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ROSA DAMASCENA EXTRACT ON ANGIOTENSIN-CONVERTING ENZYME ACTIVITY IN WISTAR RATS RECEIVING SODIUM DIET

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ABSTRACT
The prevalence of hypertension continues to rise in line with lifestyle changes. Often referred to as "the silent killer," hypertension can develop without warning. One of its contributing factors is excessive sodium intake, which disrupts the body's fluid balance regulated by the renin-angiotensin-aldosterone system. Elevated activity of the Angiotensin-Converting Enzyme within the Renin Angiotensin Aldosterone System mechanism can further lead to the development of hypertension. This study aims to investigate the impact of administering ethanol extract of Rosa damascena on the activity of Angiotensin-Converting Enzyme in Wistar rats fed a sodium-enriched diet. This experimental study utilized a post-test-only control group design. The subjects were 30 male Wistar rats, divided into five groups: 1) P0=control group; 2) P1=8% NaCl+RDEE 500mg/kgBW; 3) P2=0.35% NaCl+RDEE 500mg/kgBW; (4) P3=8% NaCl; and (5) P4=0.35% NaCl. The treatments were administered over 28 days. After the treatment period, the rats were anesthetized using a combination of Ketamine and Xylazine. The data were analyzed using a One-Way ANOVA test to assess differences among the treatment groups. A significant difference in Angiotensin-Converting Enzyme activity was observed in Wistar rats before receiving a sodium-enriched diet, with a p-value of <0.05. The ethanol extract of Rosa damascena was proven effective in reducing ACE activity in these rats, with a p-value of <0.05. The ethanol extract of Rosa damascena has demonstrated nephroprotective properties.

Keywords: ACE; hypertension; rosa damascena

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INTRODUCTION
Hypertension is still a global problem because its prevalence continues to increase. Hypertension is an increase in systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg with two examinations in two different visits. In Western Europe, cases of hypertension reach 44% while in North America the cases are around 28%. According to Kearney et al., the population of hypertension in the world will increase by around 75% in 2025, especially in developing countries. Along with the increasing adult population, the prevalence of hypertension will also continue to grow (Mills et al., 2020). Hypertension or high blood pressure is one of the chronic cardiovascular diseases that is not contagious. In general, hypertension does not have serious symptoms and is often without complaints, this is because the tissue still gets enough blood flow. However, hypertension can appear suddenly, causing various complications and even causing death. This is what is called hypertension as the silent killer (Bays et al., 2022).

According to WHO data, the incidence of hypertension in 2000 was 972 million people, or 26.5% worldwide. This figure is expected to increase to 29.2% by 2025. Africa is ranked first with the most cases of hypertension, which is around 40%, and in America, cases of hypertension are around 35%. In Southeast Asia, cases of hypertension reach 36%, while in Indonesia cases of hypertension reach 31.7% or around 63 million people (Mills et al., 2016).

Based on data from the National Health and Nutrition Examination Survey (NHNES) in 1999-2000, the hypertension rate was around 29-31% or around 58-65 million people in America. According to epidemiological data, the increasing elderly population will increase the number of hypertension cases (Oliveros et al., 2020).

In Indonesia, hypertension sufferers are around 15 million people, but only 4% are controlled hypertension and willing to seek treatment, while 50% of hypertension sufferers in Indonesia are not aware that they are sick, so their illness is more severe because they do not change their lifestyle patterns and avoid risk factors. The results of data from the 2018 Basic Health Research (Riskesdas) showed that the prevalence of hypertension reached 34.1%, the results of these figures were obtained from Indonesian people aged over 18 years, where the highest cases were in South Kalimantan (44.1%) and the lowest cases in Papua (22.2%) (Sihombing, 2022). In general, cases of hypertension occur in old age, but cases of hypertension can occur in adolescents and young adults (Meher et al., 2023). Based on previous research, it is stated that the prevalence of hypertension at the age of 20-30 years is around 45.2%. The biggest risk factors are genetics inherited from family history, sodium consumption, and obesity (Sudikno et al., 2023). Hypertension is also the main etiology of ESRD (End Stage Renal Disease), which is as much as 30%, after cases of diabetic nephropathy (Ghaderian et al., 2015). Hypertension plays a major role in cases of kidney failure, as hypertension can cause kidney damage severe enough to result in ESRD (Burnier & Damianaki, 2023). The severity of kidney damage in hypertension depends on the extent to which increased systemic pressure is transmitted to the renal microvasculature (Kohagura et al., 2024).

Hypertension is also caused by an imbalance of fluids in the body which is regulated by the renin-angiotensin-aldosterone system (RAAS) mechanism and also the cardiovascular system (Muñoz-Durango et al., 2016). In the cardiovascular system, blood pressure is determined by two main factors, namely cardiac output and peripheral resistance. In old age, there is a risk of increased vascular resistance which causes stiffness in the blood vessels, while in young age, there is often an increase in cardiac output. In addition to the cardiovascular system, RAAS also plays a role in controlling blood pressure where renin functions to convert angiotensinogen into angiotensin I, then converts it into angiotensin II by ACE (angiotensin-converting enzyme) in the lungs (Laurent & Boutouyrie, 2020). Angiotensin II is a powerful vasoconstrictor that causes an increase in blood pressure. In the adrenal glands, angiotensin II binds to angiotensin II receptors and secretes the hormone aldosterone. Aldosterone functions to regulate extracellular fluid volume by increasing sodium reabsorption from the renal tubules. When reabsorption occurs, water is absorbed, causing an increase in plasma fluid volume. An increase in plasma fluid volume causes an increase in blood volume and blood pressure (Ksiazek et al., 2024).

In the RAAS mechanism, hypertension occurs due to increased ACE activity through the RAAS. ACE activity can be inhibited through ACE inhibitors (ACE-I). ACE-I is one of the treatments for hypertension, such as captopril which is effective in lowering blood pressure in patients with essential hypertension. The side effects of captopril are generally cough, angioedema, and numbness, this is due to increased bradykinin receptors. Therefore, ACE-I derivatives have emerged which have fewer side effects such as enalapril, lisinopril, and ramipril. ACE-I can be prescribed as a single or combination treatment to lower high blood pressure (Borghi et al., 2023). In addition to pharmacological therapy, several plant extracts have been shown in vitro as ACE inhibitors. These beneficial effects come from flavonoid compounds, where complex chemical compound derivatives can reduce oxidative stress inhibit the activity of angiotensin-converting enzymes, and can provide vasodilating effects on blood vessels. Several studies have also shown that rose flower extract (Rosa damascena) can lower blood pressure and pulse rate in normotensive rats (Paiva et al., 2023). Another study also showed that rose oil aromatherapy can reduce sympathetic nerve activity by 40% and adrenaline concentration by 30% (Kawai et al., 2020). Therefore, the study aims to investigate the impact of administering ethanol extract of *Rosa damascena* on the activity of Angiotensin-Converting Enzyme in Wistar rats fed a sodium-enriched diet.

METHOD

This study is an experimental study with a post-test-only control group design, using a control group and a treatment group with simple randomization. The experimental animals used were male Wistar rats which were randomly divided into 5 groups. The research population was male Wistar rats weighing 150-200 grams. Each group has a minimum of 5 rats. To prevent a lack of samples due to death, researchers have to use 6 Wistar rats per group with a total of 5 groups, so that the total number of research subjects is 30. Blood samples for measuring ACE activity will be taken randomly as many as five per group (Hamed et al., 2024). Group P0 = consists of 6 male Wistar rats that were given regular water to drink. Group P1 = consists of 6 male Wistar rats that were given a high-sodium diet (8% NaCl solution in distilled water) and given rose extract orally at a dose of 500mg/kg body weight. Group P2 = consists of 6 male Wistar rats that were given a high-sodium diet (0.35% NaCl solution in distilled water) and given rose extract orally at a dose of 500mg/kg body weight. Group P3 = consists of 6 male Wistar rats that were given a high-sodium diet (8% NaCl solution in distilled water) and not given rose extract. Group P4 = consists of 6 male Wistar rats that were given a high-sodium diet (0.35% NaCl solution in distilled water) and not given rose extract. The high salt diet is an 8% NaCl solution, while the low salt diet is a 0.35% NaCl solution with a sonde technique on each Wistar rat in the treatment group. The administration of this salt solution is done with a sonde technique to ensure that nothing is wasted or leftover (Salim et al., 2020). ACE activity was measured by the ELISA method. Data were analyzed using ANOVA. This study has received ethical approval from the Health Research Ethics Committee, Universitas Prima Indonesia No.013/KEPK/UNPRI/II/2021.

RESULT

Table 1 shows that there are differences between treatment groups. Next, a Post Hoc analysis was conducted to determine which groups showed significant differences. The test results will be shown with differences in notation in each treatment group.

Table 1.
ACE activity of Wistar rats after treatment (ng/ml) (n=30)

Group	n	ACE (mean±SD)
P0	6	566,67±60,52
P1	6	466,09±48,19
P2	6	413,95±68,01
P3	6	664,48±75,92
P4	6	484,17±59,40

Table 2 shows that the normality test on ACE obtained normally distributed data (p>0.05). So the ANOVA test was carried out.

Table 2.
Normality test for ACE

Variable	n	Shapiro-Wilk
ACE	30	0,959

Table 3 shows that the Anova test obtained a p-value (0.00), which obtained a p-value <0.05, this indicates that there is a significant difference in ACE between the treatment groups. The results showed that ACE activity differed between groups that received rose extract (P1 and P2) and groups that did not (P3 and P4). When the control group (P0) was compared with the group that received rose extract (P1 and P2), there was also a decrease in ACE activity in P1 and P2. When P0 was compared with P3 (mice that received a high sodium diet), there was a difference. Giving a low sodium diet to P4 showed a decrease in ACE activity when compared to the control group (P0). Giving a high sodium diet (P3) showed an increase in ACE activity when compared to the control group (P0), the group of mice that received a low sodium diet (P4), and the group that received rose extract (P1 and P2). In the group of mice that received rose extract (P1 and P2), different sodium diets showed differences in ACE activity.

Table 3.
Anova test for ACE

ACE	Min-Max	p-value
P0	470,00-649,83	
P1	387,60-511,65	
P2	304,05-518,34	0,000
P3	569,47-753,78	
P4	378,68-546,16	

DISCUSSION

Giving a high sodium diet to groups P3 (high sodium diet without rose extract) and P4 (low sodium diet without rose extract) significantly increased ACE (Angiotensin Converting Enzyme) levels when compared to groups P1 and P2 which received rose extract. A high-sodium diet plays a significant role in the increasing prevalence of hypertension and subsequent risks such as kidney and heart disorders (Jaques et al., 2021). The recommended daily intake of sodium according to the Chinese Nutrition Association is 2,400 mg/day (Jiang et al., 2024). Administration of rose extract to groups P1 (high sodium diet) and P2 (low sodium diet) significantly reduced ACE, both compared to the groups that did not receive rose extract (P3 and P4), or when compared to the control group (P0). Rose flowers (Rosa damascena) contain several phytochemicals, one of which is flavonoids, where flavonoids act as enzyme inhibitors (Jariani et al., 2024). Previous research results show that flavonoid content has the potential to prevent ACE both in vitro and in vivo (Ullah et al., 2020). The quercetin-3-glucuronic acid content in flavonoids has been proven to be able to inhibit ACE so that it can maintain blood pressure regulation (Carrillo-Martinez et al., 2024).

The administration of rose flower extract with different sodium diets (high sodium diet in P1 and low sodium diet in P2) had differences. This is in line with research by Yuan et al. (2023) who reported that reducing sodium intake has been shown to reduce blood pressure levels, where sodium intake of 100 mmol/day can reduce the average systolic and diastolic pressure, namely 4.47 mmHg and 1.90 mmHg in diastolic (Filippini et al., 2021). In the research of Mallamaci and Tripepi (2024), it was found that sodium has a significant relationship with ACE. Previous research found that systolic blood pressure (mmHg) in the high-sodium diet group was 133 ± 20 while in the low-sodium diet group, it was 122 ± 17. In diastolic blood pressure (DBP) (mmHg) it was found that in the high-sodium diet group, it was 80 ± 13 while in the low-sodium diet group, it was 73 ± 11. In the mean arterial pressure (mmHg) it was found that in the high sodium diet group it was 97 ± 15 while in the low sodium diet group, it was 89 ± 12 (Graudal et al., 2017). When P1 and P2 are compared with P0, it can be seen that rose extract continues to work to inhibit ACE, both in high and low sodium conditions.

In addition to reducing sodium intake, giving antihypertensives can also lower blood pressure levels. One of the main therapies for giving antihypertensives is the ACE-inhibitor (Angiotensin Converting Enzyme) inhibitor group, where ACE-I can inhibit the change of angiotensin I (Ang I) to angiotensin II (Ang II) (Sinha & Agarwal, 2019). Where angiotensin II is a strong vasoconstrictor that can increase blood pressure. Angiotensin II also stimulates the proximal tubule of the nephron to reabsorb sodium and water, thereby increasing sodium reabsorption in the kidneys which ultimately increases blood pressure volume (Li & Zhuo, 2016).

ACE inhibitor therapy has advantages compared to other antihypertensive drugs because ACE inhibitors minimize side effects on the CNS (Central Nervous System). However, ACE inhibitors have some side effects such as cough, and rash on the body (Strauss et al., 2023). The use of natural ACE is believed to be safer and more economical to reduce blood pressure levels. One of the plants that can reduce ACE levels is the rose flower (Rosa damascena) (Boskabady et al., 2011). Rosa damascene has active components such as flavonoids that are associated with effects on the RAS (Renin-Angiotensin) system and the cardiovascular system. Rosebuds contain cyanidin-3-O-betaglucoside that significantly suppresses ACE activity, where ACE is the main enzyme in the formation of angiotensin II (Ang II). This plant has beneficial effects on cardiovascular parameters and the RAAS system (Verešová et al., 2024).

ACE inhibitor therapy can lower blood pressure by 35/20 mmHg in the group that received mental stress. ACE inhibitors work in the RAAS where ACE inhibitors can activate vasodilation of blood vessels and reduce aldosterone hormone levels. The decrease in the aldosterone hormone will reduce sodium reabsorption and ultimately reduce blood pressure (Ferrari, 2013). In one study, an aqueous ethanolic extract of Rosa damascena was shown to increase heart rate and contractility in isolated guinea pig hearts. The mechanism of this effect is unknown. However, a possible stimulatory effect of the plant on isolated guinea pig cardiac adrenoceptors is suggested. A new compound called cyanidin-3-O-β-glucoside was isolated from Rosa damascena shoots. This compound significantly suppressed ACE activity. Since ACE is a key enzyme in the production of angiotensin II, Rosa damascena may be effective in improving cardiovascular and RAAS function (Boskabady et al., 2013).

The magnitude of ACE activation inhibited by rose ethanol extract can be seen from the difference in the average ACE at P3 and P1, and the difference in the average ACE at P4 and P2. In the administration of a high sodium diet, rose extract reduced ACE to 178.39 ng/mL. Thus, the administration of the rose extract to mice receiving a high-sodium diet made ACE activity greater than that of mice receiving a low-sodium diet. Administration of rose extract as an ACE Inhibitor is better when combined with the administration of a low-sodium diet. This proves that a low-sodium diet can be done as an additional non-pharmacological therapy for people with hypertension. Previous studies have stated that the 4% high NaCl diet group showed increased expression of angiotensin II type 1 receptors and decreased expression of angiotensin II type 2 receptors in the aorta. Giving a low-sodium diet can also increase the elasticity of blood vessels, so it can reduce increased blood pressure (Wang et al., 2019). Increased ACE activity was found in P3 (mice that received a high sodium diet), both when compared with the control group (P0), the group of mice that received rose extract (P1 and P2), or the group that received a low sodium diet (P4). The decrease in sodium levels in the blood triggers the RAAS mechanism. The decrease in sodium levels will continue to activate ACE until blood pressure increases to normal levels (Ksiazek et al., 2024).

CONCLUSION

The ACE activity of Wistar rats that received rosa damascena extract was lower ($p<0.005$) compared to those that did not receive the extract. Rosa damascena extract further reduced ($p<0.05$) the ACE activity of Wistar rats that received a low diet compared to a high sodium diet.

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