Acta Medical and Health Sciences, 1 (1): 19-27 (2022)

Advance Access Publication Date: June 2022

Original Article

Potential of red guava fruitghurt in lowering blood glucose levels in streptozotocin induced rats

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ABSTRACT

Diabetes mellitus is a chronic metabolic disorder characterized by increased blood glucose levels due to decreased insulin production, insulin action or both. Red guava fruitghurt contains flavonoid phytochemical compound. This research aims to determine the effect of red guava fruitghurt on reducing blood glucose levels in rats. The study was laboratory experiment. The subjects of this study were white rats (*Rattus norvegicus*) with wistar lines, where each group needed 5 rats, therefore the total was 25 rats. The sampling technique used is simple random sampling, The experimental animals are grouped into 5 groups, negative control, positive control, treatment 1 (administration of fruitghurt), treatment 2 (administration of glibenclamide), and treatment 3 (combination of fruitghurt and glibenclamide). The data analysis was performed with paired t test, one way anova, pairwise comparison test and post hoc duncan. The study found that red guava fruitghurt can reduce blood glucose levels in rats induced by streptozotocin and show a probability value or *p value* of 0.000 (*p value* < *0.05*), meaning that there is a significant difference between Treatment 1, 2, and 3. The blood glucose level of rats after administration of fruitghurt was 75.4mg/dl, after administration of glibenclamide was 48.4mg/dl and the combination of fruitghurt and glibenclamide was 44.0mg/dl. From these data, it can be seen that the most influential treatment in reducing blood glucose levels is the combination of fruitghurt and glibenclamide. The significant effect in lowering blood glucose levels is the combination of fruitghurt and glibenclamide.

Keyword: Blood Glucose Levels, Glibenclamide, Rats, Red Guava Fruitghurt, Streptozotocin

INTRODUCTION

Diabetes Mellitus (DM) according to the American Diabetes Association (ADA) in 2010 is a metabolic disease with characteristics of hyperglycemia that occurs because there is insulin secretion, insulin action, or both that cannot produce insulin in sufficient quantities, so the body cannot use insulin effectively. The body cannot use insulin effectively, resulting in excess sugar in the blood.[1,2]

Diabetes Mellitus can be divided into two types, namely type I and type II.[3] The incidence of DM sufferers according to the World Health Organization (WHO) predicts an increase in diabetes mellitus type II. In Indonesia, it was recorded that 422 million adults suffered from DM in 2014.[4] It is estimated that in Indonesia from 8.4 million in 2000, to 21.3 million in 2030.[2] Blood glucose is very high from the maximum limit resulting in an additional 2.2 million deaths, with risk factors for cardiovascular disease and others. 43% of the 3.7 million deaths occurred before the age of 70 years.[5] The prevalence of DM according to the RISKESDAS 2018 in Indonesia based on doctor diagnoses in the population aged over 15 years from 1.5% in 2013 to 2.0% in 2018. The province with the highest prevalence is DKI Jakarta.[6]

Management of DM is generally divided into four pillars, namely education, nutritional therapy, physical exercise, and pharmacological intervention.[7] One of the ways to treat DM patients is to provide snacks such as yogurt. Yogurt with high antioxidant activity can reduce oxidative stress, thus preventing complications. Probiotic bacteria present in yogurt such as *Lactobacillus achidophillus* and *Bifidobacterium lactis* can improve antioxidant status in DM patients, by releasing Superoxide dismutase (SOD) which can inhibit or damage the process of free radical formation.[8,9] High antioxidant status is expected to prevent complications in DM patients. Antioxidants can inhibit the early stages of retinopathy, nephropathy, and neuropathy. In addition, antioxidants can also inhibit macrovascular complications, reduce the incidence of coronary heart disease, improve the autonomic nervous system of the heart, and improve vasodilation.[7]

Red guava is usually served in juice, syrup, or consumed fresh. Because the variety of processing red guava is still limited, it is processed as an ingredient in the manufacture of fruitghurt.[10] Fruitghurt is a product of fermented fruits. While yogurt is a product of fermented milk. Red guava has a distinctive taste, high content of lycopene pigment in the flesh of red guava fruit, and is able to give a natural red color.[10] Red guava is rich in carbohydrates, vitamin C, and is a good source of good iron, a good source of calcium, phosphorus, and vitamin A.[11,12] The advantage of red guava is the high content of vitamin C which is a natural antioxidant found in the flesh of red guava fruit, so it is good for maintaining health.[10] Red guava also contains lycopene, fiber and propionate which have the effect of lowering blood cholesterol. Through a non-oxidative mechanism, lycopene shows an antiatherosclerotic effect as a hypo-cholesterolemic agent by inhibiting the action of HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) reductase which plays a role in cholesterol synthesis and activates LDL receptors.[13]

Red guava can also improve health. The organoleptic properties of yogurt include the level of preference for taste, aroma, and color in yogurt.[9] Flavonoid phytochemical compounds contained in red guava fruit can reduce oxidative stress by binding to free radicals.[12,14] To reduce oxidative damage, antioxidants are needed. shows the ability of flavonoids as free radical scavengers.[15]

Probiotics are live microorganisms that are capable of exerting a beneficial effect on the health of the host when consumed in sufficient quantities.[16] The effect of probiotics on glucose metabolism is most likely due to their modulating properties of the immune system, namely by inhibiting the transfer of bacterial endotoxins into the bloodstream, and reducing circulating proinflammatory cytokines. Therefore,

probiotics can reduce insulin resistance and pancreatic β cells more efficiently.[17] In this study, the effect in reducing blood glucose levels was in yogurt fermented by *Lactobacillus acidophilus* and *Lactobacillus casei*.[17] In this study, Streptozotocin was used because in previous studies it was known that streptozotocin can cause experimental diabetic hyperglycemia conditions.[18–20] Based on this, researchers were interested in knowing the effect of guava fruitghurt. on decreasing blood glucose levels in DM rats.

METHODS AND SUBJECT

The research was a laboratory experiment to determine extent of the changes that occur after the intervention with red guava fruitghurt on rats wich was induced by Streptozotosin. Data collection was obtained from examination of blood glucose levels from rats tails, taken 3 times. The first collection was when the rats had been acclimatized for 7 days, the second was taken when the rats had been induced by streptozotocin, and the third was when the rats had been given fruitghurt and glibenclamide. The ethical approval was obtained from the Research Ethics Committee of the Faculty of Medicine, Jenderal Achmad Yani University with the number 021/UH1.10/2020.

Object of Research

The object of research in this study was 5 white rats (*Rattus norvegicus*) with the Wistar strain (based on the calculation of the Federer formula) in each treatment group, so a total of 25 animals were adapted for one week at the Veterinary Laboratory of the Faculty of Medicine, Jenderal Achmad Yani University, given standard pellet feed and induced by streptozotocin.

The Rats that will be used for this study have the following criteria: 2-3 months of age, active movement, body weight 200-300 grams, male sex, fasting blood sugar > 140 mg/dL after administration of streptozotocin

The rats were divided into 5 groups, namely a negative control group (KN), a positive control group (KP), a treatment group of 1 induced by streptozotocin and given fruitghurt (P1), a treatment group of 2 rats induced by streptozotocin given glibenclamide, and not given fruitghurt, and treatment of 3 rats induced by streptozotocin, given glibenclamide, and given Fruitghurt.

Research Material

Red guava is obtained from the Cimahi Queue Market. Red guava fruitghurt is processed at the Microbiology Laboratory, Medical Faculty, Unjani. The red guava used in this study is red guava that is ripe and fresh, with the characteristics of a yellowish skin, pink to red flesh, and a sweet taste.

Making Red Guava Fruitghurt

The selected red guava fruit washed and put into a juicer with a speed of 47 rpm to obtain fruit juice. The red guava juice obtained was added with water in a volume ratio of 1:1, after that the mixture of the two was filtered several times to obtain a guava juice that was completely clear and free from fruit fiber. Next, the clear red guava juice was put into a *Schott Duran bottle.*

At the stage of adding sucrose and *Lactobacillus acidophilus* bacteria to red guava juice requires 1 bottle of Schott Duran. Then 1 bottle of Schott Duran was filled with 225 ml of red guava juice, then added 22.5 grams of sucrose. Furthermore, the sterilization process was carried out using an autoclave for 15 minutes at a temperature of 121°C.

After the sterilization process is complete, the bottles containing the guava juice media are allowed to stand until the heat is equal to room temperature, then put 25 ml of *Lactobacillus acidophilus* suspension in each bottle and then homogenize. The bottles were then incubated at 37°C for 24 hours. The dose of streptozotocin used in this study was 50 mg/KgBW intraperitoneally.

Experimental Animal Treatment

Mice were acclimatized for 7 days, then their blood was examined for comparison before induction. Experimental animals

were given standard feed pellets of 30 g/day/head and drank ad libitum until the end of the study. Streptozotocin induction at a dose of 50 mg/KgBW intraperitoneally. Blood glucose levels were checked on day 10. Treatment for the next 7 days in each group is shown in table 1. Fruitghurt was given when streptozotocin-induced rats had hyperglycemia and were given orally in groups 3 and 5.

Table 1 Research Group

No	Group	standard feed	Streptozotosin	Glibenklamid	*Fruitghurt*	Treatment time
1	KN	+	-	-	-	18 days
2	KP	+	50 mg/kgBB	-	-	18 days
3	P1	+	50 mg/kgBB	-	1 ml	18 days
4	P2	+	50 mg/kgBB	150 mg/kgBB	-	18 days
5	P3	+	50 mg/kgBB	150 mg/kgBB	1 ml	18 days

KN : Negative control that were not induced by streptozotocin and were not given fruitghurt
KP : Positive control of streptozotocin-induced rats that were not given fruitghurt
P1 : Treatment of 1 streptozotocin-induced rats were given fruitghurt
P2 : Treatment of 2 streptozotocin-induced rats were given glibenclamide, and were not given fruitghurt
P3 : Treatment of 3 streptozotocin-induced rats were given glibenclamide, and were given fruitgurt

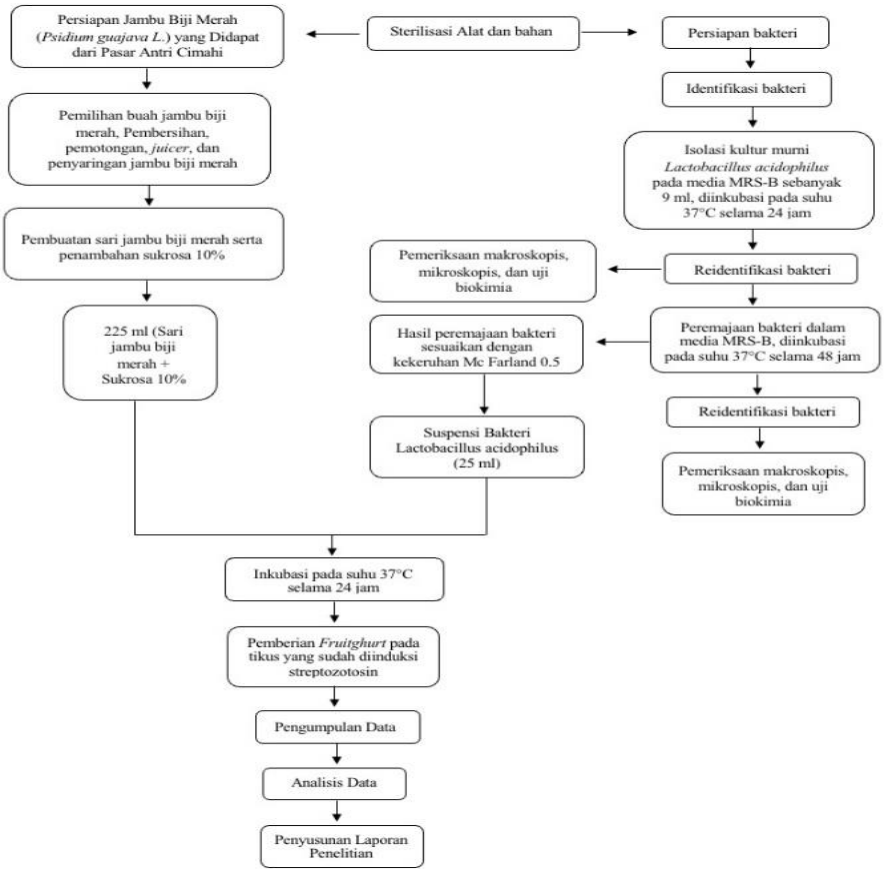

Figure 1. Research Flow

Blood Glucose Levels

Blood sampling in this study was performed from the lateral tail vein. Checking blood glucose levels using an Autocheck glucometer. In this study, blood sampling was carried out 3 times, on the 7th day after acclimatization, 10th day after being induced by streptozotocin and 18th day after being given fruitghurt. Each blood sample is taken as much as 1 ml.

Statistic Analysis

Before the statistical test was carried out, the data were tested for normality using the *Shapiro Wilk test* because the number of data was less than 50. The data were analyzed using *paired t-test* which aims to determine the difference before and after treatment. Furthermore, the *one way ANOVA test* was carried out which aims to determine the difference in blood glucose levels in rats in each group. Furthermore, *a post hoc Tukey* test was conducted to see the differences between groups.

RESULTS AND DISCUSSION

Blood Glucose Levels After Streptozotocin induction and given Fruitghurt The results show a probability value or p value of 0.000, meaning that there is a significant difference between P1, P2, P3 blood glucose of rats that have not been given fruitghurt and blood glucose of rats that have been given fruitghurt, blood glucose of rats that have been given glibenclamide and blood glucose of rats that have been given fruitghurt. given fruitghurt and glibenclamide. The results of the observations can be seen in table 2 below.

Table 2. Effect of Fruitghurt on Blood Glucose Levels In Streptozotocin-Induced Rats Before and After Treatment

Group	Blood Glucose Level (mg/dl) ± SD		*p*
	Before	After	
KN	75.80 ± 13.16	75.80 ± 13.16	
KP	147.00 ± 3.74	147.00 ± 3.74	
P1	149.80 ± 4.60	75.40 ± 12.28	0.000
P2	149.80 ± 4.60	48.40 ± 11.91	0.000
P3	145 ± 4.53	44 ± 5.52	0.000

KN : Negative control that were not induced by streptozotocin and were not given fruitghurt
KP : Positive control of streptozotocin-induced rats that were not given fruitghurt
P1 : Treatment of 1 streptozotocin-induced rats were given fruitghurt
P2 : Treatment of 2 streptozotocin-induced rats werw given glibenclamide, and not given fruitghurt
P3 : Treatment of 3 streptozotocin-induced rats were given glibenclamide, and fruitgurt

The difference in blood glucose levels before and after being given fruitghurt can be seen very clearly in all treatment groups, where there is a significant decrease in blood glucose. However, blood glucose levels with 1 ml of fruitghurt and 150 mg/kgBW of glibenclamide were much better in lowering blood glucose. Giving fruitghurt can reduce blood glucose levels caused by the mechanism of action of probiotics against the body's defenses by strengthening the *E-cadherin/Beta-cetanin complex* so that it can improve intestinal permeability, increasing the number of normal flora in the intestines in the form of gram-positive bacteria will inhibit the growth of gram-negative bacteria, so the lipopoly-saccharide produced by gram-negative bacteria can decrease and can suppress intestinal inflammatory reactions.[21]

Differences in Decreased Blood Glucose Levels After Giving Fruitghurt

The results of calculations using the One Way Anova test showed that there were differences in the decrease in blood glucose levels from various groups after giving fruitghurt. The results of observations of differences in the decrease in blood glucose levels after giving fruitghurt can be seen in table 3 below.

Table 3 One Way Anova Test for Differences in Decreased Blood Glucose Levels in Various Groups After Giving Fruitghurt

Group	Blood Glucose Level (mg/dl) ± SD	*P*
KN	75.80 ± 13.16	
KP	147.00 ± 3.74	
P1	75.40 ± 12.28	0.000
P2	48.40 ± 11.91	
P3	44 ± 5.52	

KN : Negative control that were not induced by streptozotocin and were not given fruitghurt
KP : Positive control of streptozotocin-induced rats that were not given fruitghurt
P1 : Treatment of 1 streptozotocin-induced rats were given fruitghurt
P2 : Treatment of 2 streptozotocin-induced rats werw given glibenclamide, and not given fruitghurt
P3 : Treatment of 3 streptozotocin-induced rats were given glibenclamide, and fruitgurt

Table 3 shows that there was a decrease in blood glucose levels from various groups after giving fruitghurt. Analyzed using one way ANOVA in the treated group showed there was a significant difference, *p value = 0.000 (p <0.05)*. Proving that red guava fruitghurt can lower blood glucose levels. Red guava has a high content of flavonoids and total phenolic which works as a potent inhibitor of GLUT2 and SGLT1 both in vitro and in vivo, this study has shown antihyperglycemic and hypoglycemic effects.[21]

Rat Blood Glucose Levels After Giving Fruitghurt and Glibenclamide

Based on Duncan's Post Hoc test, it was found that P3 and P2 were in subset 1, which means that they have been able to reach normal blood glucose levels, while P1 is in subset 2, which means they are almost close to normal blood glucose levels, therefore it can be concluded that fruitghurt and glibenclamide were effective in reducing blood glucose levels. The results of observations of blood glucose levels of rats induced by streptozotocin after being given fruitghurt and glibenclamide can be seen in table 4 below. Based on the Post Hoc Tukey Test, it was found that the three groups had significant differences in each group (p=1,000).

The decrease in blood glucose is probably due to the mechanism of action of the drugs glibenclamide and fruitghurt. Glibenclamide will stimulate β pancreatic cells to increase insulin secretion.16

This happens because glibenclamide is able to stimulate insulin secretion stored in the granules of pancreatic cells through its interaction with ATP-sensitive K channels on the β pancreatic cell membrane which is then assisted by Lactobacillus acidophillus in fruitghurt which has the effect of lowering blood glucose levels by improving permeability intestines and suppress the inflammatory process by inhibiting pro-inflammatory cytokines so as to minimize damage to β pancreatic cells. In addition, the flavonoid content in red guava in fruitghurt has the effect of reducing oxidative stress caused by streptozotocin induction by binding to free radicals, and has the effect of inhibiting GLUT2 in intestinal epithelial cells which can inhibit glucose absorption in the intestine. The mechanism of fruitghurt and glibenclamide will result in a significant and better reduction in blood glucose in rats when compared to giving fruitghurt and glibenclamide alone.

Table 4. Duncan's Advanced Test Results on Blood Glucose Levels of rats induced by streptozotocin after being given fruitghurt and glibenclamide

		Subset for alpha = 0.05		
Group	N	1	2	3
P3	5	44.0		
P2	5	48.4		
P1	5		75.4	
KN	5		75.8	
KP	5			147.0
Sig.		.957	1.000	1.000

KN : Negative control that were not induced by streptozotocin and were not given fruitghurt
KP : Positive control of streptozotocin-induced rats that were not given fruitghurt
P1 : Treatment of 1 streptozotocin-induced rats were given fruitghurt
P2 : Treatment of 2 streptozotocin-induced rats were given glibenclamide, and not given fruitghurt
P3 : Treatment of 3 streptozotocin-induced rats were given glibenclamide, and fruitgurt

The mechanism of action of glibenclamide is to increase insulin secretion or stimulate insulin release from β pancreatic cells.[22] Meanwhile, the decrease in blood glucose in fruitghurt is caused by a mechanism of action that has local and systemic effects. The local mechanism of action in fruitghurt may be due to the action of the *E-cadherin/Beta-cetanin complex* to improve intestinal permeability. Improved intestinal permeability will cause systemic effects resulting from probiotics, namely the possibility of suppressing the inflammatory process caused by lipopoly-saccharides produced from gram-negative bacteria, by inhibiting proinflammatory cytokines that induce cell damage so as to minimize damage from β pancreatic cells.[21] The decrease in blood glucose can also be caused by the flavonoid content of red guava which may have the effect of reducing oxidative stress by binding to free radicals caused by streptozotocin induction.[23]

The mechanism of action of glibenclamide is to increase insulin secretion or stimulate insulin release from pancreatic cells.[22] Meanwhile, the decrease in blood glucose in fruitghurt is caused by a mechanism of action that has local and systemic effects.

Probiotic drinks have many benefits, including: reducing lactose intolerance, shortening the frequency and duration of diarrhea, stimulating immunity modulation, increasing antitumor and antimutagenic activity, helping mineral absorption, and antioxidants.[24,25] The ability of probiotics to increase and maintain immunity has the potential to prevent metabolic syndromes such as type 2 diabetes mellitus.

Not only reducing inflammation, probiotics also have an important role in modulating the gut microbiota so that it affects the production of intestinal peptides in glucose metabolism.[25] Probiotics can also improve antioxidant status in patients with type 2 diabetes mellitus. High antioxidant status can prevent complications of disease in people with diabetes mellitus. Antioxidants can inhibit the early stages of retinopathy, nephropathy, and neuropathy. In addition, antioxidants can also inhibit microvascular complications, repair the cardiac autonomic nervous system, and improve vasodilation.[8]

CONCLUSION

Red guava fruitghurt can reduce blood glucose levels in streptozotocin-induced rats. Blood glucose levels after

administration of fruitghurt was 75.4 mg/dl. After administration of glibenclamide was 48.4mg/dl and the combination of fruitghurt and gliben- clamide was 44.0 mg/dl. It can be seen that the most influential in lowering blood glucose levels is the combination of fruitghurt and glibenclamide.

ACKNOWLEDGEMENTS

Our gratitude goes to the UNJANI Research and Community Service Institute which has provided funds and opportunities to conduct this research as well as to the Dean and his staff who have given the author the opportunity to conduct and complete this research.

The authors also thank the professionals who have helped in the preparation and research such as colleagues, students, assistants to the Microbiology Laboratory and Animal Laboratory, Faculty of Medicine, Achmad Yani University General. And all parties who have helped so that this research can be carried out.

DECLARATION OF INTERESTS

The author hereby declares that there is no conflict of interest in the scientific articles that we write.

FUNDING

This research received funding from the Institute Research and Community Service UNJANI Bandung.

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