

## Decreased Effects of Hypertension Therapy Caused By Interaction Between Angiotensin Converting Enzyme Inhibitors (ACE-Inh) And Bananas

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**Abstract.** Prevalence of hypertension in Indonesia is quite high at 25.8%. Drug of choice for therapeutic treatment of hypertension is the class of Angiotensin Converting Enzyme Inhibitor. ACE-inhibitors can increase potassium that have a role in blood pressure regulation. Bananas are a source of high potassium. When ACE-inhibitors are consumed with bananas, interactions may occur and will lead to adverse drug reactions such as hyperkalemia and decreased effects of blood pressure therapy. This study aimed to investigate the interaction of bananas with captopril and lisinopril against systolic and diastolic blood pressure in hypertensive rats. This was an experimental study with pre test-post test control group design. Thirty rats were randomly divided into 6 groups, without treatment (negative control), hypertension (positive control), hypertension with treatment 1 (captopril 2.25mg/kgBW once a day), hypertension with treatment 2 (lisinopril 0.6mg/kgBW once a day), hypertension with treatment 3 (captopril with banana) and hypertension with treatment 4 (lisinopril with banana). Blood pressure was measured using Non Invasive Blood Pressure technique equipped with Non Invasive Blood Pressure System (CODA®) at before, after 3 days of treatment. Data were analyzed by One Way Anova. The results showed that there was a significant difference in systolic blood pressure between groups and there was no difference in diastolic blood pressure ( $p>0.05$ ). Consumption of captopril or lisinopril along with bananas for 3 days can lower systolic blood pressure but not lower diastolic blood pressure.

### 1. Introduction

In 2013 the incidence of hypertension in Indonesia was quite high, ranging from 25.8%. This figure is only limited to cases of hypertension detected so there are still many cases of hypertension that have not been diagnosed. Primary hypertension is a common case (90-95%) of secondary hypertension 5-10%. Hypertension is a risk factor for cardiovascular disease. Mechanism of regulating blood pressure through sympathetic nerve activity, the renin angiotensin hormone system and fluid and electrolyte balance in the kidneys.

Management of hypertension can be done with a non-pharmacological approach, namely lifestyle modification, such as dietary diet. If the diet is not able to reduce blood pressure, the next approach is pharmacological therapy for anti-hypertensive drugs. five classes of antihypertensive drugs as initial or combination therapy in the management of hypertension, consisting of thiazid diuretics, beta blockers, calcium channel blockers (CCB), angiotensin converting enzyme inhibitors (ACE-Inh) and angiotensin receptor blockers (ARB) [13]. Treatment of hypertension requires a long time so that it has the opportunity to have high drug and food interactions [12].

Drug interactions can predict the emergence of drug side effects. This is in line with studies in the United States showing that the incidence of drug interactions that cause side-effect reactions is 7.3% often in hospitals and more than 88% occur in geriatric patients. Whereas in Indonesia there is no data.[1] Drug levels that are too high in plasma can cause adverse side effects. Conversely, drug levels that are too low can cause therapy failure.

Drug interactions with food are one of the forms of drug interactions that use both of them together as a result there are effects arising from nutrients from food interacting with active drug substances. Bananas are one of the most commonly consumed food choices with drugs. In the case of hypertension, first-line drugs that became drug of choice are ACE-inhibitors such as captopril and lisinopril. Bananas are one of the fruits that have high potassium content. According to some studies, ACE-inhibitor drugs taken together with high potassium supplements can increase potassium levels in the blood. With high levels of potassium in the blood will affect the work of the heart and risk to someone who has a history of hypertension.

Several studies report, bananas have high potassium content and can reduce blood pressure. A research stated that the therapy for Ambonese banana diet (*Musa paradisiaca* var. *Sapientum* Linn), which is 3-5 fruits a day which is given for 7 days can reduce blood pressure in hypertensive patients.[23] The other research also reported the same thing, namely consumption of 2 ambon bananas (140g / fruit) per day for 1 week can reduce blood pressure in elderly patients with moderate hypertension.[11] These studies were carried out on hypertensive patients who were not undergoing treatment for hypertension. This study aims to determine the risk of hyperkalemia and decrease the effect of hypertension therapy due to the use of ACE-inhibitor drugs with bananas (*Musa sp.*) simultaneously.

## 2. Literature review

### 2.1. Hypertension

Hypertension is an increase in systolic blood pressure  $\geq 140$  mmHg and or diastolic blood pressure  $\geq 90$  mmHg permanently. Hypertension classification according to JNC (Join National Committee) VIII can be seen in table 1

**Table 1.** Hypertension Classification (JNC VIII).

Classification	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)
Normal	< 120	< 80
Pre Hypertension	120 – 139	80 – 89
Level I	140 – 159	90 – 99
Level II	160	100

The pathophysiology of hypertension can be explained through 3 systems that play a role in the mechanism of blood pressure regulation, namely 1) the sympathetic nervous system 2) the Renin Angiotensin-Aldosterone system and the sodium-body fluid balance (ADH / aldosterone). The role of potassium is similar to sodium, namely potassium helps maintain osmotic pressure in the intracellular space while sodium maintains osmotic pressure in the extracellular space so that high potassium levels can increase sodium excretion in the urine (natriuresis), thereby reducing blood volume and blood pressure [6,24]

### 2.2. Banana and ace-inhibitor interaction

Captopril is the first generation ACE-inhibitor. Captopril absorption is reduced by 30-40% when given with food. If bananas are given together with captopril there will be drug and food interactions in the pharmacokinetic-absorption phase. While the next generation ACE-inhibitor that lisinopril, the

absorption process is not affected by food. Disruption of the absorption of ACE-inhibitors will have an impact on the bioavailability of captopril in the blood so that the antihypertensive effect will be

#### 2.2.1. ACE-Inhibitor

ACE-inhibitors are considered second-line therapy after diuretics in most patients with hypertension. ACE-inhibitors inhibit angiotensin I changes to angiotensin II, where angiotensin II is a potent vasoconstrictor that also stimulates aldosterone secretion. ACE-inhibitors also block the degradation of bradykinin and stimulate the synthesis of substances that cause vasodilation, including prostaglandin E2 and prostacyclin. Increased bradykinin increases the effect of blood pressure reduction.[13]

Types of ACE-Inhibitors namely: captopril, enalapril, and Lisinopril. Captopril is a proline derivative which is the first ACE Inhibitor to be used. Captopril is used in mild hypertension to severe. The dose of administration of captopril depends on individual needs. Absorption of captopril is reduced by 30-40% when given with food. Compared with other ACE inhibitors, lisinopril has the advantage of its long half-life so that the frequency of use is only once a day, making it easier to observe the effects of circadian rhythm on therapy with lisinopril. In its absorption, Lisinopril is not affected by interference from food so it can reduce risk factors for drug and food interactions [14]

#### 2.2.2. Banana

Banana (*Musa sp.*) has abundant potassium mineral resources, such as Kepok banana and Ambon banana. While the content of potassium per 100 grams of ambon banana (*Musa paradisiaca* S) is 435 mg. High potassium content in bananas is useful for regulating fluid balance in the body and helps maintain blood pressure stability.[10,17] The role of potassium ions on blood pressure reduction is as a vasodilator, because of its ability to inhibit the smooth muscle contraction of blood vessels.[9] The antihypertensive effect of potassium is also related to its effect on inhibiting sodium reabsorption in the renal tubules. [9]

### 3. Method

This type of research is laboratory experimental (True Experimental). The research design used was a randomized pre and post-test control group design.

In this study there were six treatment groups, namely control negative (C-) mice group (not made hypertension), positive control (C+) rat group (hypertension), P1 or treatment rat group 1 (hypertension given captopril), P2 or group 2 treatment rat (hypertension given lisinopril), P3 or rat group treatment 3 (hypertension given captopril and banana), P4 or group treatment rats 4 (hypertension given lisinopril and banana)

#### 3.1. Tools and materials

Glassware (pyrex), analytical balance sheet (shimazu), rat scales, Sonde (5ml, Onemade), and rat blood pressure meter @CODA Male wistar strain rats were obtained from the University of Jember Pharmacy Faculty Biomedical Laboratory, sterile water for irrigation (PT. Otsuka), CMC Na (PT. Brataco), 0.9 ml NaCl (PT Otsuka), Captopril 25mg (Tensoban), Lisinopril 10 mg (Interpil), Prednison 5mg (PT.Phapros), Banana, Rat feed @ratbio.

#### 3.2. Determination of dosage

##### 3.2.1. Hypertension rat induction dosage

Hypertension treatment was carried out in the positive control group and treatment by giving 2% NaCl solution and Prednisone 0.15 mg / ml solution in 0.5% CMC Na with a dose of 1.5 mg / Kg BW once daily for 7 days and solution 8% NaCl and Prednisone 0.15 mg / ml solution in 0.5% CMC Na with a dose of 1.5 mg / Kg BB once a day for 7 days.

### 3.2.2. Dosage of captopril

Administration of captopril 0.15 mg / ml solution suspended in 0.5% CMC Na with a dose of 2.25 mg / kg once daily.

### 3.2.3. Banana Dosage

Every rat is given a banana with 9g / kg BB of banana together when given the medicine.

### 3.3. Data Collection Techniques

Data collection by observation (obsevasi) of white wistar strain rats. The data obtained in the form of systolic blood pressure, diastole at the time of initial determination of the study sample, after induction and after administration of antihypertensive drugs and bananas. Blood pressure data was obtained from blood pressure measurements in rats by using direct tail-cuff of noninvasive method @CODA .

### 3.4. Data Analysis

Data analysis begins with the Shapiro Wilk normality test. If the normal distribution is continued with the Paired T test statistical test to see the comparison of data before and after treatment in each group and the One Way Anova statistical test followed by Post Hoc Benferroni statistical test to determine the effect of giving captopril and banana or lisinopril and bananas.

## 4. Result

The study began with rat habituation into the Habituation blood pressure measurement tool to ensure stable mouse blood pressure. Blood pressure instability causes an increase in rat blood pressure. The normal mouse blood pressure parameters for systole and diastole are guidelines for induction.

Induction was performed on rats in groups C +, C-, P1, P2, P3, P4.

On the 14th day, induction was carried out for 14 days using 15% prednisone at a dose of 1.5 mg / kg BB with a combination of 8% NaCl 3 ml daily 1 time for 14 days until the rat blood pressure was higher than before. Furthermore, the treatment group rats were given intervention in the form of drugs captopril and lisinopril with bananas.

**Table 2.** Average systolic and diastolic blood pressure before treatment

Classification	C -	C+	P 1	P 2	P 3	P 4
Sytolic (mmHg)	89,4 ±14	125±32	120,6±22	122,6±31	116,2±31	126±32
Diastolic(mmHg)	70,8±13	87,2±23	86,2±20	87±23	76,6±23	79,2±23

Table 2 shows that the average condition of systole blood pressure in the C +, P1, P2 and P4 groups had a higher blood pressure and was significantly different from the p value (<0.05) than the C-group systolic blood pressure because C- is a group that was not given an induction of 15% prednisone and 8% NaCl. Provision of 15% prednisone and 2% NaCl for 14 days can increase blood pressure. [5,20] However this did not occur in treatment group 3 which had higher systolic blood pressure but was still considered the same as C-because the post hoc test results showed p value = 0.093. This happens because the provision of prednisone is 15% and NaCl is 8% 14 days while there are studies that give 28 days of hypertension rats [16]. The average diastolic blood pressure in the C +, C-, P1, P2, P3, and P4 IV groups had no statistically significant differences with the results of ANOVA test of 0.705. This is because the nature of diastolic blood pressure tends to be stable even though it is induced with 15% prednisone and 8% NaCl. [7]

**Table 3.** Average systolic and diastolic blood pressure after treatment

Classification	C -	C+	P 1	P 2	P 3	P 4
Sytolic (mmHg)	88,2±4	121,8±29	90,4±6	96,4±27	89,8±27	96,4±26
Diastolic(mmHg)	58,8±9	76,6±19	62,6±5	61,2±19	61,6±18	61±18

Table 3 shows that the average condition of systole blood pressure at C-, P1, P2, P3, and P4 has a lower blood pressure and is significantly different from the p value of the post hoc test ( $<0.05$ ) than blood pressure systole group C + This occurs due to the administration of captopril, lisinopril, bananas together. Captopril in the P1 and lisinopril groups in P2 is an ACE inhibitor (angiotensin converting enzyme) class. This drug has a mechanism to inhibit the renin angiotensin aldosterone system, so that blood pressure drops. ACE inhibitors inhibit the enzyme to convert angiotensin I to angiotensin II (a strong vasoconstrictor). [22]

In the P3 and P4 groups, the group used ACE inhibitor and banana drugs that were given together. ACE inhibitors have a hypotensive effect with an enzyme inhibitory mechanism supplemented with bananas which also has a hypotensive effect derived from the content of potassium in bananas. Potassium in bananas has a diuretic effect so that fluid and sodium expenditure increases. This helps in the process of reducing blood pressure. Potassium can also inhibit renin release thereby altering renin angiotensin activity. [10,17] The average diastolic blood pressure between C +, C-, P1, P2, P3, P4 is not significantly different from the results of the Post Hoc Benferroni test  $p > 0, 05$ . This is because the nature of diastolic blood pressure tends to be stable even if given a single ACE-inhibitor or combination with bananas simultaneously. [7]

**Table 4.** Difference in systolic and diastolic blood pressure

Classification	C -	C+	P 1	P 2	P 3	P 4
Sytolic (mmHg)	8,8	3,2	30,2	27,4	26,4	29,6
Diastolic(mmHg)	13,6	11,8	23,6	25,8	16,2	18,2

Table 4 shows the difference between P1, P2, P3, P4 above 25 while the difference between C- and C + is only 8.8 and 3.2. Based on Benferroni's Post Hoc test, the results of the difference between P1, P2, P3, P4 and C + were significantly different with  $p < 0.05$  so that it can be said that there was an effect of drug administration of captopril, lisinopril and banana. While the difference between P1, P2, P3, P4 is not significantly different from the p value  $> 0.05$ , meaning that the effect of giving captopril, lisinopril, captopril with banana, lisinopril banana can reduce systolic blood pressure. So that giving bananas together with the drug for 3 days does not affect the hypotensive effect on ACE inhibitor drugs. While the diastole pressure difference between C +, C-, P1, P2, P3, P4 is not significantly different from the results of the Benferroni's Post Hoc test.

## 5. Conclusion

Administration of ACE inhibitors capotopril and lisinopril, Combination of Captopril with bananas and Lisinopril with bananas has an effect on systolic pressure but not on diastolic blood pressure. Giving bananas together with captopril or lisinopril for 3 days did not give effect hipotensi from captopril or lisinopril.