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Research Article

Pharmacological Properties and Toxicological Investigation on Durio zibethinus Murr. Peel Extracts

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Abstract.
The ethanol extract of the dried fruit peels of Durio zibethinusMurr. was tested for cytotoxicity, antidiabetic, antihyperuricemia, and antihypercholesterolemia activities in experimental animals. The extract showed the potential activities of antidiabetic, antihyperuricemic, and antihypercholestrol agents. As an cytotoxicity agent, the extract was not potent against vero cells with an IC50 value of 1.864 µg/mL. Overall, Durio zibethinusMurr. fruit peels extracts had the potential to be used as an ingredient in herbal medicines for antidiabetic, antihyperuricemia and anti-hypercholesterolemia.

Keywords: herbal medicine; antidiabetic; antihyperuricemia; anti-hypercholesterolemia

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1. Introduction

Durian with the scientific name Durio zibethinus is an iconic tropical fruit plant and climateric seasonal in Southeast Asia (Malaysia, Tailland, Philippines, and Indonesia)[1]. Several names for durian in Indonesia, among others; Pelangi Setururi, Salisun, Nangan, Matahari, and Sitokong. Durian peel residue is reported to have low commercial value and is even said to be non-existent and when left in the open, it will generally pollute the environment[2]. Utilization of durian fruit skins has not been carried out optimally even though the durian fruit peels have relatively high secondary metabolite compounds. Secondary metabolite compounds possessed by durian have the potential as functional food and pharmaceutical therapy in disease [3].

Secondary metabolite compounds in durian skin include flavonoids, terpenes, phenolics, saponins, tannins, and phytosterols. The antioxidant activity is thought to come from phytosterol and phenolic compounds [4]. The antidiabetic effect of durian is influenced by the content of polyphenols in controlling postprandial hyperglycemia [5]

and flavonoids in inhibiting the working α-glucosidase enzyme [6]. Saponin compounds as natural anti-cholesterol which will form a cholesterol insoluble complex bond, besides that flavonoids help reduce the absorption of bile acids and cholesterol in the intestine. Tannins suppress free radicals [7], and inhibit lipid absorption. Phytosterols reduce cholesterol synthesis in cells [8].

This article was created to describe the pharmacological effects that have been studied from research as well as the toxicity effects of the ethanol extract of durian rind (Durio zibethinus). The data obtained is expected to be used as a reference for further research scientific data and to find solutions to the problem of durian fruit skin based on its benefits, especially in medicine.

2. Methods

2.1. Plant and extraction materials

Durian peels (*Durio zibethinus Murr.*) was collected as a fresh sample obtained from Solo and its surroundings. The identification and determination of samples were carried out in the Department of Biology, FKIP UMS and the Morphistum Laboratory of Pharmacy Biology, Faculty of Pharmacy UMS. The durian peel used is dried and then pollinated. The extraction was carried out in accordance with the correct standard extraction procedure. Extraction was carried out by maceration 3 times with the extract yield about (16.93%).

2.2. Animal Test for Antidiabetic and Antihypercholesterol

Wistar strain albino male rats weighing 150-300 grams were used in this study. Animals were treated with a diet of pellets and enoughwater during the study period. To avoid any changes that may be caused by circadian rhythms, the time of the study was conducted around 08.00-10.00 am instead of at night [9].

2.3. Animals Test for Antihyperuricemia

The animals test of Swiss male mice weighing 20-35 g were used in this study. Male mice were chosen because they have less estrogen, where this hormone will affect the increase in uric acid secretion [10]. During the study period the animals were treated with

a diet of pellets and enoughwater. When the study was conducted around 08.00-10.00 am, this was done to avoid any changes that might be caused by circadian rhythms [9].

2.4. Antioxidant Test

Evaluation of antioxidant activity using Kirby and Shmidt's 1,1-diphenyl-2-picrylhydrazyl (DPPH) method [11], with a slight modification of the ethanol extract and durian fruit peel fraction. Concentration series were prepared from stock solutions (1.0 mg / mL) with several concentration series of 1000, 500, 250, 124, 62.5, 31.3, 15.6, and 7.8 µg / m. Each 0.2 mL of the sample solution was added with 3.8 mL of a mixture of 50 µM DPPH and metanol (1 mg / 50 mL) solution and allowed to stand for 30 minutes at room temperature to react. The absorbance of the solution and control mixture (without sample or standard) was measured at a wavelength of 517 nm at 0 min. The data obtained then calculated the percentage of inhibition (1%) of the DPPH.

$$\% = \frac{Ablank - Asampel}{Ablank} x\ 100 (1)$$

Exp:

1. A blank = control absorbance value (reaction of all reagents except test sample)
2. A sample = the absorbance of the sample

From IC_{50}, a plot of the percentage inhibition of the sample concentration was obtained.

All tests were carried out 3 times in duplicate with a value of IC_{50} = ± SD in triplo.

2.5. Antidiabetes Activity Evaluation

The test was carried out on 5 test groups consisting of 5 animals per group. Animals are fasted for the previous 12-15 hours and are still given adequate water prior to testing. The next treatment was for 7 days with the appropriate stages for each group. Blood draw was done to measure the blood sugar levels of mice. Blood was drawn through a lateral vein in the rat's tail. Blood sugar levels were measured after alloxan induced rats and compared with after treatment. Blood samples were given into a 0.5 mL effendrof and then to take the serum, centrifuged for 20 minutes at a speed of 12,000 rpm with minispin. A total of 10 mL of supernatant was taken and 1000 mL of the GOD-PAP reagent mixture in the cuvette was administered. The mixture was incubated at 37^{o}C for

10 minutes and the absorbance of the blank, standard, and sample was read by visible spectrophotometry at a wavelength of 500 nm.

2.6. Antihyperolesterol Activity Evaluation

All ofanimals test were pre-treated with standard food or pellets and were given enough water for 7 days. The animals test to be used were treated for 28 days with high-fat feeding (50 mL cooking oil, 10 grams of quail egg yolk, 0.1% PTU, and added with distilled water up to 100 mL;) and other feed (150 gr pellets, 20 grams of quail egg yolk, and 50 grams of margarine), and always updated and monitored by drinking 0.1 PTU of water at a dose of 2 mL / 200gb.w. For 2 weeks the cholesterol test animals (total cholesterol levels> 150 mg./dL) were given durian skin ethanol extract.

2.7. Treatment On Animal Test

The experimental animals were grouped into 5 for each test (antidiabetic and anti-hypercholesterolemic) which consisted of 5 animals in each group; The five groups, namely; Group 1 is the Control Group: the control test animal used to determine the basic parameters of the study; Group 2 is the diabetes group (rats induced by glibenclamide (0.45 mg / kgBW) so that they are considered diabetes controllers) / the cholesterol group (which are fed high cholesterol); Groups 3,4, and 5 are groups of diabetic / cholesterol animals that were given ethanol extract of durian skin in consecutive series of 500 mg / kg, 250 mg / kg, 125 mg / kg respectively.

2.8. Antihiperurisemia Activity Evaluation

Evaluation of anti-hyperuricemia activity was carried out with in vivo using white male Swiss mice aged 2-3 months weighing 20-35 grams. For 7 days, supply livestock by giving pellets and enough water. The test animals were induced using potassium oxonate 250 mg / bw until uric acid levels were more than 3.3 mg / dL. The extract suspension with 0.5% CMC was given orally to the animalstest according to body weight. Animal groups are divided into 5 groups with 3 animals each group where; group 1 negative or CMC Na 0.5%; Group 2 positive control in the form of allupurinol 10 mg / kgBW, groups 3,4, and 5 were hyperuricemic mice that were given extracts with different concentrations with series 100, 200, and 300 mg / kgBW. Blood was drawn through the eyes of mice using a capillary tube into the ophthalmic vein at 2 hours after the

potassium oxonate was induced intraperitoneally, then blood was introduced into a 0.5 mL effendrof. Enzymatic reaction with uric acid reagent FS * TBHBA is defined as the level of uric acid. The absorbance was read on the reacted sample, standard, and blank with a wavelength of 546 nm.

2.9. Cytotoxic

Cytotoxic evaluation was carried out on Vero cells and HeLa cells by extract of durian peel. In research, Hela cells were used to determine the cytotoxic activity of the durian peel extract, while Vero cells or normal cells were used as a test for the toxicity of the extract. Extract test solutions were made from stock into RPMI media and M199 media into 7 series of concentrations (100, 250, 400, 550, 700, 850, and 1000 µg / mL). HeLa cells and 10,000 (10^4) / 100 µl density cells mixed with the sample in DMSO were distributed to 96 microplates in 3 replications each concentration series. Incubation at 37^{o}C for 24 hours in 5% CO_2 incubator. At the end of each incubation, the well was filled with 110 µl of culture media (MTT 5m / mL PBS), incubated at 37^{o}C again for 4 hours to form formazone crystals. The reaction was stopped by adding SDS 10% in HCL 0.01 N 100 µL / well after 4 hours. Reincubated at room temperature for overnight and covered with aluminum foil. Readout at 595 nm wavelength with ELISA Reader. The formula used in reading the ELISA reader with a probit value of 50% as IC_{50} is;

$$\%\ living\ cell = \frac{Abstreatment - Abs\ media\ control}{Abscontrolcell - Absmedia\ control} x\ 100 (2)$$

2.10. Statistical analysis

The statistical analysis used was using SPSS version 17 software. The statistical test that was followed was mean + SEM. Measurement t-test was used with a significant difference value (P <0.05).

3. Results and Discussion

3.1. Extraction

Extraction was carried out using a mixture of two solvents, namely 96% ethanol and acetone (4:1), this addition was carried out to obtain a better extract [12]; and [13]. This happens because this mixing causes it to be more selective, non-toxic, neutral, and ethanol can be mixed with acetone in all mixtures. Ethanol solvents have a low boiling

point, tend to be safe, non-toxic and harmless. The two sides of the ethanol-OH group have polar properties, while the non-polar CH_2CH_3 group makes both polar and non-polar compounds dissolve in the solvent. The extract obtained was 338.6 grams with the extract value obtained of 16.93% from 2000 grams of powder.

3.2. Animals Test

The time of the study was carried out in the time range around 08.00 to 10.00 am because it avoided metabolic syndrome disorders or disorders of the circadian rhythm. The circadian rhythm system is a timing system that is responsible for coordinating many of the body's daily processes and metabolic processes [14]. In the system, the use of intervals hourfor research is related to deviations in the final results of the study. The use of curfews leads to an increased risk of metabolic syndrome incidence [9].

3.3. Antioxidant Test

Activity measurements are obtained from DPPH testing. The IC_{50} value shows the number of activity as an antioxidant which appears as an inhibitor of deposition of DPPH, wherein the smaller value make the higher antioxidant activity. If the IC_{50} value is <50, it indicates stronger antioxidant activity, or in the range of 50-100 ppm. Antioxidant activity is shown at IC_{50} values of more than 150 ppm [15]. The activity can be seen from the IC_{50} values obtained from the ethanol extract, chloroform fraction, and acetate fraction respectively, namely 28.83 ± 0.48; 32.81 ± 2.64; 14.91 ± 3.23, where the ethanol extract of durian peel as a whole has an antioxidant effect. Based on the IC_{50} value of the three, it shows strong antioxidant activity.The antioxidant activity of phytosterol and phenol compounds which help in scavenging free radical [4].

3.4. Antidiabetes Activity Evaluation

The experimental animals were initially induced with alloxan, until an increase in blood sugar levels. Alloxan works by forming free radicals in the pancreas, these free radicals then damage the β cells and develop insulin deficiency, and cause hyperglycemia [16]. In the alloxan test it can cause hepatotoxicity, this is evidenced by the decrease in antioxidant enzymes which are responsible for the increase in lipid aldeid peroxidase and due to oxidative stress [17]. The comparison used was glibenclamide which is a common drug for diabetes patients. Glibenclamide administration shows a decrease in

blood glucose due to the stimulating effect of residual insulin secretion on pancreatic β cells [18]. After calculating the blood levels before being induced, during treatment and after treatment, the search for the value of reducing blood sugar levels is as follows.

Table 1: Percentage of Decreased Blood Sugar Levels.

Treatment Group	Decrease in Blood Sugar Levels%
Positive control glibenklamid (0.45mg/kgBB)	41.90±13.05
Ethanol extract of durian peel (500 mg/kgBB)	**50.19±3.66**
Ethanol extract of durian peel (250 mg/kgBB)	35.09±3.84
Ethanol extract of durian peel (125 mg/kgBB)	16.55±2.99

The highest reduction in blood glucose levels was seen in animals that had been given durian peel extract as much as 500 mg / kgBW. This decrease was higher than the positive control, so it could be said that the extract was more effective than the drug administration. The test mechanism is related to the presence of flavonoid compounds that play a role in regenerating and stimulating the release of insulin from the β-pancreas [19] and inhibits the activity of the α-glucosidase enzyme [6]. Some compounds that have the potential to be antidiabetic are flavonoids cathekin and quercetin [20], as well as polyphenols with a hydroxyl group on the active side of the enzyme and forming complex bonds with it [21] and tannins [22].

3.5. Antihyperolesterol Activity Evaluation

The effect of reducing levels as a decrease in cholesterol levels in the blood. The experimental animals were given pellets and drank enough to increase their cholesterol levels. The provision of high intake of saturated fatty acids and cholesterol in pellets will increase cholesterol levels in the body of the tested animals, reduce the synthesis and activity of cholesterol receptors. Because this cholesterol will report an increase in total cholesterol levels that are not balanced and cause hypercholesterolemic conditions [23]. The extract was given thereafter for 2 weeks before measuring the reduction in blood cholesterol levels. The positive control used isnamely cholesteramine. Calculated from before being given the extract to being given the extract, the data shows that the decrease in levels.

The highest cholesterol-lowering effect was found in the group with 500mg / kg durian peel extract compared to positive controls. The reduction value in animals given

Table 2: Decrease in cholesterol levels.

Treatment Group	Decrease in Cholesterol Levels%
Negative control (CMC-Na)	13.44±15.45
Positive control (cholesteramine)	34.20±10.48
Ethanol extract of durian peel (500 mg/kgBB)	**35.82±5.00**
Ethanol extract of durian peel (250 mg/kgBB)	35.79±6.63
Ethanol extract of durian peel (125 mg/kgBB)	2.36±6.96

the extract was 35.82 ± 5.00 which showed a decrease in cholesterol levels was greater than the decrease in cholesterol levels from the positive control given to test animals. The antihypercholesterol activity of durian peel extract can be said to be greater than the drug. The role of secondary metabolite compounds in anti-hypercholesterolemia include; 1) saponins as natural anti-cholesterol, form complex bonds that are insoluble with cholesterol so that cholesterol cannot be absorbed by the intestine, 2) Flavonoids as a lowering of blood cholesterol levels, these compounds work to reduce the absorption of bile acids and cholesterol in the small intestine, increase fecal excretion, where the liver cells will increase the conversion of cholesterol into bile acids and convert lipid into energy, Tannin as a compound to fight free radicals by binding to metals in the blood, inhibiting lipid absorption [7], 4) Reducing phytosterol synthesis in cells by inhibiting binding to sterol regulatory element binding protein (SREBP) with sterol regulatory element (SRE), two proteins that play a role in the transcription of the LDL receptor gene which results in decreased HMG-CoA reductase activity [8].

3.6. Antihiperurisemia Activity Evaluation

Potassium oxonate inducers, which are potential as uricase inhibitors, which will convert uric acid into allantoin, which increases uric acid levels, were selected in this study [24]. Preliminary tests that have been carried out show that the addition of potassium oxonate significantly increases the body's uric acid levels, where the level of 3.3 mg / dl in mice can be said to be a hyperuricemic condition [25]. Potassium oxonate is intraperitonally induced. Alupurinol is used as a comparison to determine the decrease in uric acid levels, because it is generally a drug for gout sufferers. The mechanism of action of uricostaticallupurinol is to reduce uric acid by inhibiting uric acid formation. The adverse and dangerous side effects of allupurinol, especially in the intestines, are the cause of

the use of medicinal plants [26]. The data on uric acid levels that have been calculated after treatment are as follows.

The lowest uric acid level in the data above is the addition of the durian peel ethanol extract (200 mg / kgBW), namely 0.37 ± 0.25. This lowest level shows the highest decrease in uric acid levels from the initial level. The final uric acid level percentage showed that the ethanol extract of durian peel was lower than the positive control, so it could be ignored that the decrease in uric acid levels was greater in the administration of the extract. In this study, increasing the dose did not increase the response, this is related to the action of natural substances whose components are various and may allow interactions that affectof drugs effect. Another relationship is also related to the limited number of receptors, so that their effect and receptor response is limited because not all medicinal substances bind to them.

TABLE 3: Uric acid levels of mice after treatment.

Treatment Group	Levels of uric acid after treatment%
Negative control (CMC-Na)	3,47 ± 0,12
Positive control (Allupurinol 10 mg/kgBB)	1,25 ± 0,41
Ethanol extract of durian peel (100 mg/kgBB)	1,62±0,12
Ethanol extract of durian peel (200 mg/kgBB)	**0,37±0,25**
Ethanol extract of durian peel (300 mg/kgBB)	1,32±0,42

3.7. Cytotoxic

Cytotoxic testing on HeLa cells and Vero cells was performed using the MTT assay method. The tetrazolium succinate reductase system that occurs in the mitochondrial chain underlies the reaction of MTT. The toxicity observations of the ethanol extract of durian peel were seen from its effect on vero cells in inhibition. Cytotoxic test data showed that the ethanol extract of durian peel had weak activity against both HeLa and healthy cell death. Anticancer activity against cancer cells is known to be still low, because it can be associated with differences in the characteristics of cancer cells and various mechanisms of action of the extracts, so it is necessary to further study the accuracy of these two factors and other factors. The weak effect on cells was also shown by Gorinstein*et al*, 2011 with a study related to the weak antiproliferative effect of methanol extract of durian peel on cells[27]. The weakness or inability of the extract

against vero cells with an IC_{50} value of 1.864 µg / mL indicates that the extract is safe to use. Toxic or not a substance can be seen from its LD_{50} value, if more than 1000 µg / mL is said to be toxic [28]. The low value of Vero cell destruction also shows the absence of verotoxigenic properties, which means the lower incidence of virulence that causes disease. This test is performed as an in vitro cytotoxic test on healthy cells, so it is considered not to be potentially toxic for healthy cells.

4. Conclusions

Durian peel not only becomes waste but can have other benefits, such as medical effects with pharmacological effects. The pharmacological effects of the ethanol extract of durian peel include being an antioxidant, antidiabetic, anti-hypercholesterolemic, and anti-hyperuricemia. The compounds in durian skin play a role in the existence of a pharmacological effect from it. The toxicity of the durian peel was not demonstrated in the absence of an effect on Vero cells. Cytotoxic test showed extract was not potent against vero cells with an IC_{50} value of 1.864 ug / mL.

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