The Role of Bidara Leaf Extract (Ziziphus Mauritiana) on the Prevention of Renal Hypertension in Wistar Strain Rats

Dian Yuliartha Lestari, Cintantya Pramastri Yuwono, Dani Pratama Febrianto

Abstract: *Hypertension is ranked the fourth highest disease in the word. Glomerulosclerosis is the initial lesion from kidney failure in patient with hypertension. Bidara leaves have active flavonoid such as saponins and tannins are thought to prevent an increase in blood pressure and repair glomerulosclerosis. This study to prove the effect of bidara leaf extract to decrease hypertension and to prevent glomerulosclerosis. This study was true experimental with Pre and Post Test Control Group Design. This study used male white rats wistar strain. Sample divided into 5 groups (positive group, treatment group with 3 leveled dose, and medicine-control group) and were being observed in 28 days. Hypertension was measured using tail cuff blood pressure. Glomerulus observed randomly with light microscope in 5 different field of view with 400x magnification and scoring by Sclerosis Index (SI). In the linear regression test had $R^2 = 0,332$ for systolic blood pressure and $R^2 = 0,609$ for diastolic blood pressure. For glomerulosclerosis we found that the highest SI (369,69) was positive control group, while the lowest SI (84,09) was the group with a dose 400mg/kg/day. Bidara leaves extract have a significant effect on reduce hypertension and glomerulosclerosis.*

Keywords : Hypertension, Glomerulosclerosis, Bidara leaves.

I. INTRODUCTION

Hypertension in one of the most common chronic disease [1]. The prevalence of hypertension is 4th in the world [2]. Hypertension complications can reach 9.4 million deaths annually. According to the World Health Organization (WHO) and the International Society of Hypertension (IDH), there are 600 million people with hypertension worldwide, with 3 million dying each year. Seven out of every 10 sufferers do not get adequate treatment [3]. The incidence of hypertension in Indonesia obtained through measurements at the age of $\geq$ 18 years is 25.8 percent, the highest in Bangka Belitung island (30.9%), and then South Kalimantan province (30.8%), East Kalimantan province (29.6%) and the last is West Java province (29.4%)[4].

Hypertension is the second highest cause of kidney failure. Hypertension is the primary diagnosis in the United States. As many as 30,000 individuals in the United States are diagnosed with end-stage renal failure caused by hypertension each year and the number continues to increase [5]. Glomerulosclerosis is the initial lesion which most often causes kidneys tissue damaged which causes kidneys failure caused by hypertension [6]-[7].Clinically, glomerulosclerosis causes nephrotic syndrome, which consists of proteinuria, hypoalbuminemia, hypercholesterolemia and peripheral edema [7].

The bidara tree (Ziziphus mauritiana) is a plant of the family *Rhamnaceae*. Bidara tree originated from India and is now widely obtained in the tropics [8]. Bidara leaf is used in the treatment of indigestion, fever, liver damage and lung disease, but research on bidara leaf is still small [8]-[9]. Leaf bidara contains several biochemical active ingredients such as alkaloids, saponins, tannins, flavonoids, and terpenoids have their respective mechanisms in repairing and preventing the occurrence of glomerulosclerosis [10, 11, 12].

II. MATERIALS AND METHODS

This research is true experimental pre and post test group design. The sample of this study was 25 male rats (*Rattus novergicus strain wistar*) aged 2-3 months with a body weight of 15—200 grams and healthy. The sample was divided into 5 group: Negative control group, treatment control group (200mg/kgBW/day, 400mg/kgBW/day, 800mg/kgBW/day) and positive control group (captopril 1.125mg/kgBW/day po). All samples were adapted for 7 days then induced hypertension for 14 days. Hypertension induction using prednisone 1.5 mg/kgBW + NaCl 2%. After 14 days, the negative control group continued induction until 28th day, the positive control group continued with captopril 1.125mg/kgBW/day po until 28th day, and the treatment groups continued with bidara leaf extract a dose of 200mg/kgBW/day, 400 mg/kgBW/day po for 14 days

A. Measurement of Rat Blood Pressure

Blood pressure measurements are measured initially before being treated and after being treated. Blood pressure measurement using the Blood Pressure Monitor bran Coda on tail of a white rats. This method allows researchers to find out systolic and diastolic blood pressure

B. Measurement of Glomerulosclerosis

Glomerulosclerosis assessment was carried out after 28 days. The rats was killed and its kidney organs were taken and paraffin block preparations were made.

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To observe glomerulosclerosis scores using Masson Trichrome (MT) staining. The preparations were observed using a light microscope with a 400x magnification at 5 different random fields and the Sclerosis Index (IS) was determined semi-quantitatively.

The percentage of glomerulosclerosis occupied by the extracellular matrix is scored, starting with 0: 0%, 1+: 1-25%, 2+: 26-50%, 3+: 51-75%, 4+: 76-100%. Determine the Sclerosis Index (SI) with the formula: $[(0xn0+1xn1+2xn2+3xn3+4xn4)/number of glomerulus] x 100$. n0, n1, n2, n3 and n4 were the number of glomerulus with a score of 0, 1, 2, 3 and 4 [13].

C. Data Analysis

To analyzed pre and post experimental blood pressure using a General Linear Model test and linear regression analysis. To analyzed glomerulosclerosis using an ANOVA one-way test and linear regression analysis.

III. RESULTS AND DISCUSSION

The results of systole, diastolic blood pressure measurements and index sclerosis of rats in each group can be seen in the table 1.

Table I: Systole and Diastolic Blood Pressure Results in Each Group

	Systolic Blood Pressure		Diastolic Blood Pressure	
	Pre test	Post test	Pre test	Post tes
K+	130 ± 48,86	130 ± 54,11	91,67 ± 41,18	76,67 ± 26,76
K-	132,33 ± 44,79	136,33 ± 73,81	101,33 ± 47,01	108 ± 72,50
P1	158 ± 24,87	114,67 ± 24,82	120 ± 27,05	72 ± 26,96
P2	148,33 ± 27,66	114,33 ± 41,28	105,67 ± 24,17	85,33 ± 44,74
P3	152,67 ± 52,78	183 ± 53,25	119 ± 52,82	133,67 ± 53,29

Note :
K+ : positive control group
K- : negative control group
P1 : treatment group with bidara leaf extract 200mg/kgBW/day
P2 : treatment group with bidara leaf extract 400mg/kgBW/day
P3 : treatment group with bidara leaf extract 800mg/kgBW/day

Tabel II: Results of Sclerosis Index (IS) in Each Group

Group	Field					Average	IS
	1	2	3	4	5		
K-	3,75	3,70	3,83	3,5	3,91	3,74	369,69
K+	2,17	1,67	0,5	1,67	2,17	1,63	196
P1	1,75	1	1,63	1,21	1,83	1,48	143,90
P2	1,2	0,6	0,7	0,9	0,6	0,8	84,09
P3	0,88	1,25	2	1,33	0,88	1,27	135,29

Note :
K+ : positive control group
K- : negative control group
P1 : treatment group with bidara leaf extract 200mg/kgBW/day
P2 : treatment group with bidara leaf extract 400mg/kgBW/day
P3 : treatment group with bidara leaf extract 800mg/kgBW/day

The data above shows that the highest difference in systolic and diastolic blood pressure decrease was found in the P1 group (table 1), the highest Scoring Index was in the negative control group with a sclerosis index of 369.69 and the lowest sclerosis index of 84.09 for the P2 (table 2).

Before conducting data analysis, homogeneity and normality test were performed with a result of p>0.05 both blood pressure data and sclerosis index data. The result of analyzing blood pressure data using the general linear model test obtained p<0.05 (table 3), which means that there were differences significantly between groups.

Table III: Data analysis with General Linear Model

Multivariate Tests[a]		
Effect		Sig.
Group	Pillai's Trace	.066
	Wilks' Lambda	.028
	Hotelling's Trace	.015
	Roy's Largest Root	.003

One Way ANOVA test was performed to determine differences between the dose of bidara leaf extract and the number of glomeruloclerosis. Oneway ANOVA test results obtained sig = 0.000 which means there was a difference significantly between the dose of bidara leaf extract and captopril as a therapy of hypertension against glomerulosclerosis of white rats.

In the linear regression test, there are 3 variables include: Systolic blood pressure with $R^2 = 0.332$ (figure 1), and diastolic blood pressure with $R^2 = 0.609$ (figure 2), and index score glomerulosclerosis with $R^2 = 0.041$ (figure 3). The percentage role of the bidara leaf extract dose in systolic blood pressure was 3.3%, the percentage role of bidara leaf extract dose in diastolic blood pressure was 6%, and the percentage ole of the bidara leaf extract dose in index sclerosis was 40.1%.
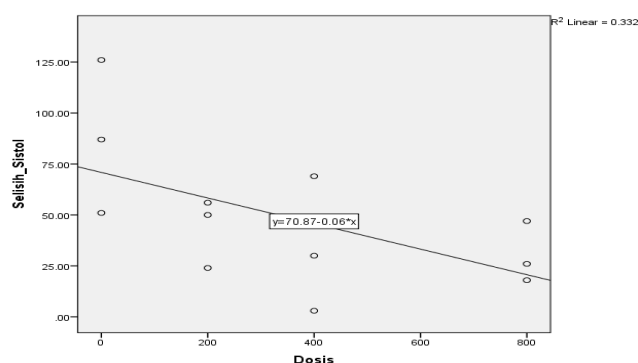

Fig 1. Systolic Blood Pressure Linear Test Graph

The process of hypertension can occur when rats with a high NaCl diet cause increased expression of the RAS system in the kidneys and brain which will stimulate renin secretion in renal juxtaglomerular cells. Activated renin converts angiotensinogen glycoprotein into angiotensin I. Angiotensin Converting Enzyme (ACE) converts Angiotensin I to produce Angiotensin II, whereas prednisone is an oral corticosteroid that has a glucocorticoid effect.

Glucocorticoids which interact with glucocorticoid receptors in smooth and endothelial blood vessels which will increase the activation of AT-1 receptors. Angiotensin II which binds to AT-1 and At-2 will induce aldosterone synthesis which will increase in plasma volume and blood pressure [9]-[11].
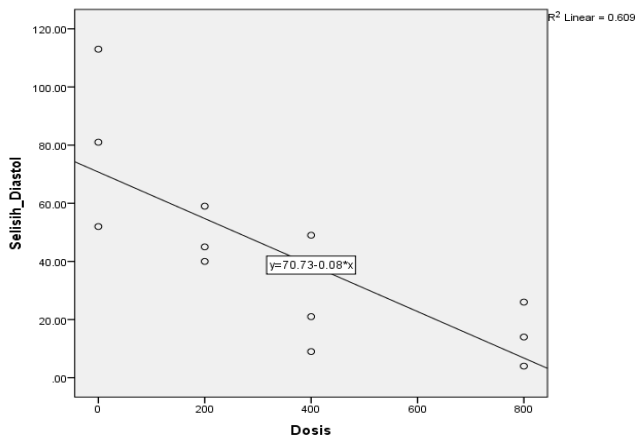

Fig 2. Diastolic Blood Pressure Linear Test Graph

Decrease blood pressure due to administration of bidara leaf extract is in accordance with [13], which said that saponin is an ingredient of bidara leaf extract can inhibit renin activity by suppressing the expression of the renin receptor in the RAAS system. Saponins, tannins, alkaloids and flavonoids which are the ingredients of bidara leaf extract are ACE inhibitors. Flavonoid compounds can also help lower blood pressure by increasing NO bioavailability by activating the e-NOS (endothelial Nitric Oxide Synthase) mechanism. E-NOS regulation will produce NO which acts as a powerful vasodilator which relaxed blood vessels and lowers blood pressure [13].

The histopathological improvement is in accordance as in [11] which showed that administration of ACE inhibitors can improve the histopathology of glomerulosclerosis by increasing the amount of plasmin by decreasing the expression of PAI-1 (Plasminogen Activator Inhibitor-1) which occurs due to a decrease in angiotensin II. The increase in plasmin levels will increase degradation of the extracellular matrix and lyse fibrin (matrix remodeling). In addition, ACE-inhibitors can also increase the intact glomerular capillary volume by 40% (capillary reorganization). [11] Saponin which is a content of bidara leas extract can suppress the expression of the renin receptor, namely PRR (Pro-Renin Receptor), inhibits the release of renin from granules, decrease the expression of TGF-β gene expression will cause a decrease in PAI-1. Decrease in PAI-1 can cause an increase in plasmin levels [13]

IV. CONCLUSION

The conclusion of this study was the bidara leaf extract (Ziziphus mauritiana) effective in reducing blood pressure in rats (Rattus novergicus strain wistar) hypertension model and remodelling glomerulosclerosis. The most effective dose of bidara leaf extract to reduce blood pressure and the amount of glomerulosclerosis in this study was 400 mg/kgBW/day

ACKNOWLEDGMENT

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Retrieval Number: C10680193S20/2020©BEIESP
DOI: 10.35940/ijitee.C1068.0193S20

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