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FULL PAPER

The effect of administering salted fish extract as a model of pregnancy hypertension in mus musculus balb-c strain through blood pressure and urinary protein measurements

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Globally, hypertension complicates approximately 6-8% of all pregnancies. Hypertension is a risk factor for the occurrence of preeclampsia are 1.591 times more likely to experience preeclampsia compared to those without a history of hypertension. Pregnant women are at risk of developing hypertension if there is a high concentration of salt (NaCl) in their blood, leading to an increase in plasma sodium levels, also known as hypernatremia, which causes the blood plasma to become hypertonic. This study aims to demonstrate the effects of salted fish extract administration as a model of pregnancy hypertension in Balb-C strain Mus musculus mice through blood pressure and urine protein measurements. This study utilized a true experimental design with a post-test only with a control group design. The experimental subjects were pregnant female Mus Musculus Balb-C mice at a gestational age of 1 day. Data analysis was conducted using the non-parametric Kruskal-Wallis test with SPSS 22 software. There were significant differences observed between the negative control group, positive control group (Anti QA-2), groups given salted fish extract with NaCl content of 17.5 mg, 52.6 mg, and 87.8 mg, and the NaCl dose of 52.6 mg, in terms of systolic blood pressure, diastolic blood pressure, mean arterial pressure (MAP), and urine protein levels. The administration of salted fish extract as a model of pregnancy hypertension has an impact on blood pressure and urine protein levels.

KEYWORDS

Extract; salted fish; hypertension; pregnancy; blood pressure; urine protein.

Introduction

The World Health Organization (WHO) mentiones that pregnancy hypertension poses a public health challenge worldwide, being one of the leading causes of maternal morbidity and mortality [1]. Globally, pregnancy hypertension complicates approximately 6-8% of all pregnancies [2]. In 2021, Indonesia recorded 7,389 maternal deaths and 1,077 cases of pregnancy hypertension [3]. Pregnancy hypertension can be classified into

four categories: chronic hypertension, preeclampsia/eclampsia, preeclampsia caused by chronic hypertension, and gestational hypertension [4].

The prevalence of pregnancy hypertension increased from 10.8% in 2017 to 13.0% in 2019, while the prevalence of chronic hypertension increased from 2.0% to 2.3% [5]. Hypertension is a risk factor for the occurrence of preeclampsia. In other words, individuals with a history of hypertension are 1.591 times more likely to experience preeclampsia compared to those without a history of hypertension [6].

Preeclampsia is a pregnancy hypertension disorder characterized by placental malperfusion and multiorgan injury. This condition accounts for approximately 14% of maternal deaths and 10-25% of perinatal deaths globally. In addition, preeclampsia also poses a risk of chronic diseases later in life for both the mother and child, such as hyperthyroidism, diabetes mellitus, and dyslipidemia [7]. According to the World Health Organization (WHO) data from 2020, an estimated 934 cases of preeclampsia occur worldwide every day. Approximately 342,000 pregnant women experience preeclampsia, and 25% of preeclampsia/eclampsia cases are the leading cause of complications during pregnancy and childbirth [8]. Preeclampsia causes 9-26% of maternal deaths in developing countries and 16% in developed countries [9].

The Bangkalan District Health Office report for the year 2019 indicates that 46% of maternal deaths were caused by preeclampsia/eclampsia [10]. Meanwhile, the primary causes of preeclampsia are mostly unknown, but it is clear that immunological components play an important pathophysiological role [11,12]. The maladaptation theory explains the disruption in trophoblast interaction with the maternal immune system, which can lead to failure in spiral artery remodeling [13]. Nutritional patterns where high levels of sodium in the blood serum are categorized as high, blood pressure will increase [14]. High salt stimulation or excessive salt levels can regulate the expression of VEGF, IL-1β, IL-6, TNF-α, and vascular endothelial growth, which initiates the onset of preeclampsia symptoms [15].

Excessive sodium consumption (>5 grams) per day has been proven to result in a significant increase in blood pressure and is associated with the onset of hypertension and cardiovascular complications. Electrolytes such as sodium (Na+) and potassium (K+) play a crucial role in pre-eclampsia and eclampsia, as they significantly contribute to the function of vascular smooth muscles. Serum Na+ levels are found to be significantly elevated in pre-eclampsia patients compared to normal pregnant women [16,17].

Pregnant women who are at risk of developing hypertension may experience high concentrations of salt (NaCl) in their blood, leading to an increase in plasma sodium levels, known as hypernatremia, which causes the blood plasma to become hypertonic. This hypertonic condition causes fluids in both the intracellular and extracellular compartments to be drawn, resulting in the contraction of cells within blood vessels, including endothelial cells, leading to endothelial cell dysfunction. This dysfunction leads to a decrease in the activation of endothelial nitric oxide synthase [eNOS], followed by a reduction in nitric oxide [NO] produced by arginine through the activation of endothelial nitric oxide synthase [eNOS] [18]. In the late second trimester of normal pregnancy, trophoblasts invade the maternal decidua up to one-third of the myometrium, replacing vascular smooth muscle [19]. The continuous release of damage-associated molecular patterns (DAMPs) from cell death and remodeling eventually contributes to a pro-inflammatory state and an increase in blood pressure [20].

Several studies have indicated a decrease in MMP-9 enzyme levels during pregnancies with preeclampsia, resulting in impaired remodeling of spiral arteries and trophoblast invasion. This is because MMP-9 plays a role in

degrading the extracellular matrix to facilitate the remodeling process of spiral arteries, and MMP-9 is a protein that acts as a proangiogenic factor. A decrease in MMP-9 leads to disturbances in the angiogenic process in the placenta associated with preeclampsia symptoms [21-23]. The objective of this study is to demonstrate the effects of administering salted fish extract as a model of pregnancy hypertension in Balb-C strain mice through blood pressure and urine protein measurements.

Experimental

The type of this study is true experimental, with a post-test only with a control group design. This study utilizes experimental animals, specifically pregnant female mice of the Mus Musculus Balb-C strain at a gestational age of 1 day, which underwent self-mating using lust synchronization techniques and has received approval from the Ethics Committee of the Faculty of Medicine, Universitas Airlangga (199/EC/KEPK/FKUA/2022). Mus Musculus mice were chosen for this research due to their frequent use in biomedical studies, genetic similarity to humans, and their ability to adapt to laboratory environments.

The inclusion criteria for the mice subjects are as follows: 1) Pregnant mice (Mus Musculus) of the Balb-C strain at a gestational age of day 1; 2) they exhibit good health, characterized by active movement and intact fur, with an average weight of 25-30 grams; and 3) they have not undergone any chemical treatment or intake. The exclusion criteria include death before completion of the research intervention or having any defects. In addition, dropouts occur if the health condition of the mice deteriorates or if they die during the study.

The total sample size for this study is 72 Balb-C Musculus mice, with details as follows: 12 mice in the negative control group, 12 mice in the positive control group, 12 mice in treatment group 1, 12 mice in treatment group 2, 12 mice in control group 3, and 12 mice in control group 4. The sampling technique involves self-mating of female Balb-C Musculus mice for the negative control and treatment groups, while the Balb/C Musculus mice that have been impregnated are conditioned to become pre-eclampsia models by injecting anti-AV-2 for the positive control group. In this study, each treatment group will be administered salted fish extract with NaCl content at the following doses: group 1: 17.5 mg/day, group 2: 52.6 mg/day, group 3: 87.8 mg/day, and group 4: with NaCl dose of 52.6 mg/day for 13 days, followed by termination on gestational day 14.

The variables in this study include: 1) independent variable: Administration of salted fish extract, and dependent variables: blood pressure and urinary protein. The research instrument consists of mouse cages equipped with sandpans covered with wire, filled with husk, and feeding, and drinking containers made of plastic materials measuring 20cm x 30cm x 40cm with room humidity at temperatures between 27-28 ˚C. The mice are fed standard pellet-shaped feed with crude protein, crude fat, calcium, and phosphorus composition, and provided with daily water intake placed in special bottles with a daily requirement of 60 ml per mouse. Data analysis is conducted using the non-parametric Kruskal-Wallis test with the assistance of SPSS 22.

Results and discussion

Blood pressure

Table 1 presents the effect of salted fish extract and NaCI on blood pressure, including systolic, diastolic, and MAP.

TABLE 1 The effect of salted fish extract and NaCl on blood pressure

Group	Group						p-value
	1 (NC)	2 (PC)	3 (Salted Fish Extract NaCl 17,5)	4 (Salted Fish Extract NaCl 52,6)	5 (Salted Fish Extract NaCl 87,8)	6 (NaCl 52,6)	
Sistole	121,50 ± 5,42 120[b]	161,00 ± 8,29 159[e]	113,80 ± 10,52 109[a]	148,80 ± 7,53 147[d]	163,11 ± 11,96 161[e]	134,33 ± 6,50 136[c]	0,000*
Diastole	77,60 ± 8,62 75[a]	103,00 ± 4,36 103[c]	83,50 ± 12,55 81,5[ab]	98,80 ± 10,90 100c	120,67 ± 11,91 124d	88,89 ± 4,99 90b	0,000*
MAP	92,23 ± 6,37 91,33[a]	122,33 ± 2,72 123,00[d]	93,60 ± 10,81 90,17[a]	115,47 ± 7,44 113,83[c]	134,81 ± 5,3317 136,67[e]	104,70 ± 5,31 106,00[b]	0,000*

Data represent the mean ± SD *Significance at α<0.05
a,b,c,d,e the same superscript in one line indicates that they are not meaningfully different

Table 1 indicates that for systolic blood pressure, the highest mean ± SD score is in the treatment group given salted fish extract with NaCl content of 87.8 mg, which is 163.11 ± 11.96, followed by the positive control group (administered with anti-QA-2) 161.00 ± 8.29, the treatment group given salted fish extract with NaCl content of 52.6 mg, 148.80 ± 7.53, the treatment group given NaCl 52.6 mg, 134.33 ± 6.50, the negative control group, 121.50 ± 5.42, and the treatment group given NaCl 17.5 mg, 113.80 ± 10.52. The highest mean ± SD score for diastolic blood pressure is in the treatment group given salted fish extract with NaCl content of 87.8 mg, which is 120.67 ± 11.91, followed by the positive control group (administered with anti-QA-2) 120.67 ± 11.91, the treatment group given salted fish extract with NaCl content of 52.6 mg, 98.80 ± 10.90, the treatment group given NaCl 52.6 mg, 88.89 ± 4.99, the treatment group given salted fish extract with NaCl content of 17.5 mg, 83.50 ± 12.55, and the negative control group, 77.60 ± 8.62. For Mean Arterial Pressure (MAP), the highest mean ± SD score is in the treatment group given salted fish extract with NaCl content of 87.8 mg, which is 134.81 ± 5.33, followed by the positive control group (administered with anti-QA-2) 122.33 ± 2.72, the treatment group given salted fish extract with NaCl content of 52.6 mg, 115.47 ± 7.44, the treatment group given NaCl 52.6 mg, 104.70 ± 5.31, the treatment group given salted fish extract with NaCl content of 17.5 mg, 93.60 ± 10.81, and the negative control group, 92.23 ± 6.37.

The analysis results systolic blood pressure, diastolic blood pressure, and MAP, p-values < 0.05 were obtained, indicating a difference between the control group and the treatment group. Therefore, it can be concluded that there is a significant difference between the negative control group, the positive control group (anti-QA-2), the group given salted fish extract with NaCl content of 17.5 mg, the group given salted fish extract with NaCl content of 52.6 mg, the group given salted fish extract with NaCl content of 87.8 mg, and the group given NaCl with a dose of 52.6 mg in terms of systolic blood pressure, diastolic blood pressure, and MAP. This means that there is an effect of salted fish extract and NaCl administration as a model of pregnancy hypertension on blood pressure in all treatment groups.

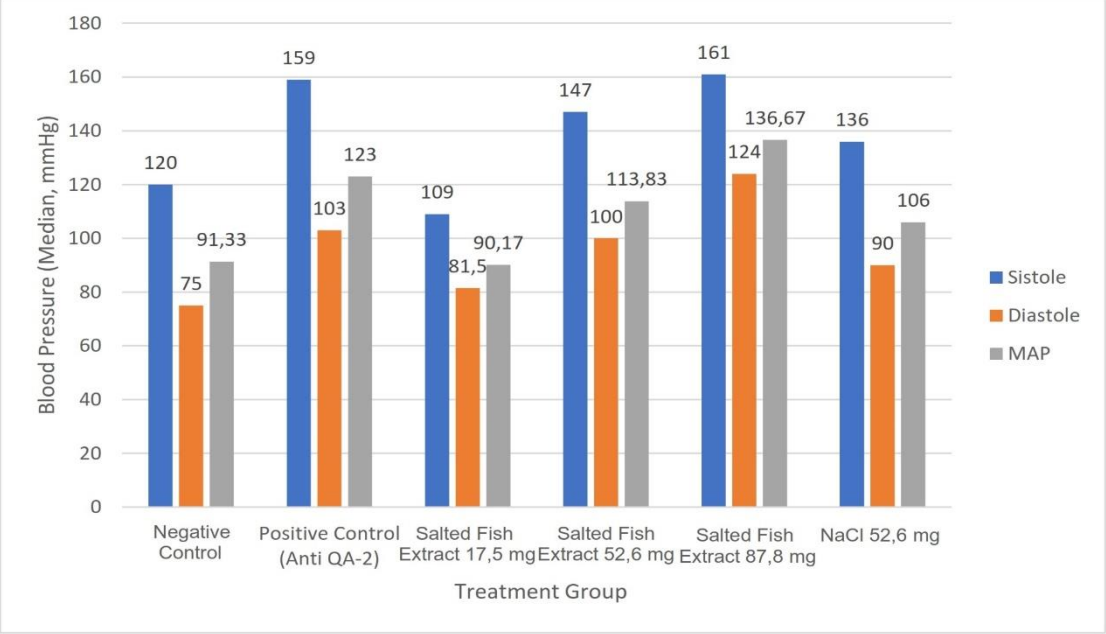

FIGURE 1 Visualization of blood pressure distribution

Figure 1 shows that the highest systolic blood pressure is in the group treated with salted fish extract containing NaCl with a dose of 87.8 mg, and the lowest is in the group treated with NaCl with a dose of 52.6 mg. The highest diastolic blood pressure is in the group treated with salted fish extract containing NaCl with a dose of 87.8 mg, and the lowest is in the negative control group. The highest MAP is in the group treated with salted fish extract containing NaCl with a dose of 87.8 mg, and the lowest is in the group treated with salted fish extract containing NaCl with a dose of 52.6 mg.

Protein urine

This section showed how the treatment groups affect protein levels.

TABLE 2 The influence of the treatment groups on urinary protein

Group	Group						p-value
	1 (NC)	2 (PC)	3 (Salted Fish Extract NaCl 17,5)	4 (Salted Fish Extract NaCl 52,6)	5 (Salted Fish Extract NaCl 87,8)	6 (NaCl 52,6)	
Protein urine	2,08±1,52 2,23^{bc}	0,59±0,50 0,32^{a}	0,76±0,59 0,62^{ab}	1,47±0,67 1,59^{c}	0,80±0,83 0,42^{ab}	0,68±0,22 0,64^{ab}	0,019*

Data represent the mean ± SD *Significance at α<0.05

^{a,b,c,d,e} the same superscript in one line indicates that they are not meaningfully different

Table 2 demonstrates that the highest mean ± SD score for urinary protein levels is in the negative control group 2.08 ± 1.52, followed by the group treated with salted fish extract containing 52.6 mg NaCl 1.47 ± 0.67, the group treated with salted fish extract containing 87.8 mg NaCl 0.80 ± 0.83, the group treated with salted fish extract containing 17.5 mg NaCl 0.76 ± 0.59, the group treated with 52.6 mg NaCl 0.68 ± 0.22, and the positive control group (Anti QA-2) 0.59 ± 0.50. The analysis of the treatment groups' data on urinary protein levels resulted in a p-value < 0.05, indicating a significant difference between the control group and the treatment groups. Thus, it can be concluded that there is a significant difference between the negative control group, the positive control group (anti-QA-2), the group

treated with salted fish extract containing 17.5 mg NaCl, the group treated with salted fish extract containing 52.6 mg NaCl, the group treated with salted fish extract containing 87.8 mg NaCl, and the group treated with 52.6 mg NaCl in terms of urinary protein levels.

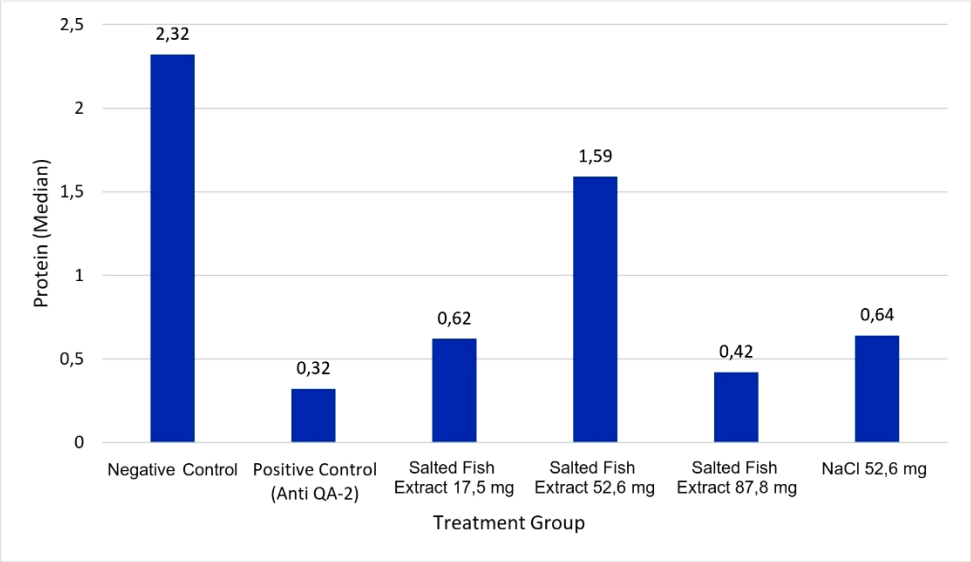

FIGURE 2 Distribution of median urinary protein across all groups

Figure 2 indicates that the negative control group has the highest median value, while the positive control group has the lowest median value.

Blood pressure

Consuming high doses of salt will increase extracellular sodium levels or "hypernatremia". This condition will cause the depletion of intracellular fluid, leading to an increase in extracellular blood volume. Furthermore, high salt levels in the bloodstream can cause the narrowing of blood vessels, known as vasoconstriction. This simultaneous increase in blood volume and vasoconstriction can potentially change the arterial pressure, ultimately contributing to an increase in blood pressure [24].

Analysis of systolic blood pressure, diastolic blood pressure, and MAP revealed significant differences among the negative control group, positive control group, and treatment group administered with salted fish extract and NaCl in terms of systolic blood pressure, diastolic blood pressure, and MAP. There are significant differences in the levels of Na+ and K+ in hypertensive and normotensive patients associated with blood pressure (14).

Clinical trials analyzing the dose response of sodium reduction show a linear correlation between sodium intake and reduction in systolic and diastolic blood pressure across the entire range of sodium exposure. Although this occurs independently of initial blood pressure, the effect of sodium reduction on blood pressure levels is more pronounced among research participants with hypertension [25].

There is no correlation between consumption of salted fish with high NaCI levels and normal levels in areas where salted fish is produced (p-value > 0.05). However, individuals who consume salted fish and live in areas where it is produced are at a greater risk of hypertension compared to those who consume salted fish normally.

This study demonstrates the effect of administering salted fish extract and NaCl as a model of pregnancy hypertension on blood pressure. These findings differ from a study conducted in Jepara, which involved 105

second-trimester pregnant women residing in coastal areas, where no significant association was found between salt intake and increased blood pressure in the second trimester. Research in Korea indicates that seafood consumption also hurts blood pressure due to the sodium content in salt-preserved seafood and the methods used in food processing. A study group in Korea reported that subjects consuming large amounts of salt-preserved seafood had a 28% higher risk of hypertension compared to those who did not consume it. The average sodium content in salt-preserved seafood is approximately 5,210 mg, whereas the recommended sodium intake for pregnant women is less than 2,300 mg per day [26].

These findings contradict other research results, which indicate that pregnant women who regularly consume sodium-rich foods every day have a 1.6 times higher risk of hypertension compared to those who do not consume them regularly [27]. Another study conducted in Korea found that respondents who consume large quantities of salt-preserved seafood have a 28% higher risk of hypertension compared to those who do not regularly consume such foods [28].

Urinary protein

The results of this study indicate that there is a significant difference between the negative control group, the positive control group, and the treatment group administered with salted fish extract and NaCl in terms of urinary protein levels. The cut-off to consider proteinuria as pathologic during pregnancy has been set at 300 mg/24 h. Due to progesterone effects on ureters and bladder muscular walls, there is a relaxation of the urinary tract, with increased vesicoureteral reflux and urinary stasis, favoring bacterial overgrowth. In these circumstances, microscopic hematuria or proteinuria in the pathologic may also be found. Urine protein levels in the negative control were higher than the positive control with anti-QA-2 injection and the treatment group induced by salted fish extract and NaCl. [29].

The 24-hour urine protein excretion measurement is the gold standard for quantifying proteinuria, but it is cumbersome, inconvenient, time-consuming, and subject to errors leading to inaccuracies in nearly half of collections [29]. Urine dipstick analysis is widely used in obstetric practice because it is simple to perform and economical, but its usefulness is impaired by low sensitivity and specificity. Several factors, such as maternal hydration status or the presence of infections, may influence its accuracy. The sensitivity and specificity of the urine dipstick test vary greatly among different studies. Moreover, this test may also overestimate the risk of significant proteinuria. Automated dipstick methods appear to have greater sensibility than visual dipstick urinalysis for the detection of proteinuria. Significant proteinuria cannot at the moment be diagnosed or excluded using only urine dipstick analysis [29].

A United States study on kidney and hypertension diseases in Africa revealed that this observational study indicates that salt intake is a major risk factor for increased urinary protein excretion, and this risk can be reduced with a slight reduction in salt intake. Interestingly, studies on salt restriction have shown a small but significant decrease in urinary protein excretion alongside heightened renin-angiotensin system activity.

Salt intake is a primary cause of elevated blood pressure and a risk factor for kidney damage. The World Health Organization (WHO) advises limiting salt intake to 5 grams or less per day. This study also indicates that reducing salt intake is associated with a significant decrease in blood pressure and urinary protein excretion. Regarding the ongoing correlation between salt intake, blood pressure, urinary protein excretion levels, and kidney and cardiovascular risk, this study demonstrates the potential long-term benefits of salt reduction in kidney and cardiovascular development [30].

Conclusion

The administration of salted fish extract as a model of pregnancy hypertension has a significant impact on increasing blood pressure and affects protein levels.

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Authors' Contributions

Novi Anggraeni: Novi Anggraeni contributed to finding concepts, literature search, definition of intellectual experiments. manuscript content and laboratory She also contributed to preparation, finalization of the manuscript.

Agus Sulistyono: Agus Sulistyono contributed to the design methodology and statistical analysis. And he also contributed to the statistical writing and discussion of this article.

Gwenny Ichsan Prabowo: Gwenny Ichsan Prabowo Focuses on data acquisition and data analysis. She also contributed to drafting and editing the results of this study.

Aditiawarman: Aditiawarman contributed to the design methodology and statistical analysis, literature search.

Conflict of Interest

There is no conflict of interest in this research.

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