/KgBW	0,5 mg/dL	2,2 mg/dL	1,7 mg/dL
5	Dose 200 mg/KgBW	0,4 mg/dL	1,8 mg/dL	1,4 mg/dL
6	Dose 400 mg/KgBW	0,5 mg/dL	1,4 mg/dL	0,9 mg/dL

The results of creatinine level measurements were obtained with an average in the negative group of pre-test = 0.5 mg/dl, post-test = 0.5 mg/dl, with no difference observed. The positive group had pre-test = 0.4 mg/dl, post-test = 2.3 mg/dl, with a difference of 1.9 mg/dl. The comparator drug group (Batugin) had pre-test = 0.6 mg/dl, post-test = 0,9 mg/dl, with an increase of 0,3 mg/dl. The ethyl acetate fraction of breadfruit leaves at a dose of 100 mg/kg BW had pre-test = 0.5 mg/dl, post-test = 2.2 mg/dl, with a difference of 1.7 mg/dl. The ethyl acetate fraction of breadfruit leaves at a dose of 200 mg/kg BW had pre-test = 0.4 mg/dl, post-test = 1.8 mg/dl, with a difference of 1,4 mg/dl. The ethyl acetate fraction of breadfruit leaves at a dose of 400 mg/kg BW had pre-test = 0.5 mg/dl, post-test = 1.4 mg/dl, with a difference of 0.9 mg/dl. The pre-test creatinine level results showed that each group's creatinine levels were within the normal range. The normal creatinine level for Wistar rats is 0.2-0.8 mg/dL (Sukmawati & Asmaliani, 2019). The post-test creatinine level results showed an increase in creatinine levels in each group, which occurred due to the administration of sodium oxalate in each group, except for the negative group.

The highest serum creatinine levels were shown by the positive group, with an average difference between the pre-test and post-test of 1.9 mg/dL, which is above the normal creatinine range. According to Sukmawati (2019), the normal creatinine level in Wistar rats is 0.2-0.8 mg/dL. The positive group experienced an increase in serum creatinine levels compared to the negative group. This increase indicates that sodium oxalate can cause kidney cell damage. The nephroprotective effect of breadfruit leaves was proven in this study. Serum creatinine levels in the groups given the ethyl acetate fraction of breadfruit leaves, namely the 100mg/kg BW, 200mg/kg BW, and 400mg/kg BW dose groups, showed lower values compared to the positive group. Effect the nephroprotective effect of the ethyl acetate fraction of breadfruit leaves is caused by various active compounds contained in the leaves. These active compounds act as antioxidants that can react with free radicals (I'syatulhasanah et al., 2017). The group receiving a dose of 400 mg/kg BW showed lower serum creatinine levels compared to the negative control group. These results indicate that the ethyl acetate fraction of breadfruit leaves at a dose of 400 mg/kg BW has a better effect in preventing an increase in creatinine levels compared to doses of 100 mg/kg BW and 200 mg/kg BW. The effect of the 400 mg/kg BW dose of the ethyl acetate fraction is consistent with research (Cahyaningsih, 2011) which states that the effectiveness of ethanol extract of breadfruit leaves increases with the administered dose.

The next data was analyzed statistically to observe the effect of preventing the increase in creatinine levels that occurred after the administration of the ethyl acetate fraction of breadfruit leaves. The data was analyzed using SPSS statistics. Normality was tested using the Shapiro-Wilk test, followed by a homogeneity test and a One Way ANOVA test. In the normality test, it was found that the creatinine level data obtained from the difference between pre-test and post-test had a significance of 0.150, meaning the data can be considered normal because the significance is > 0.05. The homogeneity test was then carried out, where results are considered normal if the significance value > 0.05. The significance value obtained was 0.024, so it can be concluded that the data is not homogeneous. The data could not proceed to the One Way ANOVA test because the requirements for the One Way ANOVA test are that the

data must be normal and homogeneous. Therefore, the data was continued with the Kruskal-Wallis test, A value of 0.019 was obtained, so the data analysis does not meet p ≥ 0.05, or H0 is rejected. This means that there is no statistically significant difference in the difference in creatinine levels between pre-test and post-test in each group across the various types of treatments.

CONCLUSIONS

From the research conducted on the nephroprotective activity test of the ethyl acetate fraction of breadfruit leaves (*Artocarpus altilis*) in male white rats, it can be concluded that the ethyl acetate fraction of breadfruit leaves (*Artocarpus altilis*) is proven to have nephroprotective effects on male white rats induced by sodium oxalate, as it can reduce serum creatinine levels.

CONFLICT OF INTEREST

In the implementation and completion of this research there is no significant problem

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