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Original Article

Effect of pomegranate extract (*Punica granatum* L.) on blood pressure and nitric oxide in gestational hypertension

Farah Salsabila [1]✉, Suharyo Hadisaputro [1], Lanny Sunarjo [1]

[1] *Postgraduate Program in Applied Health, Poltekkes Kemenkes Semarang, Central Java, Indonesia*

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CORRESPONDENCE

Phone: +6285609493973

E-mail: farahsalsabila98@gmail.com

A B S T R A C T

Background: As a complication of pregnancy, uncontrolled hypertension will continue to be a complication that harms both mother and baby. Pomegranate peel, which contains high antioxidants, is potentially used as an antihypertensive of adjuvant pharmacological therapy. However, there has been no research on the effect of pomegranate extract in lowering blood pressure, so it is necessary to do related research.

Purpose: Analyze the effect of pomegranate peel extract on blood pressure and nitric oxide levels in gestational hypertension.

Methods: This is a quasi-experiment design pre-post-test with the control group. Through purposive sampling techniques, 32 respondents were divided into two groups. During 14 days, the intervention group received nifedipine 10 mg/day with 500 mg of pomegranate peel extract, while another group was only given nifedipine 10 mg/day.

Results: The blood pressure of the intervention group decreased compared to the control group ($p<0.05$). Meanwhile, the nitric oxide level of the intervention group is increased compared to the control group ($p<0.05$).

Conclusions: Pomegranate peel extract can reduce blood pressure and enhance nitric oxide levels in gestational hypertension.

INTRODUCTION

Hypertensive disorders of pregnancy are one of the leading causes of maternal and perinatal morbidity and mortality globally.[1] The World Health Organization estimates that hypertension complicates up to 14% of the world's maternal mortality rates.[2] The pathophysiology of hypertension in pregnancy is known to be caused by placental dysfunction due to the failure of the vascular remodeling process, which then allows hypoxia and ischemia states to appear in the placenta. This condition will increase the number of free radicals and then trigger oxidative stress, resulting in endothelial dysfunction. This mechanism is a pathogenic constituent that causes gestational hypertension and preeclampsia.[3-6]

Macrominerals such as potassium, magnesium, and vitamin C effectively lower blood pressure by reducing oxidative stress.[7] Supplementation of antioxidants can reduce blood pressure and support the role of free radicals in hypertension.[8] Fruits previously researched to lower blood pressure in pregnancy with hypertension are Ambon banana and Carica papaya. The administration of 200 grams of Ambon bananas, which contain 358 mg of potassium and 3 mg of vitamin C every 100 grams two times a day for a week, can reduce blood pressure up to 10-20 mmHg.[9,10] Carica papaya, which has a potassium content of 257 mg/100 grams, can reduce systolic blood pressure by 9.61 mmHg and diastolic blood pressure by 5 mmHg with a dose of 200 grams.[11] Although previous studies have shown varying blood pressure-lowering effects, they did not highlight the role of antioxidants in Nitric Oxide levels and their effect in lowering blood pressure.

Pomegranate contains potassium (259 mg), magnesium (12 mg), vitamin C (64.6 mg), and total phenolics (56.09 mg GAE/g) and has higher macrominerals. Previous studies have shown that all parts of pomegranate have antioxidant activity with a high total content of phenolics, flavonoids, and flavonols.[12] In hemodialysis patients, a previous

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study showed that 250 mg of pomegranate peel extract is effective in improving oxidative stress and increasing antioxidant capacity.[13]

There have been evidence-based studies examining pomegranate's effect on heart activity and its relation to blood pressure. Still, no studies have developed the antihypertensive potential of pomegranate peel in the form of extracts on blood pressure about aldehydes resulting from oxidative stress in the form of nitric oxide levels in pregnancy with hypertension. This study aims to prove the effectiveness of pomegranate extract in lowering blood pressure through nitric oxide levels in gestational hypertension.

METHOD

Study Design

This is a quasi-experimental study with a pre-post-test control group design.[14]

Setting and Respondents

This research was conducted at 9 Public health centers in Bandar Lampung between February and May 2021. Respondents were pregnant women with gestational hypertension. The number of samples was 32 respondents divided into the treatment group (n=16) and the control group (n=16) randomly according to arrival.[15] The included sample criteria are gestational age >20 weeks, systolic blood pressure ≥140-160 mmHg, diastolic blood pressure ≥90-110 mmHg, no proteinuria, and consuming 10 mg/day of nifedipine. The exclusion criteria included respondents with a history of heart disease, kidney, diabetes, and hyperlipidemia. The dropout criteria are those getting proteinuria and bleeding during this experiment.

Experimental Procedure

The treatment group was given a combination of 500 mg of pomegranate extract and 10 mg of nifedipine once daily. Meanwhile, the control group was given only 10 mg of nifedipine once daily. This intervention was carried out for two weeks.

The Variables, Instruments, and Measurement

The variables measured in this study were blood pressure and nitric oxide level. The blood pressure was measured using a digital sphygmomanometer on days 1, 3, 7, and 14. In addition, 3cc of intravenous blood was taken on days 1 and 14, assisted by laboratory officers, then continued with the centrifuge process so that serum was produced, which was used to check nitric oxide levels at the GAKI Laboratory—Faculty of Medicine, Diponegoro University, Semarang.

Statistical Analysis

Data were analyzed using an Independent T-Test, Pearson correlation, and repeated measures ANOVA.

Ethical Consideration

This research has been registered with the Research Bioethics Commission of Sultan Agung Islamic University Semarang with the Ethical Clearance Number 56/III/2021/Komisi Bioetik.

RESULTS

Table 1 shows that the respondents' age characteristics are mostly above 20 years. Respondents with multigravida more than primigravida. Most of the respondents' body mass index are overweight and obese. Figure 1 shows that the average systolic blood pressure from pre to post-test measurements in the intervention group decreased by 20.94 mmHg, while in the control group, there was a decrease of 8.19 mmHg. In diastolic blood pressure, there was a decrease of 9.44 mmHg in the intervention group and 1.75 mmHg in the control group. These measurements showed that systolic and diastolic blood pressure reduction was more significant in the intervention group than in the control group. The analyzed showed a significant difference in systolic and diastolic blood pressure between the two groups ($p<0.05$).

Table 1. Characteristics of Respondent (n=32)

Characteristics	Result
Age, years	
<20	2 (6.2%)
20-35	15 (46.9%)
>35	15 (46.9%)
Parity	
Primigravida	7 (22%)
Multigravida	25 (78%)
Body Mass Index	
Normal	12 (38%)
Overweight	10 (31%)
Obese	10 (31%)

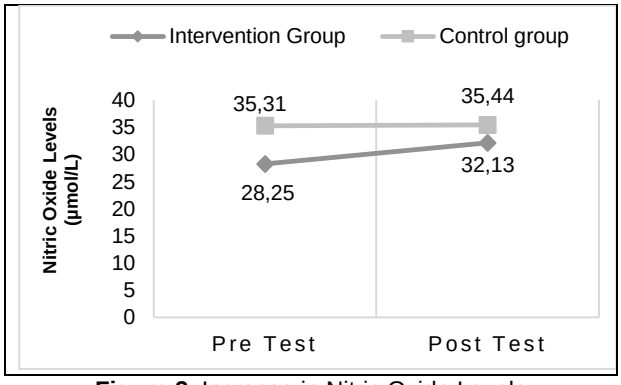

Figure 2. Increase in Nitric Oxide Levels

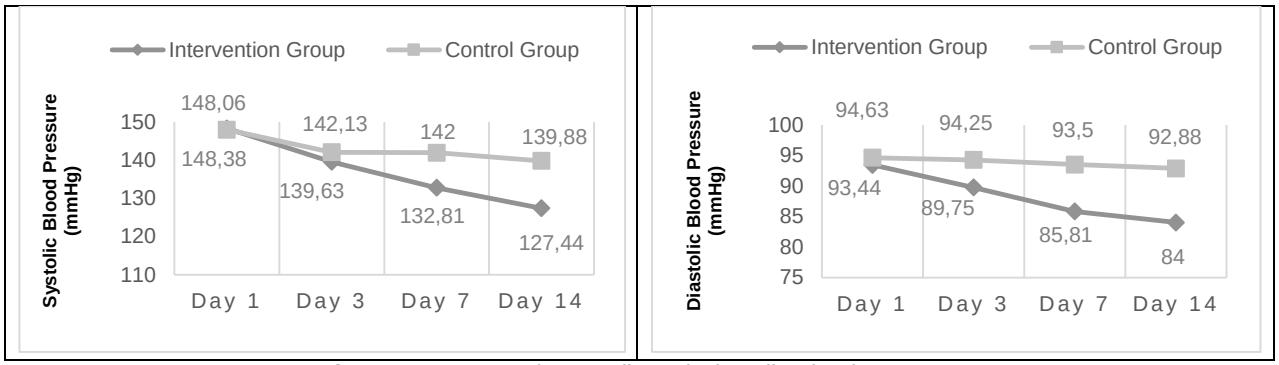

Figure 1. Decrease in Systolic and Diastolic Blood Pressure

Based on Figure 2, the average increase of nitric oxide levels in the intervention group was 3.88 µmol/L, while the control group was increased by 0.13 µmol/L. Both groups experienced an average increase in nitric oxide levels. However, the average increase in nitric oxide levels in the intervention group was more significant than in the control group. The statistics analyzed showed a significant difference in the average nitric oxide levels between the intervention and control groups.

Table 2. Correlation Nitric Oxide and Blood Pressure

	Δ Systolic		**Δ Diastolic**	
	p-value	r	p-value	r
Δ *Nitric Oxide*	0.002	-0.529	0.011	-0.445

Table 2 shows that there is a relationship between nitric oxide levels and systolic and diastolic blood pressure ($p<0.05$). The relationship between the two shows a negative direction, which means that the higher the nitric oxide level, the lower the systolic and diastolic blood pressure.

DISCUSSION

This study shows that consuming pomegranate peel extract can reduce blood pressure and increase nitric oxide in gestational hypertension. In the case of gestational hypertension, the lumen of the spiral artery does not experience vasodilation and distension, so the muscle layer of the spiral artery becomes stiff and rigid. This disrupts blood flow to the placenta, resulting in ischemia and placental hypoxia.[16] This situation will produce free radicals so that oxidative stress increases. Increased oxidative stress will make nitric oxide levels lower, resulting in endothelial dysfunction, which ends in gestational hypertension.[17]

In this study, the combination of 500 mg of pomegranate extract and 10 mg of nifedipine reduced systolic blood pressure by 14.11% (20.94 mmHg) while decreasing diastolic blood pressure by 10.1% (9.44 mmHg). The changes in systolic and diastolic blood pressure observed three times after the pre-test showed a significant decrease from the third, seventh, and fourteenth days until it reached the average category. On the other hand, nitric oxide levels measured two times in the pre-test (first day) and post-test (fourteenth day) increased by 3.88 µmol/L. The experimental group experienced a decrease in blood pressure through the levels of nitric oxide, which is thought to be because of the macrominerals content such as potassium (259 mg%), magnesium (12 mg%), vitamin C (64.6 mg%), and total phenolics (56.09 mg GAE) which play an essential role in controlling blood pressure.[18]

The content contained in the pomegranate peel has its respective role in lowering blood pressure. An increased potassium intake could have antihypertensive effects by promoting endothelium vasodilation.[19] Potassium plays a role in lowering blood pressure by inhibiting renin secretion and reducing aldosterone secretion. Potassium inhibits the absorption of water and sodium in the proximal renal tubules in the kidneys so that aldosterone secretion decreases. Renin, as an inhibitor of smooth muscle contraction of blood vessels, will be suppressed secretion by calcium to prevent the narrowing of artery and capillary walls. Plasma volume, cardiac output, and peripheral pressure will decrease in line with the decrease in blood pressure due to vasodilation. In addition, potassium helps lower the potential of membranes to provide a relaxing effect on blood vessel muscles that cause blood pressure to decrease.[20]

In addition to potassium, the high content of vitamin C, flavonoids, and polyphenols helps activate the antioxidant activity of pomegranate peel. Antioxidants work by inhibiting Reactive Oxygen Species (ROS) production and lipid peroxidation, thereby preventing endothelial dysfunction. Endothelial cells that function correctly will produce nitric oxide compounds. Nitric oxide is a potent vasodilator in dilating blood vessels to prevent high blood pressure or hypertension .[21]

Consuming fruits and vegetables rich in flavonoids significantly reduced systolic and diastolic blood pressure.[22] Regarding their potential effects on endothelial function and vascular vasodilatation, flavonoids act as endothelial oxidizers, which affect nitric oxide levels. Phenolic compounds can repair endothelial cell damage, act directly on nitric oxide metabolism, or reduce vasoconstriction

through ACE and angiotensin II receptor activity. Isoflavones interact with nitric oxide secretion by endothelial cells, resulting in increased nitric oxide levels.[23]

Nitric oxide produced by endothelial cells has a role in maintaining pressure on blood vessels. Nitric oxide exerts a vasodilating and antiproliferative effect on vascular smooth muscle cells. The production of nitric oxide by endothelial cells will make vascular smooth muscle relax. Hypertension in pregnancy is caused by endothelial dysfunction. The level of endothelial cell damage due to free radicals that cause oxidative stress will affect the amount of nitric oxide produced. The lower the level of nitric oxide in the blood, the higher the systolic and diastolic blood pressure. In gestational hypertensive patients, vasodilation disorders in endothelial cells are caused by the low availability of nitric oxide.[24]

This study's results align with previous studies, which found pomegranate peel extract to benefit serum lipid profiles and antioxidant status in osteoarthritis patients. Administration of pomegranate peel extract at a dose of 500 mg after eight weeks of intervention significantly reduced total cholesterol and triglycerides levels in patients with knee osteoarthritis and confirmed the potential antioxidant activity of pomegranate peel extract in the studied subjects. Possible effects of pomegranate peel on blood pressure. Previous research reported that pomegranate juice 200 ml/day for six weeks significantly reduced systolic and diastolic blood pressure in type 2 diabetes patients.[15,25]

CONCLUSIONS AND RECOMMENDATION

The present study demonstrated that term supplementation of 500 mg pomegranate peel extract consumption had beneficial effects on blood pressure and nitric oxide levels in gestational hypertension. Studies using other oxidative stress and antioxidant biomarkers such as malondialdehyde and superoxide dismutase are needed for more definitive results on pomegranate peel effects in managing gestational hypertension.

REFERENCES

1. Romagano MP, Williams SF, Apuzzio JJ, Sachdev D, Flint M, Gittens-Williams L. Factors associated with attendance at the postpartum blood pressure visit in pregnancies complicated by hypertension. *Pregnancy Hypertens*. 2020;22:216-219. doi:10.1016/j.preghy.2020.10.003
2. WHO. *Trends in Maternal Mortality 2000 to 2017: Estimates by WHO, UNICEF, UNFPA, World Bank Group and the United Nations Population Division: Executive Summary*. World Health Organization
3. Toljic M, Egic A, Munjas J, et al. Increased oxidative stress and cytokinesis-block micronucleus cytome assay parameters in pregnant women with gestational diabetes mellitus and gestational arterial hypertension. *Reprod Toxicol*. 2017;71:55-62. doi:10.1016/J.REPROTOX.2017.04.002
4. Li X, Tan H, Chen M, Zhou S. Transforming growth factor beta 1 related gene polymorphisms in gestational hypertension and preeclampsia: A case-control candidate gene association study. *Pregnancy Hypertens*. 2018;12:155-160. doi:10.1016/J.PREGHY.2017.11.010
5. Feng X, Liu Y, Zhang Y, et al. New views on endothelial dysfunction in gestational hypertension and potential therapy targets. *Drug Discov Today*. 2021;26(6):1420-1436. doi:10.1016/J.DRUDIS.2021.03.001
6. Reddy S, Jim B. Hypertension and Pregnancy: Management and Future Risks. *Adv Chronic Kidney Dis*. 2019;26(2):137-145. doi:10.1053/J.ACKD.2019.03.017
7. Chan Q, Wren GM, Lau CHE, et al. Blood pressure interactions with the DASH dietary pattern, sodium, and potassium: The International Study of Macro-/Micronutrients and Blood Pressure (INTERMAP). *Am J Clin Nutr*. 2022;116(1):216-229. doi:10.1093/AJCN/NQAC067
8. Sobenin IA, Andrianova I V, Fomchenkov I V, Gorchakova T V, Orekhov AN. Time-released garlic powder tablets lower systolic and diastolic blood pressure in men with mild and moderate arterial hypertension. *Hypertens Res*. 2009;32:433-437. doi:10.1038/hr.2009.36
9. Evitasari D. Efektifitas pemberian suplemen kalsium dan buah pisang ambon terhadap perubahan tekanan darah pada ibu hamil hipertensi gestasional. *J Ilm Indones*. 2020;5(10):1065-1074.
10. Porouw HS, Yulianingsih E. Pisang ambon dan hipertensi ibu hamil. *Jambura Heal Sport J*. 2019;1(2):61-70. doi:10.37311/JHSJ.V1I2.2597
11. Winda Gurnita F, Wulandari DA, Widyawati A, Karya S, Semarang H. Pengaruh konsumsi Carica Papaya L. terhadap tekanan darah ibu hamil hipertensi. *J Midwifery Public Heal*. 2020;2(1):1-6. Accessed August 11, 2023.
12. Sahebkar A, Simental-Mendía LE, Giorgini P, Ferri C, Grassi D. Lipid profile changes after pomegranate consumption: A systematic review and meta-analysis of randomized controlled trials. *Phytomedicine*. 2016;23(11):1103-1112. doi:10.1016/J.PHYMED.2015.12.014
13. Jafari T, Fallah AA, Bahrami M, Lorigooini Z. Effects of pomegranate peel extract and vitamin E on oxidative stress and antioxidative capacity of hemodialysis patients: A randomized controlled clinical trial. *J Funct Foods*. 2020;72:104069. doi:10.1016/J.JFF.2020.104069

14. White H, Sabarwal S. Quasi-Experimental Design and Methods. Published online 2014. Accessed August 11, 2023.
15. Haghighian MK, Rafraf M, Hemmati S, Haghravan S, Asghari-Jafarabadi M. Effects of pomegranate (Punica granatum L.) peel extract supplementation on serum lipid profile and oxidative stress in obese women with knee osteoarthritis: A double blind, randomized, placebo controlled study. *Adv Integr Med*. 2021;8(2):107-113. doi:10.1016/J.AIMED.2020.05.001
16. Lu M, Sferruzzi-Perri AN. Placental mitochondrial function in response to gestational exposures. *Placenta*. 2021;104:124-137. doi:10.1016/J.PLACENTA.2020.11.012
17. Keman K. Patomekanisme preeklampsia terkini: mengungkapkan teori-teori terbaru tentang patomekanisme preeklampsia dilengkapi dengan deskripsi biomokuler. Universitas brawijaya press. Published 2014. Accessed August 11, 2023.
18. Vongpatanasin W, Peri-Okonny P, Velasco A, et al. Effects of potassium magnesium citrate supplementation on 24-hour ambulatory blood pressure and oxidative stress marker in prehypertensive and hypertensive subjects. *Am J Cardiol*. 2016;118(6):849-853. doi:10.1016/J.AMJCARD.2016.06.041
19. Ndanuko RN, Ibrahim R, Hapsari RA, Neale EP, Raubenheimer D, Charlton KE. Association between the Urinary Sodium to Potassium Ratio and Blood Pressure in Adults: A Systematic Review and Meta-Analysis. *Adv Nutr*. 2021;12(5):1751-1767. doi:10.1093/advances/nmab036
20. Biswas D, Uddin MM, Dizdarevic LL, Jørgensen A, Duttaroy AK. Inhibition of angiotensin-converting enzyme by aqueous extract of tomato. *Eur J Nutr*. 2014;53(8):1699-1706. doi:10.1007/S00394-014-0676-1/METRICS
21. Yuslianti ER. Pengantar radikal bebas dan antioksidan. Deepublish. Published 2018. Accessed August 11, 2023.
22. Oteiza PI, Fraga CG, Galleano M. Linking biomarkers of oxidative stress and disease with flavonoid consumption: From experimental models to humans. *Redox Biol*. 2021;42:101914. doi:10.1016/J.REDOX.2021.101914
23. Godos J, Vitale M, Micek A, et al. Dietary Polyphenol Intake, Blood Pressure, and Hypertension: A Systematic Review and Meta-Analysis of Observational Studies. *Antioxidants 2019, Vol 8, Page 152*. 2019;8(6):152. doi:10.3390/ANTIOX8060152
24. Astutik P, Adriani M, Wirjatmadi B. Kadar radikal superoksid (O2-), nitric oxide (NO) dan asupan lemak pada pasien hipertensi dan tidak hipertensi. *J Gizi Indones*. 2014;3(1):1-6. Accessed August 11, 2023.
25. Sohrab G, Roshan H, Ebrahimof S, Nikpayam O, Sotoudeh G, Siasi F. Effects of pomegranate juice consumption on blood pressure and lipid profile in patients with type 2 diabetes: A single-blind randomized clinical trial. *Clin Nutr ESPEN*. 2019;29:30-35. doi:10.1016/J.CLNESP.2018.11.013