LEMBAR
HASIL PENILAIAN SEJAWAT SEBIDANG ATAU *PEER REVIEW*
KARYA ILMIAH : JURNAL NASIONAL TERAKREDITASI

Judul Karya Ilmiah (artikel) : Hypertension Profile of Angiotensin Receptor Blocker From Matoa Leaves Extract (Pometia Pinnata J.R. Foster & G. Foster) In Angiotensin II Induced-Male Rat With Blood Volume Parameter
Nama Penulis : Novi Elisa*, **F.X. Sulistiyanto W.S.**, Jaka Seprianto Lepangkari
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Kategori Publikasi Jurnal Ilmiah (beri √ pada kategori yang tepat)
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Hypertension Profile of Angiotensin Receptor Blocker From Matoa Leaves Extract (Pometia Pinnata J.R. Foster & G. Foster) In Angiotensin II Induced-Male Rat With Blood Volume Parameter

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ABSTRACT
Hypertension is a problem of cardiovascular disease that occurs in many people, cause of death beside stroke and tuberculosis. The leaves of matoa, which have another name, Pometia pinnata, are one of the plants used as traditional medicine for the treatment of hypertension. The active compounds of matoa leaves are flavonoids. This study aimed to observe the hypertension profile of the Angiotensin Receptor Blocker class. The test animals used in this study were 45 male Wistar rats. Each group consisted of 5 rats induced by angiotensin II, divided into groups, namely normal control, negative control, positive control, a dose of 75g/kgBW, 150g/kgBW, and 300g/kgBW, and observation were done for 14 days. The hypertension profile observed in this study was the blood volume of rats. The percentage reduction in blood volume of rats given the best matoa leaves extract was 300 mg/kgBW, extract which showed mean difference in negative control group with a significance value of <0.05.

Keywords: Hypertension, Pometia Pinnata, Angiotensin II, Blood Volume, Rat

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BACKGROUND

Hypertension is a problem of cardiovascular disease that occurs in many people. Hypertension (6.8%) is the top three diseases that can cause death beside stroke (15.4%) and tuberculosis (7.5%). World Health Organization explain that the percentation of hypertension in men (more than 25 years) is quite large than women. It is proven that 32.5% of hypertension occurs in men and 29.3% in women (Riskesdas, 2013).

Epidemiological studies show that the risk of damage to the kidneys, heart and brain is directly related to the degree of increase in blood pressure, even mild hypertension (blood pressure 140/90 mmHg) thus increases the risk of damage to various organs (heart, central nervous system, kidneys, eyes, peripheral blood vessels). Classification of antihypertensive drugs is divided according to the main regulatory place or the mechanism in which it works which includes diuretics, sympathoplegic drugs, vasodilators, drugs that inhibit angiotensin production and action (Dipiro, 2015).

Angiotensin II has two main effects that can increase arterial pressure, the first is vasoconstriction which occurs mainly in the arterioles and causes veins weakness. The occur of contraction in arterioles will increase peripheral resistance which results in increased arterial pressure. Light contraction of the veins will also increase blood flows in the veins toward heart, thereby helping the heart to fight the increased of blood pressure. Second effect, where angiotensin increases arterial pressure by working on the kidneys to decrease salt and water excretion when the pressure and volume of blood in the efferent arterioles decrease due to decreased salt intake. Enzyme renin convert a plasma protein called angiotensinogen into a peptide called angiotensin II. Angiotensin II functions as a hormone that increases blood pressure and blood volume. Angiotensin II increases blood pressure by constricting the arterioles, reducing blood flow to many peripherals including renal capillaries (Guyton and Hall, 2008).

Angiotensin Receptor Blocker (ARB) acts by blocking the AT 1 receptor to determine the pathogenesis of hypertension by treating hypertension using experimental animal, one of which uses experimental animals induced by angiotensin II selection to use angiotensin II because it produces a fast half-life in giving a hypertension effect (Sharma et al., 2010).

There are quite a lot of blood pressure-lowering drugs that have been distributed but the problem is the effectiveness of therapy and side effects of the drug (Azizah, 2008) in general, the use of antihypertensive drugs takes a long time by consuming blood pressure-lowering drugs regularly for entire life which accompanied by side effects. (Armenia et al, 2007

Secondary metabolites from matoa leaves are compounds such as alkaloids, terpenes, flavonoids, lignans, steroids, curcumin, saponins, phenolics, flavonoids, and glucosides (Suedee, 2013). *Pometia pinnata* is a member of the Sapindaceae family, widely distributed in the Asia Pacific including Papua, Indonesia (Trimedona, 2015).

Hypertension drugs based on research (Purwidyaningrum, 2017). The ACEI (Angiotensin Converting Enzym Inhibitor), CCB (Calcium Channel Blocker), BB (Beta Blocker) class of drugs have been tested as blood pressure-lowering so that researchers are interested in continuing research on antihypertensive drugs using the ARB (Angiotensin Receptor Blocker) class with hypertension profile of blood volume parameter. in male rats 200-230 kg / body induced by angiotensin II.

METHODS

Equipment that used in this research were equipments for making matoa leaves extract, such as flannel, dark colored container, analytical scales, glass beaker, oven, blender, sieve and vacuum, stirring rod, rotary evaporator. Equipments for animal testing were analytical

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scales, injection syringes 1 cc, oral syringe. Equipment for measuring blood pressure use blood pressure analyzer with tail cuff method. Equipment for determining drying losses was moisture balance.

Materials that used in this study were matoa leaves taken from the matoa plant, chemicals used in this study were 96% ethanol, n-hexane, ethyl acetate, water, negative control used was CMC, Irbesartan as a positive control, NaCl, Formaldehyde 10%, angiotensin as induction of hypertension.

The animals used were male rats (Wistar strain) with a body weight of 200-230 grams, 45 rats used for antihypertensive activity testing were grouped into 9 groups with 5 rats for each group.

Manufacture of matoa leaves powder simplicia was done by weighing the fresh matoa leaves and then washed with water flow until it free from dirt and dust. Clean matoa leaves were cut into little pieces, after that dry it in the oven at temperature of 40 °C. The dried matoa leaves were crushed using a blender to obtain the simplicia of the matoa leaves.

Manufacture of matoa leaves ethanol extract was done by putting matoa leaves simplicia as much 500 grams into a container then 96% ethanol is added in the ratio (1:10) or 500 g of extract: 5 liters of ethanol. The mixture was left for 3 days with once stirring per day. Maserat was taken using Whatman filter paper. The maserate is collected and the waste is separated (Park et al., 2014).

Characterization of Extracts. Loss of drying determination was done by gravimetric method, equipment that used in this method was Moisture Balance with 3 replications, by tare the container for the powder on moisture balance, then put 2 g of powder into the Moisture Balance, a sign of the operation is complete with the sound of the tool, then record the results of loss of drying in percent units, in the same way, repeated 2 times (Novi, 2019).

Phytochemical Screening of matoa leaves (*Pometia pinnata*). Identification of chemical to prove the presence of chemical compounds in matoa leaves extracts, such as flavonoid, alkaloid, triterpenoid, steroid, saponin, tannin (MOH, 2000).

Blood volume test of angiotensin II hypertension model rats using the noninvasive direct tail-cuff method, CODA Instrument. Blood volume testing was done at the Pharmacology and Clinical Pharmacy Laboratory in Faculty of Pharmacy Gadjah Mada University.

RESULT AND DISCUSSION

Loss of drying from matoa leaves simplicia had result from 2 g matoa leaves powder which were tested by determining the loss of drying were measured using moisture balance, simplicia that is too high in moisture content will easily being place for the growth of fungi and bacteria as well as chemical changes that can damage simplicia. Loss of drying from matoa leaves simplicia was done 3 times, with a high heating ≥ 100 °C obtained an average of 9%. This value shows that in the simplicia lossing water and volatile substances of 9%. The moisture content obtained is in accordance with the loss of drying requirements of less than 10%, the research was done in Pharmacy Technology Laboratory of Setia Budi University, Surakarta.

Identification of the chemical content of the extract showed that the results of the matoa leaves extract contained flavonoids, alkaloids, triterpenoids steroids, saponins and tannins.

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Table 1. Result of Identification of Chemical Compound Content in Matoa Leaves Extract

Chemical Compound (Coloring Reagent)	Extract
Flavonoid	+
Alkaloid:	
a. Mayer	+
b. Dragendorf	+
c. wagner	+
Triterpenoid	+
Steroid	+
Saponin	+
Tanin	+

(+) : Showed positive result
(–) : Showed negative result

Results of the identification of the chemical compounds contained in matoa (*Pometia pinnata*) leaves extract are positive results in the color test reaction:

Flavonoid. Identification of chemical content in the extract using coloring reagents showed positive result for the presence of red magenta after addition of HCl and Mg, this is in accordance with Harbone's (1987) and research by Purwidyaningrum (2017) positive results of red magenta with the addition of reagents

Alkaloid. Identification of chemical content in the extract using coloring reagents showed positive result by using mayer reagent there is a white precipitate, while at dragendorf there is a red-orange precipitate, Wagner there is a brown precipitate, this is in accordance with Harbone's (1987) research.

Terpenoid. Identification of chemical content in the extract using coloring reagents showed positive result by the red orange color, this is in accordance with research by Purwidyaningrum (2017), the presence of red-orange-purple color.

Steroid. Identification of chemical content in the extract using coloring reagents showed positive result, this is in accordance with research tested by Harbone (1987) with the addition of anhydrous acetic acid and concentrated sulfuric acid to produce red-blue color.

Saponin. Identification of chemical content in the extract using coloring reagents showed positive result by the presence of foam in the matoa leaves extract for 10 minutes which does not disappear and stable.

Tannin. Identification of chemical content in the extract using coloring reagents showed positive result by the presence of greenish black precipitate.

Table 2. Result of Blood Volume Measurement

Group Treatment	Volume Darah (mmHg.Day)			
	T0	T1	T2	T3
Normal control	54.15±11.10	53.30±17.75	49.29±3.58	52.20±2.03
Negative control	73.65±16.91	103.83±13.07	102.01±6.05	98.11±5.70
Positive control	50.57±4.91	57.23±7.93	57.89±7.42	51.29±8.74
75 mg/kgBW extract	78.37±10.40	90.88±16.63	91.60±4.47	83.08±12.62
150 mg/kgBW extract	71.44±4.38	95.06±8.25	87.36±8.96	73.85±10.16
300 mg/kgBW extract	52.17±5.87	89.92±21.54	62.51±5.14	55.49±3.79

Angiotensin II hypertension profile in rat blood volume
T0: Not given treatment
T1: Angiotensin II Induction

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T2: Angiotensin II Induction
T3: Angiotensin induction and administration of test preparation

Hypertension profile of angiotensin receptor blocker in wistar male rats with angiotensin II as the inducing agent given for 12 days. Test animals aged 2-3 months, body weight 180-230 grams, rats are used as experimental animals because they have similarities with humans in terms of physiology, anatomy, nutrition, pathology, and metabolism, the selection of male test animals is due to the effect of hormonal changes.

Generally the parameters of hypertension are systolic and diastolic, where in the previous study by Novi (2019), systolic when the heart contracts while diastolic when the heart relaxes, it has been proven that angiotensin II-induced hypertension can significantly increase blood pressure.

Hypertension parameter using blood volume seen in this study is a profile that shows an increase in blood volume where in the negative control, blood volume levels increase after being given angiotensin II without being given extracts or irbesartan as a positive control. In the extract group with a dose of 75, 150 mg / kgBW, there was a decrease in blood volume, but it was not significant. In the positive control group and the 300 mg / kgBW extract there was a significant reduction in blood volume.

So it can be interpreted that in hypertension profile angiotensin receptor blocker test with angiotensin II induction has succeeded in increasing blood volume in hypertensive rat, while the extract dose shows a significant decrease but this need to be proven further so that angiotensin takes a long time as an inducing agent for see the target of organ damage in hypertensive conditions.

Table 3. AUC Total of Extract and Percentage of Blood Volume Decrease

Group Treatment	Blood Volume (mmHg.Day)			AUC Total	% Blood Volume Decreasing Activity
	T0-T1	T1-T2	T2-T3		
Normal control	161.18±10.75	153.88±21.27	304.47±23.15	619.52±34.09 ab	47.09±5.04
Negative control	266.22±44.23	308.76±25.04	600.38±31.77	1175.36±83.78 bc	-
Positive control	176.70±14.70	172.68±22.73	276.75±71.23	626.13±36.04 ab	46.42±6.62
75 mg/kgBW extract	253.87±14.78	273.72±24.16	524.02±26.08	1051.61±58.23 bc	10.04±10.57
150 mg/kgBW extract	249.75±15.32	273.63±22.37	483.62±7.29	1007.00±32.00 bc	14.15±4.10
300 mg/kgBW extract	213.14±37.91	228.65±25.85	354.00±25.06	795.79±47.98 ab	31.91±8.40

The result of total AUC and percentage significance of blood volume derease
a. Significant against the negative control <0.05
b. Significant against the treatment group <0.05
c. Significant against the normal control <0.05

The percentage reduction of blood pressure in male rats that being made of hypertension models, blood volume parameters has been proven by giving irbesartan as a positive control (46.42 ± 6.62), variations in the extract dose of 75 mg / kgBW (10.04 ± 10.57),150 mg / kgBW (10.04 ± 10.57), 300 mg / kgBW (31.91 ± 8.40) from the percentage results there is best blood volume reduction value in the positive control group and extract 300 mg / kgBW group.

The results of One Way Anova statistical test were significant <0.05, there was a significance between the normal group and control group. Purwidyaningrum Research (2017). Suedee's (2013) study of matoa leaves contains Quercetin-3-O-rhamnoside and

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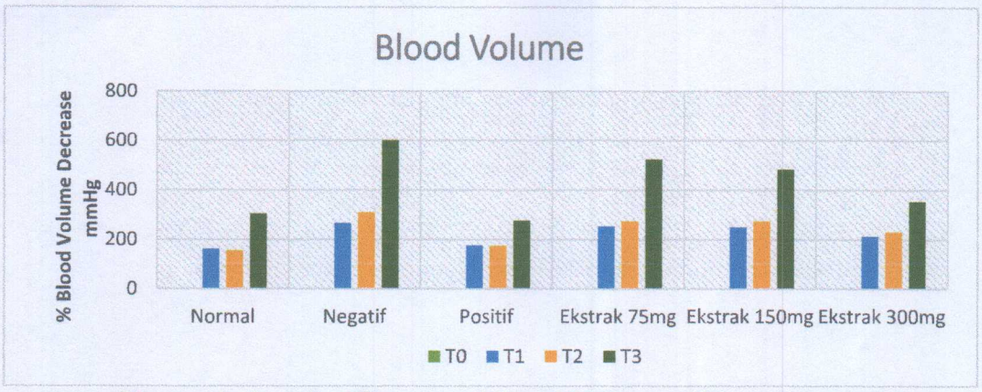
Kaemferol 3-O-rhamnoside compounds.The mechanism that occurs in ACEI inhibitors can be used as a reference for inhibitory mechanism that may occur in medicinal plant compounds, allowing compounds from matoa leaves extract to have the effect of hypertension in the ARB group.

The hypertensive profile of angiotensin receptor blockers acts by inhibiting angiotensin II type I receptors which can mediate the effect of angiotensinogen II on vasoconstriction, aldosterone release, sympathetic activity, release of antidiuretic hormones and efferent arteriolar constriction of the glomerulus.



Picture 1. Graph of Decreased Blood Volume of Hypertensive Rats

Research by Minas (2016) giving angiotensin II as an inducing agent in hypertensive model rats that given for 28 consecutive days can increase systolic and diastolic blood pressure, this is a consideration in the hypertension profile study angiotensin receptor blocker induced angiotensin II using parameters Blood volume in male Wistar rats, the percentage of blood volume has been proven that when given induction there was an increase in blood volume in the negative control, while the positive control group and the extract before being given the therapeutic dose also had a significant increase.

The induction was given for 12 consecutive days, while the therapeutic dose was given for 6 days followed by induction of angiotensin II. At the therapeutic dose group there is a decrease in blood volume, this prove that there is a significance between the negative control group and the positive control group and the extract group with a significant value <0.05, it has been proven that chemical compounds from matoa leaf extract have activity in decreasing blood volume, which means that the hypertension profile angiotensin receptor blockers have been shown to decrease blood volume in angiotensin II hypertension rats model. The normal value of hypertension in rats was 180/145 S/D, while the blood volume was 7.5% B.B according to the characteristics of Laurence et al (1964).

CONCLUSIONS

Matoa leaves extract (Pometia pinnata) has a role as a hypertension profile decrease in angiotensin II-induced rats, treatment with matoa leaves extract can reduce blood volume which contains flavonoid compounds (Quercetin-3-O-rhamnoside), effective dose of matoa leaves extract to reduce blood volume that is 300 mg / kgBW.

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SUGGESTIONS

This research needs to be done further about giving angiotensin induction in a longer time to see an increase in blood volume in cases of chronic hypertension, and continued with phytochemical testing of chemical compounds from matoa leaf extract using the TLC test.

ACKNOWLEDGMENTS

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