OSHADA JOURNAL
Oshada; Jurnal Kesehatan
https://nawalaeducation.com/index.php/O/index
Volume 1 Nomor 4, Oktober 2024
e-ISSN : 3047-017X
DOI : https://doi.org/10.62872/gbna7b66

Effectiveness Of West Sumatran *Dadiah* On Reducing Hyperglycaemia And Lipid Profile In Diabetic Rats

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ABSTRACT
The high incidence of DM (Diabetes Mellitus) has made diabetes a global health problem that is often associated with other health problems and high treatment costs. For this reason, complementary therapies such as *Dadiah* are needed. *Dadiah* is fermented buffalo milk from West Sumatra. This study aims to determine the effectiveness of *Dadiah* on reducing hyperglycaemia and lipid profile of diabetic model rats. The experimental study used 25 rats divided into five groups. Group 1 was negative control, group 2 was positive control, group 3 was DM rats with *Dadiah* intervention at a dose of 3g/300gBB, group 4 was DM with metformin 13.5mg/kgBB, and group 5 was DM with a combination of *Dadiah* and Metformin. After STZ induction, each group was given the intervention for six weeks, and the blood sugar and cholesterol levels were observed. The average decrease in blood sugar levels and cholesterol levels close to the negative control group was obtained in the *Dadiah* and metformin combination treatment group (P3) with an average blood sugar level of 124.2 mg/dL, total cholesterol level of 78.4 mg/dL, HDL level of 28.2 mg/dL, LDL level of 27.8 mg/dL and triglycerides 113.6 mg/dL. The administration of *Dadiah* and the combination of *Dadiah* with Metformin proved to have the highest effectiveness in alleviating hyperglycaemia and hypercholesterolemia in diabetes mellitus model rats.
Keywords: : Diabetes Mellitus, *Dadiah*, Hyperglycaemia, Probiotic, Lipid Profile

INTRODUCTION
Diabetes mellitus (DM) is a metabolic disorder whose main finding is chronic hyperglycaemia caused by impaired insulin secretion, insulin action, or both (Petersmann *et al*., 2019). The International Diabetes Federation (IDF) in 2019 announced that 463 million adults aged 20-79 worldwide live with diabetes. Indonesia ranks 7th in the world with 10.7 million people with diabetes, and it is estimated that by 2045, this case will increase to 16.9 million people. The number of deaths from diabetes in the world is estimated at 4.2 million people (Atlas IDFD, 2019). According to RISKESDAS (Kemenkes RI) data in 2018, the prevalence of Diabetes Mellitus in Indonesia based on doctor's diagnosis in the

population aged ≥15 years increased from 1.5% in 2013 to 2.0% in 2018. The prevalence of DM in West Sumatra is 1.6%, with 13,834 cases. The high incidence rate causes diabetes to become a global health problem.

Patients with DM will experience insulin deficiency or resistance, which disrupts protein and fat metabolism, resulting in weight loss. If the body cannot get enough energy from sugar, the body will process fat and protein into energy. Using fat and protein can cause an increase in the amount of cholesterol formed in the chain of fat and protein metabolism (Rias & Sutikno, 2017). Insulin resistance in patients with DM affects metabolism in the body, including changes in the production and disposal of plasma lipoproteins. The decreased effect of insulin on fat tissue causes reduced lipogenesis and increased lipolysis. This triggers glucotoxicity accompanied by lipotoxicity, increasing LDL (Low Density Lipoprotein) cholesterol levels (Noviyanti *et al*., 2011).

Hyperglycaemia can also cause oxidative stress, which is caused by reduced antioxidant defence activity, increased free radical production, or both (Prawitasari, 2019). Diabetes mellitus is characterized by chronic inflammation and low-grade inflammation. Levels of pro-inflammatory cytokines such as Tumour Necrosis Factor-α (TNF-α), Interleukin-6 (IL-6), and others are known to increase in DM. This condition is known as reactive oxygen species (ROS) (Mirza *et al*., 2012).

Hyperglycaemia stimulates the overproduction of superoxide in the mitochondria and the overproduction of nitric oxide (NO) in the cell, both of which can induce inducible nitric oxide synthase (iNOS) and endothelial nitric oxide synthase (eNOS). Oxidative stress and inflammatory markers are also the triggering mechanisms of insulin resistance (Prawitasari, 2019).

There are many drugs for diabetes mellitus, one of which is Metformin. Metformin is the first-line pharmacological treatment for type 2 diabetes and the most commonly prescribed drug, whether or not used in combination with insulin in blood glucose-lowering therapy. Metformin has positive effects because it can reduce glucose production in the liver. In addition, Metformin can also affect blood lipid profile levels by reducing total cholesterol and serum triglyceride levels. However, Metformin often causes adverse drug reactions due to side effects of gastrointestinal diseases (such as diarrhoea, nausea, vomiting and flatulence) (Putri *et al*., 2021).

Probiotics, according to the International Life Sciences Institute (ILSI), the Word Health Organisation (WHO), and the International Scientific Association of Probiotics and Prebiotics (ISAPP), are defined as live microorganisms which, when administered in sufficient quantities, provide health benefits to the host. Based on research conducted by Mahajan *et al*. (2019), the effect of probiotic *L. fermentum* on the progression of type 2 diabetes showed that *L. fermentum* provides antidiabetic, antioxidant and anti-inflammatory effects in type 2 diabetic rats. Probiotics also have an effect as anti-cholesterolemia. Another study also mentioned that probiotics can reduce blood cholesterol levels in experimental animals (Melia *et al*., 2023). The application of *L. fermentum* MJM60397 is also known to reduce cholesterol in experimental animals so that these isolates can be

developed into potential probiotics to reduce serum cholesterol levels (Palaniyandi *et al*., 2020).

Some *Lactobacillus* (*L. plantarum, L. fermentum, L. acidophilus*) reduce pro-inflammatory cytokines TNF-α, IL-1β, and IL-8 in the hepar of type 2 DM rats (Putra *et al*., 2022). Most *Lactobacillus* are also known to increase the antioxidant enzymes superoxide dismutase (SOD), glutathione (GSH), glutathione peroxidase (GSHPx), and catalase (CAT) in the heart of type 2 DM rats. Thus, a decrease in free radicals in the liver was observed, along with a decrease in ROS and oxidative stress marker Malondialdehyde (Setyaningsih *et al*., 2017).

Dadiah is a traditional food made from buffalo milk that is spontaneously fermented in bamboo tube containers. Each *Dadiah* product has different types of LAB depending on the producer's region. The inner bamboo wall disperses LAB, which will help in Dadiah's fermentation process. Therefore, the type of bamboo determines the quality of *Dadiah*. LAB, especially *L. fermentum* isolates from *Dadiah*, have potential as probiotic candidates isolated from *Dadiah* have potential as natural probiotics, nonpathogenic (Amelia *et al*., 2021), and have antibacterial activity (Amelila *et al*., 2020). Diabetes cases that increase from year to year will indirectly increase metformin consumption. For this reason, it is essential to discuss the role of probiotics as the primary or supporting therapy in diabetes and their effect on cholesterol levels and body weight of people with DM, one of which comes from fermented milk. Based on the problems and references from the research above, this study aims to prove that *Dadiah* effectively reduces hyperglycaemia and lipid profiles in diabetic model rats.

METHOD

This animal study was conducted at the Laboratory of Animal Experiments, Faculty of Pharmacy, Andalas University. It uses male white rats, such as Rattus norvegicus Wistar strain, with as many as 25 heads. This study will use experimental animal research with a pre-test and post-test control group design.

The study used five treatment groups in male white rats, Rattus norvegicus Wistar strain, including:

Group 1: Negative control (K-), normal rats without treatment

Group 2: Positive control (K+) Rats induced streptozotocin (STZ) without treatment

Group 3: Treatment 1 (P1), Rats induced streptozotocin (STZ) and given *Dadiah*

Group 4: Treatment 2 (P2), Rats induced streptozotocin (STZ) and given Metformin

Group 5: Treatment 3 (P3), Rats induced by streptozotocin (STZ) were given *Dadiah* and Metformin.

a. Animal Induction

Streptozotocin was dissolved in 0.01M citrate buffer, pH 4.5, and always prepared fresh for use within 10-15 minutes. STZ induction was given intraperitoneally (IP), and the dose was determined based on the rats' body weight. The dose of STZ given was 45 mg/kg BW.

b. Observations on Experimental Animals

Observations were made after six weeks of maintenance, and they included rat blood sugar levels, cholesterol levels, HDL, LDL, and triglycerides based on the method of Dharmayanti *et al*. (2018).

c. Statistical analysis

The data analysis used a normality test and SPSS to compare these between groups using paired and independent T-tests.

RESULTS AND DISCUSSION

RESULT

Blood sugar levels of experimental animals

Table 1. Mean data of blood sugar levels of rats before and after treatment

Group	Blood Sugar ± SD		P
	Before Treatment	After Treatment	
Kontrol positif	152,2 ± 19,48	152 ± 21,21	0.854
Kontrol negatif	83,6 ± 13,92	83 ± 14,26	0.675
P1	152,6 ± 17,61	130,2 ± 11,27	0.002*
P2	153 ± 13,41	124,2 ± 7,39	0.002*
P3	157 ± 21,22	125,6 ± 12,36	0.002*

Source: Data Processing

*paired T-test analysis results in $P^1 < 0.005$; there is a significant difference before and after treatment.

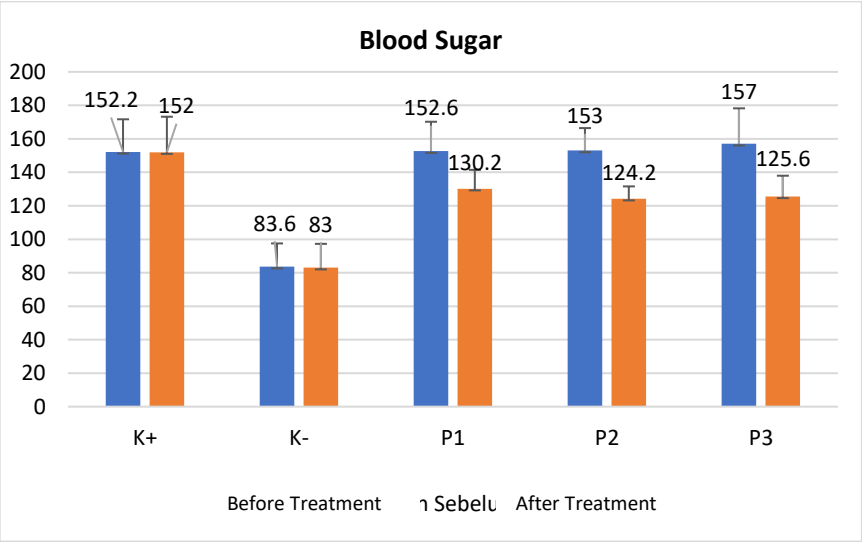

Figure 1. Graph of average blood sugar levels of rats before and after treatment
Source: Data Processing

Based on Table 1, it was found that each group that was treated experienced a decrease in blood sugar levels. The decrease in blood sugar levels of each treatment group has different results. Based on the results of SPSS analysis using paired T-test, the value of P<0.005 was obtained in each treatment. This states that there is a significant difference. The largest decrease in blood sugar levels

was found in the group (P3), with an average decrease of 31.4 mg/dL. An independent T-test was conducted to test the difference between the treatment and control groups. Each treatment group was obtained against the positive control group, with a P value of <0.005. According to these results, there is no significant difference.

Based on the study's results, it was found that rats with a body weight of 300 g without STZ induction had sugar levels of 70-98 mg/dL. After STZ induction, rats' blood sugar and cholesterol levels increased with sugar levels in the range of 136-185 mg/dL. The administration of streptozotocin gives the effect of diabetes in rats. Streptozotocin affects the sensitivity of receptors to insulin or insulin secretion, causing insulin to be not optimal in transporting blood glucose levels (Goyal *et al*., 2016).

The results showed that diabetic rats, after being treated with *Dadiah*, experienced a decrease in blood sugar levels with an average of 130.2 mg/dL due to the content of Lactic Acid Bacteria (LAB) contained in *Dadiah*. LAB isolated from *Dadiah* has the potential as a natural probiotic, nonpathogenic, viable in media with low pH and highly concentrated bile salts and has antibacterial activity. Based on the results of molecular analysis and bioinformatics from one of the studies conducted by Amelia *et al*. (2021) showed that LAB in *Dadiah* is *L. fermentum*, which has antioxidant properties and health benefits as well as additional therapy to overcome the side effects of antibiotics in the gastrointestinal tract.

Oral administration of *Dadiah* has been shown to increase sirtuin-1 (SIRT-1) production and reduce TNF-α expression, a marker of oxidative stress and inflammatory processes. *Dadiah* contains probiotics and antioxidants that can reduce oxidative stress due to chronic hyperglycaemia in diabetes mellitus. The antioxidants prevent the formation of excess reactive oxygen species (ROS) that trigger oxidative stress and cell damage (Amelia *et al*., 2023). *Dadiah* also contains bioactive peptides that can stimulate the production of endogenous antioxidants to suppress the activation of the nuclear factor kappa B (NF-kB) pathway that triggers oxidative stress and inflammation. Administration of *Dadiah* has been shown to reduce macrophage activation in producing pro-inflammatory cytokines such as TNF-α. This decrease in TNF-α will reduce systemic inflammation that plays a role in kidney damage in diabetic nephropathy. The content of *Lactobacillus fermentum* in *Dadiah* is thought to suppress inflammation by inhibiting the NF-kB pathway and the production of pro-inflammatory cytokines. *L. fermentum* is reported to have anti-inflammatory properties (Amelia *et al*., 2023). *Lactobacillus* can inhibit the translocation of LPS from intestinal to systemic. In addition, some studies report that *Lactobacillus* inhibits the infiltration and activation of macrophages into adipose tissue. Decreasing LPS in the body can reduce the systemic inflammatory response and oxidative stress associated with insulin resistance in the pathogenesis of DM (Wen *et al*., 2022).

In addition, the decrease in blood sugar levels can also be seen in P2, where the administration of Metformin can also reduce blood sugar in experimental animals. This is because Metformin is the first choice for oral antidiabetic drugs.

Metformin is a biguanid class oral antihyperglycaemia (Putri *et al*., 2021). Its primary mechanism of action is to lower glucose levels, which causes a decrease in liver gluconeogenesis and increases the sensitivity of muscle and adipose tissue to insulin. Metformin improves glycaemic control through several mechanisms: inhibiting hepatic gluconeogenesis, reducing glucose absorption from the gut and increasing glucose absorption by tissues. One of the functions of Metformin is through non-competitive inhibition of the mitochondrial enzyme glycerophosphate dehydrogenase. Inhibition of this enzyme reduces hepatic gluconeogenesis by reducing the conversion of lactate and glycerol to glucose (Baker *et al*., 2021).

Research shows that the combination of probiotics and Metformin is more effective in reducing HbA1c and fasting blood glucose than Metformin alone in patients with type 2 diabetes. The mechanism is thought to be that probiotics either directly modulate the gut microbiota or indirectly increase tolerance to Metformin, maximizing the treatment effect (Sahin *et al*., 2022).

Cholesterol Levels of Experimental Animals

Table 2. Total cholesterol level data

Group	Cholesterol level ± SD		P
	Before Treatment	After Treatment	
Control positive	91,6 ± 7,50	89,8 ± 7,56	0.009
Control negative	72 ± 9,51	71,2 ± 8,34	0.684
P1	93,6 ± 7,40	85 ± 3,16	0.023
P2	89,6 ± 3,84	80,6 ± 3,84	0.009
P3	89 ± 2,44	78,4 ± 2,40	0.001*

Source: Data Processing

* The result of paired T-test analysis $P^1 < 0.005$, there is a significant difference before and after treatment

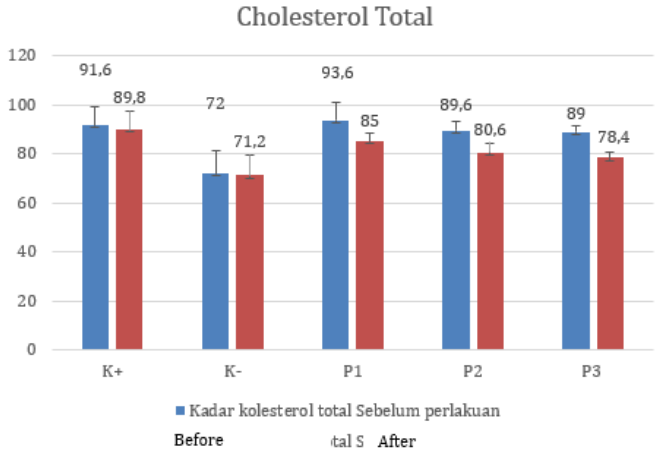

Figure 2. Graph of average blood sugar levels of rats before and after treatment

Source: Data Processing

Table 3. Average data of HDL, LDL and Triglyceride levels

Group	HDL	LDL	Triglyceride
Kontrol positive	15 ± 2,54	48,2 ± 3,42	144,2 ± 31,91
Kontrol negative	39 ± 4,12	16 ± 3,08	105,4 ± 21,61
P1	23,2 ± 4,81	36,4 ± 2,70	118,8 ± 15,05
P2	26,8 ± 2,38	29,6 ± 3,04	121,6 ± 12,68
P3	28,2 ± 3,03	27,8 ± 2,77	113,6 ± 6,18

Source: Data Processing

The table above shows that the HDL, LDL, and triglyceride levels of all groups are still in the normal range; the data is presented as mean ± SD. Value HDL is normal : 35-66 mg/dL; Normal LDL : 20-97 mg/dL; Normal triglycerides: 47-147 md/dL. Based on Table 3, the results of lipid profile in the form of average values of HDL LDL Triglycerides from control rats and rats treated with *Dadiah* (P1), metformin treatment (P2) and combined treatment of Metformin and *Dadiah* (P3).

Based on Table 2, it was found that each treated group experienced a decrease in total cholesterol levels. The decrease in total cholesterol levels from each treatment group has different results. Based on the results of SPSS analysis using paired T-test, the value of P>0.005 was obtained in treatments 1 and 2. This states that there is no significant difference. However, in treatment 3, the value of P>0.005 was obtained, stating that there was a significant difference. The largest decrease in total cholesterol levels was found in the group (P3), with an average decrease of 10.6 mg/dL. An independent T-test was conducted to test the difference between the treatment and control groups. Each treatment group was obtained against the positive control group, with a P value of <0.005. According to these results, there is no significant difference.

Another study found that curd supplementation containing probiotic L. fermentum reduced total cholesterol levels in hypercholesterolemic rats.18 Oxidative stress and inflammation play a role in the pathogenesis of hyperglycaemia and hypercholesterolemia. *Dadiah* also contains peptides that can stimulate endogenous antioxidants to inhibit NF-kB production. NF-kB is a pro-inflammatory transcription factor whose pathway activation will trigger hyperglycaemia and hypercholesterolemia (Amelia *et al*., 2023). Research shows that *Dadiah* can reduce macrophage activation in producing pro-inflammatory cytokines. This leads to decreased systemic inflammation, contributing to the pathogenesis of hyperglycaemia and hypercholesterolemia. The probiotic content in *Dadiah*, especially *Lactobacillus fermentum*, is also thought to play a role in lowering cholesterol levels by inhibiting cholesterol absorption in the intestine and reducing cholesterol production by the liver through its interaction with bile acids (Amelia *et al*., 2023).

Based on previous research, probiotic curd was generally able to reduce total cholesterol levels significantly in all treatment groups. Lactic acid bacteria are known to increase the secretion of the BSH enzyme. This will result in the

deconjugation of bile salts. BSH enzymes that produce deconjugated bile salts are present in the form of free cholic acid, which is poorly absorbed by the small intestine, resulting in reduced cholesterol absorption. Bile salts that return to the liver during enterohepatic circulation are reduced as a result, the synthesis of bile salts from serum cholesterol will increase so that the total cholesterol in the body is reduced (Evasha *et al*., 2022).

This study also states that cholesterol reduction occurs due to compounds produced, such as short-chain fatty acids from the fermentation process of probiotic curd products or due to probiotic activity in the digestive tract. Compounds that will compete with HMG-CoA bind to the enzyme HMG-CoA reductase, inhibiting cholesterol synthesis. Propionate is one of the fermented short-chain fatty acids that influences cholesterol levels. Propionate can inhibit the incorporation of acetate into plasma triacylglycerol and tends to inhibit the incorporation of acetate into plasma cholesterol. This decreases cholesterol synthesis because acetate is a precursor in cholesterol formation (Evasha *et al*., 2022).

Probiotics such as *Lactobacillus* can increase antioxidant activities in the body, such as superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase. Probiotics can also reduce free radical production. Metformin is reported to increase SOD and GPx activity and reduce malondialdehyde (MDA) levels, which is a marker of oxidative stress. Thus, combining probiotics and Metformin has an additive or synergistic effect in enhancing the body's overall antioxidant capacity. This helps protect cells from free radical-induced oxidative damage (Paquette et al., 2023).

Conclusion

Dadiah has been shown to significantly reduce blood sugar levels based on the comparison between pre-test and post-test, but there is no significant difference between blood sugar levels after *Dadiah* administration compared to the positive control. *Dadiah* can also reduce total cholesterol levels, although there is no significant difference between cholesterol levels before and after treatment and also compared to the positive control. For further research, further observations need to be made by adding the time of the *Dadiah* administration.

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