ORIGINAL ARTICLE

# Nutritional Composition of Fermented Buffalo Milk and its Effect on Blood Pressure in Diabetic Rattus Novergicus Models

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## ABSTRACT

**Introduction:** This study investigated the nutritional composition and cardiovascular health benefits of fermented buffalo milk (Dadiah), focusing on its effects on blood pressure, blood glucose, cholesterol, and the expression of ACE2 and COX-2 in experimental animals. ACE2 plays a key role in regulating blood pressure and cardiovascular health, while COX-2 is associated with inflammation and blood vessel function. **Methods:** The experimental study employed a complete randomized design (CRD) involving white Wistar rats divided into four groups: Negative Control, Positive Control, Fermented Buffalo Milk, and Ramipril treatment, with treatments lasting 8 weeks. Blood pressure was measured non-invasively, glucose and cholesterol biochemically, and ACE2 and COX-2 expressions via immunohistochemistry. Statistical analysis was performed using one-way ANOVA. **Results:** Fermented buffalo milk from Limapuluh Kota Regency was found to contain 78.33% moisture, 7.97% protein, 6.53% fat, and a total LAB count of $67 \times 10^9$ CFU/g. Compared to the Positive Control group, the milk significantly reduced blood pressure, blood glucose, and cholesterol. Both the milk and Ramipril groups suppressed ACE2 expression, with the milk showing effects comparable to Ramipril. COX-2 expression was also significantly lower in these groups. **Conclusion:** The findings suggest fermented buffalo milk may serve as an alternative to Ramipril for controlling hypertension, while also benefiting blood glucose and cholesterol regulation through ACE2 and COX-2 pathway modulation. Further clinical studies are recommended to confirm these results in humans.
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**Keywords:** Buffalo milk, Dadiah, Lactic acid bacteria, Blood pressure, Nutrition

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## INTRODUCTION

One way to process buffalo milk and increase its shelf life is to process it into dadiah. Dadiah is a traditional food of the people of West Sumatra made from buffalo milk with natural lactic acid-producing microbes organically fermented in bamboo tubes. Dadiah is a processed buffalo, cow or goat milk product that is a local wisdom from West Sumatra and has potential as a functional food (1). Dadiah also has many health benefits, including increased immunity, because it contains antioxidants with high nutritional value and the presence of lactic acid bacteria, so it can be considered a functional food (2).

Several experimental and anecdotal reports have suggested that curd may have beneficial health effects (3). Several probiotic strains have been identified from curd, which may add to its health characteristics. However, the mechanism of action underlying the health benefits of curd remains unclear. Clinical studies suggest that probiotics can lead to moderate to significant reductions in blood pressure (4). Dairy products such as cheeses, yogurts, and milk proteins, especially casein, have been employed as raw materials for producing and isolating small molecular peptides with various uses. Milk-borne bioactive peptides have a variety of health benefits, including antipyretic, anti-carcinogenic, anti-microbial, anti-hypertensive, immunomodulatory, antioxidant, appetite regulator, and energy-burning properties (5).

Previous studies have identified species of lactic acid bacteria in dadiah, including Lactobacillus plantarum 2DA isolated from dadiah Payakumbuh (6). One of the secondary metabolites of *L. plantarum* can produce Plantaricin D. Plantaricin D has similarities with 1516 drug compounds that have been circulating and approved by the FDA, showing that Plantaricin D has a fingerprint similar to Captopril, which is an ACE Blocker drug for the treatment of Blood Pressure (7). Compounds that can be ACE inhibitors are commonly referred to as

ACE inhibitors. The mechanism of ACE inhibition by compounds that work as ACE inhibitors (8).

In some studies, high-protein foods, beverages, and food sources are fermented and processed using enzymes that are efficacious as ACE-Inhibitors and anti-hypertensives, such as fermentedsoya beans, hydrolysates of various types of meat (9), hydrolytic fish protein (10;11) , buffalo milk protein hydrolysate (12), cow and goat milk protein hydrolysate (13), fermented milk (14;15) and marine organisms (16).

The indicated probiotics are potentially harmful over an intervention period of more than eight weeks among people with higher probiotic doses (≥ 1011 CFU) and higher blood pressure values (≥ 130/85 mmHg), having a more significant blood pressure-lowering effect (17). Safer hypertension prevention measures can be taken by consuming dadiah. Research by Begunova et al. (18) conducted various abilities of lactic acid bacteria to develop antioxidant and ACE-inhibiting properties during milk fermentation. The level of milk proteolysis was associated with the development of antioxidant activity in all lactic acid bacteria studied. In contrast, Lactobacillus was the bacterium that showed the most significant level of proteolytic and antioxidant activity. This is the author's background in researching the benefits and impact of giving dadiah to hypertensive-diabetic type 2 model animals on blood pressure.

## MATERIALS AND METHODS

This research was conducted at the Experimental Animal House and laboratory of the Faculty of Pharmacy, Andalas University. Fermented buffalo milk (BMF) used in this study was taken from Limapuluh Kota Regency, West Sumatra Province, Indonesia.

### Experimental Animal Preparation

The benefits of fermented buffalo milk (dadiah) were tested in vivo using 30 male Sprague Dawley rats, divided into four groups and maintained for eight weeks. The treatment groups received dadiah from Limapuluh Kota Regency or Ramipril. Type 2 diabetes was induced in the rats using streptozotocin (STZ). The rats, aged two months and weighing 250-300g, were fasted for 12 hours before receiving an STZ dose of 30 mg/kg BW. Blood glucose levels were measured on days 0 and 3 after induction to assess diabetes. Daily observations were made, and the animals were fed and housed under controlled conditions.

### Total Blood Glucose

At the start of the experiment, blood glucose degrees were measured using a glucometer to reduce the end of the rat's tail by 1 mm with scissors, then touching the rat's blood glucometer stick and recording the numbers that appeared. The glucometer displays normal diabetes conditions at 50–135 mg/dl. (21). Checking Blood glucose levels: Blood glucose levels are checked using the enzymatic method, using the Gluko-Dr® device, which reacts specifically with glucose in the blood. Glucose molecules are oxidized by the enzyme Glucose Oxidase (GOD) to produce electrons captured by the electrodes so that glucose levels are directly proportional to the received electronic signal. The blood needed to measure the blood glucose level is 2.5-4.0 µL; the blood is placed on the right side of the test strip, the blood will be absorbed automatically, and the measurement result will be read after eleven seconds on the glucose—test Gauges. Blood glucose levels are measured in mg/ dL units (22).

### Total Cholesterol

Total blood cholesterol was measured using the CHOD PAP Enzymatic Colorimeter Test in mg/dL. Stored blood serum was brought to room temperature then centrifuged for 10 minutes at 4000 rpm. The serum was collected using a micropipette and mixed with 1000 µL of kit reagent (containing cholesterol esterase, oxidase, phenol, 4-amino antipyrine, peroxidase, and buffer). The mixture was vortexed and incubated at 37°C for 5 minutes, and absorbance was measured at 573 nm. Cholesterol levels were assessed before and after the test for the positive control and after the test for the other groups.

### Blood Pressure

In this study, white Wistar rats from PT. Indo Anilab Bogor were housed in plastic cages with sawdust bedding provided with water and Indofeed™ commercial rat feed (10% of body weight daily). Following RSHP IPB's ethical guidelines, blood pressure was measured twice weekly using a non-invasive CODA® device, with rats warmed to 37°C beforehand. Six blood parameters were recorded: systolic and diastolic blood pressure, mean arterial pressure, heart rate, blood volume, and tail blood flow, with each measurement repeated ten times per rat. The room temperature was 26-27°C, cages were cleaned twice weekly, and observations were made on days 7, 14, 21, 28, 35, 42, 49, and 56.

### Analysis Immunohistochemistry Expression ACE2

Tissue samples were prepared on poly-L-Lysine slides, deparaffinized with xylol, and rehydrated with alcohol. After PBS washing (pH 7.2), antigen was retrieved by microwaving in citrate buffer (pH 6.0) at 95°C for 20 minutes. The tissue was blocked with 3% H2O2 for 30 minutes, then incubated with a primary antibody (bs1004R) for 18 hours at 4°C. Histofine® Simple StainTM MAX PO was applied for 1 hour, followed by DAB staining and counterstaining with Meyer's hematoxylin. The tissue was dehydrated, cleared with xylol, and mounted. Positive cells were brown with bluish nuclei, and ImageJ was used to analyze the proportion of positive cells.

### Analysis Immunohistochemistry COX-2
Tissue preparations were made on poly-L-Lysine-coated slides, deparaffinized with xylol, and rehydrated with alcohol. The tissue was washed with PBS (pH 7.2), followed by antigen retrieval in citrate buffer (pH 6.0) at 95°C for 20 minutes. After cooling, the tissue was rinsed with PBS and blocked with 3% H2O2 for 30 minutes. The primary antibody (COX2 polyclonal, Bioss cat: bs-10411R) was applied and incubated for 18 hours at 4°C. After PBS washes, Histofine® Simple StainTM MAX PO was added for 1 hour. DAB substrate was applied, and after 5 minutes, the reaction was stopped with water. The tissue was counterstained with Meyer's hematoxylin, dehydrated with ethanol, cleaned with xylol, and mounted with entellan. Positive cells appeared brown with bluish-purple nuclei. ImageJ was used to count positive and negative cells.

### Statistical Analysis
In interpreting the research results obtained using statistical analysis withOne Way ANOVA will be used to analyze the effect of intervention in the normal group. If a significant difference is found between groups, it is continued with the Duncan test using the SPSS application.

### Ethic Clearance
This study has been reviewed in accordance with the code of ethics regarding the use of experimental animals for research, with permission issued by the Ethics Committee of the Faculty of Medicine, Universitas Baiturrahmah, ethics permit letter number 00034/FK.unbrah.

## RESULTS

The data shown in Table I indicate that the water content values obtained in this study were 78,33%. The protein was found to be 7,97, while the fat analysis was 6.53, and the pH values were 4.2.

After 8 weeks of treatment, the positive control group still had the highest average blood glukose compared to the other groups, so positive control was valid as a comparison. Result univariate analysis, data showed that BMF can reduce blood glucose levels in type 2 diabetes rats in 8 weeks The significancy test was carried out using the one way ANOVA method and the LSD test One way ANOVA test to answer the hypothesis obtained a sig value of 0.000 < 0.05, meaning that all treatments significantly reduced blood sugar levels in 8 weeks (Table II).

**Table I. Composition Nutritional Buffalo Milk Fermented (Dadiah)**

| Analysis | Average |
|---|---|
| Water Content | 78,33 |
| Protein | 7,97 |
| Fat | 6,53 |
| pH | 4,2 |
| Total LAB | $67x10^9$ CFU/gr |

The LSD test results showed that all treatment groups significantly reduced blood sugar levels compared to the positive control (p = 0.000), confirming the effectiveness of BMF and Ramipril after 8 weeks. Further testing between the groups revealed no significant difference in their ability to lower blood sugar, indicating both treatments had equal effectiveness. However, in univariate analysis, BMF was the most effective at reducing blood glucose levels.

After eight weeks, the highest cholesterol reduction was in the Ramipril group, reaching 82.83, followed by the BMF (dadiah) group at 88.33, both within normal levels. The LSD test showed all treatment groups significantly reduced cholesterol compared to the positive control (p = 0.000). Further testing between groups revealed no significant difference between BMF (dadiah) and Ramipril, indicating both have equal effectiveness in lowering cholesterol (Table II).

The highest reduction in systolic blood pressure was in the Ramipril group, reaching 9 points, while the BMF (dadiah) group showed a decrease of 6.833 points. The LSD test confirmed that both treatments significantly lowered blood pressure compared to the control (p = 0.000) (Table III). Further comparison between the groups showed no significant difference in their effectiveness, indicating that dadiah and Ramipril have equal power to reduce systolic blood pressure. However, in univariate analysis, Ramipril was found to be the most effective at lowering systolic pressure.

In Table III the decrease in diastolic blood pressure was 11.5, corresponding to standard blood pressure. The point of decrease in systolic blood pressure was the BMF (dadiah) group, with a diastolic point of 6.333. So, there was a decrease in diastolic. All treatment groups

**Table II. Total Blood Glucose and Total Cholesterol**

| Groups | Total Blood Glucose | | Total Cholesterol | |
|---|---|---|---|---|
| | First Week | Eight Weeks | First Week | Eight Weeks |
| Control Negative | 91.25 | 98 | 111.25 | 134 |
| Control Positive | 238.75 | 338.08 | 136.5 | 205.5 |
| BMF | 282.5 | 137.83 | 145 | 88.33 |
| Ramipril | 239 | 161 | 144.67 | 82.83 |

*BMF: Buffalo Milk Fermented

**Table III. Analysis Siastole and Diastole Pressure Blood**

| Groups | Siastole | | Diastole | |
|---|---|---|---|---|
| | First Week | Eight Weeks | First Week | Eight Weeks |
| Control Negative | 108.25 | 108.25 | 58.7 | 56.25 |
| Control Positive | 141.67 | 153.75 | 75.46 | 87.5 |
| BMF | 138 | 131.17 | 81.5 | 75.17 |
| Ramipril | 138.17 | 129.17 | 78.17 | 66.67 |

*BMF: Buffalo Milk Fermented

significantly decreased diastolic blood pressure. There was no significant difference between the treatment groups, so the strength is equivalent to lowering diastolic. Combined with univariate and bivariate, Ramipril was the best substance to lower diastolic.

Staining with IHC shows normal coronary artery endothelium, which expresses a certain amount of ACE2. The ACE2 expression in the negative control is standard, as evidenced by regular blood pressure, normal blood sugar, and normal cholesterol. ACE2 expression is still found in the negative control because the rats used are old, as evidenced in HE preparations that found positive foam cells.

The positive control shows the expression of ACE2 in DM rats without treatment. IHC staining shows the expression of ACE2 in endothelial cells, the number of which will be calculated using the percentage method, namely the ratio of the number of endothelial cells that express ACE2 compared to the number of endothelial cells formed.

In the IHC image (Figure 1), the number of endothelial cells formed was very high compared to the positive control group. The IHC still showed ACE2 expression, which was quantitatively calculated by the percentage method.

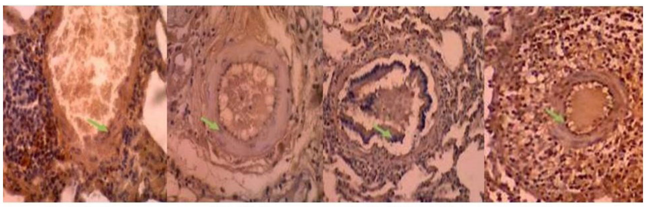


**Figure 1: Analysis Expression ACE2 with IHC**

The results (Figure 2) showed that Ramipril reduced COX-2 expression, leading to a vasodilator effect and lowered blood pressure. In the BMF group, COX-2 expression was similar to that in healthy rats, but Ramipril had lower COX-2 expression than the healthy group due to its role as an ACE inhibitor. This inhibition activates pathways that initially increase, then later decrease, COX-2 expression. Bivariate tests confirmed that both dadiah and Ramipril significantly reduced COX-2 expression in the vascular endothelium. While Ramipril showed the most significant reduction, both treatments were equally effective.

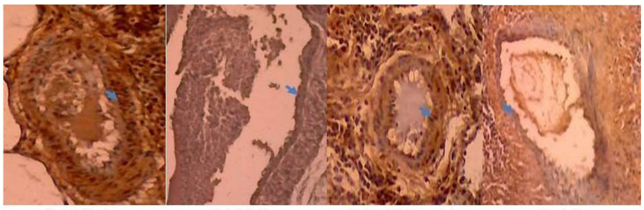


**Figure 2: Analysis Expression COX-2 with IHC**

## DISCUSSION

Dadiah, or fermented buffalo milk (BMF), is a traditional dairy product commonly made in various regions of West Sumatra, including Bukittinggi, Payakumbuh, Agam, Limapuluh Kota, Tanah Datar, Sijunjung, and Solok. Each area produces dadiah with varying nutritional compositions due to the lack of standardized production methods. For example, Alzahra et al. (23) found that dadiah from Lintau Tanah Datar Regency had a water content of 72.43-74.86%, protein levels of 7.58-8.92%, fat content of 5.60-6.18%, and a pH between 5.1-5.4. Another study by Putri et al. (24) reported that dadiah from Kapau Agam Regency had 73.55% water, 7.96% protein, 5.53% fat, and a pH of 5.16. These differences highlight the need for more consistent methods in preparing dadiah to ensure uniform quality and nutritional value across regions.

One key benefit of fermented dadiah (Bufflamo milk) is its high content of lactic acid bacteria (LAB), which act as probiotics. These probiotics can positively affect glucose metabolism and insulin sensitivity by balancing the gut microbiota. Improved gut microbiota leads to enhanced insulin sensitivity, reduced insulin resistance, and better glucose utilization by cells. LAB fermentation also produces short-chain fatty acids (SCFAs) like acetate, propionate, and butyrate, which improve energy metabolism, reduce gut inflammation, and lower blood sugar levels (25). Propionate, in particular, decreases hepatic glucose production, further aiding in blood sugar regulation. Fermented buffalo milk was chosen for its distinctive nutritional composition and significant capacity to generate bioactive peptides. Buffalo milk possesses markedly elevated concentrations of protein, calcium, phosphorus, and conjugated linoleic acid (CLA) in comparison to cow and goat milk, all of which are linked to advantageous impacts on metabolic health, including the regulation of blood pressure (26; 27).

Furthermore, buffalo milk fermentation produces a greater concentration of ACE-inhibitory peptides, crucial for regulating blood pressure by inhibiting the renin-angiotensin system. The thick consistency and elevated solids concentration of buffalo milk facilitates probiotic proliferation, augmenting its efficacy as a functional meal (28; 29). In this study, dadiah reduced blood sugar levels more effectively than Ramipril, indicating its potential as a natural treatment for hyperglycemia.

Regarding cholesterol, probiotics have been shown to significantly lower total cholesterol and LDL levels. A study administering L. casei and Saccharomyces boulardii reduced total serum cholesterol by 19% and LDL cholesterol by 37% over 42 days (30). Similarly, fermented milk containing Pediococcus acidilactici reduced total blood cholesterol within one week of consumption (31). Furthermore, lactic acid bacteria in fermented buffalo milk can bind cholesterol directly to their cell membrane or convert cholesterol to coprostanol through the enzyme cholesterol reductase. Coprostanol is non-absorbable and is expelled via feces, hence aiding in reducing circulating cholesterol (32;33). In this research, the cholesterol-lowering effects of BMF were comparable to those of Ramipril, attributed to the probiotic activity and antioxidant properties of the LAB in the fermented milk.

BMF also demonstrates potential in managing hypertension. Studies have shown that probiotics can lower blood pressure by producing bioactive peptides during fermentation that inhibit angiotensin-converting enzyme (ACE). ACE inhibitors reduce the conversion of angiotensin I to angiotensin II, a key component in raising blood pressure. LABs like L. helveticus and L. rhamnosus produce bioactive peptides with ACE-inhibiting properties during milk fermentation (19). Milk fermented for 24 hours with these strains showed significant ACE inhibition, making it a natural alternative for managing hypertension. The casein proteins in milk contribute to the antihypertensive properties of these bioactive peptides.

The study by Li et al. (34) revealed that ACE-inhibitory peptides could also be generated from milk fermented with a co-culture of LAB and yeast. Other research involving *Lactiplantibacillus plantarum* NK181 and *Lactobacillus delbrueckii* KU200171 found that probiotics in yogurt could enhance antioxidant levels, which further inhibit ACE, offering both antihypertensive and antioxidant benefits (35). Additionally, probiotics may increase ACE2 expression, a critical component in regulating blood pressure. Extracts like Hibiscus sabdariffa, when added to probiotic yogurt, enhance ACE2 activity and reduce blood pressure, offering more substantial antihypertensive effects (36).

The inhibition of ACE activity leads to a decrease in angiotensin II production, which results in the vasodilation of peripheral blood vessels, thereby reducing both systolic and diastolic blood pressure. The fermentation process generates metabolites, including short-chain fatty acids (SCFA), exopolysaccharides, and various antioxidant compounds, which exhibit anti-inflammatory and cardioprotective properties (37).

The analysis revealed increased ACE-2 expression in the tissues of rats treated with fermented buffalo milk. ACE-2 is an enzyme homologous to ACE, functioning oppositely by converting angiotensin II into angiotensin-(1-7), a peptide that exhibits vasodilatory and anti-inflammatory properties. The elevated expression of ACE-2 indicates a transition in the RAAS pathway, favoring vascular protection and hemodynamic enhancement, thereby enhancing the antihypertensive effect (38;39).

Moreover, the BMF (dadiah) effect on COX-2 expression adds to its potential health benefits. COX-2 produces prostaglandins, compounds that promote inflammation and elevate blood pressure. Probiotics help suppress COX-2 expression by balancing cytokines, reducing pro-inflammatory ones like IL-12 while increasing anti-inflammatory cytokines like IL-10 (40). This shift reduces inflammation and lowers blood pressure, making probiotics beneficial for cardiovascular health.

In addition to probiotics, BMF (dadiah) contains bioactive compounds such as peptides and antioxidants, which are vital in reducing oxidative stress and inflammation. Oxidative stress damages the vascular endothelium, leading to vasoconstriction and increased blood pressure (41). The antioxidants in dadiah protect endothelial cells, improve blood vessel function, and prevent vascular constriction. This protection against oxidative stress contributes to the overall cardiovascular benefits of dadiah, especially in managing hypertension.

Clinical studies involving fermented buffalo milk in human subjects are limited, with most research still conducted in vitro or using animal models. This emphasizes the novelty and significance of our preclinical approach utilizing diabetic Rattus norvegicus as a validated model to investigate its therapeutic potential.

Recent reviews emphasize the necessity for additional translational studies on non-bovine dairy products, given their potential functional properties (42; 43). Consequently, this study addresses a significant scientific gap and may provide a foundation for subsequent clinical trials.

The health benefits of BMF (dadiah), particularly in reducing blood sugar, cholesterol, and blood pressure, make it a promising natural alternative for managing metabolic disorders and cardiovascular health. The presence of probiotics, bioactive peptides, and antioxidants in dadiah contributes to these effects, primarily through ACE and COX-2 inhibition, enhanced insulin sensitivity, and improved gut health. However, further studies are needed to confirm its efficacy in humans and standardize its production methods to ensure consistent quality and benefits. The choice of fermented buffalo milk corresponds with the prevailing trend in functional nutrition and individualized nutritional therapy, especially in managing hypertension and metabolic disorders. By elucidating its effects in a diabetic rat model, we seek to furnish evidence-based insights into its antihypertensive potential.

## CONCLUSION

Observations of fermented buffalo milk (dadiah) from Limapuluh Kota Regency showed a water content of 78.33%, 7.97% protein, 6.53% fat, a pH of 4.2, and a total LAB count of $67x10^9$ CFU/gr. Administering dadiah to Wistar rats significantly reduced blood sugar and total cholesterol levels compared to Ramipril ($p<0.0001$). While dadiah lowered blood pressure, its effect on systolic and diastolic pressure was similar to Ramipril. Immunohistochemical analysis showed dadiah promoted cell regeneration, reducing inflammation and COX-2 expression. Thus, dadiah may serve as an antihypertensive and antidiabetic alternative, though more research is needed on its long-term effects and mechanisms in hypertension and cholesterol management.

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