



## Soy-Ipoghurt as an antidiabetic on hiperglicemic animal modelling

### *Rattus norvegicus*

### *Soy-Ipoghurt sebagai antidiabetes pada hewan coba Rattus norvegicus hiperglikemia*

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## Abstract

Treatment of Diabetes Mellitus (DM) is generally through optimizing a balanced diet. Soybeans and sweet potatoes have good antioxidants and can be developed as healthy foods for people with diabetes. Soybeans and sweet potatoes are processed into Soy-yoghurt. This study aims to determine the potential of soy yogurt as an antidiabetic in experimental animals, *Rattus norvegicus* induced by hyperglycemia, using Streptozotocin. This study used an experiment design with a total of 40 experimental animals. The research was conducted at the Medica Farma Husada Polytechnic Laboratory, Mataram, in 2022. The experimental animals that Streptozotocin (STZ) induced were then given Soy-yogurt orally at 3 ml and 3.5 ml doses. Experimental animals' Fasting Blood Glucose (FBG) levels were measured weekly using a Glucometer, while body weight (BW) was measured every three days. The results obtained were then analyzed statistically using the ANOVA test. The test results showed that there was a significant difference in blood sugar levels ( $p < 0,05$ ) in fasting given soy but no difference in BW ( $p > 0,05$ ). This study concludes that the provision of soybeans can affect the level of FBG of the experimental animals but does not affect the BW of the experimental animals.

**Keywords:** Soy-yoghurt, Diabetes Mellitus, Streptozotocin, blood glucose, Body Weight

## Abstrak

Pengobatan Diabetes Melitus (DM) umumnya melalui optimalisasi diet seimbang. Kedelai dan ubi jalar diketahui memiliki kandungan antioksidan yang baik dan berpotensi dikembangkan sebagai makanan sehat bagi penderita DM. Kedelai dan ubi jalar diolah menjadi Soy-ipoghurt. Penelitian ini bertujuan untuk mengetahui potensi soy-ipoghurt sebagai antidiabetes pada hewan coba *Rattus norvegicus* yang diinduksi hiperglikemia menggunakan Streptozotocin. Penelitian ini menggunakan desain eksperimental laboratoris dengan jumlah hewan coba sebanyak 40 ekor. Penelitian dilakukan di Laboratorium Politeknik Medica Farma Husada Mataram pada tahun 2022. Hewan coba yang telah diinduksi STZ kemudian diberikan Soy-ipoghurt secara oral dengan dosis 3 ml dan 3,5 ml. kadar Glukosa Darah Puasa (GDP) hewan coba diukur setiap minggu menggunakan Glucometer sedangkan berat badan diukur setiap 3 hari sekali. Hasil yang diperoleh kemudian dianalisis secara statistik menggunakan uji ANOVA. Hasil uji menunjukkan ada perbedaan signifikan pada kadar gula darah ( $p < 0,05$ ) puasa setelah diberikan soy-ipoghurt namun tidak adanya perbedaan pada berat badan ( $p > 0,05$ ). Kesimpulan dari penelitian ini adalah pemberian Soy-ipoghurt dapat memengaruhi kadar FBG hewan coba, namun tidak berpengaruh terhadap berat badan hewan coba.

**Kata Kunci:** Soy-ipoghurt, Diabetes Melitus, Streptozotocin, GDP, Berat badan

## Introduction

Diabetes Mellitus (DM) is a health problem among the leading cause of death worldwide. Lifestyle remains one of the main factors that increase the incidence of DM (Irwansyah & Kasim, 2021). The number of DM patients continues to increase annually (Kemenkes RI, 2020). According to previous studies, 80% of people with DM live in low- and middle-income countries, aged between 40 and 59 years (Trisnawati & Setyorogo, 2013).

DM management is usually performed using a combination of treatment and lifestyle. To date, the drug is only a supplement to the diet. It is only necessary to be administered when dietary adjustments can no longer control blood sugar levels (Wahyuningrum et al., 2020). Uncontrolled diabetes can lead to chronic and acute complications (Asmat et al., 2016). Acute complications usually include hypoglycemia, diabetic ketoacidosis, and nonketotic hyperglycemic hyperosmolar coma. Medications for people with diabetes Antihyperglycemic drugs are generally consumed throughout the patient's life (Wahyuningrum et al., 2020).

Sweet potatoes (in Indonesian called "Ketela Rambat" or "Ubi Jalar") have several advantages, including good antioxidant activity and the presence of vitamins A, B, and C, and other minerals (Windardi, 2016). Anthocyanins in strawberries have physiological functions such as anti-cancer, anti-bacterial, and protective effects against heart damage and stroke. Carbohydrates are in the Low Glycemic Index category (LGI 54) and are suitable for people with diabetes. Ubi Jalar does not drastically increase blood sugar levels when consuming foods with a high glycemic index. Ubi Jalar contains soluble fibers, which the ability of this soluble fiber can bind and control the fat/cholesterol present in the blood. Oligosaccharide fibers are attractive for the enrichment of processed products (Rosidah, 2014).

Grapefruit (*Glycine max*) is a source of vegetable protein that is widely consumed by society. Soybeans may potentially lower the blood glucose levels in patients with DM (Wagustina et al., 2020) (Nugraheni & Harnina Bintari, 2017). It is based on the contents of the phytoestrogen isoflavone (Hendriyani et al., 2018) in soybeans that have glycemic control effects, insulin sensitivity, dyslipidemia, and kidney function.

One preferred soya processing method is soymilk, which can also be further processed into yogurt. The advantage of yogurt over yogurt derived from cow milk is its higher antioxidant ability, which prevents fat oxidation (Raharjo et al., 2022). It is due to the high content of isoflavone compounds in soybeans that act as an antioxidant (Rustanti et al., 2020)

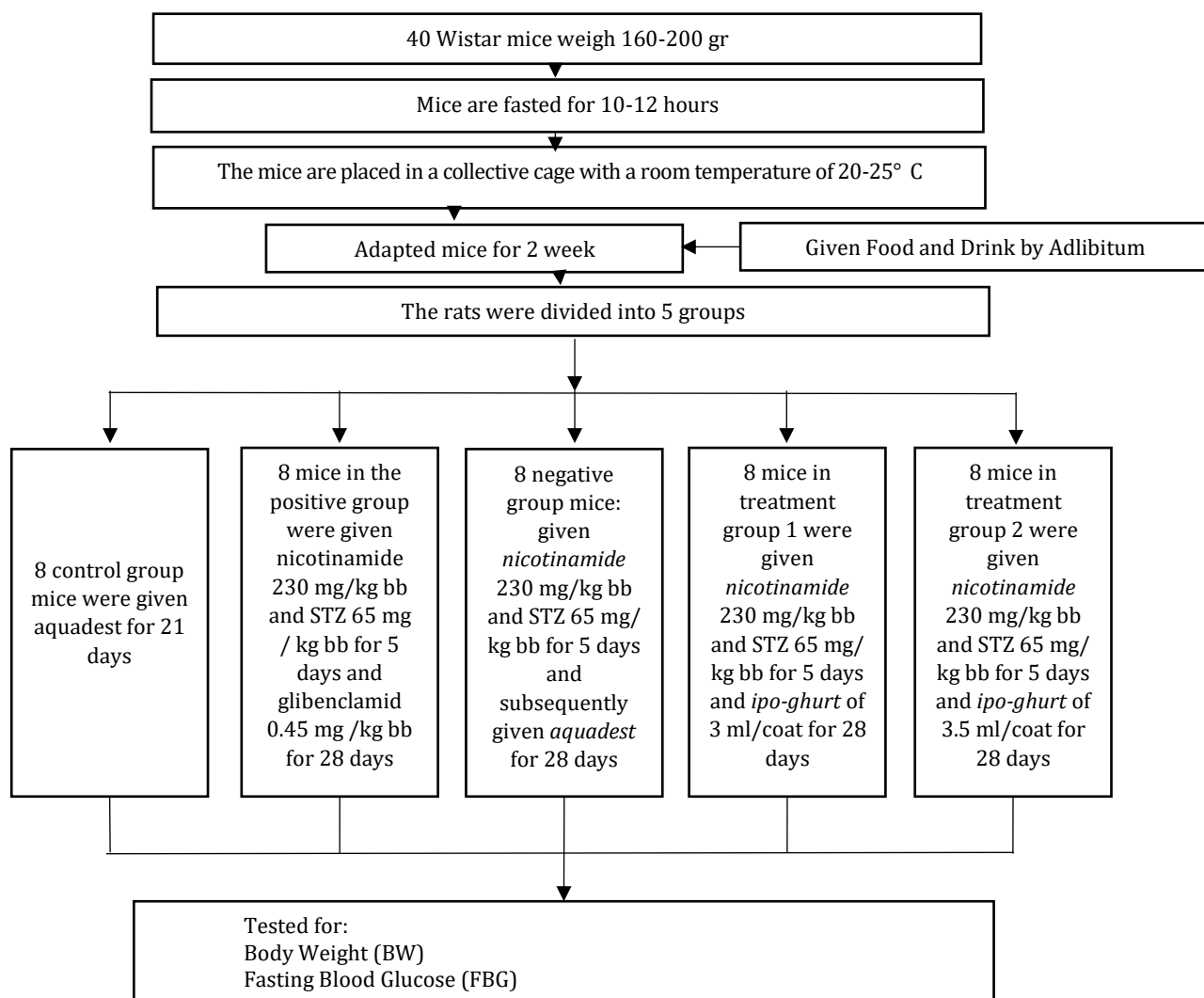
Soy yogurt is a processed product obtained from the fermentation of soybeans and adding soybeans. Soy yogurt is made by adding the thermophilic bacteria *Lactobacillus delbrueckii subsp. bulgaricus* and *Streptococcus salivary subsp.* Soy yogurt is expected to increase the nutritional value of donkeys and strawberries (Hamidah et al., 2019; Joel et al., 2019). Soy-yogurt is the development and modification of soy-yogurt products. The difference lies in the food ingredients used for the soybean combination. Soy-yogurt was used in this study (Kwanariesta 2017).

This study was conducted to examine the potential of soy yogurt as an antidiabetic agent in an animal model of *Rattus norvegicus*-induced hyperglycemia using STZ. At this stage, what was seen was the weight of the rats and a decrease in the rats' blood sugar levels were observed. Antidiabetic potential was assessed based on a decrease in fasting blood sugar levels and the weight balance of the trial animals.

## Methods

The study used an experimental laboratory design to examine the hypoglycemic effects and changes in body weight (BW) caused by the administration of soy yogurt in hyperglycemic induced trial animals. The research has obtained ethics laic with the number 60/EC-03/FK-06/UNIZAR/VIII/2022 and has been carried out at the Laboratory of Chemistry and Traditional Medicine Polytechnic Medica Farma Husada Mataram in 2022.

The sample used White male rats (*Rattus norvegicus*) were induced with *streptozotocin* (STZ) and *nicotinamide* to induce diabetic conditions. Before induction, the mice were climatized for two weeks. The animals were tested to measure their body weight and blood sugar levels before and after induction. After obtaining hyperglycemic conditions in the trial animals, they were only treated with soy yogurt. The research process starting from the manufacture of yogurt is explained later.



**Figure 1.** Research flow chart

### Starting with Yogurt

One liter of skim milk was pasteurized at 80 °C. The samples were tempered at room temperature up to 42 °C, and a commercial yogurt starter (Biokul) was added to 3 cups of food. The mixture was blended flat and tightly for 12 h at room temperature with sufficient lighting.

### Making of Ubi Jalar Ekstrakt

The Ubi Jalar (*Ipomea batatas*) was cleaned and inserted in the juicer, plus water with a ratio of Ubi Jalar to boiled water of 1:2, filtered with a filthy cloth that was blended and removed.

### Making of Soybeans Extract

Soya beans (*Glycine max*) were distorted and washed first, and then boiled for 30 min twice before and after immersion in a 0,2% NaHCO<sub>3</sub> (*Natrium bicarbonate*) solution for 30 min. The

soya skin that has been boiled is separated by washing it with water several times until it is easy to separate and preserve.

Soya beans separated by their skin are added to hot water (100 °C) in the ratio of soybeans to hot water (1:6) and then subjected to grinding or blending. Soya powder was filtered with a filament cloth that had already been bleached, and the soybeans were left on a small fire for 20 min at a temperature of 80 °C (Mayarni et al., 2020).

### Making of Soy-Yogurt

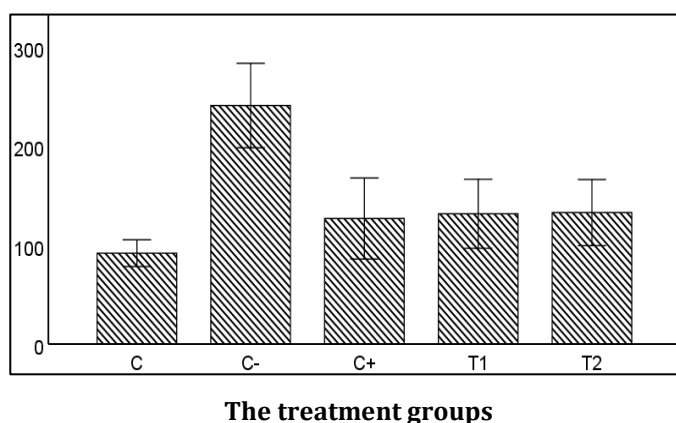
Soy yogurt was made from soybeans and Ubi Jalar beans at a 50%:50% ratio, then 15% powdered skim milk, 2% sugar, inoculated with a 3% starter addition, and mixed with 0,6% Arab gum. Next, the incubation process was closed using polyethylene plastic, and holes were added.

Incubation was performed at 40±2 °C for six hours. Soy yogurt was stored in a refrigerator at 4 °C under anaerobic conditions.

**Testing in Vivo**

Bioassay in-vivo is carried out to know the potential of soy yogurt as an antidiabetic and a decrease in blood sugar levels in diabetes conditions. The mechanism of soya yogurt research was as follows: as many as 50 mice were randomized and placed in a mouse cage at room temperature -20 to 25 °C. Rats will be fed and drunk *ad libitum*. All mice were adjusted for a week before treatment. The long experiment was carried out over 28 days, the rats' weight data were observed and measured every three days, and the rats' blood sugar levels were analyzed weekly. Mice were divided into five groups: control, positive, negative, and treatment groups. Each group consisted of 10 rats.

Mice were diagnosed with diabetes using STZ. The mice were first fed and then intraperitoneally injected with STZ at a prescribed dose of 65 mg/kg BW. Thirty minutes before STZ injection, the mice were intraperitoneally injected with nicotinamide.



**Figure 2.** Chart of blood sugar rate (mg/dL)

Based on the available data, the data analysis method used is two-way variance analysis. The binding variables were FBG and BW. The variant analysis was a two-way variant analysis with the following results. Based on Table 1, it can be seen that there is a significant difference between the treatment group with the rat FBG ratio and the time of measurement of FBG with rats FBG. The analysis can be continued (posttest). This further test determines the group pairs that are significantly different.

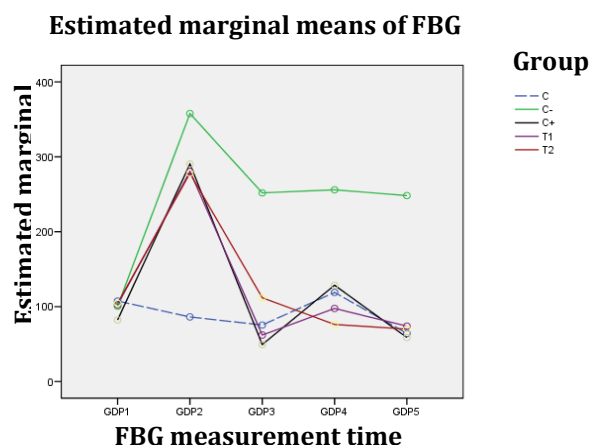
After three days, the mice were treated with soy yogurt by mouth (force-feeding) for 28 days at doses of 3,5 ml/shell and 3,0 ml/ shell.

Five days after the STZ injection, blood was collected from the rats through the tail and measured with a glucometer to ensure that the rats were in a hyperglycemic condition. Before collecting blood from mice, the mice were fasted for 16 h. Mice with fasting blood glucose levels >126 mg/dl were used.

Analysis of the hypoglycemic effects in mice (Azli Mohd Mokhtar Ruzaidi, Maleyki Mhd Jalil Abbe, Ismail Amin, 2008), weight balance, and glucose tolerance (Xie et al., 2017). Descriptive and analytical analysis using ANOVA. The results of the Shapiro-Wilk test and Levene Test at 95% CI, have shown that the data in this study are normally distributed and homogeneous ( $p > 0,05$ ).

**Result and Discussion**

Based on the study's results, the average blood sugar levels of fasting rats in each treatment are presented in Table 2-3 and Figure 2-3.



**Figure 3.** Results of FBG measurements in animals based on time

The two-way ANOVA test (Table 1) obtained FBG results, and a significant time decrease in blood sugar between behaviors to determine the difference in each treatment can be continued using the HSD test.

Based on the results of further trials between the treatment groups, the value of significance ( $p < 0,05$ ). This indicates that there was a significant difference in the blood sugar levels of fasting animals between the groups. However, no significant differences were found

among the control, positive control, and treatment groups. That is, a decrease in blood sugar levels in the positive control group (*glibenclamide*), control (no treatment), and treatment groups was equal.

**Table 1.** Summary of results of the Two-way ANOVA statistical test of fasting blood glucose (FBG)

Group	Mean $\pm$ SD	p-value
C	91,9 $\pm$ 6,654	
C- (mg/dL)	241 $\pm$ 20,926	0,000*
C+	126,9 $\pm$ 20,130	
T1	131,6 $\pm$ 17,125	
T2	132,8 $\pm$ 16,463	

\*Significant difference at 95% CI

Based on the measurement time, it can be seen that a significant change in the FBG rate began to occur at the second measurement (5 days post-induction). It suggests that STZ caused a significant increase in FBG levels in the treatment group. The subsequent measurement of the mice was already given antidiabetic candidates, so the decline in FBG rates had already begun to be visible and quite significant with the measurement of week 3.

In animal trials, the injection of STZ and nicotinamide (NAD) led to the formation of a model of type 2 Diabetes Mellitus in mice. STZ can pass through glucose carrier 2 (GLUT2) to the beta cells of the pancreas, leading to increased production of free radicals that lead to DNA damage, increased xanthine oxidase activity, and inhibition of the cancer cycle (Balakrishnan et al., 2019).

An increase in polymerase (PARP-1) activity (ADP-ribose) may be caused by the mechanism of DNA damage induced by STZ. This mechanism affects the levels of NAD (+) and intracellular ATP in cells, leading to necrosis in pancreatic beta cells. The administration of nicotinamide (NAD) can inhibit PARP-1 activity by preventing the decline in NAD (+) and intracellular ATP (Balakrishnan et al., 2019).

According to a previous study, STZ injection increases fasting blood sugar levels in white rats (Wang et al., 2020) (Saputra et al., 2018). Intravenous STZ injection increased blood glucose levels in white rats (Munjiati, 2021).

Giving soy yogurt can have a positive impact on the digestive tract because soy yogurt can increase the population of probiotic bacteria and reduce the population of pathogenic bacteria. The isoflavone content contained in soybean extract as a raw material for making yogurt can protect and improve serum lipid profiles, prevent Low-Density Lipoprotein (LDL) oxidation, and increase the activity of antioxidant enzymes in the liver. The contents of saponins and soy protein have antioxidant activity; therefore, yogurt consumption can reduce oxidative stress caused by STZ injection (Granato et al., 2010).

The high isoflavone content found in soybeans has significant benefits in decreasing blood glucose in this study, with isoflavone being able to modify cellular pathways. Isoflavone can increase antioxidants in the body by activating NRF2, which disrupts the transcription factor of endogenous antioxidants within the body that can contribute to suppressing free radicals formed under hyperglycemic conditions (Amanda et al., 2021; Kuryłowicz, 2021).

The antidiabetic effects of isoflavones produced by cell protection have been confirmed in several animal models of diabetes. In the treatment with T1 (3 mL) and T2 (3,5 mL), which represent the typical daily intake of a soy-rich diet in humans, genistein, which breaks down the derivatives of the isoflavone compound, was able to protect cells and maintain insulin production in mice and cats injected with STZ. This effect was due to the ability of genistein to proliferate and reduce apoptosis in pancreatic cells. The isoflavone compounds indirectly protect cells and stimulate insulin production (Verma et al., 2019) (Verma, Samanta, & Krishna, 2019).

Based on previous studies (Raharjo et al., 2022), the fermentation process of soymilk in yogurt products can increase the amino acid content, which can subsequently affect the decrease in blood sugar levels of the test animals. However, when viewed from the variable lipid profile that was subsequently related to BW, soy fermentation products did not have a significant impact (Astuti et al., 2020).

Furthermore, the results of the research on the BW variable, the ANOVA test was carried out

not using two-way analysis, but one-way with the following findings:

**Table 2.** Oneway Anova of BW result

Group	Mean $\pm$ SD	p-value
C	188 $\pm$ 9,591	
C-	139 $\pm$ 22,636	0,309*
C+ (mg/dL)	154 $\pm$ 26,596	
T1	142 $\pm$ 18,456	
T2	185 $\pm$ 23,979	

\*Not Significant at 95% CI

The findings (Table 2) showed no effect of yogurt administration on the BW of the mice ( $p=0,309$ ). Therefore, the five comparison groups did not affect the BW of rats. In some of the treatments given (of the five groups), the BW of mice was relatively the same or not significantly different. However, further testing is not possible.

During the research and treatment process, white rats were fed the AIN-93 standard to ensure no bias in FBG levels as a result of feeding, and to maintain the stability of the rats' weight. It is well known that weight tends to decrease in diabetic mice. This was also observed in the negative control group, which had the lowest BW compared to the other groups. This differs from previous research (Rias & Sutikno, 2017). There was a significant relationship between FBG levels and BW. In this case, the weights of diabetic rats were significantly different from those of non-diabetic rats. This is supported by related explanations of the effects of soy fermentation products on the lipid profile and body mass of trial animals (Astuti et al., 2020). However, it is necessary to determine the level of immunity and stress in experimental animals at this stage.

A limitation of this study was that no measurements were made to measure the stress levels of the experimental animals. This study did not measure the stress level of the experimental animals because of the lack of facilities to carry out these tests. In several studies, the intended measurements were not performed.

## Conclusion

Giving soy yogurt can significantly reduce the FBG levels of the trial animals, but not their BW.

Recommendations and further research should be carried out by modifying the dosage of soy yogurt. The results of this study make it

possible to socialize preventive, promotional, and rehabilitative efforts in patients with DM as an antidiabetic alternative.

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