Trop J Nat Prod Res, January 2026; 10(1): 6463 - 6466 **ISSN 2616-0684 (Print)**
ISSN 2616-0692 (Electronic)

Tropical Journal of Natural Product Research

Available online at https://www.tjnpr.org

Original Research Article

The Effect of Dadih Administration on Thromboxane, Prostacyclin, Nitric Oxide, and Endothelin-1 Levels in a Pre-eclampsia Rat Model

Budi Budi[1], Nur Indrawaty Lipoeto[2], Yanwirasti Yanwirasti[3], Donel Suheimi[4]

[1]*Doctoral Program of Biomedical Science, Faculty of Medicine, Universitas Andalas, Padang, West Sumatera, 25163, Indonesia*
[2]*Department of Nutrition, Faculty of Medicine, Universitas Andalas, Padang, West Sumatera, 25163, Indonesia*
[3]*Department of Anatomy, Faculty of Medicine, Universitas Andalas, Padang, West Sumatera, 25163, Indonesia*
[4]*Department of Obstetrics and Gynecology Faculty of Medicine Universitas Riau*

ARTICLE INFO

Article history:
Received 02 May 2025
Revised 22 December 2025
Accepted 13 January 2026
Published online 01 February 2026

ABSTRACT

Pre-eclampsia is a serious pregnancy complication characterized by hypertension, organ dysfunction, and an imbalance between thromboxane A2 (TXA2) and prostacyclin, alongside endothelial dysfunction and reduced nitric oxide (NO) production. TXA2 acts as a vasoconstrictor and pro-aggregatory eicosanoid, whereas prostacyclin functions as a vasodilator and anti-aggregatory molecule. Nitric oxide contributes to vascular relaxation and protects the endothelium. Dadih, a traditional West Sumatran fermented buffalo milk product rich in probiotics, has been shown to affect inflammation and may modulate prostanoid balance. This study aimed to evaluate the effect of Dadih administration on thromboxane, prostacyclin, nitric oxide, and endothelin-1 levels in a preeclamptic rat model. Female Wistar rats were acclimatized, mated, and induced with pre-eclampsia using oral prednisone and 2% NaCl for 14 days. The treatment group received Dadih at a dose of 0.935 g/200 g body weight daily via oral gavage. Biomarker levels were measured using ELISA, and statistical analysis was performed using SPSS version 23.0. Results showed no significant differences in endothelin-1 ($p = 0.195$), thromboxane ($p = 0.362$), prostacyclin ($p = 0.507$), or nitric oxide ($p = 0.895$) levels between groups. These findings suggest that Dadih, at the given dose and duration, does not significantly modulate these biomarkers in Pre-eclampsia.

Keywords: Pre-eclampsia, Endothelin-1, Thromboxane, Prostacyclin, Nitric Oxide

Introduction

Each year, millions of women with no previous history of hypertension develop pre-eclampsia[1,2]. Pre-eclampsia is a pregnancy-specific disorder associated with substantial maternal and perinatal complications[3]. Globally, its incidence ranges from 2–8%, with a wide range across developing countries from 0.51% to 38.4%[4]. In developed nations, maternal mortality from pre-eclampsia can reach 16%, higher than rates in Africa and Asia at around 9%[5]. In Indonesia, pre-eclampsia is the second leading cause of maternal death, after postpartum hemorrhage[6]. Data from major hospitals such as Cipto Mangunkusumo and Hasan Sadikin indicate increasing case numbers annually.

The etiology of pre-eclampsia remains unclear, involving complex interactions between immunological, genetic, epigenetic, biochemical, and environmental factors[7]. Placental dysfunction and endothelial damage are widely recognized as the main pathophysiological mechanisms. The endothelium, a single-cell layer lining blood vessels, regulates vascular tone, coagulation, and inflammatory responses[8]. Disruption of this layer leads to increased vasoconstrictor release, vascular permeability, and inflammatory damage.

Oxidative stress, triggered by an imbalance between free radicals and antioxidants, has also been implicated in endothelial dysfunction and pre-eclampsia[9,10]. Fermented dairy products, such as Dadih (a traditional probiotic-rich buffalo milk fermented in bamboo) are known to possess antioxidant, anti-inflammatory, and endothelial-modulating effects[11,12]. Studies report that Dadih contains Lactobacillus plantarum strains capable of reducing oxidative stress and improving vascular function[13]. It is rich in nutrients including proteins, fats, and organic acids, and is locally available and affordable in West Sumatra[14]. Previous studies have suggested that probiotics may regulate NO and ET-1 levels, reduce inflammation, and improve endothelial health[15,16]. The novelty of this study lies in its investigation of Dadih as a functional fermented food intervention specifically targeting vascular biomarkers (TXA2, PGI2, NO, and ET-1) in a pre-eclampsia rat model. While Dadih is traditionally consumed for gastrointestinal benefits, its role in modulating endothelial biomarkers in hypertensive pregnancy remains underexplored. This study aims to evaluate the effect of Dadih administration on the levels of TXA2, PGI2, NO, and ET-1 in a pre-eclampsia animal model. The use of ELISA (Enzyme-Linked Immunosorbent Assay) to measure these markers and the administration of Dadih in controlled doses are designed to directly assess its biological impact on endothelial function and inflammation.

*Corresponding author. Email: klinikpermataibu4@gmail.com
Tel: *+6281268186387*

Citation: Budi B, Nur IL, Yanwirasti Y, Donel S. The Effect of Dadih Administration on Thromboxane, Prostacyclin, Nitric Oxide, and Endothelin-1 Levels in A Pre-eclampsia Rat Model. Trop J Nat Prod Res. 2026; 10(1): 6463 – 6466 https://doi.org/10.26538/tjnpr/v10i1.4

Official Journal of Natural Product Research Group, Faculty of Pharmacy, University of Benin, Benin City, Nigeria

Materials and Methods

Animal Maintenance

The rats were placed in individual cages with rice husk bedding and monitored daily. The number of rats used followed the Federer formula, resulting in 18 rats in total, aged 3 months and weighing an average of 250-300 g. Animals obtained from the animal house of the biomedical laboratory of Faculty of Medicine, Universitas Andalas. All procedures were approved by the Ethics Committee of the Faculty of Medicine, Universitas Andalas (Ethical Clearance No: 415/UN.16.2/KEP-

FK/2023).
Experimental rats were divided into three groups (n = 6 per group) consisting of negative control (healthy pregnancy), positive control (pre-eclampsia model without treatment) and treatment group (pre-eclampsia + Dadih administration)
Each biomarker measurement was performed in duplicate for each sample to ensure analytical precision.

Pre-eclampsia Animal Model
Pre-eclampsia was induced by oral administration of prednisone (Prednison®, PT Kimia Farma, Indonesia; purity ≥98%, pharmaceutical grade) at a dose of 1.5 mg/kg body weight and 2% NaCl solution for 14 days, following a modified method adapted from previous studies[1]. Mating was conducted using the monomating method.

Elisa Examination
Biomarker levels of thromboxane A2, prostacyclin, nitric oxide, and endothelin-1 were measured using ELISA kits (Elabscience®, Cat. No. E-EL-0165 for TXA2, E-EL-0035 for PGI2, E-EL-0025 for NO, and E-EL-0016 for ET-1; Elabscience Biotechnology Inc., Houston, USA; 96-well format; detection range: 0.1–1000 ng/L; assay sensitivity <0.1 ng/L; 99.2% purity; analytical grade). The optical density was read at 450 nm using a microplate reader (BioTek® ELx800, Agilent Technologies Inc., USA).

Dadih Preparation and Administration
A Dadih solution with a concentration of 1 g/ml was prepared by suspending Dadih in distilled water. An oral probe containing the Dadih solution was inserted through the palate into the esophagus of the rat. Once the probe was in place, the solution was administered slowly until empty. The recommended dosage of Dadih for humans is 104-208 g/70 kg. The conversion factor from 70 kg human body weight to 200 g rat body weight is 0.018 (Laurence, 2008 in Pratama and Probosari, 2012), resulting in a Dadih concentration of 0.935 g/200 g body weight for rats.

Statistical Analysis
Data were analyzed using IBM® SPSS® Statistics software (version 23.0, IBM Corp., Armonk, NY, USA, released in 2015). Data distribution was tested using the Shapiro-Wilk test. One-way ANOVA was applied for normally distributed data, and the Kruskal–Wallis test was used for non-normally distributed data. Significant results were followed by post hoc analysis using Tukey's HSD. Significance was defined at $p < 0.05$.

Results and Discussion

The levels of thromboxane, prostacyclin, nitric oxide, and endothelin-1 were assessed using ELISA, which provided absorbance values that were subsequently converted into concentration values. These measurements allowed for the evaluation of these biomarkers across different experimental groups.
As shown in Table 1, ET-1 levels in the treatment group (Dadih) were elevated (148.87 ± 25.72 ng/L) compared to both the negative control group (130.51 ± 17.30 ng/L) and the positive control pre-eclampsia model group (134.40 ± 21.98 ng/L). However, the increase was not statistically significant (p = 0.195). This suggests that Dadih treatment did not reduce ET-1 levels, which remain elevated during pre-eclampsia. Elevated ET-1 levels are consistent with ongoing endothelial dysfunction.

Table 1: Endothelin-1 Levels in Urine Samples of the Pre-eclampsia Rat Model

Group	ET-1 (ng/L)	P Value
Control	130.51 ± 17.30	
Hypertension Pre-Eclampsia Model	134.40 ± 21.98	0.195
Dadih Treatment	148.87 ± 25.72	

According to Table 2, the TXA2 levels in the Dadih-treated group were 147.32 ± 20.99 ng/L, slightly higher than in the untreated pre-eclampsia group (133.80 ± 22.79 ng/L) and the normal control group (134.98 ± 21.68 ng/L). No significant difference was observed across groups (p = 0.362), indicating that Dadih administration did not significantly modulate thromboxane synthesis or vasoconstrictive activity in this model.

Table 2: Thromboxane Levels in Urine Samples of the Pre-eclampsia Rat Model

Group	Thromboxane (ng/L)	P Value
Control	134.98 ± 21.68	
Hypertension Pre-Eclampsia Model	133.80 ± 22.79	0.362
Dadih Treatment	147.32 ± 20.99	

Table 3 shows that prostacyclin levels decreased slightly in the Dadih group (8.78 ± 8.64 ng/mL) compared to both the control group (9.28 ± 8.14 ng/mL) and the pre-eclampsia model (9.38 ± 8.24 ng/mL). This reduction was not statistically significant (p = 0.507). The reduction in PGI2 levels, although not significant, aligns with the pathological imbalance commonly seen in pre-eclampsia between vasoconstrictors and vasodilators.

Table 3: Prostacyclin Levels in Urine Samples of the Pre-eclampsia Rat Model

Group	Prostacyclin (ng/mL)	P Value
Control	9.28 ± 8.14	
Hypertension Pre-Eclampsia Model	9.38 ± 8.24	0.507
Dadih Treatment	8.78 ± 8.64	

As reported in Table 4, NO levels were lowest in the Dadih group (131.43 ± 209.76 µM), followed by the pre-eclampsia group (259.24 ± 239.06 µM), while the highest concentration was observed in the control group (399.08 ± 545.71 µM). The p-value (0.895) indicates a non-significant difference. The observed decrease in NO level in the treatment group suggests Dadih may not sufficiently restore endothelial NO production under the current dosage and treatment duration.

Table 4: Nitric Oxide Levels in Urine Samples of the Pre-eclampsia Rat Model

Group	NO (µM)	P Value
Control	399.08 ± 545.71	
Hypertension Pre-Eclampsia Model	259.24 ± 239.06	0.895
Dadih Treatment	131.43 ± 209.76	

During pre-eclampsia development, various vasoactive substances are released by the endothelium during inflammation, including nitric oxide (NO), also known as endothelial-derived relaxing factor (EDRF), endothelial-derived hyperpolarizing factor (EDHF), prostacyclin (PGI2), bradykinin, acetylcholine, serotonin, and histamine. Vasoconstrictor substances include endothelin, platelet-activating factor (PAF), angiotensin II, prostaglandin H2, thrombin, and nicotine. Further progression of these responses exacerbates pre-eclampsia, particularly influenced by hypertension[15].
In this study, the administration of Dadih did not significantly alter the levels of ET-1, TXA2, PGI2, or NO. The increase in ET-1 indicating that Dadih, at the given dose and duration, was insufficient to suppress endothelin-1 release. The elevated ET-1 levels are due to endothelial dysfunction that triggers excessive ET-1 release, leading to severe a vasoconstriction, increased blood pressure, and worsening pre-eclampsia. Additionally, ET-1 contributes to endothelial dysfunction, a key feature of pre-eclampsia. Disrupted endothelium fails to produce adequate, which amplifies the vasoconstrictor effects of ET-1. ET-1 is also involved in the inflammatory processes associated with pre-eclampsia, where increased ET-1 leads to endothelial and leukocyte activation, aggravating inflammation and vascular damage, and

increasing the risk of serious complications. Given ET-1's central role in pre-eclampsia pathophysiology, inhibiting the ET-1 pathway has been considered a potential therapeutic approach for managing or preventing pre-eclampsia[16,17,18].

Our results align with the findings of Naruszewicz et al.[20], where probiotics like *Lactobacillus plantarum* were shown to suppress ET-1 in smokers, but only after extended administration. This suggests that 14 days of Dadih intake may be insufficient, and a longer treatment duration might be needed to elicit vascular benefits.

In pre-eclampsia, nitric oxide (NO) production is often disrupted, contributing to vasoconstriction, increased blood pressure, and endothelial dysfunction, all hallmarks of the condition. Studies have shown that women with pre-eclampsia have lower NO levels compared to pregnant women without complications[20]. Research by Shaamash et al.[21]indicated that women with pre-eclampsia had significantly lower plasma NO levels compared to control groups, supporting the hypothesis that NO deficiency plays a role in pre-eclampsia pathogenesis. Furthermore, other studies suggest that supplementation with NO donors or agents that enhance NO production may help reduce blood pressure and improve endothelial function in at-risk pregnant women[21].

Lactic acid bacteria, particularly those found in Dadih such as *Lactobacillus plantarum*, have been reported to mitigate NO hyperactivity. Kang et al.[23] demonstrated the efficacy of *L. plantarum* in reducing NO hyperactivity. However, in our study, NO levels were significantly lower in the Dadih group compared to the pre-eclampsia model and control groups ($p = 0.895$), indicating that the antioxidant or endothelial-protective effects were not adequately activated within the study timeframe.

This finding is contrary to expectations, and may be explained by the possibility that bioactive peptides and metabolites in Dadih require specific gut microbial processing or bioavailability timeframes to activate NO signaling pathways, which did not occur in the short experimental duration. The results also suggest that probiotic effects may not be linear or dose-independent in systemic inflammation contexts such as pre-eclampsia.

Thromboxane, especially in its active form, thromboxane A2 (TXA2), is an eicosanoid critical in coagulation and vasoconstriction processes. In pre-eclampsia, there is an imbalance between thromboxane, which is a vasoconstrictor and pro-aggregatory, and prostacyclin, which is a vasodilator and anti-aggregatory. This imbalance results in increased thromboxane production and decreased prostacyclin, contributing to excessive vasoconstriction, increased blood pressure, and vascular complications. Thromboxane also plays a role in endothelial dysfunction, exacerbating vasoconstriction and reducing the production of vasodilators such as nitric oxide (NO). Additionally, thromboxane enhances platelet aggregation, which can elevate the risk of thrombosis, contributing to serious complications like HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count) and preterm birth. In therapeutic contexts, inhibiting the thromboxane–prostacyclin pathway has been a focus, with low-dose aspirin shown to inhibit thromboxane synthesis without significantly affecting prostacyclin, effectively reducing pre-eclampsia risk in high-risk women[23,24].

Prostacyclin (PGI2) is an eicosanoid produced by endothelial cells that acts as a potent vasodilator and platelet aggregation inhibitor. In normal pregnancy, prostacyclin is crucial for maintaining blood flow to the placenta and preventing thrombus formation, both vital for healthy fetal development. In pre-eclampsia, there is an imbalance between prostacyclin and thromboxane A2 (TXA2), where TXA2 production increases while prostacyclin production decreases. This imbalance contributes to vasoconstriction, elevated blood pressure, and platelet aggregation, characteristic of pre-eclampsia. Reduced prostacyclin production can also lead to endothelial dysfunction, worsening the condition. Studies indicate that lower prostacyclin levels in pregnant women with pre-eclampsia compared to normal pregnancies support the idea that prostacyclin deficiency may play a role in pre-eclampsia pathogenesis. Interventions that increase prostacyclin levels or correct the imbalance between prostacyclin and thromboxane could potentially manage or prevent pre-eclampsia. For instance, low-dose aspirin is often recommended for high-risk women to reduce thromboxane synthesis without significantly affecting prostacyclin[24].

The role of probiotics in thromboxane and prostacyclin modulation is still limited in the literature. However, it is hypothesized that their antioxidant effects may indirectly restore this balance. In our study, however, prostacyclin levels slightly decreased in the Dadih group, suggesting that the intervention did not correct the TXA2–PGI2 ratio. This may be due to insufficient systemic circulation of the active probiotic-derived metabolites within the short observation period. However, considering its probiotic and antioxidant properties, further research is recommended using higher doses, extended treatment duration, and more sensitive vascular or oxidative markers. This study contributes to understanding the limitations and future potential of functional probiotic foods in pregnancy-related vascular disorders.

Conclusion

In summary, our study highlights that while Dadih contains promising bioactive compounds, its short-term administration did not yield statistically significant changes in key biomarkers. The lack of statistical significance (all $p > 0.05$) across ET-1, NO, TXA2, and PGI2 levels indicates that either the dose, frequency, or bioavailability was inadequate under the current experimental design. Nonetheless, this study provides an important baseline for future investigations into functional food-based interventions for vascular dysfunction in pre-eclampsia models.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

References

1. Raghupathy R. Cytokines as key players in the pathophysiology of preeclampsia. Med Princ Pract. 2013;22(Suppl 1):8–19. doi:10.1159/000354200
2. Say L, Chou D, Gemmill A, Tunçalp Ö, Moller AB, Daniels J. Global causes of maternal death: a WHO systematic analysis. Lancet Glob Health. 2014;2(6):e323–333. doi:10.1016/S2214-109X(14)70227-X
3. Cunningham FG. Williams obstetrics. 24th ed. New York: McGraw-Hill Education; 2014.
4. Jeyabalan A. Epidemiology of preeclampsia: impact of obesity. Nutr Rev. 2013;71(Suppl 1):S18–25. doi:10.1111/nure.12055
5. Hutcheon JA, Lisonkova S, Joseph KS. Epidemiology of pre-eclampsia and other hypertensive disorders of pregnancy. Best Pract Res Clin Obstet Gynaecol. 2011;25(4):391–403. doi:10.1016/j.bpobgyn.2011.01.006
6. Ministry of Health of the Republic of Indonesia. National Health Survey 2007. Jakarta: Ministry of Health of the Republic of Indonesia; 2008.
7. Fox R, Kitt J, Leeson P, Aye CYL, Lewandowski AJ. Preeclampsia: risk factors, diagnosis, management, and cardiovascular impact on the offspring. J Clin Med. 2019;8(10):1625. doi:10.3390/jcm8101625
8. Godo S, Shimokawa H. Endothelial functions. Arterioscler Thromb Vasc Biol. 2017;37(9):e1–12. doi:10.1161/atvbaha.117.309813
9. Granger JP, Alexander BT, Llinas MT, Bennett WA, Khalil RA. Pathophysiology of hypertension during preeclampsia linking placental ischemia with endothelial dysfunction. Hypertension. 2001;38(3):718–22. doi:10.1161/01.Hyp.38.3.718
10. Phoswa WN, Khaliq OP. The role of oxidative stress in hypertensive disorders of pregnancy (preeclampsia, gestational hypertension) and metabolic disorders of pregnancy (gestational diabetes mellitus). Oxid Med Cell Longev. 2021;2021:5581570. doi:10.1155/2021/5581570

11. Clare DA, Swaisgood HE. Bioactive milk peptides: a prospectus. J Dairy Sci. 2000;83(6):1187–95. doi:10.3168/jds.S0022-0302(00)74983-6
12. Korhonen H, Pihlanto A. Bioactive peptides: production and functionality. Int Dairy J. 2006;16(9):945–60. doi:10.1016/j.idairyj.2005.10.012
13. Usmiati S, Risfaheri. Development of dadih as a functional probiotic food native to West Sumatra. J Litbang Pertan. 2015;32(1):20–9.
14. Putri MT, Juliyarsi I, Roza E, Purwati E. Proximate analysis of dadih from Kapau, Agam Regency, West Sumatera, Indonesia. IOP Conf Ser Earth Environ Sci. 2021;888:012044. doi:10.1088/1755-1315/888/1/012044
15. Villa PM, Hämäläinen E, Mäki A, Räikkönen K, Pesonen AK, Taipale P, et al. Vasoactive agents for the prediction of early- and late-onset preeclampsia in a high-risk cohort. BMC Pregnancy Childbirth. 2013;13:110. doi:10.1186/1471-2393-13-110
16. Jain A. Endothelin-1: a key pathological factor in pre-eclampsia? Reprod Biomed Online. 2012;25(5):443–9. doi:10.1016/j.rbmo.2012.07.014
17. Saleh L, Verdonk K, Visser W, van den Meiracker AH, Danser AHJ. The emerging role of endothelin-1 in the pathogenesis of pre-eclampsia. Ther Adv Cardiovasc Dis. 2016;10(5):282–93. doi:10.1177/1753944715624853
18. Naruszewicz M, Johansson ML, Zapolska-Downar D, Bukowska H. Effect of Lactobacillus plantarum 299v on cardiovascular disease risk factors in smokers. Am J Clin Nutr. 2002;76(6):1249–55. doi:10.1093/ajcn/76.6.1249
19. Sutton EF, Gemmel M, Powers RW. Nitric oxide signaling in pregnancy and preeclampsia. Nitric Oxide. 2020;95:55–62. doi:10.1016/j.niox.2019.11.006
20. Shaamash AH, Elsonosy ED, Zakhari MM, Radwan SH, El-Dien HM. Placental nitric oxide synthase activity and nitric oxide production in normal pregnancy, pre-eclampsia and eclampsia. Int J Gynaecol Obstet. 2001;72(2):127–33. doi:10.1016/S0020-7292(00)00314-3
21. Kang CH, Han SH, Kim JS, Kim Y, Jeong Y, Park HM, et al. Inhibition of nitric oxide production, oxidative stress prevention, and probiotic activity of lactic acid bacteria isolated from the human vagina and fermented food. Microorganisms. 2019;7(4):109. doi:10.3390/microorganisms7040109
22. Roberge S, Nicolaides K, Demers S, Hyett J, Chaillet N, Bujold E. The role of aspirin dose on the prevention of preeclampsia and fetal growth restriction: systematic review and meta-analysis. Am J Obstet Gynecol. 2017;216(2):110–20.e6. doi:10.1016/j.ajog.2016.09.076
23. Wang Y, Zhang Y, Canzoneri BJ, Gu Y, Philibert L, Lewis DF. Prostacyclin and thromboxane levels in women with severe preeclampsia undergoing magnesium sulfate therapy during antepartum and postpartum periods. Hypertens Pregnancy. 2008;27(1):17–27. doi:10.1080/10641950701825721
24. Goulopoulou S. Maternal vascular physiology in preeclampsia. Hypertension. 2017;70(6):1066–73. doi:10.1161/Hypertensionaha.117.08821