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Antidiabetic Activity of Durian (*Durio zibethinus* Murr.) and Rambutan (*Nephelium lappaceum* L.) Fruit Peels in Alloxan Diabetic Rats

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Abstract

The present study was carried out to evaluate the in alloxan (150 mg/kgb.wt) induced diabetic rats. The ethanolic extract of Durian (Durio zibethinus Murr.) and rambutan (Nephelium lappaceum L.) fruit peels administered orally to the diabetic rats for 11 days, produced significant decrease in the level of blood glucose. The highest percentage reduction in blood glucose levels were shown of rambutan fruit peels extract with dose 500 mg/kgb.w and the value of persentage reduction were 61.76±4.26%.

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Keywords: Antidiabetic activity, Durio zibethinus Murr., Nephelium lappaceum L., Alloxan, Ethanolic extract

INTRODUCTION

Diabetes mellitus (DM) is defined as a disease or chronic metabolic disorder with multiple etiologies is characterized by high blood glucose levels with impaired metabolism of carbohydrates, lipids and proteins as a result of insufficiency of insulin function [1]. In Indonesia is estimated at about 50% people with diabetes have not been diagnosed. In addition, only two-thirds of the undiagnosed are undergoing treatments, both pharmacological and non-pharmacological. WHO and IDF (International Diabetes Federation) predicts an increase in the prevalence of diabetes reaches 2 to 3 times in 2030 so a lot of research in the prevention and management of diabetes and its complications [2].

Diabetes disease management requires a multidisciplinary treatment with pharmacological therapy and non-pharmacological therapies [3]. The use of modern drugs such as sulfonylurea group had side effects such as water retention with hyponatremia. While the use of α-glucosidase inhibitors and biguanides can cause

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gastrointestinal disturbances [4].

In 1980 the WHO recommended that an examination of the plant which has the effect of hypoglycemia due to the use of modern drugs that are less safety [5]. Two of the result of in vitro studies which explain that the ethanol extract of durian rind [6] and rambutan fruit peels had antihyperglycemic activity[7]. Based on the research of Batubara [8] ethanol extract the inner and outer skin of durian fruit had antioxidant activity. Durian acts as an antioxidant [9] and antiproliferative [10]. The content of polyphenols and flavonoids can inhibit rise high enough plasma lipids and plasma antioxidant activity in vivo tests on Wistar rats were weighed cholesterol [11]. Rambutan fruit peels contain flavonoids, tannins and saponins [12]. Rambutan peel ethanol extract contains epigallocatechin-3-gallate [13] which have activity as antihyperglycemia [14] as well as powerful antioxidants [15]. Rambutan fruit peels ethanol extract be known to have a greater ability to capture as an antioxidant free radical DPPH compared with vitamin E [16,9]. Haruenkit et al. [10] explained that the content of polyphenols, flavonoids, flavanols, tannins and ascorbic acid acts as an antioxidant. Polyphenols and antioxidant phenols such as catechin can capture free radicals and reduce oxidative stress.

Based on the above it is expected that this study can determine whether there is the effect of the ethanolic extract of durian (*Durio zibethinus* Murr.) and rambutan (*Nephelium lappaceum* Linn.) fruit peels to decrease blood glucose levels in alloxan diabetic rats. The results of this study will provide the benefits of obtaining antidiabetic drugs materials from peels of Indonesian fruits.

MATERIALS AND METHODS

Plant material and extraction

Durian (*Durio zibethinus* Murr.) and rambutan (*Nephelium lappaceum* Linn.) fruit peels were collected fresh from the waste fruit traders in the market areas in Surakarta, Central of Java, Indonesia and dried in the shade and then powdered. The plant was identified by experts team from the pharmaceutical biology, Pharmacy Faculty, Universitas Muhammadiyah Surakarta. Ethanolic extracts of TC were prepared according to the standard extract procedure. The yield of extracts from the extraction of three times maceration was approximately 16.93% and 27.16%, respectively.

Animals

Male albino rats of inbred Wistar strain (body wt. 150-300 g) were used in this study. The animals were fed on a pellet diet and water ad libitum throughout the study period. All the experiments were carried out in between 8 and 10 A.M in order to avoid circadian rhythm induced changes.

Experimental groups

All the experimental animals were divided into 8 groups with each group consisting of 5 animals as follows:

Group 1- Control: This group was used for studying the baseline values of the parameters studied. Group 2- Diabetic control: This group consisted of glibenclamide induced diabetic rats with dose 0.45 mg/kg b.w. Group 3- Diabetic rats treated with (500 mg/kg b.w.) ethanolic extract of durian rind. Group 4- Diabetic rats treated with (250 mg/kg b.w.) ethanolic extract of durian rind. Group 5- Diabetic rats treated with (125 mg/kg. b.w) ethnolic extract of durian rind. Group 6- Diabetic rats treated with (500 mg/kg. b.w.) ethnaolic extract of rambutan peel. Group 7- Diabetic rats treated with (250 mg/kg. b.w.) ethnaolic extract of rambutan peel. Group 8- Diabetic rats treated with (125 mg/kg. b.w.) ethnaolic extract of rambutan peel.

Experimental induction of diabetes

Before the animals treated with blood glucose levels were measured initially as a baseline. High blood glucose levels (diabetes) is made by injecting alloxan intraperitoneally at a dose of 150 mg / kg b.w [17]. The solution of alloxan was prepared by dissolving alloxan monohydrate in water for injection. The next four days were measured in blood glucose levels compared with rats for glucose injected rats before induced alloxan. In the event of an increase in blood glucose levels to ± 200 mg / dL, were considered diabetic rats.

Antidiabetic activity testing

The testing was performed on each group of ethanolic extract of durian rind and rambutan fruit peels. The white male rats are grouped into 8 treatment groups. Each group consisted of 5 tails. Prior to testing, the animals were fasted 12-15 hours and still be given to drink ad libitum. The rats treated with the appropriate treatment groups for 7 days and blood glucose levels of rats were measured again for comparison with blood glucose levels of rats after alloxan induced. Blood sampling is done through the lateral tail vein of rats were collected in 0.5 mL Eppendorf tubes and then centrifuged using minispin for 20 minutes at 12,000 rpm to obtain serum. Subsequently, the supernatant was taken using a micropipette as much as 10 mL and then inserted into the cuvette and added 1000 mL GOD-PAP reagent mixture were then incubated for 10 min at 37 ° C. Then blank, standard and sample absorbance was read using a visible spectrophotometer at λ 500 nm.

Statistical analysis

Blood glucose measurement data of rats were analyzed by statistical tests using SPSS version 17 for windows. The statistical testing was used the normal distribution (Shapiro-Wilk test), homogeneity testing (Testing of Homogenecity of Variance). Then Kruskal-Wallis testing was used to see the difference in glucose levels between treatment groups of rats and Mann-Whitney testing to see the significance of the average difference between the treatment groups.

RESULTS AND DISCUSSION

Extraction by maceration method was using a solvent mixture of 96% ethanol and acetone (4: 1 L) for every 2000 grams of powder. Usage a solvent mixture of ethanol and acetone to extract more than a single solvent because the solvent mixture is not toxic, neutral, heat required to lower concentration and ethanol can be mixed with acetone in all comparisons [18]. The weight of durian rind extracts obtained was 338.6 grams with a yield of 16.93% from 2000 grams of powder. The weight of rambutan fruit peel extract was 543.2 grams with a yield of 27.16%.

Alloxan is selectively toxic to pancreatic β cells that produce insulin due to the accumulation of alloxan through the GLUT2 transporter. Toxic action of alloxan on β cells is initiated by free radicals formed by redox reactions. In vitro assays known mechanisms of alloxan to the pancreatic β cell destruction by inducing expenditure of the mitochondria calcium ions resulting in impaired cell oxidation process and result in disruption of homeostasis [19]. Animal tests with glucose ± 200 mg / dL declared diabetes [20]. The results of the measurement of blood glucose levels during treatment of mice 7 days can be seen in Table 1.

Statistical calculation of the data begined with the antidiabetic activity tests for normality of distribution using the Shapiro-Wilk testing that showed the data from each group were normally distributed ($p > 0.05$). Then followed a statistical test of Homogenecity of Variance Test against alloxan and glucose levels obtained post significance of 0.008 ($p < 0.05$). In the testing on blood glucose levels obtained the 0.022 significance ($p < 0.05$) so that both the data stated were not homogeneous. This result showed that the treatment groups were from different populations. Statistical analysis followed by Kruskal-Wallis testing obtained 0.000 ($p < 0.05$) showed that there were significant differences in blood glucose levels among the eight treatment groups. Then continued on the statistical analysis of non-parametric Mann-Whitney testing which gived the results significantly different between treatment groups bark ethanol extract and ethanol extract of durian fruit rambutan skin with the negative control group.

In Table 2, the calculation of the percentage of decrease in blood glucose levels showed an increase in the percentage of decrease with increasing dose administration of durian and rambutan fruit peels ethanol extracts.

Tabel 1. Decreased Blood Glucose Data

Treatment		Early Blood Glucose (*pre*) (mg/dL)	Blood glucose Post alloxan induced (mg/dL)	End Blood glucose (*post*) (mg/dL)
Group I Negative control CMC-Na 0,5%	1	103	208	198
	2	104	238	212
	3	63	210	239
	4	68	203	247
	5	60	230	235
Means ± SD		**79.6±22.01**	**217.8±15.27**	**226.5±20.44**
Group II Positive control Glibenklamid 0,45 mg/kg b.w.	1	75	222	140
	2	60	213	156
	3	63	230	133
	4	73	193	81
	5	62	210	148
Means ± SD		**66.6±6.88**	**213.6±13.94**	**131.6±29.57**
Group III Ethanolic extract of durian rind 500 mg/kg b.w.	1	70	248	107
	2	97	225	110
	3	65	219	123
	4	99	248	104
	5	67	246	120
Means ± SD		**79.6±16.90**	**237.2±14.06**	**112.8±8.29**
Group IV Ethanolic extract of durian rind 250 mg/kg b.w.	1	117	225	145
	2	93	212	149
	3	109	228	158
	4	99	201	134
	5	104	227	149
Means ± SD		**104.4±9.21**	**218.6±11.76**	**147±8.69**
Group V Ethanolic extract of durian rind 125 mg/kg b.w.	1	60	230	187
	2	59	243	190
	3	106	232	200
	4	71	210	186
	5	81	211	182
Means ± SD		**75.4±19.32**	**225.2±14.30**	**189±6.78**
Group VI Ethanolic extract of Rambutan fruit peel 500 mg/kg b.w.	1	107	192	78
	2	115	208	76
	3	104	196	98
	4	126	209	87
	5	117	199	94
Means ± SD		**113.8±8.70**	**200.8±7.46**	**86.6±9.63**
Group VII Ethanolic extract of Rambutan fruit peel 250 mg/kg b.w.	1	111	244	124
	2	74	268	113
	3	114	288	122
	4	89	231	107
	5	67	223	111
Means ± SD		**91±21.2**	**250.8±26.88**	**115.4±7.30**
Group VIII Ethanolic extract of Rambutan fruit peel 125 mg/kg b.w.	1	67	230	173
	2	79	225	169
	3	67	232	176
	4	70	237	162
	5	88	220	176
Means ± SD		**74.2±9.15**	**228.8±6.53**	**171.2±5.89**

Tabel 2. Average Percentage Decrease Blood Glucose Levels (% DBGL)

Groups of Treatment	DBGL (%)
Positive control Glibenklamid (0.45 mg/kg b.w.)	41.90±13.05
Durian rind ethanolic extract (500 mg/kg b.w.)	50.19±3.66
Durian rind ethanolic extract (250 mg/kg b.w.)	35.09±3.84
Durian rind ethanolic extract (125 mg/kg b.w.)	16.55±2.99
Rambutan fruit peel ethanolic extract (500 mg/kg b.w.)	61.76±4.26
Rambutan fruit peel ethanolic extract (250 mg/kg b.w.)	49.05±3.22
Rambutan fruit peel ethanolic extract (125 mg/kg b.w.)	22.65±2.10

The ethanolic extracts of durian and rambutan friut peels with dose of 500 mg/kg b.w. had a greater percentage decrease than Glibenclamide 0.45 mg/kg b.w as positive control. The ability of ethanolic extract of durian and rambutan fruit peels were in reducing blood glucose levels presumably because flavonoids constituents. Presumed mechanism of action of flavonoids which were to regenerate and stimulate the release of insulin by pancreatic β cells [21]. In addition there were three mechanism of the decrease in blood glucose levels as a potential antidiabetic plants, among others are: 1) have the ability as an adstringen to be able precipitate the intestinal mucous membrane protein and forms a layer that protects the intestine, so as to inhibit the intake of glucose, 2) accelerate the release of glucose from the circulation by accelerating filtration and renal excretion, 3) accelerating the release of glucose through increased metabolism or incorporate into fat deposits, a process involving the pancreas to produce insulin [22].

Durian had reported contains flavonoids, namely catechin and quercetin [23] as well as polyphenols and tannins [10]. Quercetin had activity Aldos reductase inhibitors that could potentially be used in therapeutic antihyperglycemia [24]. In the rambutan fruit peels contained flavonoids and tannins [12]. Ethanolic extract of rambutan fruit peels contained quercetin, geraniin [13] and epigallocatechin-3-gallate (EGCG) which had antihyperglycemia activity [14] as well as powerful antioxidants [15]. Based on the content of flavonoids catechin, quercetin and EGCG and polyphenols and tannins, a mechanism thought to decrease blood glucose levels in diabetic rats through inhibition of glucose absorption, stimulates the release of insulin and indirect mechanisms through the antioxidant processes.

Glucose binds to proteins can be oxidized and produce Reactive Oxygen Species (ROS). The combination of glycation and oxidation of glucose produces AGEs (advanced glycogen end-products) in which this process was irreversible long-lasting and can caused tissue damage. That glycated proteins and AGEs-modified proteins can lead to oxidative stress which can trigger the diabetic condition [22]. Another mechanism that was thought to have the effect of decreasing blood glucose levels in test animals, with the occurrence geraniin in rambutan fruit peel extract which had the ability to prevent the formation of AGEs [13].

This research has proven that the ethanol extract of durian rind and rambutan fruit peel can lowered blood glucose levels of alloxan-induced rats. However, the mechanism of the antidiabetic activity of the ethanol extract of durian and rambutan fruit peels was not certainly. So the evaluation to determine the mechanism of molecular pharmacology decrease in blood glucose levels that occurs, needs to be done. In addition it is necessary to ensure what the active compounds are most responsible for its pharmacological activity.

CONCLUSION

The ethanolic extract of durian and rambutan fruit peels with each dose of 125, 250, and 500 mg/kg b.w. had antidiabetic effects on male white rats alloxan induced. Percentage reduction in blood glucose levels of durian and rambutan fruit peels ethanol extract with dose of 125, 250, and 500 mg/kg b.w. are 16.55 ± 2.99%, 35.09 ± 3.84%, 50.19 ± 3.66%, 22.65 ± 2.10%, 49.05 ± 3.22%, 61.76 ± 4.26%, respectively.

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