The Antidiabetic Effect of Black Glutinous Tapai Beverage in Metabolic Syndrome Rats

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Abstract: Metabolic syndrome (MetS) known as insulin resistance syndrome, is recognized as a risk factor for type 2 diabetes mellitus. Management of MetS involves a combination of lifestyle changes and pharmacological interventions. Black glutinous tapai beverage (BGTB) as local food contains *Lactobacillus spp*., which can be a potential source of probiotics to improve hyperglycemia. This study aimed to determine the efficacy of BGTB as an antidiabetic in rat models of MetS. This study used 30 male Sprague Dawley rats which were divided into five groups, one as a normal group (N) given a standard diet, and the other four groups were given a high-fat diet for 2 weeks and induced by Streptozotocin (STZ) and Nicotinamide (NA), i.e. negative control (KN) was given a standard diet, positive control (KP) was given metformin 9 mg, treatment 1 (P1) and treatment 2 (P2) were given BGTB 0,9 ml 200 gr-1 rat BW and 1,8 ml 200 gr-1 rat BW, respectively for four weeks. The result showed a significant difference (p=0.000) in blood glucose and HbA1c after giving BGTB. This study showed that BGTB has the potential to be developed as a functional beverage and source of probiotics for people with MetS.

1 INTRODUCTION

Metabolic syndrome (MetS), known as insulin resistance syndrome, is recognized as one of the risk factors for cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM). Obesity and insulin resistance are considered significant factors in the development of MetS (Limanan & Prijanti, 2013; Rochlani et al., 2017; Srikanthan et al., 2016). The prevalence of MetS in Indonesia is 28% in men and 46.2% in women. In Indonesia, hyperglycemia (51%) is the second component of MetS after hypertension (61,0%) (Sigit et al., 2020).

MetS management involves a dual approach, combining lifestyle changes and pharmacological interventions. Emphasis on environmental and lifestyle factors such as excessive calorie consumption, lack of fiber intake, and low physical activity as major contributors to MetS (PERKENI, 2021; Rochlani et al., 2017). There is no single treatment for MetS, requiring several types of drugs and a long period to improve each component. The development of functional and nutraceutical foods can be used to limit drug use and minimize side effects (Ayivi et al., 2020; Rochlani et al., 2017).

Functional foods are intended to reduce the risk of, slow down, or prevent certain diseases and improve immunity, and are not medicines or dietary supplements (Goetzke & Spiller, 2014). Black glutinous tapai is known as a functional food obtained from the fermentation process of black glutinous rice. Black glutinous rice contains high fiber, anthocyanins, phenols, and antioxidant activity which can be an alternative healthy snack for people with dyslipidemia, MetS, and constipation. Consumption of black glutinous tapai >11.5 grams per day, has a protective benefit against MetS by 16 times compared to individuals who consume <11.5 grams (Fauziyah, 2018; Yulianto, 2022).

The International Scientific Association for Probiotics and Prebiotics (ISAPP) explained that some types of fermented foods contain probiotics that can benefit health (Marco et al., 2021). Probiotics are microorganisms in the form of bacteria that are given in sufficient doses to provide health benefits to their hosts (Scavuzzi et al., 2014).

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Black glutinous tapai, in previous studies, was studied to have several lactic acid bacteria, such as *Lactobacillus fermentum 1 BK 2-5* which have the potential to become probiotic candidates in black glutinous tapai (Panjaitan, 2018).

It was mentioned that the water content formed from the fermentation of black sticky rice reached 55.18% on the 3rd day of fermentation (Fauziyah, 2018). This water content is referred to as black glutinous tapai beverage. Research on utilizing black glutinous rice juice against MetS conditions currently does not exist.

In previous studies, BGTB contained 3×10^9 *Lactobacillus spp*.,. Some types of *Lactobacillus* can suppress fasting and postprandial blood glucose. In addition, it can help activate insulin signaling for glucose absorption (Bobga et al., 2022; Choi et al., 2020; Yadav et al., 2018). Black glutinous rice is a good probiotic carrier because it does not need to go through another processing process that can reduce the amount of probiotics before consumption (Nuraida, 2015). In addition, the deep purple color of BGTB indicates the presence of anthocyanins have function as a prebiotic. Black sticky rice contains 257 ppm of anthocyanins (Fauziyah & Pardina, 2020). Anthocyanins can function as a prebiotic which can significantly increase the number of *Lactobacillus* spp., (Wang et al., 2020; Zhu, 2018).

This study aims to see if black glutinous tapai beverage can be an alternative functional food for antidiabetics and patients with MetS.

2 MATERIAL AND METHOD

2.1 Production of BGTB

Making BGTB begins with separating black glutinous rice from foreign objects and washing it. Black glutinous rice is then soaked overnight or for approximately 8 hours. Subsequently, black glutinous rice is steamed for 1 hour. After that, prepare hot water that has just been brought to a boil in a ratio of 1:1.2, then put the steamed black glutinous rice into the boiling water and stir again until evenly distributed. Cover the pot, and let stand for 30 minutes. Prepare the steaming pot again, then steam the black sticky rice for ± 1 hour until cooked. Remove and cool the black glutinous rice. After cooling, mix the sticky rice with the mashed yeast, then stir until smooth. Store the tapai in a closed container and let it sit for ± 3 days. After standing for 3 days at room temperature, the black glutinous rice is squeezed and the black glutinous rice liquid is taken, which we call BGTB, and stored in a sterilized glass bottle.

2.2 Induction of Test Animal

Thirty male Sprague Dawley rats were weighed with an average weight of 200 grams. For 2 weeks, rats were given HFD and distilled water ad libitum. After that, rats will be induced using STZ + NA. The STZ dose was dissolved in citrate buffer (pH 4.5) and nicotinamide was dissolved in normal physiological saline. Rats were induced with nicotinamide (110 mg/kg bw) in the intraperitoneal section and 15 minutes later induced with STZ (45 mg/kg bw).

Samples that met the criteria for metabolic syndrome based on NCEP-ATP III (FBG (>250 mg/dL), triglyceride (≥150 mg/dL), and HDL (<40 mg/dL) levels) were considered to have metabolic syndrome and were used as experimental animals (Aydin et al., 2014). This research has received ethical clearance approval from KEPK FK UNS (61/UN27.06.11/KEP/EC/2023).

2.3 Testing the Antidiabetic Activity of Black Glutinous Tapai Beverage

This study was a laboratory experimental study, using a randomized pretest and posttest-controlled group design. Divided into five groups of 6 rats, one group as a normal group and four MetS groups:

- KN: Normal (without treatment)
- K-: MetS (without treatment)
- K+: Administration of metformin 9 mg/kg BW
- P1: Administration of 0.9 mL BGTB
- P2: Administration of 1.8 mL BGTB

2.4 Measurement of Blood Glucose Levels by GOD-PAP

Blood glucose measurements (FBG and PBG) were conducted before and after treatment for 28 days. Qualitative measurements used the Enzymatic calorimetric Test GOD-PAP method. Glucose in the sample was oxidized to form gluconic acid and hydrogen peroxide. Hydrogen peroxide 4-Aminoatypirene with phenol indicator was catalyzed with POD to form quinonimine and water. Serum (sample) was obtained from blood centrifuged at 3000 rpm for 10 minutes, 10 µl of serum was taken and mixed with 1000 µl of standard sugar, then incubated at 37 C or 10 minutes. Absorbance was measured by comparing the results of the test solution with standard glucose levels at a wavelength of 500 nm with a UV-Vis spectrophotometer (Subiyono et al., 2016). Blood glucose measurements (FBG and PBG) were conducted before and after treatment for 28 days. Qualitative measurements used the Enzymatic calorimetric Test GOD-PAP method. Glucose in the sample was oxidized to form gluconic acid and hydrogen peroxide. Hydrogen peroxide 4-Aminoatypirene with phenol indicator was catalyzed with POD to form quinonimine and water. Serum (sample) was obtained from blood centrifuged at 3000 rpm for 10 minutes, 10 µl of serum was taken and mixed with 1000 µl of standard sugar, then incubated at 37 ˚C or 10 minutes. Absorbance was measured by comparing the results of the test solution with standard glucose levels at a wavelength of 500 nm with a UV-Vis spectrophotometer (Subiyono et al., 2016).

2.5 Measurement of HbA1c by Elisa Method

Measurement of HbA1c levels was carried out after 28 days of treatment, using the sandwich enzyme immunoassay technique. First, the plate was washed with wash buffer 2 times. Then 100 µl of standard, sample, and control were added into each well, sealed, and incubated for 90 minutes at 37oC. The plate was washed with wash buffer 2 times without soaking. 100 µl biotin solution was added into each well and incubated for 60 minutes at 37oC. Washed the plate with wash buffer 3 times soaking for 1 minute each time. Then, 100 µl of SABC solution was added into the wells and incubated for 30 minutes at 370. After that, wash the plate again by using wash buffer 5 times and soak it for 1 minute for each wash. add 90 µl TMB substrate in each well and incubate for 10-20 minutes at 37 ºC. Added 50 µl stop solution in each well. Read the absorption with a microplate reader at a wavelength of 450 nm and calculated the levels (Triyono, 2016).

2.6 Data Analyze

Data were analyzed using the One-way ANOVA test and continued using the Post Hoc Tukey HSD test. This test is used to determine the impact of giving black glutinous rice juice on FBG, PBG, and HbA1c levels. If the data is not normally distributed, it will be continued with the Kruskal Wallis non-parametric test and then continued using the Games-Howell test.

3 RESULT

As the result shown in Table 1, both FBG and PBG in the K+, P1, and P2 groups decreased, with the highest decrease in the P2 group. Based on the

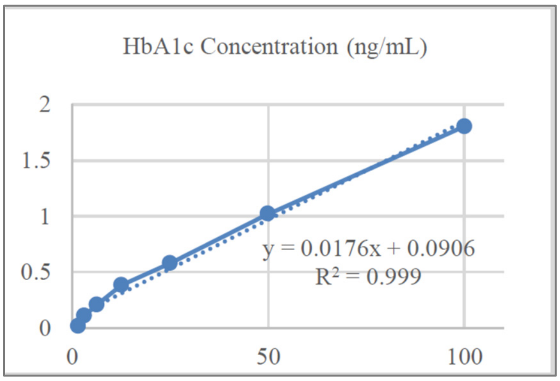

Figure 1: Standard Curve HbA1c.

Kruskall-Walis statistical test, there were differences in each group ($p < 0.05$). Followed by Games-Howell post hoc test shows no difference in influence between groups K+ and P2.

The HbA1C level was calculated by substituting the absorbance value (y) of the sample at 450 nm wavelength into the logarithm regression equation y = (equals to) ax + b, which was obtained from the standard HbA1C curve so that the HbA1C concentration value (x) was obtained. Based on the Kruskal Walis test, black glutinous rice juice had a significant effect on HbA1c levels between groups.

Post Hoc Tukey HSD test showed a significant difference ($P < 0.05$) between doses of intervention groups. From the difference in comparison with the K- group in the intervention group, the P2 group had a better effect of 55.28%.

4 DISCUSSION

The high-fat diet (HFD) formula adds a fat component of up to 40%-50% of total calories for 4-8 weeks (Gao & Zheng, 2014). The HFD is made by the modern human diet which is currently found to be higher in fat than the recommended diet (20%-25%) (KEMENKES RI, 2019). The characteristics obtained from HFD are obesity, impaired glucose tolerance, and insulin resistance (Husna et al., 2019). High levels of fat in the blood affect the ability of insulin receptors and cause the expression of glucose transporter type 4 (GLUT 4) to decrease. The decrease in GLUT 4 expression causes glucose transportation into the cell membrane to be disrupted, decreasing glucose transport activity. Therefore, HFD can cause high blood glucose levels (Rahmawati et al., 2017).

Blood glucose levels after intervention in KN and K-groups increased by 1.89% and 0.4%, respectively. The increase in FBG in the normal group can be caused by the age of the rats entering early adulthood (Nurmawati, 2017), which was 14 weeks old at the end of the intervention. Physiologically, increasing age causes a decrease in the function of pancreatic β-cells (Setiyorini & Wulandari, 2017). Along with age, the ability of pancreatic β-cells will weaken until they are damaged, which triggers hyperglycemia (Rahmawati et al., 2017).

The increase in FBG in the K- group may be due to the administration of HFD for two weeks and STZ+NA induction without BGTB administration. Furthermore, the results of this study showed that the average FBG levels in K+, P1, and P2 experienced a significant decrease after the administration of BGTB ($p<0.05$). For the FBG pre-test and post-test from the analysis results using paired t-test, treatment groups K +, P1, and P2 showed the effect of BGTB administration. Similar results of research on rice bran fermented using *Lactobacillus fermentum* MF423, it is known to improve hyperglycemia conditions in vitro and in vivo and increase the antioxidant capacity of diabetic rats (Ai et al., 2021). In addition, it was found that *L. rhamnosus BSL* and *L. rhamnosus R23* have potential as probiotic foods and are promising agents for managing T2DM (Eko Farida et al., 2020). The *Lactobacillus* bacteria in BGTB can help maintain the gut microbiota. This effect inhibits the transfer of bacterial endotoxins into the bloodstream and reduces circulating lipopolysaccharides and proinflammatory cytokines, which in turn decreases inflammation resulting in decreased insulin resistance and controlled blood glucose levels (Hindri et al., 2020).

Some LAB strains were reported to inhibit the enzyme α-glucosidase and have antioxidant activity. Inhibition of this enzyme will reduce glucose absorption and thus reduce blood glucose levels. α-glucosidase is an enzyme in the filamentous peripheral membrane that catalyzes the process of carbohydrate digestion, and inhibiting the activity of α-glucosidase has been demonstrated to decrease glucose absorption and reduce blood glucose levels (E. Farida & Jennie, 2019). Inhibition of the enzyme α-glucosidase is one of the therapeutic approaches to reduce PBG levels because by inhibiting the enzyme α-glucosidase, it can delay the breakdown of oligosaccharides and disaccharides into monosaccharides so that compounds that can inhibit the work of the enzyme α-glucosidase can be used as oral drugs for patients with type 2 diabetes (Febrinda et al., 2013).

Table 1: Blood Glucose on rats with different treatments.

Blood Glucose	Treatment Group				
	KN	K-	K+	P1	P2
Fasting (mg/dL)					
Pre-test	69.08±1.77	270.66 ±2.18	269.70 ±2.37	269.76 ±4.11	267.39 ±2.16
Post-test	70.39±1.52	271.79 ±2.39	96.82 ±4.04	126.37 ±5.13	88.46 ±2.97
Δ Mean±SD*	1.31±-0.25[a]	1.13±0.21 [a]	-172.88 ±1.67 [b]	-143.39 ±1.02[c]	-178.93 ±0.81 [b]
p pre-post**	0.000	0.001	0.262	0.782	0.462
Postprandial (mg/dL)					
Pre-test	88.23±1.37	285.30 ±1.98	284.06 ±2.54	284.06 ±3.49	283.84 ±2.72
Post-test	92.49±2.12	293.65 ±2.43	117.15 ±3.85	142.41 ±5.13	117.27 ±13.02
Δ Mean±SD*	4.26±0.75[a]	8.35±0,45[b]	-166.9 1±1.31[c]	-141.65 ±1,64[d]	-166,57 ±10,3[c]
p pre-post**	0.000	0.028	0.028	0.000	0.028

*Delta value (different mean between pre and post-test): positive number indicated an increase and negative indicated a decrease.
**$p<0.05$ in each column indicated a significant difference between pre and post-test.
[a,b,c,d])Numbers followed by the same letter indicate no significant difference

Probiotics produce short-chain fatty acid (SCFA), namely propionic acid, which can inhibit gluconeogenesis in the liver to suppress glucose production and reduce insulin resistance (Bishehsari et al., 2018). Probiotics can act as inhibitors of the enzyme α-glucosidase found in intestinal microfili so that they can cause a decrease in blood glucose levels (Gomes et al., 2014). A meta-analysis showed that consuming probiotics can improve glucose metabolism at a modest level (Zhang et al., 2016). From the results of Hindri's research, it is stated that the administration of *Lactobacillus fermentum* can reduce blood glucose levels, and HbA1c (Hartini, 2016).

HbA1c levels were compared in each group, from the results of Kruskal Walis there were differences in each treatment group ($p<0.05$). Followed by the Howell games test, there was an effect of BGTB administration on HbA1c. In both FBG and PBG, there was no difference in the K+ and P2 groups, where 1.8 ml BGTB had similarities with metformin in reducing blood glucose levels. The improvement of MetS conditions by metformin is associated with increased GLP-1 expression, AMPK activation, and improved gut microbiota composition so it will have an impact on increasing insulin sensitivity and decreasing the process of lipolysis (Wang et al., 2020).

The administration of BGTB was more effective in reducing blood glucose levels presumably due to the role of anthocyanins as antioxidants. Antioxidants capture free radicals and reduce inflammation by suppressing TNF-α production. Decreased TNF-α production can improve insulin sensitivity through increased autophosphorylation of insulin receptors, increased tyrosine kinase activity on insulin receptors, and increased GLUT-4 expression. Increased GLUT-4 expression causes the transportation of blood glucose to the cell membrane to increase and blood glucose levels to decrease. Anthocyanins as antidiabetics are also able to activate AMPK in adipose tissue, muscle, and liver. Tasked with maintaining energy balance in cells, AMPK will suppress glyconeogenesis and lipolysis by phosphorylating acetyl-CoA carboxylase and AcetylCoA Oxidase, thus preventing glucose formation in the liver and FFA formation and increasing insulin sensitivity (Herrera-balandrano et al., 2021; Takikawa et al., 2010). In addition, it can also increase GLUT-4 (Glucose Transporter type 4), so that glucose uptake into cells will increase (Ifadah et al., 2021).

5 CONCLUSION

Black glutinous tapai beverage contains *Lactobacillus* sp., and anthocyanins, which had been demonstrated to have an antidiabetic effect. Our study showed that BGTB could improve blood glucose (FBG and PBG) and HbA1c of metabolic syndrome rats. These effects might be beneficial to further extend the application of BGTB as a potential probiotic and prebiotic for metabolic syndrome.

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