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Research Article

Antihyperglycemic Effect of Rambutan Honey in Alloxan-induced Diabetic Wistar Rats

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Abstract

Background and Objective: Diabetes mellitus is a chronic metabolic disorder characterized by inappropriate hyperglycemia due to lack of or resistance to insulin and free radicals involved. Honey is known to have an antioxidant and antihyperglycemic effect in community. However, the mechanisms of rambutan honey action as antihyperglycemic have poorly understood. The objectives of this study were to investigate the effect of rambutan honey toward to decrease blood glucose level and to histopathology-changing aspects in the pancreas of diabetic Wistar rat. **Materials and Methods:** The research methods were an experimental laboratory. The samples ($n = 30$) were divided into six groups, the negative control which normal blood glucose (NC), Positive Control (PC), the group of rambutan honey 0.5, 1 and 2 g kg⁻¹ b.wt. and glibenclamide 0.065 mg/200 g b.wt. Diabetes was induced in rats by an intraperitoneal injection of alloxan. Rambutan honey was orally administered to normal and diabetic rats for a period of 21 days. Blood glucose level was observed on day 0, 7th, 14th and 21st and the last day of the pancreas histopathologic examination stained with haematoxylin-eosin. Data were statistically analyzed using ANOVA and paired t-test. **Results:** Rambutan honey 0.5 g kg⁻¹ b.wt. decrease blood glucose level significantly on day 21 ($p = 0.047$) with blood glucose level means of 195.2 ± 19.83 mg dL⁻¹ (PC), 127.6 ± 25.46 mg dL⁻¹ (0.5 g kg⁻¹ b.wt.), 187.6 ± 54.83 mg dL⁻¹ (1 g kg⁻¹ b.wt.) and 243.6 ± 77.62 mg dL⁻¹ (2 g kg⁻¹ b.wt.), respectively and had no significant differences compared with glibenclamide. **Conclusion:** Rambutan honey exhibits antihyperglycemic activity in alloxan-induced diabetic rats. Thus our finding provides clear evidences that rambutan honey have a potential as an adjuvant along with antidiabetics agent treatment. However, such effects need to be confirmed on human in clinical condition.

Key words: Honey, antihyperglycemic, diabetic, glucose level, glibenclamide

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Diabetes mellitus is a group of metabolic diseases in which a person has high blood glucose either because the body does not produce enough insulin or because cells do not respond to the insulin that is produced by the pancreas. This resulting high blood sugar produces the classical symptoms of polyuria: Frequent urination polydipsia (increased thirst) and polyphagia (increased hunger)^{1,2}.

Dangers that can be caused on the condition of diabetes mellitus are a long-term loss of vision, kidney failure due to nephropathy and neuropathy¹.

People who have diabetes mellitus in the world until 2014, namely 347 million and 80% of cases were in developing countries. In 2012, approximately 1.5 million people died from diabetes and it is estimated by 2030 will increase up to 2 times³.

Diabetes mellitus require pharmacology and non-pharmacology treatment. Oral antidiabetic drugs such as glitazon class of thiazolidinediones, insulin secretagogues groups such as tolbutamide and glibenclamide and alpha-glucosidase inhibitors such as acarbose. In certain circumstances when the need for insulin greatly increases the required insulin parenterally. Treatments of diabetes were known to have side effects, such as lactic acidosis, indigestion, weight gain and impaired liver enzymes⁴.

Now-a-days many people use traditional medicine as an alternative treatment. Traditional medicine is believed to be safer when compared with modern medicine because traditional medicine has relatively fewer side effects when use in the right materials, the right dosage, the right usage and the exact time of administration⁵. One is the traditional treatment with honey. Several studies have shown that honey can be used as an antioxidant, anti-inflammatory, wound healing and recent research showed that honey has anti-diabetic effects. Honey is a natural ingredient that has been used widely as a component of its efficacious. It has been reported that honey has about 200 components, such as glucose, fructose, amino acids, flavonoid, vitamins and minerals. Flavonoids are components that act as antioxidants and anti-inflammatory in damaged cells. Rambutan honey is monofloral honey with a high flavonoid might have a good potential in lowering blood glucose levels due to lack of insulin secretion and insulin action. In diabetes mellitus patients have known that increased oxidative stress will exacerbating pancreatic β -cells damaged flavonoids protect pancreatic β -cells by reducing oxidative stress. Fructose in honey is known to be able to stimulate insulin secretion and activate glucokinase enzyme which improves glucose metabolism and transform glucose

into glucose 6-phosphate thus reducing blood glucose. Fructose in honey might contribute to the hypoglycemic effect of honey⁶. One of traditional and modern uses of natural honey in human disease is thought to help lowering blood glucose levels of patients with diabetes mellitus⁷ type 1 and 2.

Based on the above and the limited explanation of the antihyperglycemic effect of honey in the case of diabetes mellitus, then study was conducted on the effects of rambutan honey to the blood glucose levels and pancreatic tissue of alloxan induced mice compared with glibenclamide. Glibenclamide is sulfonylurea class of oral antidiabetic drugs the second generation that has a major effect in increasing insulin secretion from the pancreas^{8,9}.

The objectives of this study were to investigated the effect of rambutan honey in decreasing blood glucose level and to histopathology-changing aspects in the pancreas of diabetic Wistar rat.

MATERIALS AND METHODS

Rambutan honey samples: Samples were taken from Indonesia National Beekeeping Centre (Pusbahnas).

Experimental animals: Animal samples of 30 rats were taken from the Central Laboratory of Biological Sciences ITB Bandung. Rats ($n = 5$ group⁻¹) were divided into negative control, positive control, 0.5 g kg⁻¹ b.wt. (1), 1 g kg⁻¹ b.wt., (2), 2 g kg⁻¹ b.wt., rambutan honey (3) and 0.065 mg/200 g b.wt., glibenclamide. Glucose level was observed on day 0, 7, 14, 21 and administered orally twice for 3 weeks treatment¹⁰.

Negative controls were only given food and drink, the positive control were induced by alloxan. Group 1, 2 and 3 were induced by alloxan of 120 mg kg⁻¹ b.wt., i.p. and then after 72 h and blood glucose levels increasing, the mice were given rambutan honey were orally with doses of 0.5, 1 and 2 g kg⁻¹ b.wt. Glibenclamide group were induced by alloxan of 120 mg kg⁻¹ b.wt., i.p. and then after 72 h, the rats were given with 0.065 mg/200 b.wt., glibenclamide.

Diet given to rats and the same dosed each day. Examination of blood glucose levels of Wistar rats performed on days 0, 7th, 14th and 21st. The last day of the pancreas histopathologic examination stained with haematoxylin-eosin and observations were made with the objective magnification of 40 times.

Statistical analysis: Data were statistically analyzed by paired t-test for the analysis of Wistar rats blood glucose levels before and after alloxan induced and one way ANOVA and

Tukey *post hoc* test for effect of rambutan honey to blood glucose levels, after affirming the normality and homogeneity of variances assumptions of data sets. The $p < 0.05$ were considered to be significantly different.

Research ethics aspects: Ethical approval was obtained from the Research Ethics Committee Hasan Sadikin Hospital (RSHS) Bandung with No. 151/UN6.C1.3.2/KEPK/PN/2016 and based on the principle of the '3R' American Veterinary Medical Association¹¹.

RESULTS

Effect of alloxan-induced on blood glucose levels: Effect of alloxan-induced on blood glucose levels Wistar rats 72 h after induction had increased significantly compared with before induction ($p < 0.05$) (Table 1).

Effect of rambutan honey on blood glucose levels: Effect of rambutan honey on blood glucose levels were seen using one way ANOVA test on the results of blood glucose levels on day 7th, 14th and 21st (Table 2).

On day 7 ($p = 0.02$), there were significant differences on blood glucose levels in all treatment groups. On day 14 and 21 ($p = 0.00$), there were significant differences on blood glucose levels in all treatment groups. Tukey *post hoc* test was then performed to determine the difference between the treatment groups (Table 3).

Based on Table 3, it is shown that there were significant differences on blood glucose levels between rambutan honey 0.5 and 2 g kg⁻¹ b.wt., on day 14. On day 21, it is found significant differences in blood glucose levels between rambutan honey 0.5 g kg⁻¹ b.wt., and positive control and between rambutan honey 0.5 g kg⁻¹ b.wt. and 2 g kg⁻¹ b.wt. ($p < 0.05$). Result of data analysis indicates that there were effects of 3 weeks treatment of rambutan honey on blood glucose levels of Wistar rats. The difference between blood glucose levels after induction day 0-21 at a dose of 0.5 g kg⁻¹ b.wt., amounted to 42.4 mg dL⁻¹ and at a dose of 1 g kg⁻¹ b.wt., was approximately 4.8 mg dL⁻¹ (Fig. 1).

Rambutan honey effective dose to decrease blood glucose levels: Rambutan honey effective dose in lowering blood glucose levels can be seen by analyzing the data at day 21 in the group rambutan honey 0.5, 1 and 2 g kg⁻¹ b.wt., compared to positive control (Table 4).

Effect of rambutan honey on blood glucose levels means significantly at day 21 ($p = 0.000$). Blood glucose levels mean 195.2 mg dL⁻¹ (positive control), 127.6 mg dL⁻¹

(rambutan honey 0.5 g kg⁻¹ b.wt.), 187.6 g dL⁻¹ (rambutan honey 1 g kg⁻¹ b.wt.) and 243.6 mg dL⁻¹ (rambutan honey 2 g kg⁻¹ b.wt.).

Results of *post hoc* test between rambutan honey 0.5, 1, 2 g kg⁻¹ b.wt. and a positive control showed

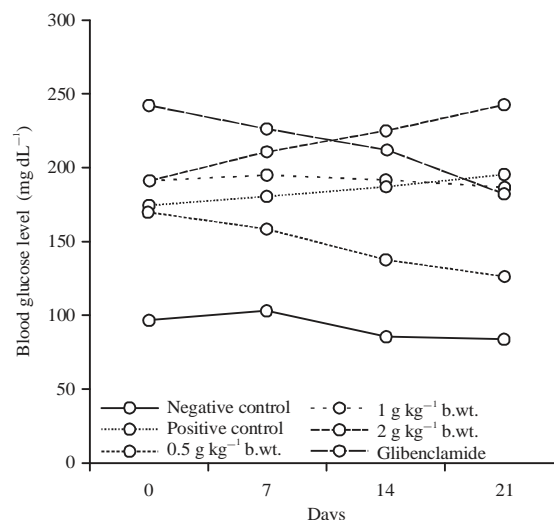


Fig. 1: Effect of 3 weeks treatment of rambutan honey doses 0.5, 1 and 2 g kg⁻¹ b.wt., on blood glucose levels compared to glibenclamide days 0, 7th, 14th and 21st

Table 1: Effect of alloxan on rat blood glucose levels

Groups	Blood glucose level (mg dL ⁻¹) before induction	Blood glucose level (mg dL ⁻¹) after induction	p-value
	Mean ± SD	Mean ± SD	
Negative control	91.40 ± 6.73	98.20 ± 5.81	0.178
Positive control	91.40 ± 9.81	174.8 ± 28.89	0.001*
0.5 g kg ⁻¹ b.wt.	91.00 ± 18.97	170.0 ± 40.09	0.015*
1 g kg ⁻¹ b.wt.	92.80 ± 15.62	192.4 ± 39.02	0.004*
2 g kg ⁻¹ b.wt.	106.4 ± 17.45	192.2 ± 55.87	0.027*
Glibenclamide	94.40 ± 13.13	243.2 ± 49.18	0.003*

Paired t-test, * $p < 0.05$ significantly

Table 2: Rambutan honey influence on blood glucose levels on the day 7th, 14th and 21st

Days	Groups	n	Mean ± SD	Min-max	*p-value
7	Positive control	5	181.0 ± 26.22	149.0-215.0	0.002
	0.5 g kg ⁻¹ b.wt.	5	158.8 ± 36.21	123.0-199.0	
	1 g kg ⁻¹ b.wt.	5	195.2 ± 36.02	159.0-252.0	
	2 g kg ⁻¹ b.wt.	5	211.4 ± 64.77	142.0-309.0	
	Positive control	5	188.0 ± 23.15	158.0-218.0	0.000
14	0.5 g kg ⁻¹ b.wt.	5	138.8 ± 30.50	102.0-185.0	
	1 g kg ⁻¹ b.wt.	5	192.0 ± 45.12	138.0-262.0	
	2 g kg ⁻¹ b.wt.	5	226.4 ± 70.39	145.0-325.0	
	Positive control	5	195.2 ± 19.83	176.0-224.0	0.000
21	0.5 g kg ⁻¹ b.wt.	5	127.6 ± 25.46	95.0-164.0	
	1 g kg ⁻¹ b.wt.	5	187.6 ± 54.83	124.0-274.0	
	2 g kg ⁻¹ b.wt.	5	243.6 ± 77.62	160.0-355.0	

ANOVA test, * $p < 0.05$ significantly

that for 0.5 g kg⁻¹ b.wt., group (p = 0.047), indicated that there were significant differences

in blood glucose level between the positive control and the 0.5 g kg⁻¹ b.wt.

Table 3: Differences in blood glucose levels between the treatment groups

Days	Groups	p-value
7	0.5 g kg ⁻¹ b.wt. vs positive control	0.958
	0.5 vs 1 g kg ⁻¹ b.wt.	0.745
	0.5 vs 2 g kg ⁻¹ b.wt.	0.383
	1 g kg ⁻¹ b.wt. vs positive control	0.994
	1 vs 2 g kg ⁻¹ b.wt.	0.989
	2 g kg ⁻¹ b.wt. vs positive control	0.858
14	0.5 g kg ⁻¹ b.wt. vs positive control	0.462
	0.5 vs 1 g kg ⁻¹ b.wt.	0.378
	0.5 vs 2 g kg ⁻¹ b.wt.	0.034*
	1 g kg ⁻¹ b.wt. vs positive control	1.000
	1 vs 2 g kg ⁻¹ b.wt.	0.790
	2 g kg ⁻¹ b.wt. vs positive control	0.707
21	0.5 g kg ⁻¹ b.wt. vs positive control	0.047*
	0.5 vs 1 g kg ⁻¹ b.wt.	0.138
	0.5 vs 2 g kg ⁻¹ b.wt.	0.005*
	1 g kg ⁻¹ b.wt. vs positive control	0.994
	1 vs 2 g kg ⁻¹ b.wt.	0.646
	2 g kg ⁻¹ b.wt. vs positive control	0.912

Post hoc Tukey test, *p<0.05 significantly

Table 4: Differences in blood glucose levels between doses of rambutan honey on day 21 compared to positive control

Groups	p-value
0.5 g kg ⁻¹ b.wt. vs positive control	0.047*
1 g kg ⁻¹ b.wt. vs positive control	0.994
2 g kg ⁻¹ b.wt. vs positive control	0.912

Post hoc Tukey test, *p<0.05 significantly

Antihyperglycemic effect of rambutan honey compared with glibenclamide: Effect of rambutan honey compared with glibenclamide to the blood glucose levels can be done by comparing the blood glucose levels of each group with glibenclamide result on day 21 (Table 5).

Table 5 shows that there were no significant difference on blood glucose levels between rambutan honey 0.5 and 1 g kg⁻¹ b.wt., compared with glibenclamide.

Effect of rambutan honey to pancreatic histopathology:

Histological observation according to the observation made through a light microscope. Examination of histological sections of pancreas showed that the shape of β -cell and acinar cell in the islet of Langerhans all group were normally preserved in the pancreas tissues (Fig. 2).

Table 5: Comparison of blood glucose levels in rambutan honey 0.5 g kg⁻¹ b.wt. and glibenclamide

Groups	n	p-value
Rambutan honey 0.5 g kg ⁻¹ b.wt.	5	0.212
Glibenclamide	5	
Rambutan honey 1 g kg ⁻¹ b.wt.	5	1.000
Glibenclamide	5	

Post hoc Tukey test, p<0.05 significantly

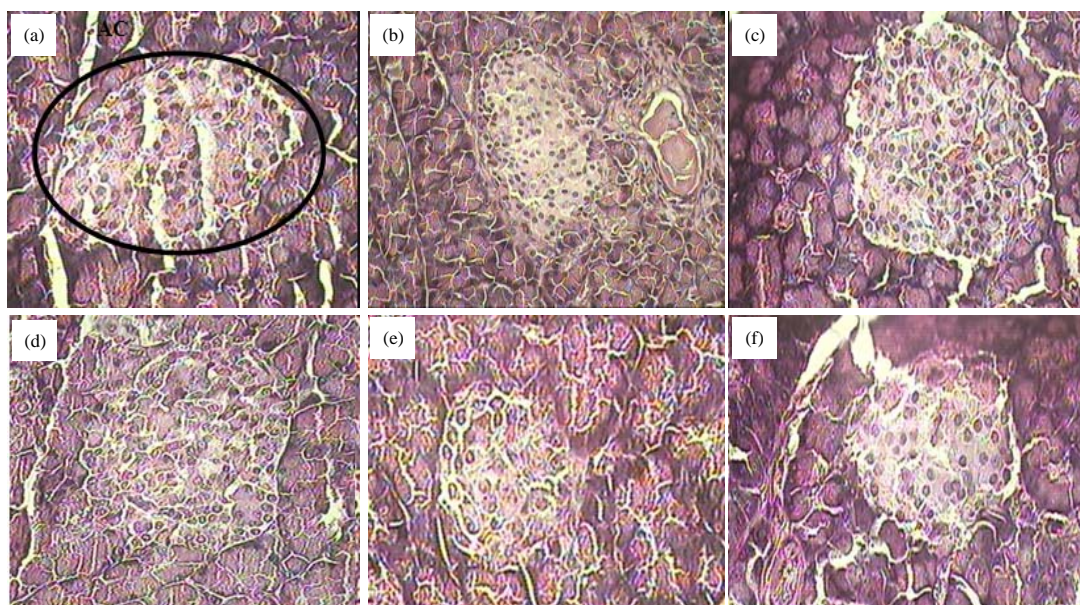


Fig. 2(a-f): Effect of 3 week's treatment of rambutan honey on histoarchitecture of the pancreas (H and E stain, with the objective magnification of 40 times), (a) In normal rat, the pancreas architectures were well preserved, islet of Langerhans (circle), AC (Acinar cells), (b) In alloxan treated rat, decrease of acinar cells and vacuoles were observed (arrowheads), (c-e) In alloxan+0.5, 1 and 2 g kg⁻¹ b.wt., honey treated rat, the pancreas architectures were relatively well preserved and (f) In glibenclamide treated rat, the pancreas architectures were well preserved

DISCUSSION

In this study it is shown that alloxan can cause diabetic rats by damage to the pancreatic β -cells which increasing blood glucose levels. This was consistent with study of Suarsana *et al.*¹², that the administration alloxan into the body will cause the metabolic oxidation-reduction which produces free radicals and radical alloxan. These free radicals and radical alloxan cause damage to the pancreatic β -cells. On the islets of Langerhans in the pancreas showed reduction in mass of cells, starting to shrink, crushed, even disappeared. As a result of the pancreatic β -cell damage, then the pancreas was unable to produce the hormone insulin that causes a state of hyperglycemia in the body. The hyperglycemia also will aggravate from β -cell damage¹³. Hyperglycemia condition tend to increase the formation of free radicals. Reactive Oxygen Species (ROS) were form through metabolic pathways auto-oxidation glucose such as glucose, metabolism methylglucose formation metabolism and oxidative phosphorylation. Excessive reactive oxygen species can cause damage to the pancreatic β -cells¹⁴.

Rambutan honey 0.5 g kg⁻¹ b.wt., dose have showed effective in decreasing blood glucose levels in diabetic rats. This was likely due rambutan honey has several nutritious components such as fructose and flavonoids which causes increased secretion of insulin in diabetics. Increased secretion of insulin will decrease blood glucose levels. In addition, there were also components of honey oligosaccharides which may contribute to lower pancreatic β -cell apoptosis¹⁵.

The results were consistent with Erejuwa *et al.*⁸ that gelam honey orally administered to streptozotocin-induced diabetic rats can lower blood glucose levels and increase insulin serum. Honey can lower blood glucose levels by activating glucokinase, an enzyme that plays a role in glucose metabolism. Fructose in honey can catalyze change glucose into glucose-6 phosphate thus lowering glucose in the blood. In addition, fructose can also stimulate insulin secretion from pancreatic β -cells. Blood glucose and fructose level has been shown to increase hepatic glucose phosphorylation by activating glucokinase and inhibits glycogenolysis through an emphasis phosphorylase. Fructose in honey can increase hepatic glucose uptake also the synthesis and storage of glycogen thus improving glycemic control in diabetes mellitus^{6,8,16}.

The results of this study were also consistent with Fasanmade and Alabi⁹ that the honey treatment 10 mL kg⁻¹ b.wt./5 mL of distilled water for three consecutive weeks in diabetic rats induced alloxan can give the effect of

a decrease in blood glucose levels significantly. Alloxan was a diabetogenic agent that can damage the pancreatic β -cells, causing a decrease in insulin and causing diabetes mellitus. Alloxan was used to induce diabetes in experimental animals as research purposes^{9,13}.

Fructose, the sugar in the form of oligosaccharides contained in honey can also thought to have the effect of lowering blood glucose levels. Oligofructose can improve glucose tolerance and reduce hyperglycemia conditions. The beneficial effects of oligofructose on blood glucose, partly mediated through increased glucagon-like peptide-1 (GLP-1). Glucagon-like peptide-1 was a hormone that has a function to increase insulin and lower the glucagon when the levels of glucagon increased; resulting in lower blood sugar, in addition to the GLP-1 stimulates the proliferation and lowers apoptosis on β pancreas cell^{6,17,18}.

Honey also contains some minerals such as zinc, selenium, calcium, chromium, manganese and potassium, which plays a role in insulin secretion in pancreatic β -cells. The mineral components in honey can be used to prevent chronic disease in adults¹⁹. Although the mineral levels in honey was not too much, but if honey was taken continuously for 4 weeks may contribute to the hypoglycemic effect⁸.

Honey also contains antioxidants such as catalase, ascorbic acid, phenolic acid, derivatives of carotenoids organic acids, maillard reaction products, amino acids, proteins and also flavonoids. Flavonoids are a group of secondary metabolites that were mostly found in plants and included in the class of phenolic compounds with a chemical structure C₆-C₃-C₆. Flavonoid skeleton consisting of aromatic ring A, aromatic ring B and middle ring in the form of oxygen-containing heterocyclic ring and the oxidized form which was used as the basis flavonoid division into sub-sub-group. These compounds have biological effects such varied activities immunomodulatory, antioxidants, hypolipidemia, hypoglycemia and relaxes blood vessels^{20,21}. The results of this study supported previous studies by study of Yuslianti²² that rambutan honey has antioxidant activity *in vitro* and *in vivo* so that the possibility can protect pancreatic β -cell damage induced alloxan potentially lowering blood glucose levels.

Antidiabetic effects of flavonoids have also been proven through the study of Erejuwa *et al.*⁸ that flavonoids may modulate lipid metabolism, abnormal glucose, improve peripheral insulin resistance and reduce the complications of diabetes caused by abnormal lipid profile and insulin resistance. The action of flavonoids that were beneficial in diabetes mellitus was through its ability to avoid the absorption of glucose or improve glucose tolerance.

Flavonoids can stimulate taking glucose in peripheral tissues, regulating the activity and expression of enzymes involved in carbohydrate metabolism pathways and act resembling insulin by affecting insulin signaling mechanisms⁸. Rutin flavonoid content in honey can also cause the effect of lowering blood glucose by stimulating the pancreatic β -cells in the islets of Langerhans to secrete insulin so that blood insulin levels will increase. Rutin is the glycoside between the flavonols quercetin and the saccharide, rutinose. Rutin exerts antidiabetic, antithrombotic, anti-inflammatory, antioxidant, cytoprotective, hepatoprotective, vasoprotective, smooth muscle relaxing and tissue protein glycation inhibiting activities²³. Flavonoid also protects pancreatic cells damage by decreasing oxidative stress levels in circulating C-peptide that can increase insulin levels^{8,16}.

Rambutan honey contains antioxidant flavonoids and vitamin C found to have a free radical reduction activity both *in vitro* and *in vivo* that can protect pancreatic β -cell damage induced alloxan and potentially lowering blood glucose levels¹⁰. Vitamin C improves endothelium dependent vasodilation in patients with insulin-dependent diabetes mellitus²⁴. The content of fructose, flavonoids and vitamin C in rambutan honey chances of causing a decrease in blood glucose levels in diabetic rats.

The increase in the blood glucose at a concentration of 2 g kg^{-1} b.wt. can occur because of fructose excessive levels can be converted into glucose. In the metabolism of fructose there was a change lane change fructose to fructose 1-phosphate by fructokinase then into dihydroxyacetone phosphate and glyceraldehyde 3-phosphate by aldolase B. Both these compounds were intermediates in glycolysis and the liver was converted to glucose, glycogen or fatty acids. Dihydroxyacetone phosphate and glyceraldehyde 3-phosphate in the liver can be converted into glucose 6-phosphate through the reverse reaction of the glycolytic pathway (gluconeogenesis pathway) and released into the blood stream in the form of glucose or converted to glycogen by way fructose turns into fructose 1,6 bisphosphate by a aldolase A and B and into fructose 6-phosphate to fructose 1,6 bisphosphate. Fructose 6-phosphate can be converted into glucose 6-phosphate isomerase. Once into glucose 6-phosphate, it can be converted into glucose and enter the blood vessels or deposited in the form of glycogen¹⁴. Rambutan honey can potential in lowering blood glucose levels in diabetics when given the effective dosage.

In this study, it was found that rambutan honey of 0.5 g kg^{-1} b.wt. was the most effective dose in lowering blood glucose level, different from the results of Erejuwa *et al.*⁸, that the use of gelam honey dose of 1 g kg^{-1} b.wt. orally in diabetes

mice was a most effectively dose in lowering blood glucose levels and increase insulin serum. The content of fructose was known to activate glucokinase which was an enzyme that plays a role in intracellular glucose metabolism. The enzyme catalyzing change glucose into glucose-6-phosphate which will cause a decrease in blood glucose levels, in addition to the fructose also stimulates insulin secretion in pancreatic β -cells. Honey also contains elements such as zinc, chromium, potassium, manganese and others who play a role in the improvement of glucose tolerance and insulin secretion. Besides zinc plays a role in the metabolism of glucose and insulin.

The results showed that the effect of rambutan honey orally compared with oral hypoglycemic drugs glibenclamide had no significant differences in blood glucose levels of diabetic rats, so between rambutan honey and glibenclamide have nearly the same effectiveness in lowering blood glucose levels. This study proves that glibenclamide can lower blood glucose levels due to it have a working mechanism of increasing the release of insulin from the pancreas by binding to receptors sulfonylurea with a molecular weight of 140 kDa and a high affinity associated with potassium gates in one direction-sensitive ATP in the cell- β pancreas inside. Glibenclamide inhibits reflux calcium through the canal and cause depolarization. Depolarization will lead to the opening of calcium channels, causing release of insulin²⁵. The ability of glibenclamide in reducing glucose levels was similar to the mechanism of flavonoid content in honey in lowering blood glucose. In rambutan honey dietary intake which contains large enough flavonoids can reduce blood glucose levels by increasing insulin secretion and increase insulin sensitivity²⁶. Besides the effects of flavonoids also have more advantages than glibenclamide which can improve decision glucose in peripheral tissues, regulating the activity and expression of enzymes involved in the metabolic pathways of carbohydrates and affect the mechanism of insulin signaling and rambutan honey contains antioxidant flavonoids quite high and vitamin C as well as proven has an activity of free radicals reduction both *in vitro* and *in vivo* that can protect pancreatic β -cells.

Increased free radical generation represents in alloxan induced diabetic Wistar rats. Antioxidant therapy has been an easy and well-known choice to reduce free radicals in diabetes. This paradigm has gradually shifted as further studies demonstrated that antioxidant therapy alone is not sufficient, results with various antioxidants, namely, vitamins E and C have had disappointing results^{19,24}. Now it is almost certain that antioxidant therapy is an option that must be used in combination with other therapies to diabetes.

Effect of rambutan honey to pancreatic histopathology on day 21 can be seen from examination of histological section diabetics and normal rats pancreas showed there no damage to cells of the pancreas characterized. It must be evaluated for the further research to observed pancreatic histopathology on day 0, 7, 14, 21 not only histo-architecture of the Langerhans islet but also number of β islet, acinar cells and lymphocytes infiltration.

Effect of honey on the ratio of glucose levels in the 3rd and 7th days of treatment showed a very significant change. The test results showed that the honey can improve the condition of the diabetic rat, causing blood glucose levels return to near normal conditions.

CONCLUSION

It is stated that rambutan honey showed effect on blood glucose levels decrease in Wistar rats induced alloxan with a decline on day 21 at a dose of 0.5 g kg^{-1} b.wt. Rambutan honey with a dose of 0.5 g kg^{-1} b.wt., was the most effective dose effect on blood glucose levels decrease in alloxan-induced Wistar rats. Rambutan honey 0.5 , 1 g kg^{-1} b.wt. and glibenclamide have nearly the same effect in lowering blood glucose levels of alloxan-induced Wistar rats. Hence, it may be a useful antihyperglycemic in cases of diabetes mellitus and can be used as an adjuvant along with clinically effective antidiabetic agent. Further, study is needed to determine the role of flavonoids on rambutan honey in lowering blood glucose levels as well as the need to perform a clinical trial.

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