



**POTENTIAL ROLE OF *ZINGIBER CASSUMUNAR* ROXB. RHIZOME  
IN LOWERING BLOOD PRESSURE AND HEART RATE ON  
FRUCTOSE-INDUCED HYPERTENSION RATS MODEL**

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**ABSTRACT**

Treatment of hypertension in general needs a longer period of time. The side effects of antihypertensive drugs usually cause a failure of the hypertension treatment. The safety factor long-term drug use is a major concern for any of these medicines. One of the plants that are often used in traditional medicine and has potential as antihypertensive is *Zingiber cassumunar* Roxb. This study aimed to determine the activity of ethanolic extract of the *Zingiber cassumunar* Roxb. Rhizome as an antihypertensive. Rats were divided into 6 groups randomly. All groups except the normal group were induced by 25% fructose in the drinking water for 21 consecutive days. Parameters measured were

urine volume, systolic and diastolic blood pressure, and heart rate. Ethanol extract of *Zingiber cassumunar* Roxb. dose of 50 mg/kg showed effective as a diuretic, lowered systolic and diastolic blood pressure and normalize heart rate. Ethanol extract of *Zingiber cassumunar* Roxb. dose of 50 mg/kg showed the best antihypertension activity.

**KEYWORDS:** Amlodipine, Fructose, Furosemide, Hypertension, *Zingiber cassumunar* Roxb.

**INTRODUCTION**

Hypertension is a risk factor for cardiovascular disease or stroke characterized by persistent increases in blood pressure. Hypertension can attack almost all groups of people around the world. The number of people with hypertension continues to increase from year to year.<sup>[1]</sup> In

2012, WHO (World Health Organization) recorded as many as 1 billion people of the world suffer from hypertension. This number will continue to increase and can be predicted by 2025 the number reached 29% or 1.6 billion people worldwide will suffer from hypertension.

Increased systolic and diastolic blood pressure accompanied by increased heart rate.<sup>[2]</sup> The increased heart rate increases the likelihood of sudden death.<sup>[3]</sup> The relationship between heart rate and systolic blood pressure has been widely confirmed in both adults and children. Blood pressure during childhood has a significant association with blood pressure in adulthood. Increased blood pressure in childhood will increase the likelihood of hypertension and complications in adulthood.<sup>[4]</sup>

Epidemiological studies of healthy volunteers show that fructose consumption of more than 74 grams per day may increase blood pressure.<sup>[5]</sup> Studies in Wistar rats, giving 10% of fructose in drinking water for 7 days or more caused hypertension followed by elevated levels of insulin, glucose, and triglycerides in the blood.<sup>[6]</sup> Feeding containing 66% fructose causes hypertension within 15 days.<sup>[7]</sup> Giving 25% of fructose daily in drinking water for 21 days significantly resulted in hyperlipidemia in mice.<sup>[8]</sup> In addition, a high-fructose diet can be expected to result in metabolic syndrome.<sup>[9]</sup> Metabolic syndrome refers to hyperglycemia, obesity, dyslipidemia (hypertriglyceridemia, decreased HDL, and elevated cholesterol) and hypertension.<sup>[10]</sup>

Treatment of hypertensive diseases in general needs a long period of time. Side effects arising from antihypertensive drugs can result in failure of hypertension therapy. Therefore, the safety factor of long-term drug use is an important concern in drug selection. Currently, there is a tendency to return to nature, increasing the use of natural medicine to overcome hypertension.

One of the natural medicine ingredients that are often used in traditional medicine and has potential as antihypertensive is *Zingiber cassumunar* Roxb rhizomes. *Zingiber cassumunar* Roxb is a family Zingiberaceae plant that is often used in the community as a source of bioactive compounds. Part of the *Zingiber cassumunar* Roxb which is often used in medicine is the rhizomes. In Indonesia, *Zingiber cassumunar* Roxb rhizome has been widely used to treat fever, headache, cough with phlegm, colds, constipation, jaundice, intestinal worms, stiffness and obesity. The *Zingiber cassumunar* Roxb rhizome contains active compounds such as cassumunin A and cassumunin B, a complex curcuminoid that has anti-inflammatory

and antioxidant activity.<sup>[11]</sup> Contain phenylbutenoids as anticancer and anti-inflammatory,<sup>[12]</sup> immunostimulant,<sup>[13]</sup> and inhibitors of Angiotensin Converting Enzyme (ACE-I).<sup>[14]</sup>

Based on the description above, this research was conducted to determine the antihypertensive activity of ethanol extract of *Zingiber cassumunar* Roxb rhizome in fructose-diet rats. The results of this study are expected to provide information on the benefits of ethanol extract rhizome *Zingiber cassumunar* Roxb as antihypertensive.

## METHODS

This study was conducted *in-vivo* in white male Wistar strain test animals. This study aimed to determine the effect of ethanol extract of *Zingiber cassumunar* Roxb rhizome in Wistar rats induced hypertension with dietary fructose. The dose of fructose used was 25% in drinking water for 21 days. The test material used in this study includes 96% ethanol (purchased from Brataco, Bandung, Indonesia), *Zingiber cassumunar* rhizome (obtained from Manoko plantation, Lembang, Bandung, Indonesia and determination of plants was done in the laboratory Taxonomy, Department of Biology, Faculty of Mathematics and Natural Sciences, Padjadjaran University of Bandung (no. 120/HB/01/2016), fructose (obtained from Brataco, Bandung, Indonesia), furosemide tablet (generic drug Dexa Medica, Indonesia), amlodipine tablet (generic drug Dexa Medica, Indonesia) and animal feed (obtained from a local animal feed store). Diuretic activity was conducted by the Lipschitz method by measuring the volume of urine. Measurement of systolic and diastolic blood pressure by using noninvasive blood pressure instrument for rodents (CODA Kent Scientific, USA). Heart rate was monitored using tools developed by Biomedical Engineering, ITB, Bandung, Indonesia.<sup>[15]</sup>

### Material Collection and Preparation

*Zingiber cassumunar* Roxb rhizomes were washed, wet sorting, dry sorting and drying. The rhizomes were dried in the sun until the rhizomes dried. The dried rhizomes were milled and extracted with a maceration method using 96% ethanol solvent for 3 days at room temperature. The assurance of characteristic of the extract was done to know the quality of extract includes determination of total ash content, water content, water-soluble extract, ethanol soluble concentration. The phytochemical examination was performed on *Zingiber cassumunar* Roxb rhizome extract to determine secondary metabolite content including flavonoids, alkaloids, saponins, tannins, steroids, triterpenoids.

### Animal preparation

This study was conducted on 2-month-old male Wistar white rat with body weight range of 200-250 g. The procedures in this study have been approved by the local ethics committee with no 315 / UN6.C1.3.2 / KEPK / PN / 2016. Prior to the treatment, a total of 30 rats were acclimatized in animal cages for 14 days with free access to food and drinking water.

### **Diuretic activity**

Diuretic tests were performed by the Lipschitz method by measuring the volume of urine. Test animals were given test drugs and then measured the volume of urine obtained for 5 hours after administration of the drug test. The urine volume greater than the normal group indicates the activity of diuretics.

A total of 25 rats were grouped randomly into 5 groups consisting of group 1 (receiving drug carrier), group 2 (receiving furosemide suspension 3.6 mg/kg) group 3-5 (receiving extract dose 30, 50, 100 mg/kg). All groups except the normal group received 5 mL warm water orally, then the test drugs were administered according to the group. All animals were enclosed in a metabolic cage to hold urine every hour for 5 hours.

### **Antihypertensive activity**

The animal model of hypertension was achieved by providing 25% fructose in drinking water in Wistar white male rats. Blood pressure testing was performed using a non-invasive CODA<sup>®</sup> tool.

A total of 30 male Wistar strains were grouped randomly into 6 groups consisting of group 1 (receiving drug carrier), group 2 (receiving drug carrier), group 3 (receiving amlodipine suspension 0.45 mg/kg) group 4-6 (receiving extract dose 30, 50, 100 mg/kg). All groups except group 1 received 25% fructose in drinking water for 21 days. Measurement of systolic and diastolic blood pressure, and heart rate were performed on days 0, 7, 14 and 21.

The heart rate was calculated by the previously published method, an electrocardiogram device designed by biomedical engineering, Bandung Institute of Technology, ITB, Bandung, Indonesia.

### **Data analysis**

The data obtained were analysed statistically. There was a significant difference between treatment groups at  $p < 0.05$ .

## **RESULTS**

The yield of extraction by maceration method was 8.5%. The results of phytochemical screening tests of *Zingiber cassumunar* Roxb rhizome extract contain flavonoids, tannins, triterpenoids and steroids (Table 1). The results of quality inspection of the extract are presented in table 2.

**Table 1: The phytochemical screening of *Zingiber cassumunar* Roxb rhizome extract.**

Compound	Phytochemical contents	
	Dried rhizome	Rhizome extract
Alkaloids	-	-
Flavonoids	+	+
Tannin	+	+
Saponins	-	-
Triterpenoids	+	+
Steroids	+	+

+ presented

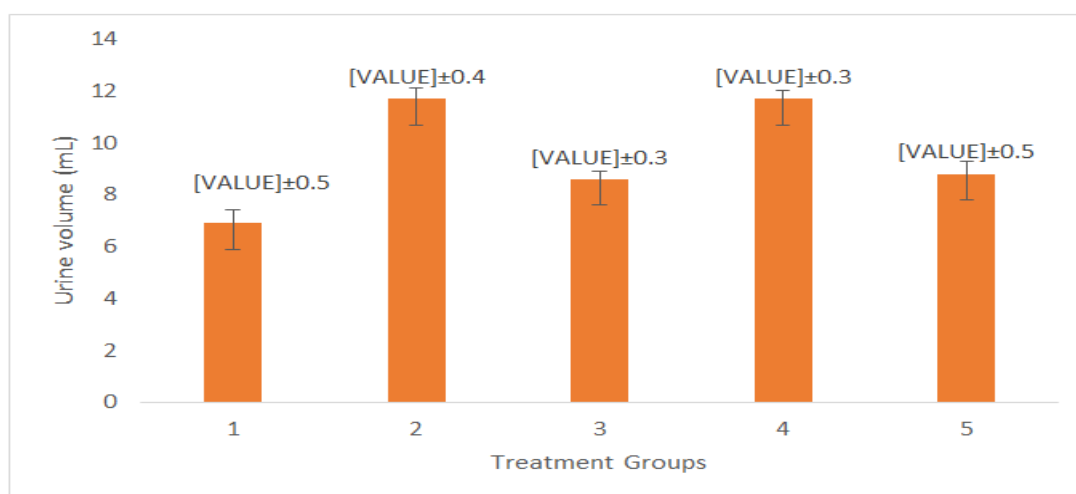
- Not presented

**Table 2: Results of quality inspection of *Zingiber cassumunar* Roxb rhizome extract.**

Examination	Result (%)
Total ash content	9.5
Water content	10
Water-soluble content	72.4
Ethanol soluble content	87.7

### Diuretic Activity

The average urine volume obtained for 5 hours of observation for all treatment groups is shown in Fig. 1.



**Figure 1. The average of urine volume in all treatment groups for 5 hours after administration of the test drug (n = 3).**

(\*): There are significant differences compared to the normal group (p<0.05)

Group 1: received 5 mL of warm water and 1% NaCMC suspension

Group 2: received 5 mL of warm water and furosemide 3.6 mg/kg

Group 3: received 5 mL of warm water and extract dose 30 mg/kg

Group 4: received 5 mL of warm water and extract dose 50 mg/kg

Group 5: received 5 mL of warm water and extract dose 100 mg/kg

### Systolic Blood Pressure

The result of measurement of systolic blood pressure after giving 25% fructose in drinking water on days 0, 7, 14 and 21 is given in table 3.

**Table 3: Average of systolic blood pressure for 21 days for all treatment groups (n = 3).**

Group	Average of systolic blood pressure $\pm$ SD			
	Day 0	Day 7	Day 14	Day 21
1	113.6 $\pm$ 2.07	107.4 $\pm$ 3.43 <sup><math>\alpha</math></sup>	109.4 $\pm$ 1.14 <sup><math>\alpha</math></sup>	108.0 $\pm$ 2.09 <sup><math>\alpha</math></sup>
2	114.4 $\pm$ 1.67	128.6 $\pm$ 1.81 <sup>*</sup>	144.0 $\pm$ 1.73 <sup>*</sup>	160.6 $\pm$ 2.50 <sup>*</sup>
3	112.6 $\pm$ 2.96	107.2 $\pm$ 1.30 <sup><math>\alpha</math></sup>	109.6 $\pm$ 1.67 <sup><math>\alpha</math></sup>	109.2 $\pm$ 2.48 <sup><math>\alpha</math></sup>
4	112.6 $\pm$ 1.51	121.4 $\pm$ 2.88 <sup><math>\alpha</math></sup>	121.2 $\pm$ 3.03 <sup><math>\alpha</math></sup>	126.8 $\pm$ 3.34 <sup><math>\alpha</math></sup>
5	110.4 $\pm$ 3.64	111.6 $\pm$ 2.96 <sup><math>\alpha</math></sup>	114.2 $\pm$ 2.48 <sup><math>\alpha</math></sup>	108.4 $\pm$ 1.34 <sup><math>\alpha</math></sup>
6	111.6 $\pm$ 3.57	115.6 $\pm$ 3.04 <sup><math>\alpha</math></sup>	116.2 $\pm$ 3.34 <sup><math>\alpha</math></sup>	126.2 $\pm$ 2.48 <sup><math>\alpha</math></sup>

\*: There are significant differences compared to the group 1 (p<0.05)

$\alpha$ : There are significant differences compared to the group 2 (p<0.05)

Group 1: received NaCMC 1% suspension

Group 2: received fructose 25% and 1% NaCMC suspension

Group 3: received fructose 25% and amlodipine 0.45 mg/kg

Group 4: received fructose 25% and extract dose of 30 mg/kg

Group 5: received fructose 25% and extract dose of 50 mg/kg

Group 6: received fructose 25% and extract dose of 100 mg/kg

### Diastolic Blood Pressure

The results of measurement of diastolic blood pressure on days 0, 7, 14, and 21, after giving 25% fructose in drinking water are shown in table 4.

**Table 4: Average of diastolic blood pressure for 21 days for all treatment groups (n = 3).**

Group	Average of diastolic blood pressure $\pm$ SD			
	Day 0	Day 7	Day 14	Day 21
1	80.4 $\pm$ 3.20	81.0 $\pm$ 4.52 <sup><math>\alpha</math></sup>	75.4 $\pm$ 3.50 <sup><math>\alpha</math></sup>	77.9 $\pm$ 1.58 <sup><math>\alpha</math></sup>
2	81.2 $\pm$ 1.78	90.0 $\pm$ 4.35*	96.2 $\pm$ 2.77*	104.8 $\pm$ 2.68*
3	78.0 $\pm$ 0.70	83.0 $\pm$ 2.44 <sup><math>\alpha</math></sup>	77.4 $\pm$ 4.03 <sup><math>\alpha</math></sup>	78.2 $\pm$ 3.76 <sup><math>\alpha</math></sup>
4	79.8 $\pm$ 3.27	87.4 $\pm$ 3.97*	85.2 $\pm$ 4.14 <sup><math>\alpha</math></sup>	80.4 $\pm$ 2.60 <sup><math>\alpha</math></sup>
5	79.2 $\pm$ 4.60	78.6 $\pm$ 2.40 <sup><math>\alpha</math></sup>	82.8 $\pm$ 4.20 <sup><math>\alpha</math></sup>	82.6 $\pm$ 3.36 <sup><math>\alpha</math></sup>
6	78.2 $\pm$ 3.49	85.6 $\pm$ 1.94 <sup><math>\alpha</math></sup>	85.0 $\pm$ 3.08 <sup><math>\alpha</math></sup>	86.2 $\pm$ 3.83 <sup><math>\alpha</math></sup>

\*: There are significant differences compared to the group 1 ( $p < 0.05$ )

$\alpha$ : There are significant differences compared to the group 2 ( $p < 0.05$ )

Group 1: received NaCMC 1% suspension

Group 2: received fructose 25% and CMC 1%

Group 3: received fructose 25% and amlodipine 0.45 mg/kg

Group 4: received fructose 25% and extract dose of 30 mg/kg

Group 5: received fructose 25% and extract dose of 50 mg/kg

Group 6: received fructose 25% and extract dose of 100 mg/kg

### Heart rate

Heart rate measurements in rats was designed to determine any changes, after fructose administration in drinking water for 21 days. Heart rate measurement data are presented in Tables 5. The results obtained were analysed statistically.

**Tabel 5: The average of heart rate (HR) on day 21 after 25% fructose administration in drinking water for all treatment groups (n = 3).**

Group	Mean of Heart Rate (HR) $\pm$ SD			
	Day 0	Day 7	Day 14	Day 21
1	422.1 $\pm$ 10.9	422.0 $\pm$ 7.8 <sup><math>\alpha</math></sup>	425.5 $\pm$ 5.6 <sup><math>\alpha</math></sup>	424.9 $\pm$ 4.9 <sup><math>\alpha</math></sup>
2	419.6 $\pm$ 18.3	488.2 $\pm$ 16.4*	488.6 $\pm$ 22.9*	531.5 $\pm$ 18.3*
3	425.9 $\pm$ 14.3	424.4 $\pm$ 6.3 <sup><math>\alpha</math></sup>	425.9 $\pm$ 15.2 <sup><math>\alpha</math></sup>	425.5 $\pm$ 4.2 <sup><math>\alpha</math></sup>
4	423.4 $\pm$ 13.0	451.2 $\pm$ 21.2 <sup><math>\alpha</math></sup>	457.4 $\pm$ 29.1 <sup><math>\alpha</math></sup>	456.7 $\pm$ 7.1 <sup><math>\alpha</math></sup>
5	425.1 $\pm$ 11.0	428.8 $\pm$ 22.7 <sup><math>\alpha</math></sup>	458.9 $\pm$ 11.8 <sup><math>\alpha</math></sup>	462.3 $\pm$ 7.2 <sup><math>\alpha</math></sup>
6	423.9 $\pm$ 10.9	436.5 $\pm$ 24.2 <sup><math>\alpha</math></sup>	496.9 $\pm$ 25.9*	499.7 $\pm$ 18.8 <sup><math>\alpha</math></sup>

\*: There are significant differences compared to the group 1 ( $p < 0.05$ )

$\alpha$ : There are significant differences compared to the group 2 ( $p < 0.05$ )

Group 1: received CMC 1% suspension

Group 2: received fructose 25% and 1% NaCMC suspension

Group 3: received fructose 25% and amlodipine 0.45 mg/kg

Group 4: received fructose 25% and extract dose of 30 mg/kg

Group 5: received fructose 25% and extract dose of 50 mg/kg

Group 6: received fructose 25% and extract dose of 100 mg/kg

## DISCUSSION

### Diuretic activity

The administration of the 30, 50 and 100 mg/kg dose extracts showed significantly different diuresis effects than the normal group (Fig. 1). The effect of diuresis on the group receiving extract doses of 50 mg/kg did not differ significantly ( $p > 0.05$ ) against the group receiving furosemide 3.6 mg/kg. This suggests that the diuresis effect of the dose extract of 50 mg/kg was similar to that of furosemide 3.6 mg/kg.

### Antihypertension activity

The result of measurement of systolic blood pressure, the group receiving fructose 25% in drinking water for 21 days showed a significant increase in blood pressure (table 2). On day 0, the results of systolic blood pressure measurements showed no significant difference in all treatment groups. Furthermore, systolic blood pressure at day 7 was significantly different ( $p < 0.05$ ) between groups. Systolic blood pressure in group 2 began to increase significantly compared to group 1 (normal) ( $p < 0.05$ ). The group that receiving extracts of 30, 50, and 100 mg/kg showed a decrease in systolic blood pressure on day 7 which was statistically significant compared to group 2 ( $p < 0.05$ ).

The result of measurement of systolic blood pressure on day 14, group 2 showed an increase in systolic blood pressure up to an average of 144 mmHg (Table 2). The results of Jena, et al (2013) reported that giving fructose 66% in the diet for 14 days, increased systolic blood pressure to 148 mmHg. This suggests that giving 25% fructose in drinking water is effective in increasing systolic blood pressure compared to the 66% fructose in the diet. Group that received doses of 30, 50 and 100 mg/kg showed a decreased of systolic blood pressure compared to group 2 ( $p < 0.05$ ).

Measurement of systolic blood pressure on day 21, group 2 continued to increase systolic blood pressure. The group that received extract doses of 30, 50 and 100 mg/kg showed a decrease in systolic blood pressure compared to group 2 ( $p < 0.05$ ). Extract doses of 50 mg/kg had the effect of normalizing systolic blood pressure comparable to the amlodipine 0.45 mg/kg ( $p > 0.05$ ).



The results of measurement of diastolic blood pressure on day 0 showed no significant difference in all treatment groups. The results of measurement of diastolic blood pressure on day 7 there was a significant difference ( $p < 0.05$ ) between groups. Diastolic blood pressure in group 2 showed significant differences ( $p < 0.05$ ) compared to group 1. On day 7, diastolic blood pressure in group 4 showed significant differences ( $p < 0.05$ ) against groups 1, 2 and 3 (Table 3). The administration of 30 mg/kg extract for 7 days can prevent the increase of diastolic blood pressure but weaker than amlodipine 0.45 mg/kg. Administration of the dose extract of 50 mg/kg can normalize diastolic blood pressure and stronger than amlodipine 0.45 mg/kg. Diastolic blood pressure of group 6 showed the significantly different result ( $p < 0.05$ ) compared to group 1 and 2, while group 3 showed no significant difference ( $p > 0.05$ ). This suggests that giving 100 mg/kg extracts lowered diastolic blood pressure comparable to the 0.45 mg/kg amlodipine drug but still can not normalize diastolic blood pressure at day 7. It can be concluded that, a dose of 50 mg/kg showed an effective result in normalizing diastolic blood pressure on day 7.

Measurement of blood pressure on day 14, group 2 showed elevated in diastolic blood pressure (Table 3). This implies that giving 25% fructose in drinking water for 14 days can increase diastolic blood pressure significantly ( $p < 0.05$ ). Diastolic blood pressure in the group receiving the extract doses of 30, 50 and 100 mg/kg had a significant difference ( $p < 0.05$ ) against groups 1, 2 and 3. This suggests that these three dose variations prevented the rise in diastolic blood pressure but have not been able to normalize. Diastolic blood pressure of the group receiving the extract doses of 30, 50 and 100 mg/kg showed no significant difference which means that these three dose variations have the same strength in preventing the rise in diastolic blood pressure on day 14. In the group that received dose of 30 and 100 mg/kg had the effect of preventing the rise in diastolic blood pressure on day 14. While the group that received dose of 50 mg/kg has shown an effect on day 7.

The measurement of diastolic blood pressure on day 21, group 2 still experienced increased in diastolic blood pressure. Diastolic blood pressure in group 4 did not differ significantly ( $p > 0.05$ ) Compared to groups 1 and 3. Diastolic blood pressure of the group receiving a dose of 30 mg/kg can normalize diastolic blood pressure and be comparable to amlodipine 0.45 mg/kg (Table 3). Diastolic blood pressure in the group receiving doses of 50 and 100 mg/kg had the effect of preventing elevated diastolic blood pressure but not yet normalizing. The results of this study concluded that the best dose in normalizing diastolic blood pressure on

day 21 was 30 mg/kg while the doses of 50 and 100 mg/kg were only able to prevent the increase of diastolic blood pressure on the 21st day.

### **Heart rate**

Heart rate (HR) result on day 0 showed no significant difference for each treatment group. Giving extract 30 mg/kg for 7 days can not normalize heart rate but can prevent the increase in heart rate. Giving extracts dose of 50 and 100 mg/kg for 7 days can normalize the heart rate ( $p > 0.05$ ).

Giving fructose 25% in drinking water for 14 days can increase the frequency of heart rate compared to group 2 ( $p < 0.05$ ). Provision of 30 and 50 mg/kg dose extracts can normalize the heart rate frequency. While administration of 100 mg/kg dose extract cannot prevent the increase in heart rate frequency.

Giving fructose 25% in drinking water for 21 days increase heart rate. Giving doses of 30, 50, and 100 mg/kg can prevent a significant increase in heart rate frequency statistically compared to group 2 ( $p < 0.05$ ). Administration of dose extracts that have the best potential in normalizing and preventing heart rate increase are doses of 50, 30 and 100 mg/kg respectively.

Giving of fructose 25% for 21 days in drinking water showed a significant increase in heart rate starts from day 7. The group that received amlodipine showed stable heart rate. This is in line with the antihypertensive mechanism of amlodipine as a peripheral arterial vasodilator which can lead to decreased vascular resistance which in turn causes a decrease in blood pressure. Effects on the heart muscle will reduce the heart rate. This effect, will further lower the workload of the heart.<sup>[16]</sup> Previous studies have reported that administration of amlodipine in animal models of fructose-induced hypertension can lower blood pressure by inhibiting the L-type calcium channel located in the vascular smooth muscle.<sup>[17]</sup>

Addition of 25% fructose in drinking water for 21 days increases systolic and diastolic blood pressure and an increase in heart rate. These results are consistent with previous studies that reported that fructose administration may increase systolic and diastolic blood pressure. Previous studies have reported that fructose administration interfered with endothelial activity and at day 28 increases blood pressure.<sup>[18]</sup> Fructose disrupts endothelial function that plays an

important role in regulating vascular tone through the release of nitric oxide compounds by the enzyme nitric oxide synthase.<sup>[19,20]</sup>

Based on the results of this study it can be concluded that *Zingiber cassumunar* Roxb rhizome extracts effective dose of 50 mg/kg can increase urine expenditure and prevent the increase and normalize the heart rate. The results of this study explain the mechanism of rhizome extract of *Zingiber cassumunar* Roxb in lowering systolic and diastolic blood pressure.

## CONCLUSION

Based on this research can be concluded that the ethanolic extract of *Zingiber cassumunar* Roxb rhizome has antihypertensive activity. The decrease in systolic and diastolic blood pressure is believed to occur through a mechanism as a diuretic, decreasing and normalizing the heart rate.

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