The Effect of Rambutan Honey and Rutin on Decrease Blood Glucose and Increase Streptozotocin-Induced Rat Plasma Insulin

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Abstract. Diabetes mellitus (DM) is a chronic metabolic disease characterized by hyperglycemia due to insulin work disorders, insulin secretion disorders, or both. Rambutan honey as a natural ingredient has been studied to reduce oxidative stress, protect pancreatic beta cells from damage, and can increase insulin secretion from pancreatic beta cells. Rutin as secondary antioxidants can increase insulin secretion, reduce free radical formation, and can stimulate pancreatic progenitor cells to form new cells. This study aims to determine the effect of rambutan honey on blood glucose and insulin levels in rats induced by streptozotocin compared to rutin. This research is a pure experimental study with a total sample of 24 experimental animals consisting of 4 groups, namely negative control (NC), positive control (PC), and 2 treatment groups (T1–T2). Glucose levels were measured using the GOD-PAP method and were analyzed statistically (T-dependent $p < 0.05$, Anova, Duncan $p < 0.05$). Insulin levels were measured using a mouse insulin ELISA-kit and were statistically analyzed (Anova, Duncan $p < 0.05$). The results showed that rambutan honey and rutin could significantly reduce blood glucose levels ($p = 0.008$ and $p = 0.010$). Data on insulin levels showed significant differences between groups ($p = 0.000$). The conclusion of this study is that rambutan honey and rutin can reduce blood glucose level and increase insulin levels because they are antioxidant agents which have antihyperglycemic effects.

Keywords: Blood glucose · Diabetes · Insulin · Rambutan honey · Rutin

1 Introduction

Diabetes mellitus (DM) is a chronic metabolic disease characterized by hyperglycemia due to insulin work disorders, insulin secretion disorders, or both [1]. There are complications of DM, including acute complications in the form of hyperglycemia, diabetic

Y. Y. Kumala et al. (Eds.): ASCMF 2022, AHSR 53, pp. 84–94, 2023.
https://doi.org/10.2991/978-94-6463-060-2_13

ketoacidosis, and hyperglycemia hyperosmolar status, as well as chronic complications such as coronary heart disease, stroke, and diabetic retinopathy [2]. The International Diabetes Federation (IDF) records that as many as 9.3% of the world's population aged 20–79 years suffer from diabetes. The IDF predicts that this number will increase in 2030 and 2045 by 10.2% and 10.9%. Indonesia ranks the 7th highest prevalence of DM after China, India, USA, Pakistan, Brazil, and Mexico according to the IDF in 2019 [3]. The prevalence of diabetes mellitus in Indonesia according to 2018 Riskesdas has increased, from 6.9% in 2013 to 8.5% in 2018 [4]. Management of DM is divided into non-pharmacological and pharmacological. Non-pharmacological therapy consists of medical nutritional therapy, increased physical activity, and education. Pharmacological therapy in the form of oral antidiabetic drugs and insulin injection. These medications have side effects, including nausea, vomiting, diarrhea, metallic taste, malabsorption, flatulence, abdominal bloating, weight gain, edema, increasing plasma volume, and worsening congestive heart failure [5, 6].

Nowadays traditional medicine is used as an alternative treatment which is widely accepted by society. The advantages of natural medicine over modern are lower side effects, have been known and used from ancient times, are easy to obtain, affordable, and relatively safe. There are natural ingredients to treat diabetes mellitus because it has been scientifically researched to have anti-hyperglycemic effects, including red pine (*Pinus densiflora*), aloe vera (*Aloe vera*), sambiloto (*Andrographis paniculata*), shallots (*Allium cepa*), bratawali (*Tinospora crispa*), jaka tuwa (*Scoparia dulcis*), pomegranate (*Punica granatum*), noni (*Morinda citrifolia*), garlic (*Allium sativum*), sweet potato (*Ipomeae batatas*), and rambutan honey (*Nephelium lappaceum*) [7–9]. Rambutan honey is honey that comes from the nectar-sucking bee of rambutan flowers (*Nephelium lappaceum*). Rambutan honey has about 200 ingredients, including glucose, fructose, amino acids, vitamins, minerals, and flavonoids. Flavonoids are natural antioxidants with various biological effects, such as anti-inflammatory, antibacterial, and vasodilator action. Flavonoids as antioxidants are able to scavenge free radicals to help regenerate cells, including free radicals that are generated from oxidative stress due to hyperglycemia. Yuslianti reported that rambutan honey contains antioxidant flavonoids of the rutin group of 130.02 $\mu g\ ml^{-1}$ [10, 11]. Rakhmat et al. reported that the use of rambutan honey at a dose of 0.5 $g\ kg^{-1}$ b.wt. was effective in reducing blood glucose levels in alloxan-induced rats [12].

DM is known to be associated with oxidative stress and chronic inflammation. Oxidative stress is an imbalance between the oxidative and antioxidant systems of cells and tissues. Oxidative stress is the result of excessive production of oxidative free radicals and associated reactive oxygen species (ROS). Antioxidants are compounds that can slow down, delay, and prevent the formation of free radicals [13–15]. The most exogenous antioxidants in nature are the flavonoid quercetin which is included in the flavonol class. Among the flavonoid derivatives are rutin. According to research by Niture et al., rutin at a dose of 50 $mg\ kg^{-1}$ b.wt. and 100 $mg\ kg^{-1}$ b.wt. in diabetic rats can reduce blood glucose levels. Inhibiting cytokines as an inflammatory mediator and activating endogenous antioxidants is rutin mechanism in lowering blood glucose [16]. It is explained in the research of Abdelmoety et al., that the flavonoid quercetin can regenerate the pancreas so that insulin deficiency can be overcome, it is also able to suppress the apoptosis

of pancreatic beta cells without change the proliferation of pancreatic beta cells [17]. Based on this background, the authors wanted to know the effect of rambutan honey on streptozotocin-induced blood glucose and plasma insulin levels in rats compared to rutin.

2 Material and Methods

The research was conducted at the Biochemistry Laboratory of Medical Faculty of Jenderal Achmad Yani University Cimahi, the Biochemistry Laboratory of Medical Faculty of Brawijaya University Malang, and the Pharmacology Laboratory of Medical Faculty of Padjajaran University Bandung from September 2020 to February 2021. Ethical approval was obtained from the Research Ethics Committee of the Faculty of Medicine, Padjadjaran University with number 1017/UN6.KEP/EC/2020.

2.1 Research Design

This research is a laboratory experimental study with pre and post-test only control group design. The research consisted of making pharmaceutical standardized honey and honey dissolving, induction of streptozotocin, giving treatment, checking blood glucose levels using the GOD-PAP method, and checking plasma insulin levels with mouse insulin ELISA-kit.

2.2 Object of Research

The white rats of the Wistar strain (*Rattus norvegicus*) obtained from the SITH ITB animal development laboratory which had standardized strains were 24 rats (based on the calculation of the Federation formula). The rats were divided into 4 groups, namely the negative control group (NC), the positive control group (PC), the 500 mg kg^{-1} b.wt. rambutan honey treatment group (T1), and the 50 mg kg^{-1} b.wt. rutin treatment group (T2).

2.3 Research Materials

Rambutan honey is obtained from the national beekeeping centre (PUSBAHNAS) in Bogor, harvested in the range of September, and has a dark reddish colour with a pH of 4.21. The dose of rambutan honey used in this study was 500 mg kg^{-1} b.wt. The hydrate rutin is obtained from the sigma company with a yellow-green colour, in the form of powder, can dissolve in Pyridine 50 mg mL^{-1}, DMSO, aqueous base, and has a 25 g preparation with a barcode 4022536002446. Rutin hydrate have the molecular formula $C_{27}H_{30}O_{16}.xH_2O$ and is a synthetic rutin that binds to a water molecule. The dose of the rutin used in this study was 50 mg kg^{-1} b.wt [18, 19].

2.4 Making Standardized Honey and Honey Dissolution

Rambutan honey is filtered with filter paper or gauze attached to a funnel and measuring cup. The honey is then incubated in a water bath with a temperature of 70 °C for 30 min then stored in an airtight lid for 24 h to remove any remaining water. Rambutan honey is calculated and weighed according to the needs of each rat (dose 500 mg kg^{-1} b.wt.). Furthermore, honey is dissolved in physiological NaCl to a volume of 2 mL. Each mouse was given 2 mL of rambutan honey solution.

2.5 Induction of Streptozotocin Method

The streptozotocin dose used for this study was 35 mg kg^{-1} b.wt. The injection is done intraperitoneally. The streptozotocin required for each rat was dissolved in a citrate buffer pH 4.4 0.1 M until the volume reached 1 mL.

2.6 Treatment of Experimental Animals

After 7 days of acclimatization (on the 1st day of the study), NC was fed standard pellets 30 g/day/head and was given drinking ad libitum until the end of the study. PC, T1, and T2 were given high fat feed for 14 days. PC, T1, and T2 were induced by streptozotocin on the 15th day. The blood glucose levels of the four groups were analyzed on day 18. T1 was given rambutan honey on the 19th day at a dose of 500 mg kg^{-1} b.wt. For 14 days and T2 was given rutin at a dose of 50 mg kg^{-1} b.wt. For 14 days. Examination of blood glucose and plasma insulin levels was carried out on the 34th day for all experimental groups. Rats fasted 12 h before blood glucose testing and 1.5 h before checking insulin levels. The mice were terminated with ketamine.

2.7 Examination of Blood Glucose and Plasma Insulin Levels

Examination of blood glucose levels was carried out by the GOD-PAP method and examination of plasma insulin levels was carried out by using the mouse insulin ELISA-kit [20–22].

2.8 Statistical Analysis

The data from this study were statistically analyzed using SPSS 25.0. The data will be presented in a table. Blood glucose levels were tested by paired T-Test, one-way ANOVA, and Duncan's post-hoc with $p < 0.05$. Plasma insulin levels were tested by one-way ANOVA and post-hoc Duncan with $p < 0.05$.

3 Results

3.1 Effect of Streptozotocin-Induced and High-Fat Diet on Blood Glucose Levels

Streptozotocin combined with a high-fat diet can increase the blood glucose levels of rats after 96 h post induction with a significant p value (Table 1).

Table 1. Effect of streptozotocin and high-fat diet 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	
NC	98.83 ± 4.17	99.81 ± 6.12	0.655
PC	111.50 ± 16.30	281.76 ± 61.41	0.005*
T1	103.46 ± 11.36	306.39 ± 109.52	0.005*
T2	98.83 ± 10.94	226.57 ± 80.35	0.007*

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

Table 2. Rats blood glucose levels after induction and after being treated with rambutan honey

Variables	Mean ± SD (mg dL^{-1})	Difference	p value
Blood glucose before treatment of rambutan honey 500 mg/kgBW	306.39 ± 109.52	196.53	0.008
Blood glucose after treatment of rambutan honey 500 mg/kgBW	109.86 ± 22.30		

T-Test result: p value < 0.05 (significant).

Table 3. Rats blood glucose levels after induction and after being given rutin treatment

Variables	Mean ± SD (mg dL^{-1})	Difference	p value
Blood glucose before treatment of rutin 50 mg/kgBW	226.57 ± 80.35	131.71	0.010
Blood glucose after treatment of rutin 50 mg/kgBW	94.85 ± 7.64		

T-Test result: p value < 0.05 (significant).

3.2 Effect of Rambutan Honey and Rutin on Blood Glucose Levels

Both of rambutan honey and rutin can significantly reduce blood glucose levels based on the paired t-test (Tables 2 and 3), but rambutan honey has a better effect of lowering blood glucose levels compared to rutin (Fig. 1).

3.3 Effect of Rambutan Honey and Rutin on Plasma Insulin Levels

One-way ANOVA test was carried out to see the effect of rambutan honey and rutin in increasing plasma insulin levels and a significant p value was obtained (Table 4). The Duncan's post hoc test was carried out to see the differences between all groups (Table 5). Based on Duncan's post hoc test, rutin can increase insulin plasma close to negative

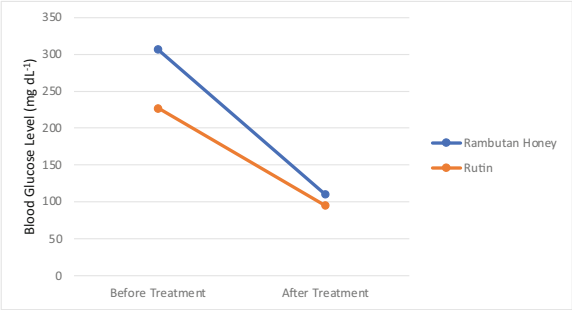

Fig. 1. The effect of rambutan honey on reduce blood glucose levels compared to rutin.

Table 4. The difference in the plasma insulin levels after administration of rambutan honey and rutin

Treatment	Plasma insulin levels after treatment (pg dL^{-1})	p-value
	Average ± SD	
NC	51,03 ± 6,42	0,000
PC	187,88 ± 24,49	
T1	69,47 ± 4,99	
T2	48,03 ± 8,49	

One-way ANOVA test: p-value < 0,05 (significant). NC: Negative control, PC: Positive control, T1: Treatment of rambutan honey, T2: Treatment of rutin.

Table 5. The comparison of differences in plasma insulin levels between treatment groups

Treatment	Plasma Insulin Levels After Treatment ($\alpha = 0.05$)		
	1	2	3
T2	48.03		
NC	51.03		
T1		69.47	
PC			187.88

Note: Duncan's Post-hoc test. NC: Negative control, PC: Positive control, T1: Treatment of rambutan honey, T2: Treatment of rutin

control and rambutan honey can increase insulin levels above the negative control. The positive control has the highest insulin levels.

4 Discussion

Induction of streptozotocin causes diabetes in experimental rats. Induction of streptozotocin combined with a high-fat diet can represent type 2 diabetes mellitus as well as in the study of Niture, et al. [16]. A high-fat diet combined with streptozotocin has been used widely for type 2 diabetes studies [16]. Streptozotocin selectively accumulates in pancreatic beta cells via the low affinity GLUT-2 in the plasma membrane. The toxicity of streptozotocin depends on the alkylating activity of DNA from the methylnitrosurea portion. Transfer of the methyl group from streptozotocin to the DNA molecule causes damage which, during a certain series of events, results in DNA fragmentation. The increased dephosphorylation of ATP after the induction of streptozotocin supplies the substrate for xanthine oxidase which results in the formation of superoxide radicals. As a result, hydrogen peroxide and hydroxyl radicals are also generated. Streptozotocin releases a number of nitric oxide (NO) which plays a role in DNA damage. These free radicals and DNA damage result in pancreatic beta cell's necrosis [23–26].

High-fat diet also play a role in insulin resistance which is the cause of type 2 diabetes. The relationship between obesity and insulin resistance is explained by several mechanisms. First, the role of free fatty acids (FFAs). Intracellular triglyceride levels in obese individuals are high, especially in the liver and muscle tissue. This may occur due to high levels of FFA in the blood that are deposited in these organs. Intracellular triglycerides and the metabolism products of FFA are potent inhibitors of insulin signalling that causing insulin resistance. The lipotoxic effect of FFA is thought to be mediated through decreased activity of insulin signalling proteins. Second, the role of adipocytokines. Adipocytokines are hormones (proteins) released into circulation by adipose tissue. Leptin, adiponectin, and resistin are the examples of adipocytokines. Adiponectin plays a role in insulin sensitivity in peripheral tissues and the condition of obesity makes adiponectin decrease, resulting in decreased insulin sensitivity (insulin resistance). Resistin is a hormone that causes insulin resistance and the levels of this hormone are increased in obese individuals. Finally, a protein called sirtuin can improve glucose tolerance, stimulate insulin secretion from pancreatic beta cells, and increase adiponectin production. Sirtuin abnormalities are also involved in the pathogenesis of type 2 DM [27].

Rambutan honey at a dose of 0.5 g kg^{-1} b.wt. proven to significantly reduce blood glucose levels as in the study of Rakhmat, et al. [12]. Honey contains fructose which can inhibit glycogenolysis and activate glucokinase, an enzyme that plays a role in glucose metabolism so that hepatic glucose phosphorylation increases. This effect is a hypoglycemic effect. Honey also contains minerals such as zinc which plays a role in insulin secretion in the beta cells of the pancreas, thereby reducing blood glucose levels [12, 18].

Rutin at a dose of 50 mg kg^{-1} b.wt. also proven to significantly reduce blood glucose levels. This match the research by Niture, et al. [16]. Rutin works to lower blood glucose levels by increasing insulin secretion by changing the calcium uptake in pancreatic beta cells through intracellular calcium conversion and the PKC signalling pathway which can increase the fusion of insulin-filled vesicles. Rutin can also scavenge free radicals and prevent chain reactions through carboxyl groups capable of chelating Fe metal,

breaking free radical initiation reactions by hydrogen atom transfer or electron transfer and inhibiting fatty chain autooxidation reactions in the termination process [16, 28].

Rambutan honey can lower blood glucose levels better than rutin. This difference occurs because the various content of honey, not only rutin flavonoids, so that the mechanism for reducing blood glucose levels is also more diverse than rutin. Honey contains fructose which can inhibit glycogenolysis and activate glucokinase, an enzyme that plays a role in glucose metabolism so that hepatic glucose phosphorylation increases. The flavonoids in honey can reduce oxidative stress, which can worsen pancreatic beta cell damage. Ascorbic acid or vitamin C functions as an inhibitor of the aldose reductase enzyme so that fructose and glucose 6 phosphate levels decrease. Reduced levels of fructose and glucose 6 phosphate minimize the formation of AGEs. Apart from being an aldose reductase inhibitor, vitamin C also plays a role in reducing free radicals and oxidation reactions. Tocopherol improves free radical defence potential, improves glucose transport, insulin sensitivity, improves sympathovagal balance associated with oxidative stress, and decreases the activity of protein kinase C (PKC), an enzyme that is directly linked to an increase in reactive oxygen compounds.

The rutin group can increase plasma insulin levels to near NC and the rambutan honey group increase plasma insulin levels beyond NC. This difference occurs because the rutin works to increase the fusion of insulin-filled vesicles by changing the calcium uptake in pancreatic beta cells through intracellular calcium conversion and the protein kinase C (PKC) signalling pathway. The end result of this process is an increase in plasma insulin levels. Rutin can also scavenge free radicals and prevent chain reactions through carboxyl groups capable of chelating Fe metal, breaking free radical initiation reactions by transferring hydrogen atoms or electron transfers and inhibiting fatty chain autoxidation reactions in the termination process [16, 28, 29].

The content of honey which plays a role in increasing insulin secretion is zinc. Zinc plays a key role in insulin biosynthesis as part of the hexameric structure of this hormone, and in sensitivity to insulin in target tissues through stimulation of insulin receptors. Calcium (which the uptake is increased by rutin) and potassium regulate voltage dependent channels in pancreatic beta cells, which are important for insulin exocytosis. Because calcium is a mineral that causes insulin exocytosis and zinc is a mineral that plays a role in insulin biosynthesis, the insulin levels of rambutan honey are higher than rutin [30].

Honey also contains fructose which can inhibit glycogenolysis and activate glucokinase, an enzyme that plays a role in glucose metabolism so that hepatic glucose phosphorylation increases. Flavonoids in honey can reduce oxidative stress, which worsens the damage to pancreatic beta cells. Ascorbic acid or vitamin C functions as an inhibitor of the enzyme aldose reductase so that the reduced glucose levels decrease. The decrease of the reduced glucose levels minimize the formation of AGEs. Apart from being an aldose reductase inhibitor, vitamin C also plays a role in reducing free radicals and oxidation reactions. Tocopherol improves the potential for free radical defence, improves glucose transport, insulin sensitivity, improves sympathovagal balance associated with oxidative stress, and reduces the activity of protein kinase C (PKC), an enzyme that is directly linked to an increase in reactive oxygen species. Phenolic acid compounds in honey can scavenge free radicals, provide hydrogen, cool singlet oxygen, chelate metal ions and

serve as a substrate for radicals such as superoxide and hydroxyl. This mechanism exerts a protective effect on pancreatic beta cells [31–34].

The positive control group insulin levels are the highest. This can occur due to high-fat feeding coupled with streptozotocin induction and the absence of treatment with antioxidant compounds in rats. Blood insulin levels are determined by the balance between insulin production from pancreatic beta cells with insulin degradation by hepatic proteins and other tissues (kidneys, muscles, and heart). Insulin that has been secreted by pancreatic beta cells will then enter the liver through the portal vein. Fifty percent of the insulin will be degraded in the liver, while the rest will return to the systemic circulation. A study by Bergman et al. in 2018 was conducted to measure the insulin levels of rats before and after giving a high-fat diet. The results of these studies indicate a decrease in insulin clearance or insulin degradation by the liver from 60% to only 44%. Decreased insulin clearance means that a larger fraction of newly secreted insulin reaches the systemic circulation. Bergman et al. concluded that insulin degradation by the liver can change due to environmental factors, such as a high-fat diet. They also concluded that decreased liver insulin degradation contributes to compensated hyperinsulinemia due to insulin resistance [35].

5 Conclusion

Rambutan honey at a dose of 500 mg kg^{-1} b.wt. can reduce blood glucose levels and increase insulin plasma levels of streptozotocin-induced rats better than rutin so it can be used to treat diabetes mellitus as an adjuvant therapy.

Acknowledgments. Thank you to the National Beekeeping Centre (Pusbahnas) Perhutani, Indonesia office which has provided samples of pure isolate rambutan honey.

Competing Interest. Thank you to LPPM Unjani Indonesia which has funded this research.

Grant Information. No competing interests were disclosed.

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