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Effects of Pamelo Orange Peel (*Citrus maxima*) Ethanol Extract on Macroscopic Kidney and Heart of Hypertensive Rats

(*Efek Ekstrak Etanol Kulit Jeruk Pamelo (Citrus maxima) pada Makroskopik Ginjal dan Jantung Tikus Hipertensi*)

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ABSTRACT

Background: Hypertension, characterized by elevated blood pressure (≥140/90 mmHg), leads to kidney and heart damage. Hypertension causes increased heart rate, heart enlargement, risk of heart failure, and damage to kidney blood vessels. One way to treat hypertension is by administering drugs such as herbal medicines. Pamelo oranges (*Citrus maxima*) are starting to be developed in the treatment of diseases. The ethanol extract of pomelo orange peel (EEKJP) contains flavonoid compounds which have antihypertensive activity as a natural Angiotensin Converting Enzyme (ACE) inhibitor, diuretic, increases Nitric Oxide Synthase (NOS) activity and activates Endothelium Derived Relaxing Factor (EDRF). **Objectives:** This study aims to examine the effect of ethanol extract of pomelo orange peel on the macroscopic features of the heart and kidneys of hypertensive rats (*Rattus norvegicus*). **Methods:** This research uses The Posttest-Only Control Group Design. Thirty rats were divided into six groups, namely naive control, negative control (NaCMC 1%), positive control (Captopril 0,45 mg/200 gramBB), EEKJP 100 mg/KgBW group, EEKJP 150 mg/KgBW group, and EEKJP 200 mg/KgBW group. Hypertension condition through induction with prednisone 1.5 mg/KgBW and NaCl 2% for 21th days. The test preparation was administered orally for 14th days. Next, all rats were dissected to remove the heart and kidney organs for macroscopic observations. **Results:** The results of the study showed that ethanol extract of pomelo (*Citrus maxima*) orange peel had a varied effect on the macroscopic appearance of the heart and kidneys of rats with hypertension. The heart organ shows structural improvements, while the kidneys have not shown any improvement. **Conclusions:** Extract with a dose of 100 mg/KgBW has no changes in the macroscopic appearance of the heart so it is thought to be able to repair damage to the heart organ.

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INTRODUCTION

Hypertension is an abnormal condition of arterial blood pressure which is characterized by blood pressure values above normal values (systolic: ≥140 mmHg and diastolic: ≥ 90 mmHg) (Singh et al, 2017). Globally, hypertension has a prevalence of 1.13 billion, while the national hypertension rate reaches 34.1% (Noviati et al., 2022). If hypertension is not treated immediately, it can cause serious health conditions and become a major risk factor for coronary heart disease, stroke, kidney failure, dementia, vision problems and other diseases. There are around 54% of cases of stroke and coronary heart disease caused by high blood pressure which accounts for 33% of global deaths (Rajadurai, 2017).

Epidemiological research shows that mild hypertension (blood pressure ≥ 140/90) in young or middle-aged adults will ultimately increase the risk of damage to body organs (Erawati, 2007). Organ damage is one of the complications resulting from uncontrolled or prolonged hypertension. Hypertension also increases the work of the heart. Prolonged workload will eventually cause heart enlargement and increase the risk of heart failure and heart attack (Bangsawan et al., 2013).

Another primary impact of increasing blood pressure is damage to the kidney blood vessels, resulting in a decrease in kidney function. Hypertension causes barotrauma stimulation of the glomerular capillaries and increases the glomerular capillary pressure. This will cause glomerulusclerosis and can stimulate chronic hypoxia which causes kidney damage (Maritha et al., 2021).

One way to reduce the prevalence of hypertension which leads to organ damage is through administering medication (Muliani, 2021). However, long-term use can cause drug side effects such as hypotension, kidney problems, and even impotence. Therefore, alternative treatments are needed that have minimal side effects and toxicity.

One plant that is beneficial to humans is the pomelo (*Citrus maxima*). Pamelo oranges are a type of orange that is widely cultivated in Indonesia. Pamelo orange peel contains bioactive components such as alkaloids, flavonoids, vitamin C and lycopene (Base, 2018). Polyphenolic compounds such as flavonoids have antihypertensive activity as natural Angiotensin Converting Enzyme (ACE) inhibitors, diuretics, increase Nitric Oxide Synthase (NOS) activity and activate Endothelium Derived Relaxing Factor (EDRF) which plays a role in vasodilation (Abed, 2021). In addition, flavonoids can work through antioxidant mechanisms. Based on the research results of Gupta et al. (2021) who compared the antioxidant value of each part of the pomelo fruit, it was found that the highest antioxidant value was found in the flavedo skin (Gupta et al, 2021).

Based on the description above, preliminary research has been carried out on the effect of ethanol extract of pomelo (*Citrus maxima*) orange peel on the macroscopic appearance of the kidneys and heart of rats

with hypertension. Thus, it is hoped that this research can add scientific data, namely that pomelo peel extract can have an antihypertensive effect that is safe for heart and kidney tissue and as a basis for further research to test the pharmacological effects of pomelo peel with other parameters.

MATERIAL AND METHODS

Materials

The tools used in this research are grinder machine (Fomac FCT-Z500), maceration container, sieve, rotary vacuum evaporator (IKA™ RV 10 V), animal cage, non-invasive blood pressure measuring device (CODA), magnetic stirrer (Mixer Vortex), analytical balances (Kern) and surgical equipment. Ingredients used in this research: male white rats (UMI Pharmacology Laboratory), pomelo orange peel (Ma'rang, Pangkep), prednisone (Ibnusina Pharmacy), captopril (Ibnusina Pharmacy), ampoule ketamine (Ibnusina Pharmacy), NaCl 2% (Ibnusina Pharmacy), distilled water, 96% ethanol, Na -CMC (Sumber Rejeki ALKES Store), standard feed and husks.

Methods

This research has received an ethical certificate from the Research Ethics Committee (KEP) of the Indonesian Muslim University with number 600/A.1/KEP-UMI/XII/2023.

Preparation of ethanol extract of pomelo orange peel (EEKJP)

The process of making pomelo peel extract is carried out using the maceration method, namely crushed pomelo peel powder is added to 96% ethanol solution until the sample is completely submerged while stirring periodically and leaving for 3 x 24 hours. Then filtration is carried out to obtain liquid extract of pomelo orange peel and residue. After that, the residue is macerated again. Next, the liquid extract of pomelo peel is collected then concentrated using a rotary vacuum evaporator and evaporated using a water bath until a thick extract of pomelo is obtained (Filbert et al., 2023).

Preparation of Pamelo Orange Peel Ethanol Extract Suspension

The ethanol extract of pomelo orange peel will be made in three variations, namely 100 mg/KgBB, 150 mg/KgBB and 200 mg/KgBB. Weighed 80 mg, 100 mg, and 160 mg of ethanol extract of pomelo orange peel respectively according to calculations. After that, 1% NaCMC was suspended until homogeneous, put into a 100 ml measuring flask and filled to the mark line (Safrina et al., 2018).

Treatment of Test Animals

In the initial stage, 30 rats were adapted for 14 days and their initial blood pressure was measured using a Tail Cuff Blood Pressure Analyzer on day 0 (T0). Next, they were grouped into 6 groups. Apart from group 1, rats were given 1.5 mg/Kg prednisone and 2% NaCl for 21 days as an inducer for the

hypertensive rat model. On day 22 (T1), the blood pressure of the rat was measured after being induced with a blood pressure target of > 174/145 mmHg. Days 23-36 are given the following treatment:

1) Group I, given standard feed (normal control)
2) Group II, given Na-CMC 1% orally (negative control)
3) Group III, given captopril 0,45 mg/200 gramBB orally (positive control)
4) Group IV, given EEKJP 100 mg/kgBB orally
5) Group V, given EEKJP 150 mg/kgBB orally
6) Group VI, given EEKJP 200 mg/kgBB orally

On day 37 (T2), blood pressure was measured again (Elisa et al., 2021).

On the 38th day, all test animals were anesthetized for sacrifice, then the kidneys and heart were removed using a set of surgical instruments. The organs taken were washed with physiological NaCl solution. Observations for changes in color, surface and consistency were carried out on fresh organs. Before color changes are detected, each organ is labeled to avoid data errors (Sutomo et al., 2019; Ceriana & Rejeki, 2023).

RESULTS AND DISCUSSION

This study aims to provide a macroscopic picture of the kidney and heart organs of rats experiencing hypertension after administration of ethanol extract of pomelo (*Citrus maxima*) orange peel. Testing the effect of ethanol extract of pomelo orange peel (EEKJP) with varying doses of 100 mg/kgBB; 150 mg/KgBW and 200 mg/kgBW were carried out on experimental rat. The inclusion criteria in this study were that experimental rat experienced an increase in blood pressure in both systole and diastole after being induced by 1.5 mg/Kg prednisone and 2% NaCl for 21 days, where all rats had blood pressure above the normal limit, namely > 174/145 mmHg. This is because prednisone is a corticosteroid drug which can cause hypertension directly or indirectly. Indirect influence through mineralocorticoid effects with a working mechanism of increasing sodium and water resistance in the kidneys so that blood volume increases. Meanwhile, the direct influence of corticosteroids on the cardiovascular system includes capillaries, arterioles and heart muscle through the effects of glucocorticoids (Lestari et al., 2023; Raisania et al., 2012).

Hypertension caused by corticosteroids depends on the therapeutic dose. Full dose prednisone therapy has a higher dose than the alternating dose, namely 2 mg/kgBW/day (maximum 80 mg/day) while the alternating dose is given at 1.5 mg/kg BW/day (maximum 60 mg/day). The greater the dose of corticosteroid therapy, the greater the side effects. There is a positive correlation between side effects and the cumulative dose of corticosteroids (Raisania et al., 2012). Apart from that, one of the factors causing an increase in blood pressure is consuming excessive salt intake. Where, excessive sodium consumption can cause the sodium concentration in the extracellular fluid to increase (Rauf et al., 2018).

In this study, using 2% NaCl can increase blood pressure by stimulating the formation of renin, resulting in vasoconstriction and increasing blood volume (Aria et al., 2021).

Experimental animals that had hypertension were then given EEKJP with three dose variations for 14 days to see its effect on the kidneys and heart. This is based on the connection between these two organs and hypertension. Organ damage is a general term used for complications resulting from uncontrolled or prolonged hypertension. Hypertension causes enlargement of the heart and increases the risk of heart failure and heart attack (Bangsawan et al., 2013). Another primary impact, hypertension causes barotrauma stimulation of the glomerular capillaries and increases glomerular capillary pressure. This will cause glomerulusclerosis and can stimulate chronic hypoxia which causes kidney damage (Maritha et al., 2021).

The results of macroscopic observations of the kidney organs of hypertensive rats after being induced by ethanol extract of pomelo orange peel can be seen in table 1 and figure 1.

Table 1. Macroscopic observation data on the kidneys of hypertensive rats after treatment for 14 days

Groups	Replication	Macroscopic observation of kidney organs		
		Color	Surface	Consistency
Normal Control	1	Brownish red	Smooth	Springy
	2	Brownish red	Smooth	Springy
	3	Brownish red	Smooth	Springy
Negative Control NaCMC 1%	1	Brownish red	Spotted	Springy
	2	Brownish red	Smooth	Springy
	3	Brownish red	Smooth	Springy
Positive Control Captopril 0,45 mg/200 gramBB	1	Brownish red	Smooth	Springy
	2	Brownish red	Smooth	Springy
	3	Brownish red	Rough	Springy
EEKJP 100 mg/Kg BW	1	Brownish red	Smooth	Springy
	2	Brownish red	Smooth	Springy
	3	Brownish red	Spotted	Springy
EEKJP 150 mg/Kg BW	1	Brownish red	Smooth	Springy
	2	Brownish red	Smooth	Springy
	3	Brownish red	Rough	Springy
EEKJP 200 mg/Kg BW	1	Brownish red	Smooth	Springy
	2	Brownish red	Smooth	Springy
	3	Brownish red	Spotted	Springy

Note. EEKJP (Pamelo Orange Peel Ethanol Extract)

Table 1 shows that the macroscopic appearance of rat kidneys does not show any striking differences in color or morphological changes between all treatment groups. All rats had brownish red kidney color (Figure 1.). Based on the explanation by Ceriana and Sari (2016) in their research, macroscopic observations of the kidneys showed that the color of the kidneys was pale and the size of the organ increased when given nephrotoxic test materials (Septiva et al., 2019). Another observation parameter is the surface and consistency of the kidney organs among the six groups that changed the most, namely NaCMC 1% group (negative control) was followed by the 100 mg/KgBW and 200 mg/KgBW extract groups with spotty surfaces, while the EEKJP 150 mg/KgBW and Captopril groups had rough surfaces. This proves that the administration of ethanol extract of pomelo orange peel has not shown any better changes in the macroscopic appearance of the kidneys of hypertensive rats.

Captopril is an antihypertensive drug that works as an ACE (Angiotensin Converting Enzyme) inhibitor, namely as an inhibitor of the angiotensin converting enzyme by reducing the formation of angiotensin II (Mulyani et al., 2015). This drug has been widely used for the therapy of arterial hypertension and cardiovascular diseases. Treatment with captopril in conditions of kidney damage due to hypertension can reduce blood pressure, repair kidney injury, and suppress kidney inflammation and inhibit activation of nuclear factor-kB NF-kB (Gan et al., 2018).

The macroscopic profile of the kidneys of hypertensive rats after treatment with ethanol extract of pomelo orange peel (EEKJP) for 14 days is shown in Figure 1 below :

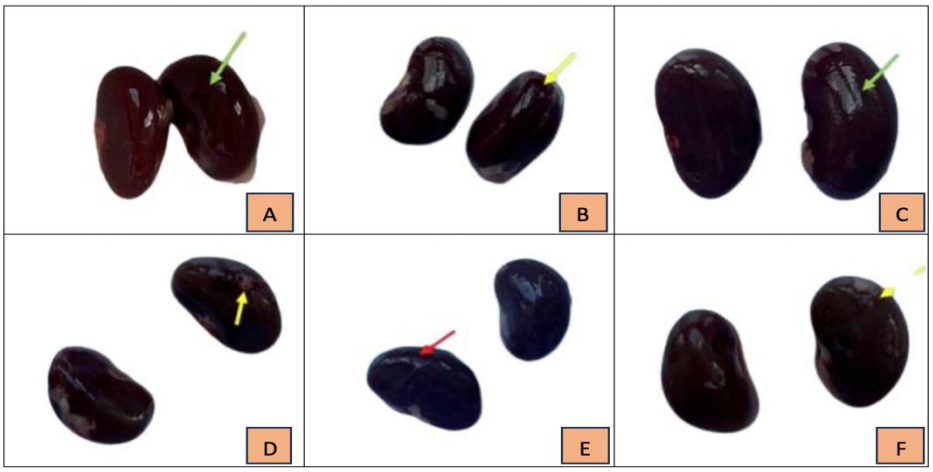

Figure 1. Morphology of the kidneys of hypertensive rats after treatment for 14 days
(A = Normal control; B = Negative control, C = Captopril positive control, D = EEKJP 100 mg/KgBW, E = EEKJP 150 mg/KgBW, and F = EEKJP 200 mg/KgBW; Yellow arrow = Spotted surface, Green arrow = Smooth surface, Red arrow = Rough surface, Blue arrow = Pale red color)

Macroscopic observations made on the heart organ include color, surface and consistency. The macroscopic observation data on the heart organs of rats experiencing hypertension after being treated for 14 days can be seen in table 2 and figure 2.

Table 2. Macroscopic observation data on the heart of hypertensive rats after treatment for 14 days

Groups	Replication	Macroscopic observation of the heart organ		
		Color	Surface	Consistency
Normal Control	1	Brownish red	Smooth	Springy
	2	Brownish red	Smooth	Springy
	3	Red	Smooth	Springy
Negative Control NaCMC 1%	1	Blackish red	Spotted	Hard
	2	Brownish red	Spotted	Hard
	3	Pale red	Smooth	Springy
Positive Control Captopril 0,45 mg/200 gramBB	1	Brownish red	Smooth	Springy
	2	Brownish red	Spotted	Springy
	3	Brownish red	Smooth	Springy
EEKJP 100 mg/Kg BW	1	Brownish red	Spotted	Springy
	2	Brownish red	Smooth	Springy
	3	Brownish red	Smooth	Springy
EEKJP 150 mg/Kg BW	1	Brownish red	Rough	Springy
	2	Brownish red	Smooth	Springy
	3	Pale red	Smooth	Springy
EEKJP 200 mg/Kg BW	1	Brownish red	Rough	Hard
	2	Brownish red	Smooth	Springy
	3	Pale red	Smooth	Springy

Note. EEKJP (Pamelo Orange Peel Ethanol Extract)

A normal heart has a brownish red color with a smooth surface and does not experience hardening, while an abnormal heart will experience color changes, hardening, and have a spotty surface (Anggraeni et al., 2017; Sutomo et al., 2019). Based on the data in table 2, it shows that the negative control group showed a structure with several changes, namely a blackish red and pale red color, experienced hardening and a spotty surface (Figure 2). This indicates that damage has occurred to cells and tissues. This is in accordance with research by Hakimah et al. (2021), that hypertension can change the structure and tissue of cells, so that it can potentially lead to a fatal condition, namely cell death (Hakimah et al., 2021). The test group for ethanol extract of pomelo orange peel which did not have changes in macroscopic morphology was the 100 mg/kg BW dose group. Thus, it can be concluded that the ethanol extract of pomelo orange peel at a dose of 100 mg/kgBW is thought to be able to repair heart damage. This happens because the dose of the active substance is thought to have an effect on cell regeneration in the heart in greater numbers so that damaged cells can regenerate again (Tandi et al., 2017).

The macroscopic profile of the heart of hypertensive rats after treatment with ethanol extract of pomelo orange peel (EEKJP) for 14 days is shown in Figure 2 below:

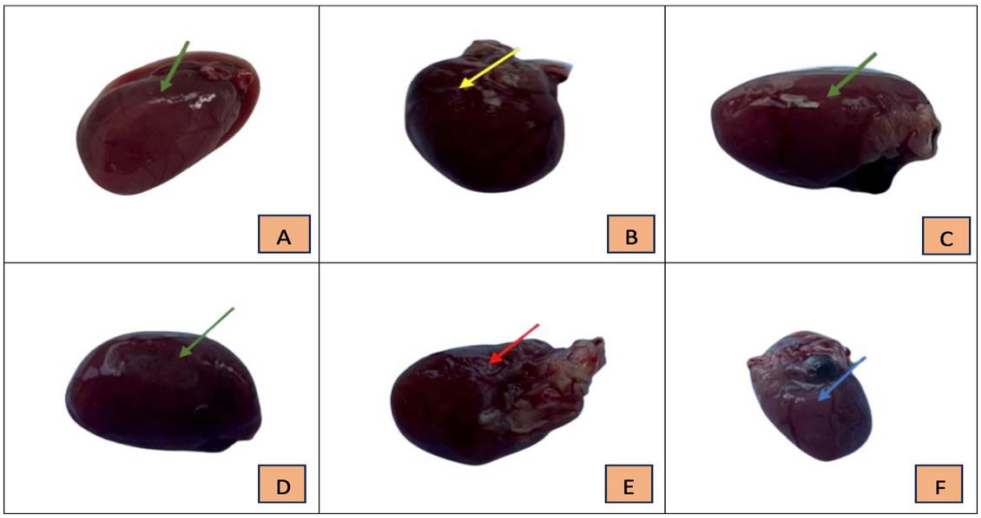

Figure 2. Morphology of the heart of hypertensive rats after treatment for 14 days
(A = Normal control; B = Negative control, C = Captopril positive control, D = EEKJP 100 mg/KgBW, E = EEKJP 150 mg/KgBW, and F = EEKJP 200 mg/KgBW; Yellow arrow = Spotted surface, Green arrow = Smooth surface, Red arrow = Rough surface, Blue arrow = Pale red color)

Based on the description above, the ethanol extract of pomelo orange peel specifically at a dose of 100 mg/KgBW did not have any changes in the macroscopic heart of rats with hypertension. This is possibly because pomelo orange peel contains bioactive components such as alkaloids, flavonoids, vitamin C and lycopene (Base, 2018). The content of these compounds functions as an antioxidant intake. Antioxidants function as the body's defense against free radicals that induce oxidative stress and reactive oxygen compounds in plasma and cells so that cell damage does not occur (Tandi et al., 2017). Polyphenolic compounds such as flavonoids have antihypertensive activity as natural ACE inhibitors, can act as diuretics and increase NOS activity and activate EDRF which plays a role in vasodilation of blood vessels (Abed, 2020). Apart from that, the flavonoid compounds contained in plants act as diuretic agents so they can increase the glomerular filtration rate. This causes nephrotoxic substances that enter the kidneys to be excreted quickly due to increased urination (Septiva et al., 2019).

CONCLUSION

Ethanol extract of pomelo orange peel has varied effects on the macroscopic appearance of the heart and kidneys of rats with hypertension. The extract at a dose of 100 mg/KgBW does not have any macroscopic changes to the heart so it is thought to be able to repair heart damage. Furthermore, further tests should be carried out regarding the microscopic appearance of the heart and kidneys of hypertensive rats given the extract.

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CONFLICT OF INTEREST

The authors declare no conflict of interest

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