

# Ethanol Extract Combinations Effect of Celery Herb (*Apium graveolens* L.) and Bay Leaf (*Syzygium polyanthum* W.) Toward Hypertensive Mice Induced by NaCl and High Fat Feed

Widyasari Putranti, Moch. Saiful Bachri, Resalianti Sintiana Devie

<sup>a,b,c,d</sup> Faculty of Pharmacy, Ahmad Dahlan University, Yogyakarta

Prof. Dr. Soepomo Street, Janturan, Warungboto, Yogyakarta 55164

<sup>a)</sup>widyasari@pharm.uad.ac.id

**Abstract:** Hypertension is defined by the increase of blood pressure systolic and diastolic which is  $\geq 140/90$  mmHg. Hypertension prevalence in Indonesia or in the world is increasing every year. Herb medicine is alternative option in hypertension treatment because it is relatively secure for long term usage. Plant which can be used for anti-hypertension therapy is combination of celery herb (*Apium graveolens*) and bay leaf ethanol extract (*Syzygium polyanthum*). This research aims to determine the activity of a combination of celery herb ethanol extract (EESE) and bay leaf ethanol extract (EESA) and find out how much the decrease of blood pressure on the combination of celery herb and bay leaf ethanol extract toward male Wistar mice. The design of this research used an experimental design with pre-post control group design. Hypertensive mice are induced with high fat feed and orally with NaCl 8%, then the mice are supplied with combinations of celery herb and bay leaf ethanol extract with the dose of 1,125 : 6,25 , 2,25 : 12,5 and 4,5 : 25 mg/kgBB, mice Hydrochlorotiazide 2,25 mg/kgBB, Simvastatin 0,9 mg/kgBB, EESE 4,5 mg/kgBB, EESA 25 mg/kgBB and control CMC-Na 0,5%. Research result shows that the combination of celery herb and bay leaf can decrease systole blood pressure in the 22<sup>nd</sup> day. The ethanol extract combination of celery herb and bay leaf has anti-hypertension effect (it is able to decrease systole blood pressure  $\geq 20$  mmHg) and it is not significantly different with normal group ( $p < 0,05$ ). Based on the research, it can be concluded that ethanol extract combination of celery herb and bay leaf can decrease systole blood pressure.

**Keywords:** Anti-hypertension, *Apium graveolens*, *Syzygium polyanthum*, Combination of Extract, Blood Pressure.

## Introduction

Hypertension is a medical condition where there is an increase in blood vessel contraction resulting in blood vessel resistance and cause an increase in blood pressure in blood vessels [1]. Hypertension is one of the main cause of the increasing amount of diseases related to cardiovascular. Based on the research Basic Health Research (Riskesmas) in 2013, hypertension prevalence in Indonesian citizens who are more than 18 years old age is 25,8% [2].

The good treatment for hypertension is to use anti-hypertension drugs to reduce blood pressure. However the treatment of hypertension requires no small cost because the usage will be for long terms. Moreover, the treatment can cause various side effects because of long term usage [3]. Those cases make people choose to plant medicine or herb as the alternative treatment for hypertension.

Traditional medicine plants or herbs that are commonly used by people to overcome hypertension are celery herb and bay leaf. Celery herb (*Apium graveolens*) is a plant which is often cooked for food and used as traditional medicine. Celery herb contains Apigenin, prevents from blood vessels constriction and phtalides, that can relax blood vessels [4]. Based on initial test, celery herb with dose of 4,5 mg/kgBB can decrease blood pressure toward male Wistar mice induced with NaCl.

Bay leaf (*Syzygium polyanthum*) is a spice producing plant which is commonly used in food by Indonesian society and use as a drug plant. Bay leaf had been known by the people to decrease blood pressure because it contains essential oil, tannin, and flavonoid [5]. Bay leaf is also as antihyperlipidemia because it contains tannin, saponin, niacin, and flavonoid which can decrease blood cholesterol level and control HDL cholesterol [6]. Based on initial test, ethanol extract of bay leaf with dose of 25 mg/kgBB has function as anti-hypertension and anti-hyperlipidemia.

Based on the background, the research needs to be conducted on the effect of ethanol extract combination of celery leaf and bay leaf in blood pressure decrease toward white male Wistar mice, it is expected that by giving ethanol extract celery leaf, as anti-hypertension, combined with ethanol extract bay leaf, as anti-hypertension and anti-hyperlipidemia, will be able to decrease blood pressure through cholesterol decrease in blood pressure as well. This is because hyperlipidemia can also cause an increase in blood pressure. Therefore, giving combination of celery leaf and bay leaf ethanol extract is expected to be more effective in reducing blood pressure in white male Wistar mice induced with sodium chloride and high fat feed.

## **Materials and Methods**

### **Plant Materials**

Celery herb and bay leaf was obtained from Beringharjo market Yogyakarta and identified in Biology Laboratory of Ahmad Dahlan University. Simplicia powder was made from delicate pieces of simplicia or simplicia complete which has been dried through powder making process with tools without damaging or eliminating chemical compound in the simplicia, then it was stirred until obtained powder. Ethanol extract of celery herb and bay leaf was made using maceration method with ratio of comparison between simplicia and solvent was 1 : 10. Maceration is done during the first 6 hours while stirring occasionally, then let stand for 18 hours. Then macerate was separated by filtering. Filtrate gained was kept as filtrate I, whereas sediment was re-macerated. Macerate was separated from the pulp. Filtrate was mixed with filtrate I and then it was evaporated using *rotary evaporator* until obtained thick extract [7].

### **Animals**

White furrow male wistar mice with 2-3 month old, weighing 150-250 gram, as much as 25 mice used for this research. The tested animal was placed in constant temperature ( $22 \pm 2^{\circ}\text{C}$ ) with the moisture relatively constant ( $55 \pm 10\%$ ) and had free access for food and water. Animal handling protocol of the research was adapted by the animal treatment manual of the Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Ahmad Dahlan University.

### **Experimental Design**

The mice were divided into nine groups (5 mice per group) and treatment was conducted for 22 days. Normal group: the mice were only provided with food and water for 21 days. Control Group: the mice were supplied with NaCl 8% and high fat feed (14 days) and CMC-Na 0.5% (7 days). Hydrochlorothiazide: the mice were supplied with NaCl 8% and high fat feed (14 days) and hydrochlorothiazide 2,25 mg/kgBB with volume of 2 ml/200 g mice (7 days). Symvastin group: the mice were supplied with NaCl 8% and high fat feed (14 days) and were supplied with symvastin 0,9 mg/kgBB kgBB on volume of 2 ml/200 g mice (7 days).

Extract group: the mice were induced with NaCl and high fat feed (14 days) and were supplied with extract (7 days). EESE group: the mice were supplied with ethanol extract of celery herb of 4,5 mg/kgBB (7 days). EESA group: the mice were supplied with ethanol extract bay leaf of 25 mg/kgBB (7 days). Combination Group I: the mice were supply with EESE 1,125 mg/kgBB and EESA 6,25 mg/kgBB. Combination group 2: the mice were supplied with EESE 2,25 mg/kgBB and EESA 12,5 mg/kgBB. Combination group 3: the mice were supplied with EESE 4,5 mg/kgBB and EESA 25 mg/kgBB. The administration of extract toward combination of groups was given individually and there was paused after the first extract administration.

### **Blood Pressure Measurement**

Mice blood pressure was measured by *Tail Cuff Method* which used *blood pressure analyzer* called CODA. The method of measurement using this tool was the mice to be measured was put into the holder. Mice must be in a state of no stress due to cold or heat and in a calm state when in the holder. The mice tail was put in the tied cuff and the mice blood pressure was measured [8]. Hypertension in mice was happened after the blood pressure reached 150/90 mmHg. The mice blood pressure measurement was conducted in the day 0, 14, 17, 19, and 22.

### **Statistical Analysis**

Data attained was processed statistically using SPSS. Analysis test conducted was homogeneity test and normal distribution test. Then, to know the relationship between treatment groups will be conducted by one way variant analysis test (ANOVA). If there were significant different between groups, it will be

conducted by smallest actual different analysis test (BNT). However, if the data were not normally distributed and homogeneity, then it will be conducted with non-parametric Kruskal-Wallis analysis to know any differences existed. If there were significant differences then it continued with non-parametric analysis Mann Whitney [9].

## Result and Discussion

### Extraction Result

Based on the conducted research, it was attained extraction as the result of celery herb with thick dark green extract and had characteristic smelt, whereas bay leaf extraction result was attained thick brown blackish color, tasted bitter and characteristic smelt. The result of celery herb and bay leaf ethanol extraction can be seen in Table 1.

**Table 1.** Celery Herb (*Apium graveolens* L.) and Bay Leaf (*Sizygium polyanthum* W.) Extraction Result

No	Sample	Sample Weight	Extract Weight	Rendemen
1.	Celery Leaf	2,6 kg	177,185 g	6,815 %
2.	Bay Leaf	2,2 kg	112,44 g	5,111 %

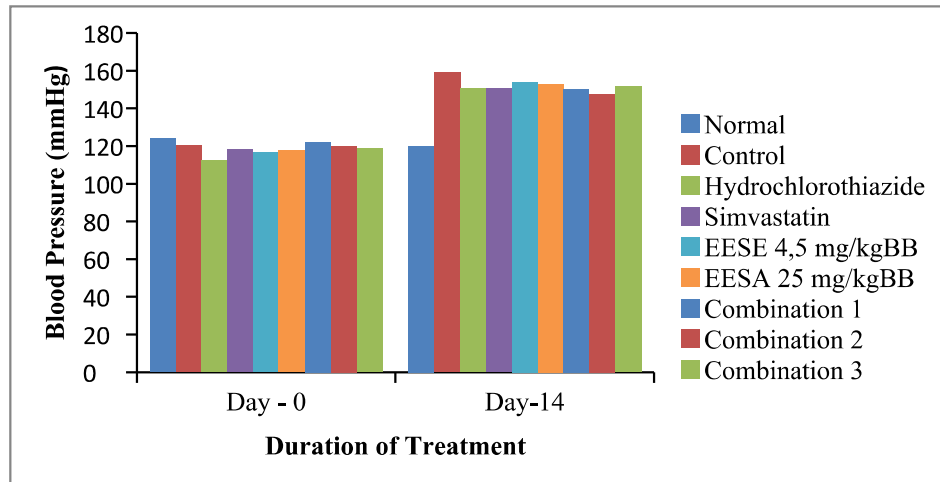
### Anti-hypertension Activity Test

Artery blood pressure is a pressure occurred in the blood vessel artery pumped by the heart to all over the body in the millimeter mercury unit (mmHg). There are two artery blood pressure, systole blood pressure and diastole blood pressure [10]. The measurement of blood pressure toward mice used *Tail Cuff Method* with *blood pressure analyzer* tool called CODA.

Systole blood pressure is blood pressure when the heart is in contraction. Mice systole blood pressure in the day-0 was normal and lower than the mice systole blood pressure in the day-14. Based on statistics analysis result shows that there are no significant difference ( $p > 0,05$ ) on all of tested mice groups. This shows that all mice groups tested were the same and normal. Average systole blood pressure data in the day-0 and 14 can be seen in Table 2.

**Tabel 2.** Average  $\pm$  SD Systole Blood Pressure induced by NaCl 8% and High Fat Feed

Group	Dose (mg/kgBB Mice)	Systole Blood Pressure (mmHg)	
		Day-0	Day-14
Normal		124 $\pm$ 5,788	120 $\pm$ 1,225
Control		120,2 $\pm$ 12,133	159 $\pm$ 5,916
Hydrochlorothiazide	2,25	112,4 $\pm$ 13,315	150,4 $\pm$ 8,961
Simvastatin	0,9	118,2 $\pm$ 7,155	150,6 $\pm$ 6,309
EESA	4,5	116,4 $\pm$ 13,012	154 $\pm$ 5,612
EESA	25	117,6 $\pm$ 8,849	153 $\pm$ 1,871
Combination 1	1,125 : 6,25	122 $\pm$ 7,583	150,2 $\pm$ 2,280
Combination 2	2,25 : 12,5	120 $\pm$ 13,472	147,6 $\pm$ 7,503
Combination 3	4,5 : 25	118,8 $\pm$ 15,515	151,4 $\pm$ 2,510



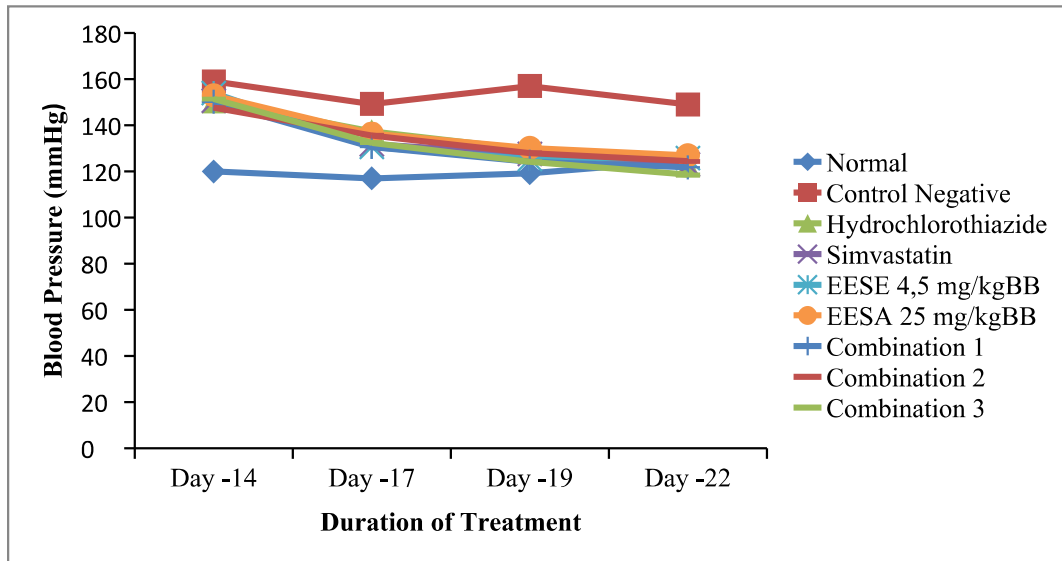
**Gambar 1.** Histogram of Systole Average Blood Pressure Before and After Induced by NaCl 8% and High Fat Feed

Systole blood pressure in the day-14 increased after supplied with NaCl 8% and high fat feed. The increase of systole blood pressure can be seen in Picture 1. After induction for 14 days, the blood pressure was concluded as light hypertension. Based on Krinke (2009), hypertension is categorized light when systole blood pressure on the range of 149-199 mmHg and diastole blood pressure >97 mmHg [11]. Over consumption of salt can cause blood pressure because it can increase sodium levels in delicate muscle cells in arterial walls. High sodium levels can cause arterial contracting and constricting [12]. Constricting blood vessel makes the heart must work harder to pump increasing-blood volume through narrow space, thus causes blood pressure becomes high.

The measurement result of systole blood pressure in day-14 after induced NaCl 8% and high fat feed in mice groups were increasing and the blood pressure was higher compared to average normal systole blood pressure which is  $120 \pm 1,225$ . Based on statistics analysis result shows that there are significant difference ( $p < 0,05$ ) between normal group and those seventh groups, meanwhile in control group with average systole blood pressure of  $159 \pm 5,916$  shows that there are no significant differences ( $p > 0,05$ ) with those seventh groups. It can be said that induction of NaCl 8% and high fat feed for 14 days can cause mice systole blood pressure increased significantly.

Group	Dose (mg/kgBB mice)	Systole Blood Pressure (mmHg)				Decreasing (%)
		Day-14	Day-17	Day-19	Day-22	
Normal		120 ±	117 ±	119,2 ±	124,8 ±	-4*
		1,225	3,240	10,330	5,805	
Control		159 ±	149,2 ±	157 ±	149 ±	6,289
		5,916	5,263	5,874	9,301	
HCTZ	2,25	150,4 ±	137,4 ±	129,4 ±	122,6 ±	18,484*
		8,961	4,722*	5,320*	0,894*	
Simvastatin	0,9	150,6 ±	131,8 ±	127,6 ±	123 ±	18,327*
		6,309	7,396*	5,320*	2,000*	
EESE	4,5	154 ±	130,6 ±	125,4 ±	125,8 ±	18,312*
		5,612	4,506*	1,817*	5,167*	
EESA	25	153 ±	136,4 ±	130,2 ±	127 ±	16,993*
		1,871	1,949*	5,630*	8,718*	
Combination 1	1,125 : 6,25	150,2 ±	130,6 ±	124,2 ±	121,8 ±	18,908*
		2,280	6,914*	6,419*	8,585*	
Combination 2	2,25 : 12,5	147,6 ±	135,6 ±	128 ±	124,4 ±	15,718*
		7,503	4,980*	5,148*	4,827*	
Combination 3	4,5 : 25	151,4 ±	132,4 ±	124,2 ±	118,6 ±	21,664*
		2,510	5,814*	1,483*	3,050*	

Information: \* $p < 0,05$  Significantly different compared to Control group.



**Gambar 2.** Histogram of Average Systole blood pressure in Day-14,17,19 and 22.

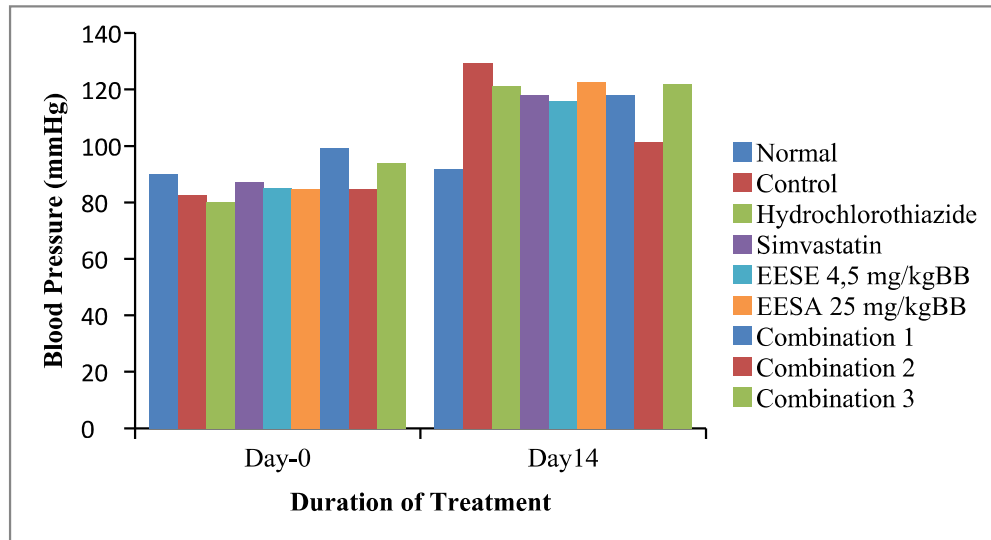
Based on average result of systole blood pressure during treatment on Table 2, systole blood pressure has significant difference ( $p < 0,05$ ) with control group and it is not significantly different with normal group ( $p > 0,05$ ). This can be said that systole blood pressure during rendering with extract was decreasing and almost reached normal systole blood pressure group. The decreasing is not different significantly ( $p > 0,05$ ) compared with HCTZ group. The biggest decreasing of blood pressure is group of Combination 3.

**Table 3.** Average  $\pm$  SD Mice Diastole Blood Pressure Induced with NaCl 8% and High Fat Feed

Group	Dose (mg/kgBB Mice)	Diastole Blood Pressure (mmHg)	
		Day-0	Day-14
Normal		90 $\pm$ 13,874	92 $\pm$ 8,860
Control		82,8 $\pm$ 5,020	129,4 $\pm$ 11,83
HCTZ	2,25	80,2 $\pm$ 11,300	121,2 $\pm$ 18,820
Simvastatin	0,9	87,2 $\pm$ 9,257	118 $\pm$ 12,748
EESE	4,5	85,2 $\pm$ 11,077	116 $\pm$ 6,205
EESA	25	84,6 $\pm$ 9,476	122,6 $\pm$ 16,009
Combination 1	1,125 : 6,25	99,2 $\pm$ 6,419	118 $\pm$ 10,464
Combination 2	2,25 : 12,5	84,6 $\pm$ 11,171	101,2 $\pm$ 20,644
Combination 3	4,5 : 25	94 $\pm$ 12,981	121,8 $\pm$ 13,609

Diastole blood pressure was reaching when the heart finished contracting. Average diastole blood pressure in day-0 is diastole normal blood pressure before induced with NaCl 8% and high fat feed. The measurement result of diastole blood pressure can be seen in Table 3. Based on statistics analysis shows that there are no significant differences ( $p > 0,05$ ) in all of tested groups. This case shows that diastole blood pressure is normal in all tested mice groups.

Diastole blood pressure at day-14 in group of mice, supplied with NaCl 8% and high fat feed, was increasing and not different significantly ( $p > 0,05$ ) with Control Group, meanwhile compared with normal group there were significant difference ( $p < 0,05$ ). This shows that Induction of NaCl 8% and high fat feed for 13 days also can increase diastole blood pressure. Diastole blood pressure can be seen in Picture 3.



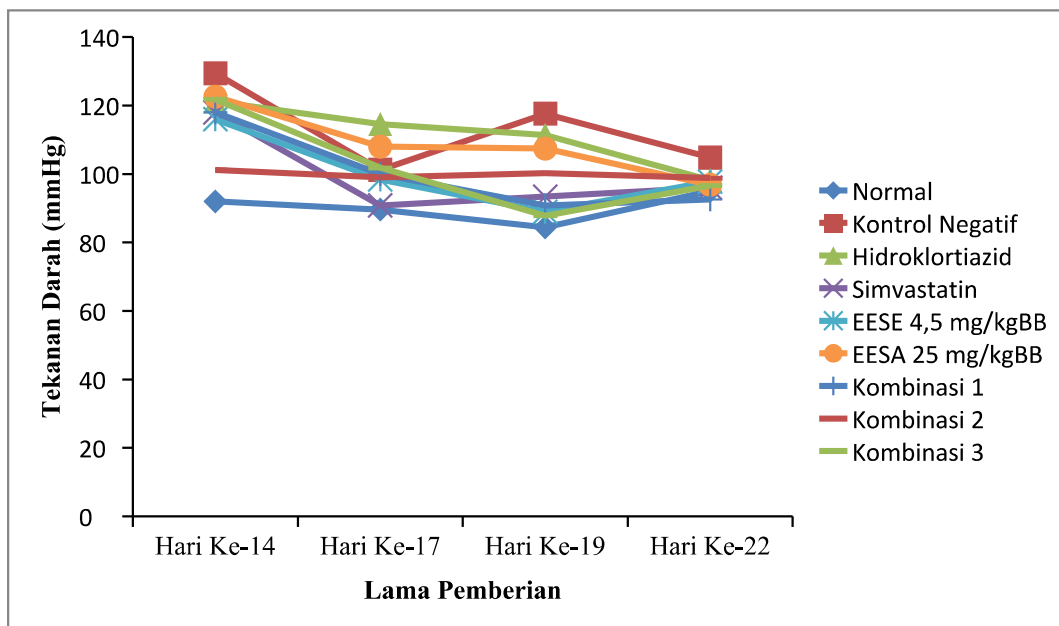
**Picture 3.** Histogram of Diastole Average Blood Pressure Before and After being induced by NaCl 8% and High Fat Feed

**Table 4.** Average  $\pm$  SD Diastole Blood Pressure Day - 14, 17, 19 and 22.

Group	Dose (mg/kgBB Mice)	Diastole Blood Pressure (mmHg)				Decreasing (%)
		Day-14	Day-17	Day-19	Day-22	
Normal		92 $\pm$ 8,860	89,6 $\pm$ 11,908	84,4 $\pm$ 12,857	95 $\pm$ 18,207	- 3,261
Control		129,4 $\pm$ 11,83	101,2 $\pm$ 12,154	117,6 $\pm$ 18,487	104,8 $\pm$ 19,396	19,011
HCTZ	2,25	121,2 $\pm$ 18,820	114,6 $\pm$ 10,644	111,4 $\pm$ 13,088	98,2 $\pm$ 10,803	18,482
Simvastatin	0,9	118 $\pm$ 12,748	90,8 $\pm$ 17,908	93,4 $\pm$ 3,578*	96 $\pm$ 8,155	18,644
EESE	4,5	116 $\pm$ 6,205	98,4 $\pm$ 7,797	89 $\pm$ 9,055*	97,8 $\pm$ 9,094	15,690
EESA	25	122,6 $\pm$ 16,009	108 $\pm$ 15,508	107,4 $\pm$ 17,329	96,8 $\pm$ 28,455	21,044
Combination 1	1,125 : 6,25	118 $\pm$ 10,464	100 $\pm$ 7,071	90,8 $\pm$ 6,261*	92,6 $\pm$ 15,274	21,525
Combination 2	2,25 : 12,5	101,2 $\pm$ 20,644	99 $\pm$ 9,772	100,2 $\pm$ 10,686	98,8 $\pm$ 5,263	2,372
Combination 3	4,5 : 25	121,8 $\pm$ 13,609	101,8 $\pm$ 17,196	87,8 $\pm$ 19,292*	96,6 $\pm$ 10,383	20,690

Information : \*p < 0,05 Significantly Different Compared with Control Group.

Based on average result of mice diastole blood pressure test, on Table 4 during treatment, shows that extract treatment can decrease diastole blood pressure however it is not significant. Diastole blood pressure in day-22 not does not show significant difference (p>0,05) with control group. Diastole blood pressure decrease can be seen in Picture 4.



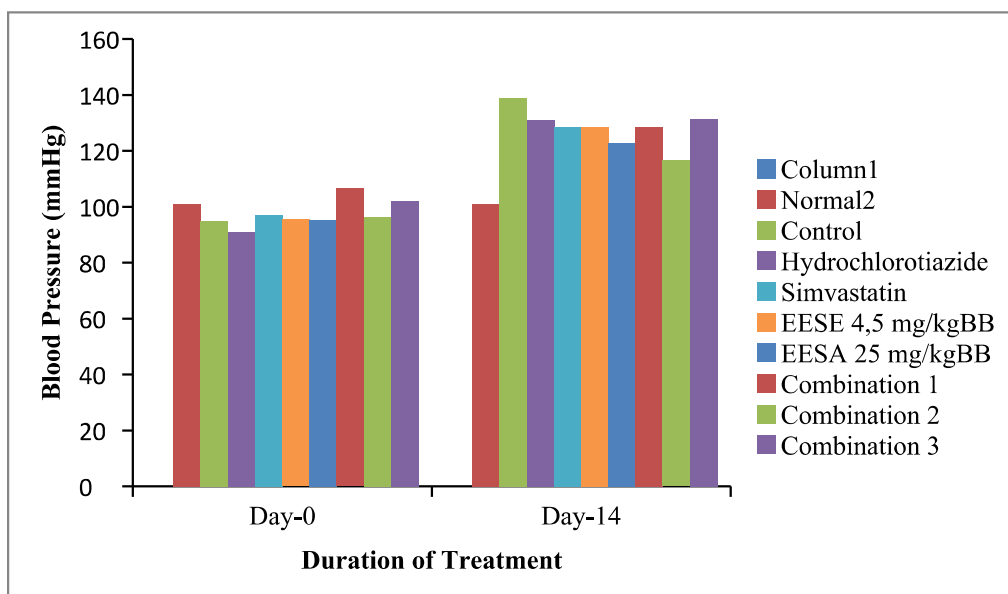
**Picture 4.** Graphic on Diastole Average Blood Pressure on Day-14, 17, 19 and 22.

Beside systole and diastole blood pressure, it is also conducted average blood pressure to mice. Blood pressure throughout the contracted heart cycle. During the heart's contracting cycle, two-thirds of the time is spent in diastole and one-third in systole [10]. Average blood pressure or called MAP is the main factor for viewing the condition of tissue perfusion. High MAP can cause cardiovascular and cause organ disorder, whereas low MAP can cause perfusion tissue disorder which is critical condition [13]. .

**Table 5.** Average  $\pm$  SD Mice Blood Pressure Induced With NaCl 8% and High Fat Feed.

Group	Dose (mg/kgBB mice)	Average Blood Pressure (mmHg)	
		Day-0	Day-14
Normal		101 $\pm$ 10,840	101 $\pm$ 5,701
Control		95 $\pm$ 6,856	138,8 $\pm$ 9,524
HCTZ	2,25	91 $\pm$ 11,979	130,8 $\pm$ 14,973
Simvastatin	0,9	97,2 $\pm$ 8,379	128,4 $\pm$ 10,455
EESE	4,5	95,4 $\pm$ 11,567	128,4 $\pm$ 5,983
EESA	25	95,2 $\pm$ 8,556	122,6 $\pm$ 16,009
Combination 1	1,125 : 6,25	106,6 $\pm$ 5,177	128,4 $\pm$ 7,635
Combination 2	2,25 : 12,5	96,2 $\pm$ 11,735	116,4 $\pm$ 14,673
Combination 3	4,5 : 25	102 $\pm$ 13,472	131,2 $\pm$ 10,001

Measurement result of average blood pressure can be seen on Table 5. Average blood pressure day-0 is normal average blood pressure before induced with NaCl 8% and high fat feed. Based on statistics analysis result, there are no significant difference ( $p > 0,05$ ) to all of tested mice groups. This shows that average blood pressure of all tested mice is normal.



**Picture 5.** Histogram of Average Blood Pressure Before and After Induced NaCl 8% and High Fat Feed.

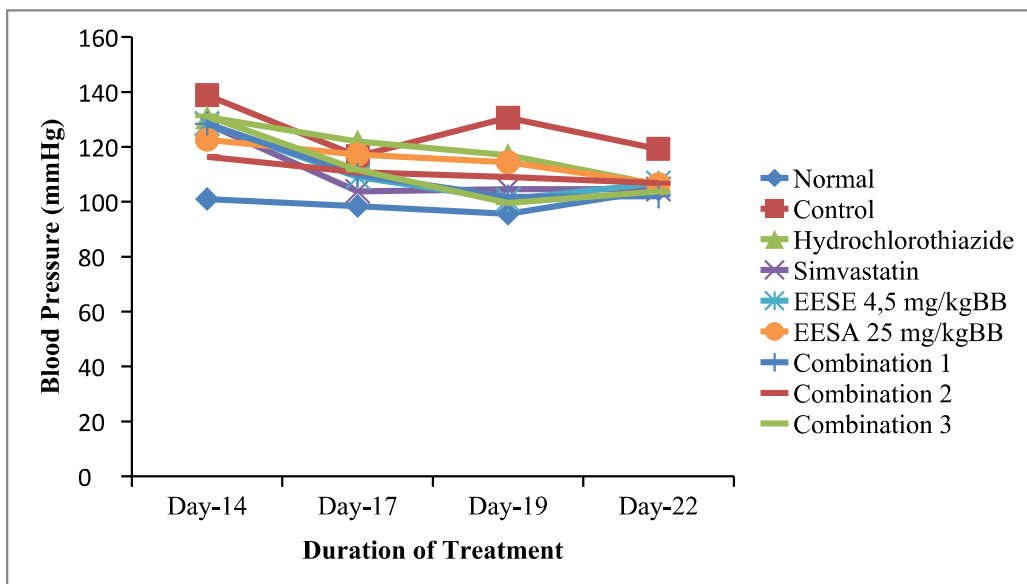
Statistics analysis result average blood pressure on Day-14 shows that there are significant differences ( $p < 0,05$ ) between the five groups with normal group and there are no significant differences ( $p > 0,05$ ) with control groups. This shows that induction of NaCl 8% and high Fat Feed can also increase average blood pressure. The increase of blood pressure can be seen in Picture 5.

**Table 6.** Average  $\pm$  SD Average Mice Blood Pressure Induced by NaCl 8% and High Fat Feed

Group	Dose (mg/kgBB Mice)	Average Blood Pressure (mmHg)				Decreasing (%)
		Day-14	Day-17	Day-19	Day-22	
Normal		101 $\pm$ 5,701	98,4 $\pm$ 7,403	95,6 $\pm$ 9,556	104,4 $\pm$ 13,259	-3,366*
Control		138,8 $\pm$ 9,524	116,6 $\pm$ 9,737	130,6 $\pm$ 13,465	119,2 $\pm$ 15,707	14,121
HCTZ	2,25	130,8 $\pm$ 14,973	122 $\pm$ 7,517	117 $\pm$ 10,247*	106,2 $\pm$ 7,120	18,807
Simvastatin	0,9	128,4 $\pm$ 10,455	103,8 $\pm$ 9,576	104,6 $\pm$ 3,912*	104,6 $\pm$ 5,683	18,409
EESE	4,5	128,4 $\pm$ 5,983	109 $\pm$ 8,633	100,8 $\pm$ 6,221*	106,8 $\pm$ 7,294	16,822
EESA	25	122,6 $\pm$ 16,009	117,2 $\pm$ 10,474	114,4 $\pm$ 11,589*	106,4 $\pm$ 20,526	13,214
Combination 1	1,125 : 6,25	128,4 $\pm$ 7,635	109,8 $\pm$ 6,870	101,8 $\pm$ 5,805*	102 $\pm$ 12,227*	20,561
Combination 2	2,25 : 12,5	116,4 $\pm$ 14,673	110,8 $\pm$ 6,535	109 $\pm$ 8,631*	106,8 $\pm$ 4,550	8,247
Combination 3	4,5 : 25	131,2 $\pm$ 10,001	111,6 $\pm$ 12,462	99,6 $\pm$ 13,278*	103,8 $\pm$ 6,686*	20,884

Information: \*  $p < 0,05$  Significantly different compared with Control Group.





**Picture 6.** Graphic Average Blood Pressure in Day -14, 17, 19, and 22.

Based on average blood pressure test during treatment on Table 6 shows that extract treatment can decrease average blood pressure however the decreasing is not significant. Average blood pressure decrease in day-22 does not show the significant different ( $p > 0,05$ ) compared with Control group. The decreasing average blood pressure for 7 days treatment can be seen in Picture 6.

Based on the research conducted by Ismiyati, bay leaf can decrease average blood pressure significantly [14]. This is also shows in the research that bay leaf can decrease average blood pressure after 7 days treatment.

Although the mechanism of action of each plant is different in lowering blood pressure but when combined, it can reduce blood pressure which is almost the same as the hydrochlorothiazide comparison group. This is because bay leaf contains compound flavonoid which can decrease cholesterol levels. One of the flavonoid contained in bay leaf is kuersetin. Kuersetin can hampers oxidation LDL which modified by Marofag. Moreover bay leaf also can decrease blood pressure because of the flavonoid compound. Based on the previous research, Ismiyati shows that bay leaf ethanol extract can decrease blood pressure due to induction fenileprin [14]. Celery herb also contains flavonoid that works in decreasing blood pressure through blood vessel vasodilatation. Flovonoid compound type is bioactive medicine plant compound which is commonly has the ability to hamper ACE activity. ACE has important role in creating angiotensin II which is the cause of hypertension [5].

Based on research conducted by Dianat, celery leaf ethanol extract can decrease systole blood pressure because celery leaf contains flavonoid apigenin that has strong antioxidant effect and can prevent tissure damaging due to oxidant stress [15]. Based on the research conducted by muflikhatur also shows that ethanol extract of bay leaf doses 0,034 gram can decrease cholesterol level totally [16]. Bay leaf contains flavonoid which can hamper HMG-CoA reductase and hamper fat absorption in intestine. This case is much related with blood pressure decrease when the two plants are combined, because based on the research conducted by a Doctor in America on 2006 stated that the higher cholesterol level can increase the risk of hypertension [17]. Therefore, the research used the two plants for the synergy effect in eliminating blood pressure with much better.

Based on mice vital organ analysis result with haematoxylin and eosin, it shows that there are no pathology changing in liver, kidney, and heart organ after rendered combinations of celery and bay leaf ethanol extract. However, in comparison groups of simvastatin there is foki necrotic Centro lobular in the liver.

Based on the previous research, combination of celery leaf (*Apium graveolens*) and bay leaf (*Sizygium polyanthum*) ethanol extract can decrease systole blood pressure, diastole and average blood pressure. However, diastole blood pressure decrease is less than systole blood pressure, so the blood pressure decrease is more through a decrease in mice systole blood pressure. Combinations of celery and bay leaf ethanol extract can be used as alternative medicine because it is taken from the nature and seen from the percent reduction was greater than the comparison group hydrochlorothiazide.

## Conclusions

Based on the conducted research, it can be concluded that giving combinations of celery herb conducted (*Apium graveolens*) and bay leaf (*Syzygium polyanthum*) ethanol extract can decrease systole blood pressure significantly and it is not significantly different with comparison of hydrochlorothiazide group.

## Acknowledgement

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Faculty of Mathematics and Natural Sciences,  
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Jl. Jend. Ahmad Yani Km. 36 Banjarbaru,  
Kalimantan Selatan, Indonesia 70714

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Moch. Saiful Bachri<sup>1, a</sup>, Widyasari Putranti<sup>2, b\*</sup>, Lina Widiyastuti<sup>3, c</sup>, ,  
Resalianti Sintiana Devie<sup>4, d</sup>

<sup>1,2,3,4</sup>Faculty of Pharmacy, Ahmad Dahlan University, Prof. Dr. Soepomo Street, Janturan,  
Warungboto, Yogyakarta, Indonesia 55164

[1msaifulbachri@yahoo.co.id](mailto:msaifulbachri@yahoo.co.id), [2widyasari@pharm.uad.ac.id](mailto:widyasari@pharm.uad.ac.id), [3lina.widiyastuti@pharm.uad.ac.id](mailto:lina.widiyastuti@pharm.uad.ac.id), ,  
[4resalianti17@gmail.com](mailto:resalianti17@gmail.com)

**Keywords:** Anti-hypertension, *Apium graveolens*, *Syzygium polyanthum*, Combination of Extract, Blood Pressure.

**Abstract:** Hypertension is defined by the increase of blood pressure systolic and diastolic which is  $\geq 140/90$  mmHg. Hypertension prevalence in Indonesia or in the world is increasing every year. Herb medicine is alternative option in hypertension treatment because it is relatively secure for long term usage. Plant which can be used for anti-hypertension therapy is combination of celery herb (*Apium graveolens*) and bay leaf ethanol extract (*Syzygium polyanthum*). This research aims to determine the activity of a combination of celery herb ethanol extract (EASE) and bay leaf ethanol extract (EESA) and find out how much the decrease of blood pressure on the combination of celery herb and bay leaf ethanol extract toward male Wistar mice. The design of this research used an experimental design with pre-post control group design. Hypertensive mice are induced with high fat feed and orally with NaCl 8%, then the mice are supplied with combinations of celery herb and bay leaf ethanol extract with the dose of 1,125 : 6,25 , 2,25 : 12,5 and 4,5 : 25 mg/kgBB, mice Hydrochlorotiazide 2,25 mg/kgBB, Simvastatin 0,9 mg/kgBB, EASE 4,5 mg/kgBB, EESA 25 mg/kgBB and control CMC-Na 0,5%. Research result shows that the combination of celery herb and bay leaf can decrease systole blood pressure in the 22<sup>nd</sup> day. The ethanol extract combination of celery herb and bay leaf has anti-hypertension effect (it is able to decrease systole blood pressure  $\geq 20$  mmHg) and it is not significantly different with normal group ( $p < 0,05$ ). Based on the research, it can be concluded that ethanol extract combination of celery herb and bay leaf can decrease systole blood pressure.

## Introduction

Hypertension is a medical condition where there is an increase in blood vessel contraction resulting in blood vessel resistance and cause an increase in blood pressure in blood vessels [1]. Hypertension is one of the main cause of the increasing amount of diseases related to cardiovascular. Based on the research Basic Health Research (Riskesdas) in 2013, hypertension prevalence in Indonesian citizens who are more than 18 years old age is 25,8% [2].

The good treatment for hypertension is to use anti-hypertension drugs to reduce blood pressure. However the treatment of hypertension requires no small cost because the usage will be for long terms. Moreover, the treatment can cause various side effects because of long term usage [3]. Those cases make people choose to plant medicine or herb as the alternative treatment for hypertension.

Traditional medicine plants or herbs that are commonly used by people to overcome hypertension are celery herb and bay leaf. Celery herb (*Apium graveolens*) is a plant which is often cooked for food and used as traditional medicine. Celery herb contains Apigenin, prevents from blood vessels constriction and phtalides, that can relax blood vessels [4]. Based on initial test, celery herb with dose of 4,5 mg/kgBB can decrease blood pressure toward male Wistar mice induced with NaCl

Bay leaf (*Sizygium polyanthum*) is a spice producing plant which is commonly used in food by Indonesian society and use as a drug plant. Bay leaf had been known by the people to decrease blood pressure because it contains essential oil, tannin, and flavonoid [5]. Bay leaf is also as antihyperlipidemia because it contains tannin, saponin, niacin, and flavonoid which can decrease blood cholesterol level and control HDL cholesterol [6]. Based on initial test, ethanol extract of bay leaf with dose of 25 mg/kgBB has function as anti-hypertension and anti-hyperlipidemia.

Based on the background, the research needs to be conducted on the effect of ethanol extract combination of celery leaf and bay leaf in blood pressure decrease toward white male Wistar mice, it is expected that by giving ethanol extract celery leaf, as anti-hypertension, combined with ethanol extract bay leaf, as anti-hypertension and anti-hyperlipidemia, will be able to decrease blood pressure through cholesterol decrease in blood pressure as well. This is because hyperlipidemia can also cause an increase in blood pressure. Therefore, giving combination of celery leaf and bay leaf ethanol extract is expected to be more effective in reducing blood pressure in white male Wistar mice induced with natrium chloride and high fat feed.

## Materials and Methods

**Plant Materials.** Celery herb and bay leaf was obtained from Beringharjo market Yogyakarta and identified in Biology Laboratory of Ahmad Dahlan University. Simplicia powder was made from delicate pieces of simplicia or simplicia complete which has been dried through powder making process with tools without damaging or eliminating chemical compound in the simplicia, then it was stirred until obtained powder. Ethanol extract of celery herb and bay leaf was made using maceration method with ratio of comparison between simplicia and solvent was 1 : 10. Maceration is done during the first 6 hours while stirring occasionally, then let stand for 18 hours. Then macerate was separated by filtering. Filtrate gained was kept as filtrate I, whereas sediment was re-macerated. Macerate was separated from the pulp. Filtrate was mixed with filtrate I and then it was evaporated using *rotary evaporator* until obtained thick extract [7].

**Animals.** White furrow male wistar mice with 2-3 month old, weighing 150-250 gram, as much as 25 mice used for this research. The tested animal was placed in constant temperature ( $22 \pm 2^\circ\text{C}$ ) with the moisture relatively constant ( $55 \pm 10\%$ ) and had free access for food and water. Animal handling protocol of the research was adapted by the animal treatment manual of the Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Ahmad Dahlan University.

**Experimental Design.** The mice were divided into nine groups (5 mice per group) and treatment was conducted for 22 days. Normal group: the mice were only provided with food and water for 21 days. Control Group: the mice were supplied with NaCl 8% and high fat feed (14 days) and CMC-Na 0.5% (7 days). Hydrochlorothiazide: the mice were supplied with NaCl 8% and high fat feed (14 days) and hydrochlorothiazide 2,25 mg/kgBB with volume of 2 ml/200 g mice (7 days). Symvastin group: the mice were supplied with NaCl 8% and high fat feed (14 days) and were supplied with symvastin 0,9 mg/kgBB kgBB on volume of 2 ml/200 g mice (7 days).

Extract group: the mice were induced with NaCl and high fat feed (14 days) and were supplied with extract (7 days). EESE group: the mice were supplied with ethanol extract of celery herb of 4,5 mg/kgBB (7 days). EESA group: the mice were supplied with ethanol extract bay leaf of 25 mg/kgBB (7 days). Combination Group I: the mice were supply with EESE 1,125 mg/kgBB and EESA 6,25 mg/kgBB. Combination group 2: the mice were supplied with EESE 2,25 mg/kgBB and EESA 12,5 mg/kgBB. Combination group 3: the mice were supplied with EESE 4,5 mg/kgBB and EESA 25 mg/kgBB. The administration of extract toward combination of groups was given individually and there was paused after the first extract administration.

**Blood Pressure Measurement.** Mice blood pressure was measured by *Tail Cuff Method* which used *blood pressure analyzer* called CODA. The method of measurement using this tool was the

mice to be measured was put into the holder. Mice must be in a state of no stress due to cold or heat and in a calm state when in the holder. The mice tail was put in the tied cuff and the mice blood pressure was measured [8]. Hypertension in mice was happened after the blood pressure reached 150/90 mmHg. The mice blood pressure measurement was conducted in the day 0, 14, 17, 19, and 22.

**Statistical Analysis**Data attained was processed statistically using SPSS. Analysis test conducted was homogeneity test and normal distribution test. Then, to know the relationship between treatment groups will be conducted by one way variant analysis test (ANOVA). If there were significant different between groups, it will be conducted by smallest actual different analysis test (BNT). However, if the data were not normally distributed and homogeneity, then it will be conducted with non-parametric Kruskal-Wallis analysis to know any differences existed. If there were significant differences then it continued with non-parametric analysis Mann Whitney [9].

## Result and Discussion

**Extraction Result.** Based on the conducted research, it was attained extraction as the result of celery herb with thick dark green extract and had characteristic smelt, whereas bay leaf extraction result was attained thick brown blackish color, tasted bitter and characteristic smelt. The result of celery herb and bay leaf ethanol extraction can be seen in Table 1.

**Table 1.** Celery Herb (*Apium graveolens* L.) and Bay Leaf (*Sizygium polyanthum* W.) Extraction Result

No	Sample	Sample Weight	Extract Weight	Rendemen
1.	Celery Leaf	2,6 kg	177,185 g	6,815 %
2.	Bay Leaf	2,2 kg	112,44 g	5,111 %

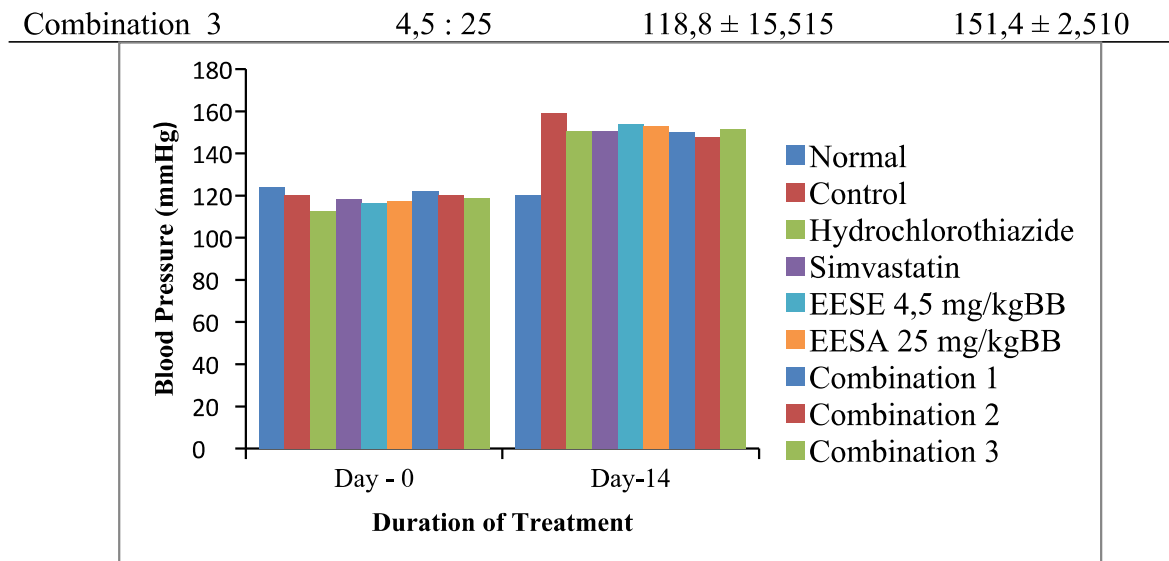
**Anti-hypertension Activity Test.** Artery blood pressure is a pressure occurred in the blood vessel artery pumped by the heart to all over the body in the millimeter mercury unit (mmHg). There are two artery blood pressure, systole blood pressure and diastole blood pressure [10]. The measurement of blood pressure toward mice used *Tail Cuff Method* with *blood pressure analyzer* tool called CODA.

Systole blood pressure is blood pressure when the heart is in contraction. Mice systole blood pressure in the day-0 was normal and lower than the mice systole blood pressure in the day-14. Based on statistics analysis result shows that there are no significant difference ( $p > 0,05$ ) on all of tested mice groups. This shows that all mice groups tested were the same and normal. Average systole blood pressure data in the day-0 and 14 can be seen in Table 2.

**Table 2.** Average  $\pm$  SD Systole Blood Pressure induced by NaCl 8% and High Fat Feed

Group	Dose (mg/kgBB Mice)	Systole Blood Pressure (mmHg)	
		Day-0	Day-14
Normal		124 $\pm$ 5,788	120 $\pm$ 1,225
Control		120,2 $\pm$ 12,133	159 $\pm$ 5,916
Hydrochlorothiazide	2,25	112,4 $\pm$ 13,315	150,4 $\pm$ 8,961
Simvastatin	0,9	118,2 $\pm$ 7,155	150,6 $\pm$ 6,309
EESE	4,5	116,4 $\pm$ 13,012	154 $\pm$ 5,612
EESA	25	117,6 $\pm$ 8,849	153 $\pm$ 1,871
Combination 1	1,125 : 6,25	122 $\pm$ 7,583	150,2 $\pm$ 2,280
Combination 2	2,25 : 12,5	120 $\pm$ 13,472	147,6 $\pm$ 7,503





**Fig. 1.** Histogram of Systole Average Blood Pressure Before and After Induced by NaCl 8% and High Fat Feed

Systole blood pressure in the day-14 increased after supplied with NaCl 8% and high fat feed. The increase of systole blood pressure can be seen in Figure 1. After induction for 14 days, the blood pressure was concluded as light hypertension. Based on Krinke (2009), hypertension is categorized light when systole blood pressure on the range of 149-199 mmHg and diastole blood pressure >97 mmHg [11]. Over consumption of salt can cause blood pressure because it can increase sodium levels in delicate muscle cells in arterial walls. High sodium levels can cause arterial contracting and constricting [12]. Constricting blood vessel makes the heart must work harder to pump increasing-blood volume through narrow space, thus causes blood pressure becomes high.

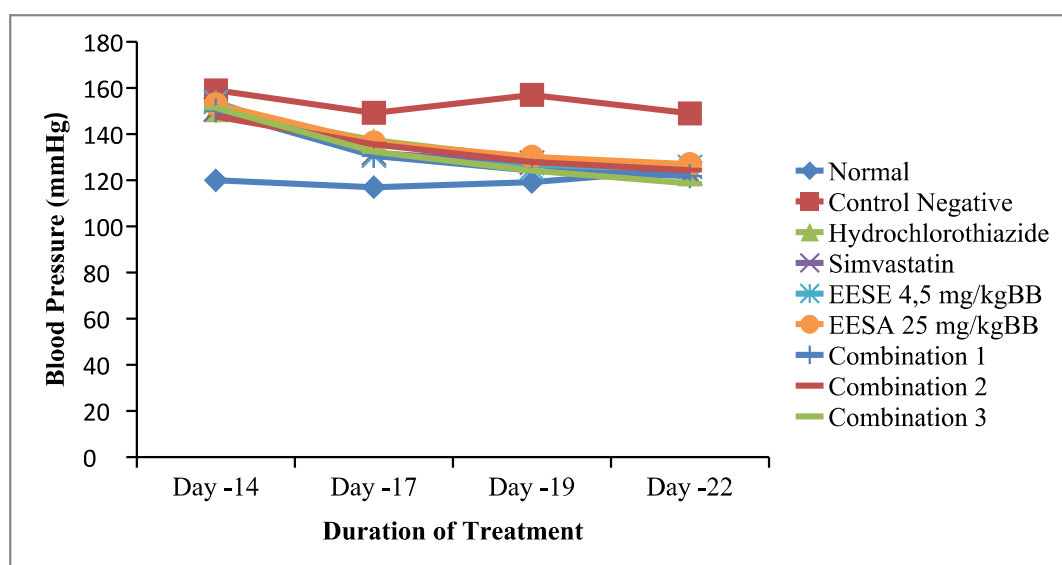
The measurement result of systole blood pressure in day-14 after induced NaCl 8% and high fat feed in mice groups were increasing and the blood pressure was higher compared to average normal systole blood pressure which is  $120 \pm 1,225$ . Based on statistics analysis result shows that there are significant difference ( $p < 0,05$ ) between normal group and those seventh groups, meanwhile in control group with average systole blood pressure of  $159 \pm 5,916$  shows that there are no significant differences ( $p > 0,05$ ) with those seventh groups. It can be said that induction of NaCl 8% and high fat feed for 14 days can cause mice systole blood pressure increased significantly.

**Table 3.** Average ± SD Systole Blood Pressure Day-14, 17, 19, and 22

Group	Dose (mg/kgBB mice)	Systole Blood Pressure (mmHg)				Decresin g (%)
		Day-14	Day-17	Day-19	Day-22	
Normal		$120 \pm$	$117 \pm$	$119,2 \pm$	$124,8 \pm$	-4*
		1,225	3,240	10,330	5,805	
Control		$159 \pm$	$149,2 \pm$	$157 \pm$	$149 \pm$	6,289
		5,916	5,263	5,874	9,301	
HCTZ	2,25	$150,4 \pm$	$137,4 \pm$	$129,4 \pm$	$122,6 \pm$	18,484*
		8,961	4,722*	5,320*	0,894*	
Simvastatin	0,9	$150,6 \pm$	$131,8 \pm$	$127,6 \pm$	$123 \pm$	18,327*
		6,309	7,396*	5,320*	2,000*	
EESE	4,5	$154 \pm$	$130,6 \pm$	$125,4 \pm$	$125,8 \pm$	18,312*
		5,612	4,506*	1,817*	5,167*	
EESA	25	$153 \pm$	$136,4 \pm$	$130,2 \pm$	$127 \pm$	16,993*
		1,871	1,949*	5,630*	8,718*	

Combination 1	1,125 : 6,25	150,2 ± 2,280	130,6 ± 6,914*	124,2 ± 6,419*	121,8 ± 8,585*	18,908*
Combination 2	2,25 : 12,5	147,6 ± 7,503	135,6 ± 4,980*	128 ± 5,148*	124,4 ± 4,827*	15,718*
Combination 3	4,5 : 25	151,4 ± 2,510	132,4 ± 5,814*	124,2 ± 1,483*	118,6 ± 3,050*	21,664*

Information: \*p < 0,05 Significantly different compared to Control group.



**Fig. 2.** Histogram of Average Systole blood pressure in Day-14,17,19 and 22.

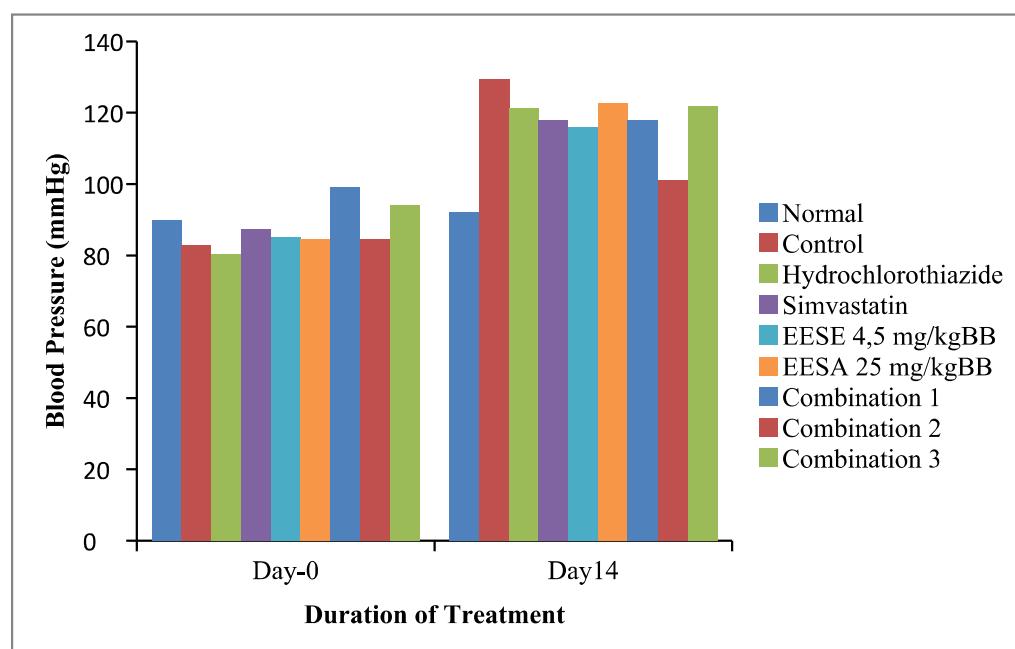
Based on average result of systole blood pressure during treatment on Table 3, systole blood pressure has significant difference ( $p < 0,05$ ) with control group and it is not significantly different with normal group ( $p > 0,05$ ). This can be said that systole blood pressure during rendering with extract was decreasing and almost reached normal systole blood pressure group. The decreasing is not different significantly ( $p > 0,05$ ) compared with HCTZ group. The biggest decreasing of blood pressure is group of Combination 3.

**Table 4.** Average ± SD Mice Diastole Blood Pressure Induced with NaCl 8% and High Fat Feed

Group	Dose (mg/kgBB Mice)	Diastole Blood Pressure (mmHg)	
		Day-0	Day-14
Normal		90 ± 13,874	92 ± 8,860
Control		82,8 ± 5,020	129,4 ± 11,83
HCTZ	2,25	80,2 ± 11,300	121,2 ± 18,820
Simvastatin	0,9	87,2 ± 9,257	118 ± 12,748
EESE	4,5	85,2 ± 11,077	116 ± 6,205
EESA	25	84,6 ± 9,476	122,6 ± 16,009
Combination 1	1,125 : 6,25	99,2 ± 6,419	118 ± 10,464
Combination 2	2,25 : 12,5	84,6 ± 11,171	101,2 ± 20,644

Diastole blood pressure was reaching when the heart finished contracting. Average diastole blood pressure in day-0 is diastole normal blood pressure before induced with NaCl 8% and high fat feed. The measurement result of diastole blood pressure can be seen in Table 4. Based on statistics analysis shows that there are no significant differences ( $p>0,05$ ) in all of tested groups. This case shows that diastole blood pressure is normal in all tested mice groups.

Diastole blood pressure at day-14 in group of mice, supplied with NaCl 8% and high fat feed, was increasing and not different significantly ( $p>0,05$ ) with Control Group, meanwhile compared with normal group there were significant difference ( $p<0,05$ ). This shows that Induction of NaCl 8% and high fat feed for 13 days also can increase diastole blood pressure. Diastole blood pressure can be seen in Figure 3.



**Fig. 3.** Histogram of Diastole Average Blood Pressure Before and After being induced by NaCl 8% and High Fat Feed

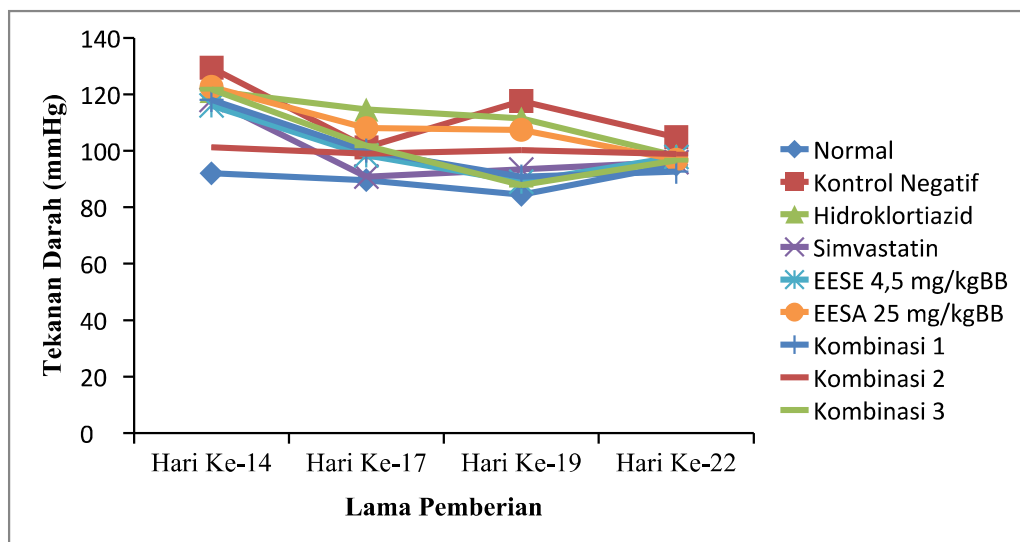
**Table 5.** Average ± SD Diastole Blood Pressure Day - 14, 17, 19 and 22.

Group	Dose (mg/kgBB Mice)	Diastole Blood Pressure (mmHg)				Decreasi ng (%)
		Day-14	Day-17	Day-19	Day-22	
Normal		92 ± 8,860	89,6 ± 11,908	84,4 ± 12,857	95 ± 18,207	- 3,261
		Control	129,4 ± 11,83	101,2 ± 12,154	117,6 ± 18,487	
HCTZ	2,25	121,2 ± 18,820	114,6 ± 10,644	111,4 ± 13,088	98,2 ± 10,803	18,482
		Simvastatin	118 ± 12,748	90,8 ± 17,908	93,4 ± 3,578*	
EESE	4,5	116 ± 6,205	98,4 ± 7,797	89 ± 9,055*	97,8 ± 9,094	15,690
		EESA	122,6 ± 108 ±	108 ± 107,4 ±	107,4 ± 96,8 ±	

Combination 1	1,125 : 6,25	16,009 118 ± 10,464	15,508 100 ± 7,071	17,329 90,8 ± 6,261*	28,455 92,6 ± 15,274	21,525
Combination 2	2,25 : 12,5	101,2 ± 20,644	99 ± 9,772	100,2 ± 10,686	98,8 ± 5,263	2,372
Combination 3	4,5 : 25	121,8 ± 13,609	101,8 ± 17,196	87,8 ± 19,292*	96,6 ± 10,383	20,690

Information : \*p < 0,05 Significantly Different Compared with Control Group.

Based on average result of mice diastole blood pressure test, on Table 5 during treatment, shows that extract treatment can decrease diastole blood pressure however it is not significant. Diastole blood pressure in day-22 not does not show significant difference (p>0,05) with control group. Diastole blood pressure decrease can be seen in Figure 4.



**Fig. 4.** Graphic on Diastole Average Blood Pressure on Day-14, 17, 19 and 22.

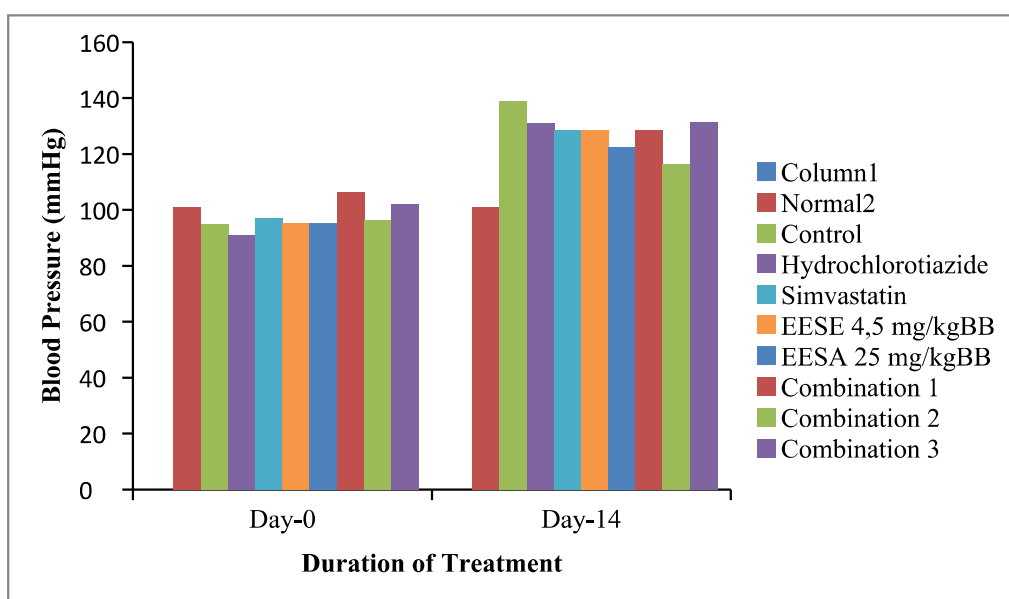
Beside systole and diastole blood pressure, it is also conducted average blood pressure to mice. Blood pressure throughout the contracted heart cycle. During the heart's contracting cycle, two-thirds of the time is spent in diastole and one-third in systole [10]. Average blood pressure or called MAP is the main factor for viewing the condition of tissue perfusion. High MAP can cause cardiovascular and cause organ disorder, whereas low MAP can cause perfusion tissue disorder which is critical condition [13].

**Table 6.** Average ± SD Mice Blood Pressure Induced With NaCl 8% and High Fat Feed.

Group	Dose (mg/kgBB mice)	Average Blood Pressure (mmHg)	
		Day-0	Day-14
Normal		101 ± 10,840	101 ± 5,701
Control		95 ± 6,856	138,8 ± 9,524
HCTZ	2,25	91 ± 11,979	130,8 ± 14,973
Simvastatin	0,9	97,2 ± 8,379	128,4 ± 10,455
EESE	4,5	95,4 ± 11,567	128,4 ± 5,983

EESA	25	95,2 ± 8,556	122,6 ± 16,009
Combination 1	1,125 : 6,25	106,6 ± 5,177	128,4 ± 7,635
Combination 2	2,25 : 12,5	96,2 ± 11,735	116,4 ± 14,673
Combination 3	4,5 : 25	102 ± 13,472	131,2 ± 10,001

Measurement result of average blood pressure can be seen on Table 6. Average blood pressure day-0 is normal average blood pressure before induced with NaCl 8% and high fat feed. Based on statistics analysis result, there are no significant difference ( $p>0,05$ ) to all of tested mice groups. This shows that average blood pressure of all tested mice is normal.



**Fig. 5.** Histogram of Average Blood Pressure Before and After Induced NaCl 8% and High Fat Feed.

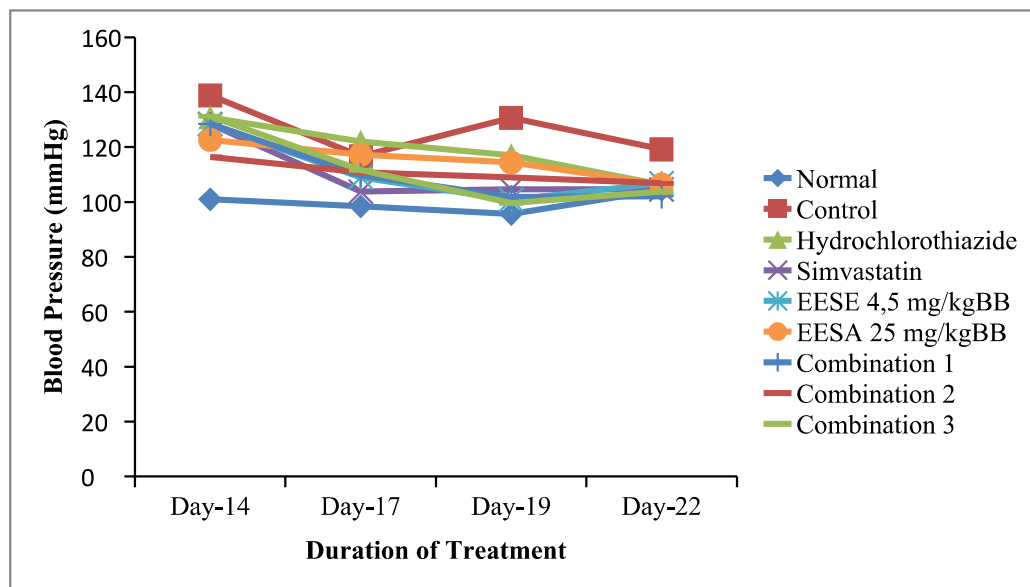
Statistics analysis result average blood pressure on Day-14 shows that there are significant differences ( $p<0,05$ ) between the five groups with normal group and there are no significant differences ( $p>0,05$ ) with control groups. This shows that induction of NaCl 8% and high Fat Feed can also increase average blood pressure. The increase of blood pressure can be seen in Figure 5.

**Table 7.** Average ± SD Average Mice Blood Pressure Induced by NaCl 8% and High Fat Feed

Group	Dose (mg/kgBB Mice)	Average Blood Pressure (mmHg)				Decreasing (%)
		Day-14	Day-17	Day-19	Day-22	
Normal		101 ± 5,701	98,4 ± 7,403	95,6 ± 9,556	104,4 ± 13,259	-3,366*
Control		138,8 ± 9,524	116,6 ± 9,737	130,6 ± 13,465	119,2 ± 15,707	14,121
HCTZ	2,25	130,8 ± 14,973	122 ± 7,517	117 ± 10,247*	106,2 ± 7,120	18,807
Simvastatin	0,9	128,4 ± 10,455	103,8 ± 9,576	104,6 ± 3,912*	104,6 ± 5,683	18,409
EESE	4,5	128,4 ± 5,983	109 ± 8,633	100,8 ± 6,221*	106,8 ± 7,294	16,822

EESA	25	122,6 ± 16,009	117,2 ± 10,474	114,4 ± 11,589*	106,4 ± 20,526	13,214
Combination 1	1,125 : 6,25	128,4 ± 7,635	109,8 ± 6,870	101,8 ± 5,805*	102 ± 12,227*	20,561
Combination 2	2,25 : 12,5	116,4 ± 14,673	110,8 ± 6,535	109 ± 8,631*	106,8 ± 4,550	8,247
Combination 3	4,5 : 25	131,2 ± 10,001	111,6 ± 12,462	99,6 ± 13,278*	103,8 ± 6,686*	20,884

Information: \*  $p < 0,05$  Significantly different compared with Control Group.



**Fig. 6.** Graphic Average Blood Pressure in Day -14, 17, 19, and 22.

Based on average blood pressure test during treatment on Table 7 shows that extract treatment can decrease average blood pressure however the decreasing is not significant. Average blood pressure decrease in day-22 does not show the significant different ( $p > 0,05$ ) compared with Control group. The decreasing average blood pressure for 7 days treatment can be seen in Figure 6.

Based on the research conducted by Ismiyati, bay leaf can decrease average blood pressure significantly [14]. This is also shows in the research that bay leaf can decrease average blood pressure after 7 days treatment.

Although the mechanism of action of each plant is different in lowering blood pressure but when combined, it can reduce blood pressure which is almost the same as the hydrochlorothiazide comparison group. This is because bay leaf contains compound flavonoid which can decrease cholesterol levels. One of the flavonoid contained in bay leaf is kuersetin. Kuersetin can hampers oxidation LDL which modified by Marofag. Moreover bay leaf also can decrease blood pressure because of the flavonoid compound. Based on the previous research, Ismiyati shows that bay leaf ethanol extract can decrease blood pressure due to induction fenileprin [14]. Celery herb also contains flavonoid that works in decreasing blood pressure through blood vessel vasodilatation. Flovonoid compound type is bioactive medicine plant compound which is commonly has the ability to hamper ACE activity. ACE has important role in creating angiotensin II which is the cause of hypertension [5].

Based on research conducted by Dianat, celery leaf ethanol extract can decrease systole blood pressure because celery leaf contains flavonoid apigenin that has strong antioxidant effect and can prevent tissue damaging due to oxidant stress [15]. Based on the research conducted by

muflikhatur also shows that ethanol extract of bay leaf doses 0,034 gram can decrease cholesterol level totally [16]. Bay leaf contains flavonoid which can hamper HMG-CoA reductase and hamper fat absorption in intestine. This case is much related with blood pressure decrease when the two plants are combined, because based on the research conducted by a Doctor in America on 2006 stated that the higher cholesterol level can increase the risk of hypertension [17]. Therefore, the research used the two plants for the synergy effect in eliminating blood pressure with much better.

Based on mice vital organ analysis result with haematoxylin and eosin, it shows that there are no pathology changing in liver, kidney, and heart organ after rendered combinations of celery and bay leaf ethanol extract. However, in comparison groups of simvastatin there is foki necrotic Centro lobular in the liver.

Based on the previous research, combination of celery leaf (*Apium graveolens*) and bay leaf (*Sizygium polyanthum*) ethanol extract can decrease systole blood pressure, diastole and average blood pressure. However, diastole blood pressure decrease is less than systole blood pressure, so the blood pressure decrease is more through a decrease in mice systole blood pressure. Combinations of celery and bay leaf ethanol extract can be used as alternative medicine because it is taken from the nature and seen from the percent reduction was greater than the comparison group hydrochlorothiazide.

## Conclusions

Based on the conducted research, it can be concluded that giving combinations of celery herb conducted (*Apium graveolens*) and bay leaf (*Sizygium polyanthum*) ethanol extract can decrease systole blood pressure significantly and it is not significantly different with comparison of hydrochlorothiazide group.

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## Ethanol Extract Combinations Effect of Celery Herb (*Apium graveolens* L.) and Bay Leaf (*Syzygium polyanthum* W.) Toward Hypertensive Mice Induced by Sodium Chloride and High Fat Feed

MOCH Saiful Bachri<sup>1,a</sup> WIDYASARI Putranti<sup>1,b\*</sup>, LINA Widiyastuti<sup>1,c</sup>,  
RESALIAN TI Sintiana Devie<sup>1,d</sup>

<sup>1</sup>Faculty of Pharmacy, Ahmad Dahlan University, Prof. Dr. Soepomo Street, Janturan, Warungboto, Yogyakarta, Indonesia 55164

<sup>a</sup>msaifulbachri@yahoo.co.id, <sup>b</sup>widyasari@pharm.uad.ac.id, <sup>c</sup>lina.widiyastuti@pharm.uad.ac.id, ,  
<sup>e</sup>resalianti17@gmail.com

**Keywords:** Anti-hypertension, *Apium graveolens*, *Syzygium polyanthum*, Combination of Extract, Blood Pressure.

**Abstract:** The combination of herb medicine is alternative option in hypertension because it has more potential for treatment with complications like hyperlipida. Plant which can be used for anti-hypertension therapy is combination of celery herb (*Apium graveolens*) and bay leaf ethanol extract (*Syzygium polyanthum*). This research aims to determine the activity of a combination of celery herb ethanol extract (CHEE) and bay leaf ethanol extract (BLEE) and find out how much the decrease of blood pressure on the combination of both toward hypertension with high fat Wistar mice. The design of this research used an experimental design with pre-post control group design. Hypertensive mice are induced with high fat feed and orally with sodium chloride 8%, then the mice are supplied with combinations extract with the dose of 1.125 ; 6.25 ; 2.25 ; 12.5 and 4.5 ; 25 mg/kg, hydrochlorotiazide 2.25 mg/kg, Simvastatin 0.9 mg/kg, CHEE 4.5 mg/kg, BLEE 25 mg/kg and CMC-Na 0.5%. Research result shows that the combination can decrease systole blood pressure in the 22<sup>nd</sup> day. The extract combination has anti-hypertension effect (it is able to decrease systole blood pressure  $\geq 20$  mmHg) and it is not significantly different with normal group ( $p < 0.05$ ). Based on the research, it can be concluded that ethanol extract combination can decrease systole blood pressure with high fat complications after using it for 22 days.

### Introduction

Hypertension is a medical condition where there is an increase in blood vessel contraction resulting in blood vessel resistance and cause an increase in blood pressure in blood vessels [1]. Hypertension is one of the main cause of the increasing amount of diseases related to cardiovascular. Based on the research Basic Health Research (Riskesdas) in 2013, hypertension prevalence in Indonesian citizens who are more than 18 years old age is 25.8% [2].

The good treatment for hypertension is to use anti-hypertension drugs to reduce blood pressure. However the treatment of hypertension requires no small cost because the usage will be for long terms. Moreover, the treatment can cause various side effects because of long term usage [3]. Those cases make people choose to plant medicine or herb as the alternative treatment for hypertension.

Traditional medicine plants or herbs that are commonly used by people to overcome hypertension are celery herb and bay leaf. Celery herb (*Apium graveolens*) is a plant which is often cooked for food and used as traditional medicine. Celery herb contains apigenin, prevents from blood vessels constriction and phtalides, that can relax blood vessels [4]. Based on initial test, celery herb with dose of 4.5 mg/kg can decrease blood pressure toward male wistar mice induced with sodium chloride.

Bay leaf (*Syzygium polyanthum*) is a spice producing plant which is commonly used in food by Indonesian society and use as a drug plant. Bay leaf had been known by the people to decrease blood pressure because it contains essential oil, tannin, and flavonoid [5]. Bay leaf is also as antihyperlipidemia because it contains tannin, saponin, niacin, and flavonoid which can decrease

blood cholesterol level and control HDL cholesterol [6]. Based on initial test, ethanol extract of bay leaf with dose of 25 mg/kg has function as anti-hypertension and anti-hyperlipidemia.

Based on the background, the research needs to be conducted on the effect of ethanol extract combination CHEE and BLEE in blood pressure decrease toward white male wistar mice, it is expected that by giving CHEE, as anti-hypertension, combined with BLEE, as anti-hypertension and anti-hyperlipidemia, will be able to decrease blood pressure through cholesterol decrease in blood pressure as well. This is because hyperlipidemia can also cause an increase in blood pressure. Therefore, giving the combination of ethanol extract is expected to be more effective in reducing blood pressure in white male wistar mice induced with sodium chloride and high fat feed.

## Materials and Methods

**Plant Materials.** Celery herb and bay leaf was obtained from Beringharjo market Yogyakarta and identified in Biology Laboratory of Ahmad Dahlan University. Simplicia powder was made from delicate pieces of simplicia or it complete which has been dried through powder making process with tools without damaging or eliminating chemical compound in the simplicia, then it was grinded until obtained powder. Ethanol extract of celery herb and bay leaf was made using maceration method with ratio of comparison between simplicia and solvent was 1: 10. Maceration was done during the first 6 hours while stirring occasionally, then let stand for 18 hours. Then macerate was separated by filtering. Filtrate gained was kept as filtrate I, whereas precipitate was re-macerated. Macerate was separated from the pulp. Filtrate was mixed with filtrate I and then it was evaporated using *rotary evaporator* until obtained thick extract [7].

**Animals.** White furrow male wistar mice with 2-3 month old, weighing 150-250 gram, as much as 25 mice used for this research. The tested animal was placed in constant temperature ( $22 \pm 2^\circ\text{C}$ ) with the moisture relatively constant ( $55 \pm 10\%$ ) and had free access for food and water. Animal handling protocol of the research was adapted by the animal treatment manual of the Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Ahmad Dahlan University. All studies were approved by the Research Ethics Committee Ahmad Dahlan University (Ethical Approval Number 011805079).

**Experimental Design.** The mice were divided into nine groups (5 mice per group) and treatment was conducted for 22 days. Normal group: the mice were only provided with food and water for 21 days. Control Group: the mice were supplied with Sodium chloride 8% and high fat feed (14 days) and CMC-Na 0.5% (7 days). Hydrochlorothiazide: the mice were supplied with Sodium chloride 8% and high fat feed (14 days) and hydrochlorothiazide 2.25 mg/kg with volume of 2 mL/200 g mice (7 days). Simvastatin group: the mice were supplied with Sodium chloride 8% and high fat feed (14 days) and were supplied with simvastatin 0.9 mg/kg on volume of 2 mL/200 g mice (7 days). Extract group: the mice were induced with Sodium chloride and high fat feed (14 days) and were supplied with extract (7 days). CHEE group: the mice were supplied with ethanol extract of celery herb of 4.5 mg/kg (7 days). BLEE group: the mice were supplied with ethanol extract bay leaf of 25 mg/kg (7 days). Combination Group I: the mice were supply with CHEE 1.125 mg/kg and BLEE 6.25 mg/kg. Combination group 2: the mice were supplied with CHEE 2.25 mg/kg and BLEE 12.5 mg/kg. Combination group 3: the mice were supplied with CHEE 4.5 mg/kg and BLEE 25 mg/kg. The administration of extract toward combination of groups was given individually and there was paused after the first extract administration.

**Blood Pressure Measurement.** Mice blood pressure was measured by *Tail Cuff Method* which used *blood pressure analyzer* called CODA. The method of measurement using this tool was the mice to be measured was put into the holder. Mice must be in a state of no stress due to cold or heat and in a calm state when in the holder. The mice tail was put in the tied cuff and the mice blood pressure was measured [8]. Blood pressure measurement in mice was carried out on day 14 after blood pressure reached 150/90 mmHg and at the time of treatment on days 17, 19, 22.

**Statistical Analysis** Data attained was processed statistically using SPSS. Analysis test conducted was homogeneity test and normal distribution test. Then, to know the relationship between treatment groups will be conducted by one way variant analysis test (ANOVA). If there were significant

different between groups, it will be conducted by smallest actual different analysis test (BNT). However, if the data were not normally distributed and homogeneity, then it will be conducted with non-parametric Kruskal-Wallis analysis to know any differences existed. If there were significant differences then it continued with non-parametric analysis Mann Whitney [9].

## Result and Discussion

**Extraction Result.** Based on the conducted research, it was attained extraction as the result of celery herb with thick dark green extract and had characteristic smelt, whereas bay leaf extraction result was attained thick brown blackish color, tasted bitter and characteristic smelt. The result of celery herb and bay leaf ethanol extraction can be seen in Table 1.

**Table 1.** Celery Herb (*Apium graveolens* L.) and Bay Leaf (*Syzygium polyanthum* W.) Extraction Result

No	Sample	Sample Weight (kg)	Extract Weight (g)	Rendemen (%)
1.	Celery Herb	2.6	177.185 g	6.815 %
2.	Bay Leaf	2.2	112.44 g	5.111 %

**Anti-hypertension Activity Test.** Artery blood pressure is a pressure occurred in the blood vessel artery pumped by the heart to all over the body in the millimeter mercury unit (mmHg). There are two artery blood pressure, systole blood pressure and diastole blood pressure [10]. The measurement of blood pressure toward mice used *Tail Cuff Method* with *blood pressure analyzer* tool called CODA.

Systole blood pressure is blood pressure when the heart is in contraction. Mice systole blood pressure in the day-0 was normal and lower than the mice systole blood pressure in the day-14. Based on statistics analysis result shows that there are no significant difference ( $p > 0.05$ ) on all of tested mice groups. This shows that all mice groups tested were the same and normal. Average systole blood pressure data in the day-0 and 14 can be seen in Table 2.

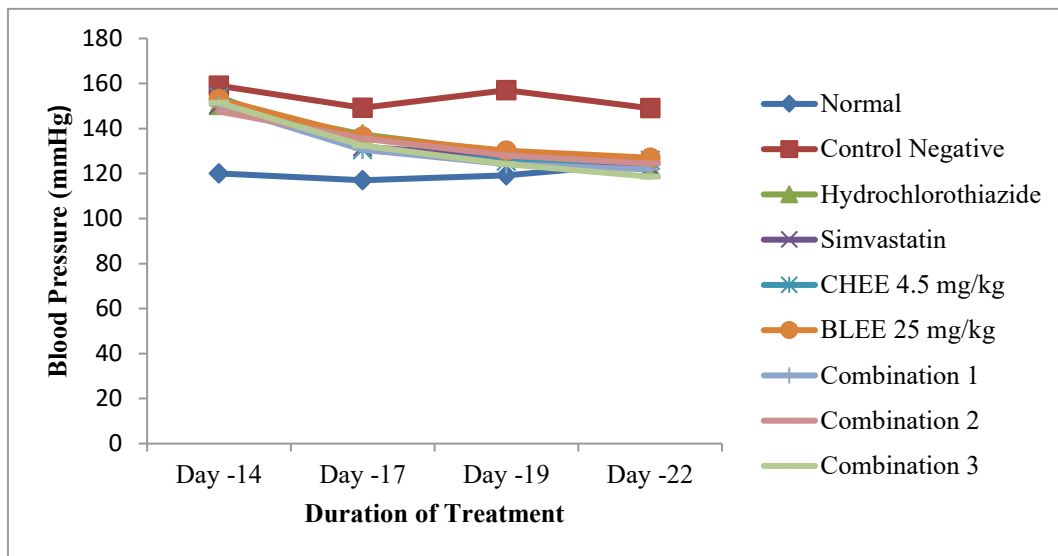
Systole blood pressure in the day-14 increased after supplied with Sodium chloride 8% and high fat feed. After induction for 14 days, the blood pressure was concluded as light hypertension. Based on Krinke (2009), hypertension is categorized light when systole blood pressure on the range of 149-199 mmHg and diastole blood pressure  $> 97$  mmHg [11]. Over consumption of salt can cause blood pressure because it can increase sodium levels in delicate muscle cells in arterial walls. High sodium levels can cause arterial contracting and constricting [12]. Constricting blood vessel makes the heart must work harder to pump increasing-blood volume through narrow space, thus causes blood pressure becomes high.

The measurement result of systole blood pressure in day-14 after induced Sodium chloride 8% and high fat feed in mice groups were increasing and the blood pressure was higher compared to average normal systole blood pressure which is  $120 \pm 1.225$ . Based on statistics analysis result shows that there are significant difference ( $p < 0.05$ ) between normal group and those seventh groups, meanwhile in control group with average systole blood pressure of  $159 \pm 5.916$  shows that there are no significant differences ( $p > 0.05$ ) with those seventh groups. It can be said that induction of Sodium chloride 8% and high fat feed for 14 days can cause mice systole blood pressure increased significantly.

**Table 2.** Average  $\pm$  SD Systole Blood Pressure

Group	Dose (mg/kg)	Systole Blood Pressure (mmHg)					Decreasing (%)
		Day-0	Day-14	Day-17	Day-19	Day-22	
Normal		124 $\pm$ 5.788	120 $\pm$ 1.225	117 $\pm$ 3.240	119.2 $\pm$ 10.330	124.8 $\pm$ 5.805	-4*
Control		120.2 $\pm$ 12.133	159 $\pm$ 5.916	149.2 $\pm$ 5.263	157 $\pm$ 5.874	149 $\pm$ 9.301	6.289
HCTZ	2,25	112.4 $\pm$ 13.315	150.4 $\pm$ 8.961	137.4 $\pm$ 4.722*	129.4 $\pm$ 5.320*	122.6 $\pm$ 0.894*	18.484*
Simvastatin	0,9	118.2 $\pm$ 7.155	150.6 $\pm$ 6.309	131.8 $\pm$ 7.396*	127.6 $\pm$ 5.320*	123 $\pm$ 2.000*	18.327*
CHEE	4,5	116.4 $\pm$ 13.012	154 $\pm$ 5.612	130.6 $\pm$ 4.506*	125.4 $\pm$ 1.817*	125.8 $\pm$ 5.167*	18.312*
BLEE	25	117.6 $\pm$ 8.849	153 $\pm$ 1.871	136.4 $\pm$ 1.949*	130.2 $\pm$ 5.630*	127 $\pm$ 8.718*	16.993*
Combination 1	1.125 : 6.25	122 $\pm$ 7.583	150.2 $\pm$ 2.280	130.6 $\pm$ 6.914*	124.2 $\pm$ 6.419*	121.8 $\pm$ 8.585*	18.908*
Combination 2	2.25 : 12.5	120 $\pm$ 13.472	147.6 $\pm$ 7.503	135.6 $\pm$ 4.980*	128 $\pm$ 5.148*	124.4 $\pm$ 4.827*	15.718*
Combination 3	4.5 : 25	118.8 $\pm$ 15.515	151.4 $\pm$ 2.510	132.4 $\pm$ 5.814*	124.2 $\pm$ 1.483*	118.6 $\pm$ 3.050*	21.664*

Information: \*P < 0.05 Significantly different compared to Control group.

**Fig. 1.** Histogram of Average Systole blood pressure in Day-14,17,19 and 22.

Based on average result of systole blood pressure during treatment on Table 2, systole blood pressure has significant difference ( $p < 0.05$ ) with control group and it is not significantly different with normal group ( $p > 0.05$ ). This can be said that systole blood pressure during rendering with extract was decreasing and almost reached normal systole blood pressure group. The decreasing is not different significantly ( $p > 0.05$ ) compared with HCTZ group. The biggest decreasing of blood pressure is group of Combination 3.

Diastole blood pressure was reaching when the heart finished contracting. Average diastole blood pressure in day-0 is diastole normal blood pressure before induced with Sodium chloride 8% and high fat feed. The measurement result of diastole blood pressure can be seen in Table 3. Based on statistics analysis shows that there are no significant differences ( $p>0.05$ ) in all of tested groups. This case shows that diastole blood pressure is normal in all tested mice groups.

Diastole blood pressure at day-14 in group of mice, supplied with Sodium chloride 8% and high fat feed, was increasing and not different significantly ( $p>0.05$ ) with Control Group, meanwhile compared with normal group there were significant difference ( $p<0.05$ ). This shows that Induction of Sodium chloride 8% and high fat feed for 13 days also can increase diastole blood pressure

**Table 3.** Average  $\pm$  SD Diastole Blood Pressure

Group	Dose (mg/kgBB Mice)	Diastole Blood Pressure (mmHg)					Decreasing (%)
		Day-0	Day-14	Day-17	Day-19	Day-22	
Normal		90 $\pm$	92 $\pm$	89.6 $\pm$	84.4 $\pm$	95 $\pm$	- 3.261
		13.874	8.860	11.908	12.857	18.207	
Control		82.8 $\pm$	129.4 $\pm$	101.2 $\pm$	117.6 $\pm$	104.8 $\pm$	19.011
		5.020	11.83	12.154	18.487	19.396	
HCTZ	2.25	80.2 $\pm$	121.2 $\pm$	114.6 $\pm$	111.4 $\pm$	98.2 $\pm$	18.482
		11.300	18.820	10.644	13.088	10.803	
Simvastatin	0.9	87.2 $\pm$	118 $\pm$	90.8 $\pm$	93.4 $\pm$	96 $\pm$ 8.155	18.644
		9.257	12.748	17.908	3.578*		
CHEE	4.5	85.2 $\pm$	116 $\pm$	98.4 $\pm$	89 $\pm$	97.8 $\pm$	15.690
		11.077	6.205	7.797	9.055*	9.094	
BLEE	25	84.6 $\pm$	122.6 $\pm$	108 $\pm$	107.4 $\pm$	96.8 $\pm$	21.044
		9.476	16.009	15.508	17.329	28.455	
Combination 1	1.125 : 6.25	99.2 $\pm$	118 $\pm$	100 $\pm$	90.8 $\pm$	92.6 $\pm$	21.525
		6.419	10.464	7.071	6.261*	15.274	
Combination 2	2.25 : 12.5	84.6 $\pm$	101.2 $\pm$	99 $\pm$ 9.772	100.2 $\pm$	98.8 $\pm$	2.372
		11.171	20.644		10.686	5.263	
Combination 3	4.5 : 25	94 $\pm$	121.8 $\pm$	101.8 $\pm$	87.8 $\pm$	96.6 $\pm$	20.690
		12.981	13.609	17.196	19.292*	10.383	

Information: \* $p < 0.05$  Significantly Different Compared with Control Group.

Based on average result of mice diastole blood pressure test, on Table 3 during treatment, shows that extract treatment can decrease diastole blood pressure however it is not significant. Diastole blood pressure in day-22 not does not show significant difference ( $p>0.05$ ) with control group.

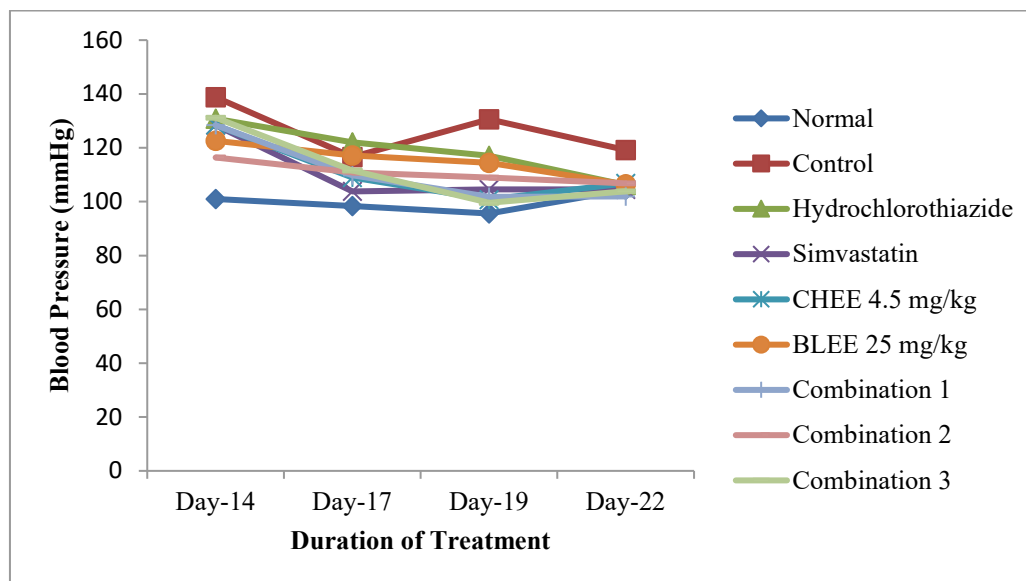
Beside systole and diastole blood pressure, it is also conducted average blood pressure to mice. Blood pressure throughout the contracted heart cycle. During the heart's contracting cycle, two-thirds of the time is spent in diastole and one-third in systole [10]. Average blood pressure or called MAP is the main factor for viewing the condition of tissue perfusion. High MAP can cause cardiovascular and cause organ disorder, whereas low MAP can cause perfusion tissue disorder which is critical condition [13].

Measurement result of average blood pressure can be seen on Table 4. Average blood pressure day-0 is normal average blood pressure before induced with Sodium chloride 8% and high fat feed. Based on statistics analysis result, there are no significant difference ( $p>0.05$ ) to all of tested mice groups. This shows that average blood pressure of all tested mice is normal. Statistics analysis result average blood pressure on Day-14 shows that there are significant differences ( $p<0.05$ ) between the five groups with normal group and there are no significant differences ( $p>0.05$ ) with control groups. This shows that induction of Sodium chloride 8% and high Fat Feed can also increase average blood pressure.

**Table 4.** Average  $\pm$  SD Average Mice Blood Pressure

Group	Dose (mg/kg)	Average Blood Pressure (mmHg)					Decreasing (%)
		Day-0	Day-14	Day-17	Day-19	Day-22	
Normal		101 $\pm$ 10.840	101 $\pm$ 5.701	98.4 $\pm$ 7.403	95.6 $\pm$ 9.556	104.4 $\pm$ 13.259	-3.366*
Control		95 $\pm$ 6.856	138.8 $\pm$ 9.524	116.6 $\pm$ 9.737	130.6 $\pm$ 13.465	119.2 $\pm$ 15.707	14.121
HCTZ	2.25	91 $\pm$ 11.979	130.8 $\pm$ 14.973	122 $\pm$ 7.517	117 $\pm$ 10.247*	106.2 $\pm$ 7.120	18.807
Simvastatin	0.9	97.2 $\pm$ 8.379	128.4 $\pm$ 10.455	103.8 $\pm$ 9.576	104.6 $\pm$ 3.912*	104.6 $\pm$ 5.683	18.409
CHEE	4.5	95.4 $\pm$ 11.567	128.4 $\pm$ 5.983	109 $\pm$ 8.633	100.8 $\pm$ 6.221*	106.8 $\pm$ 7.294	16.822
BLEE	25	95.2 $\pm$ 8.556	122.6 $\pm$ 16.009	117.2 $\pm$ 10.474	114.4 $\pm$ 11.589*	106.4 $\pm$ 20.526	13.214
Combination 1	1.125 : 6.25	106.6 $\pm$ 5.177	128.4 $\pm$ 7.635	109.8 $\pm$ 6.870	101.8 $\pm$ 5.805*	102 $\pm$ 12.227*	20.561
Combination 2	2.25 : 12.5	96.2 $\pm$ 11.735	116.4 $\pm$ 14.673	110.8 $\pm$ 6.535	109 $\pm$ 8.631*	106.8 $\pm$ 4.550	8.247
Combination 3	4.5 : 25	102 $\pm$ 13.472	131.2 $\pm$ 10.001	111.6 $\pm$ 12.462	99.6 $\pm$ 13.278*	103.8 $\pm$ 6.686*	20.884

Information: \*  $p < 0.05$  significantly different compared with Control Group.

**Fig. 2.** Graphic Average Blood Pressure in Day -14, 17, 19, and 22.

Based on average blood pressure test during treatment on Table 4 shows that extract treatment can decrease average blood pressure however the decreasing is not significant. Average blood pressure decrease in day-22 does not show the significant different ( $p > 0.05$ ) compared with Control group. The decreasing average blood pressure for 7 days treatment can be seen in Fig. 2.

Based on the research conducted by Ismiyati, bay leaf can decrease average blood pressure significantly [14]. This is also shows in the research that bay leaf can decrease average blood pressure after 7 days treatment.

Although the mechanism of action of each plant is different in lowering blood pressure but when combined, it can reduce blood pressure which is almost the same as the hydrochlorothiazide comparison group. This is because bay leaf contains compound flavonoid which can decrease cholesterol levels. One of the flavonoid contained in bay leaf is kuersetin. Kuersetin can hampers oxidation LDL which modified by Marofag. Moreover bay leaf also can decrease blood pressure because of the flavonoid compound. Based on the previous research, Ismiyati shows that bay leaf

ethanol extract can decrease blood pressure due to induction phenylephrin [14]. Celery herb also contains flavonoid that works in decreasing blood pressure through blood vessel vasodilatation. Flavonoid compound type is bioactive medicine plant compound which is commonly has the ability to hamper ACE activity. ACE has important role in creating angiotensin II which is the cause of hypertension [5].

Based on research conducted by Dianat, CHEE can decrease systole blood pressure because celery herb contains flavonoid apigenin that has strong antioxidant effect and can prevent tissue damaging due to oxidant stress [15]. Based on the research conducted by muflikhatur also shows that ethanol extract of bay leaf doses 0,034 gram can decrease cholesterol level totally [16]. Bay leaf contains flavonoid which can hamper HMG-CoA reductase and hamper fat absorption in intestine. This case is much related with blood pressure decrease when the two plants are combined, because based on the research conducted by a Doctor in America on 2006 stated that the higher cholesterol level can increase the risk of hypertension [17]. Therefore, the research used the two plants for the synergy effect in eliminating blood pressure with much better.

Based on mice vital organ analysis result with haematoxylin and eosin, it shows that there are no pathology changing in liver, kidney, and heart organ after rendered combinations of celery and bay leaf ethanol extract. However, in comparison groups of simvastatin there is foki necrotic Centro lobular in the liver.

Based on the previous research, combination of celery herb (*Apium graveolens*) and bay leaf (*Syzygium polyanthum*) ethanol extract can decrease systole blood pressure, diastole and average blood pressure. However, diastole blood pressure decrease is less than systole blood pressure, so the blood pressure decrease is more through a decrease in mice systole blood pressure. Combinations of celery and bay leaf ethanol extract can be used as alternative medicine because it is taken from the nature and seen from the percent reduction was greater than the comparison group hydrochlorothiazide.

## Conclusion

Based on the conducted research, it can be concluded that giving combinations of celery herb conducted (*Apium graveolens*) and bay leaf (*syzygium polyanthum*) ethanol extract can decrease systole blood pressure significantly specially on combination 3 (4.5:25 mg/kg) and it is not significantly different with comparison of hydrochlorothiazide group.

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