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POTENTIAL DIURETIC ACTIVITY FROM ZINGIBERACEAE FAMILY AND ITS EFFECT ON THE LEVELS OF POTASSIUM AND SODIUM IONS IN THE URINE

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ABSTRACT

Diuretic is a class of drugs that increase urinary expenditure to overcome various diseases such as hypertension, heart failure, kidney failure. The use of loop diuretics such as furosemide is very useful, but has side effects of hypokalemia and hyponatremia. The purpose of this study was to determine the potential of zingiberaceae (20 species) as diuretics. A total of 66 male Wistar strains were grouped randomly into 22 groups (n = 3) consisting of group 1 (receiving drug carrier suspension), group 2 (receiving furosemide suspension 3.6 mg/kg) and group 3-22 received ethanol extract of zingiberaceae rhizome dose 50 mg/kg. All the groups received 5 mL of warm water orally and 10 minutes later received the test drug. The animals were placed in metabolic cages to hold urine for 5 hours. The data obtained were analyzed statistically by ANOVA method. The results showed that 19 rhizome of zingiberaceae has diuretic activity, while rhizomes of *Alpinia galanga* did not have diuretic activity. The diuretic activity of 10 species of zingiberaceae rhizomes, are comparable to furosemide ($p>0.05$). Five species of zingiberaceae did not increase the expenditure of sodium and potassium ions in urine different from furosemide ($p<0.05$). This study can be concluded that zingiberaceae rhizomes potentially strong as potassium-sparing diuretics.

KEYWORDS: Diuretic, furosemide, potassium, sodium, zingiberaceae.

INTRODUCTION

Cardiovascular disease has been recognized as the leading cause of death worldwide.[1] Some of the major risk factors for the incidence of cardiovascular disease include hypertension, hyperlipidemia obesity, renal diseases, diabetes mellitus.[2-6]

Several studies have reported the effectiveness of diuretic drugs as antihypertensives. Diuretic drug is the drug of choice for primary hypertension, hypertension with chronic renal impairment isolated systolic hypertension in the elderly.[7-9]

The prevalence of hypertension continues to increase every year, especially in Indonesia. This suggests that existing therapy has not been able to control hypertension. So it is an opportunity to find new drugs that are safer and more effective in treating hypertension. The search for new drugs can be done through herbal medicine. Natural medicines are believed to be safe and effective in preventing and treating various diseases including hypertension. The rhizomes of zingiberaceae have long been used to treat various diseases including hypertension. Zingiberaceae species are easily cultivated in tropical countries including Indonesia. The zingiberaceae family has played an important role for hundreds of years because the infusions and tinctures of these plants have been used and are still in use today, as a component of herbal remedies for various diseases.

Until now, the zingiberaceae rhizome is a plant that is widely studied and is a potential source of medicinal plants. Various studies have shown that *Zingiber officinale* var rubrum has the potential to lower total cholesterol and triglyceride, lower glucose levels by improving HbA1c value, diuretic and antioxidants.[10-14] Previous research has reported that 16 species of the zingiberaceae rhizomes inhibit the alpha-glucosidase enzyme.[15]

Various study of *Kaempferia galanga*, that rich with phytochemical sources, showed strong antioxidant and anti-inflammatory activity.[16,17] Kaempferol as an active compound of *Kaempferia galanga* showed anti-obesity by regulating lipid metabolism, inhibit lipase enzyme activity.[18,19] Petroleum ether extract of *Kaempferia galanga* Linn showed diuretic activity.[20] *Kaempferia galanga* showed anti-hyperglycemia, anti-inflammatory.[21]

Based on the description above, it strengthens the potential rhizome of zingiberaceae in various pharmacological effects including diuretics. This study aimed to determine the potential of zingiberaceae rhizome as a diuretic and its effect on the levels of potassium and sodium ions in the urine.

MATERIALS AND METHODS

Plant materials

The study was conducted using 20 species of zingiberaceae, namely: *Zingiber littorale Nor, Zingiber aromaticum Val, Zingiber zerumbet* (L) *J.E. Smith, Zingiber cassumunar Roxb, Zingiber ottensi Val, Zingiber officinale var officinarum, Zingiber officinale var. Amarum, Zingiber officinale var. Rubrum, Kaempferia galanga L, Alpinia galanga (L) Sw, Curcuma mango Val, Boesenbergia pandurata Roxb, Curcuma Aeroginosa Roxb, Xanthorrhiza Curcuma Roxb, Curcuma domestica Val, Curcuma Zedoaria, Curcuma petiolata Roxb, Curcuma soloensis, Curcuma purpurascens Val, Curcuma heyneana* Val Twenty rhizomes of zingiberaceae were obtained from Manoko Lembang, Bandung, West Java, Indonesia. The rhizomes were botanically determined at the Laboratory of Biology, Faculty of Science, University of Padjadjaran, Bandung, West Java, Indonesia.

Preparation of extract

Twenty species of zingiberaceae rhizome were washed and cleaned of dirt, then cut into small pieces and dried under the sun. The rhizome, which has been dried, was extracted using 96% ethanol solvent (purchased from Brataco, Bandung, Indonesia) by maceration for 3 days. The filtrate was filtered, and concentrated using rotary evaporator at 60 ° C and dried over a water bath at 60°C.

Screening of phytochemical

Phytochemical screening was performed on an ethanolic extract of the zingiberaceae rhizome. Phytochemical screening aim to identified the classes of secondary metabolite compounds contained in zingiberaceae rhizomes such as alkaloids, flavonoids, tannins, saponins, steroids/triterpenoids, and quinones.

Animal preparation

Male 2-month Wistar rats weighing 200-250 grams obtained from D'Wistar (laboratory animal supply provider), Majalaya, Bandung, West Java, Indonesia. Animals acclimatized for 7 days in a cage with standard feed and drinking water, as well as 12 hours dark-light cycle. All animal treatment during the study was approved by the Ethics Committee of the Faculty of Medicine, Padjadjaran University, Bandung, West Java, Indonesia (No:26 / UN6.C.10 / PN / 2018).

Study of diuretic activity

Test diuretic activity performed using Lipschitz methods by measuring the volume of urine. After acclimatization the test animals were grouped randomly into 22 groups (n = 3). Groups 1-20 were given 50 mg/kg dose extract test and group 21 was given furosemide (generic drug from Dexa Medica) dose 3.6 mg/kg, and group 22 was given drug carrier (2 mL of CMC-Na 1%). Prior to the administration of test drugs, all groups were given warm drinking water 5 mL orally. The test animals were placed in a metabolic cage, the urine volume of were measured and collected for 5 h. Urine volume greater than the normal group showed diuretic activity. The levels of sodium and potassium ions in urine were determined by atomic absorption spectrophotometer method. This measurement aimed to determine the effects of hyponatremia and hypokalemia in groups receiving zingiberaceae extracts compared with furosemide.

Statistic analysis

All data were presented as the mean ± standard deviation (SD). The data obtained were analyzed statistically by one-way ANOVA and followed by LSD multiple comparison tests. A significant difference of $p<0.05$ was considered, compared to control group.

RESULTS AND DISCUSSION

Yields of extraction

Zingiberaceae rhizome extracted by maceration using ethanol 96% for 3 days. Yields of extraction presented in Table 1. The largest amount of extract was *Zingiber cassumunar* Roxb.

Table 1: Yields of ethanolic extract of zingiberaceae rhizomes.

No.	Zingiberaceae	Yield (%)
1	*Zingiber cassumunar Roxb*	2.9
2	*Ottensi Zingiber Val*	2.8
3	*Zingiber officinale var.Amarum*	2.5
4	*Zingiber officinale var.Rubrum*	2.2
5	*Zedoaria Curcuma*	2.1
6	*Zingiber zerumbet (L) J.E. Smith*	1.9
7	*Curcuma purpurascens Val*	1.9
8	*Zingiber littorale Nor*	1.8
9	*Curcuma Xanthorrhiza Roxb*	1.8
10	*Kaempferia galanga L.*	1.7
11	*Alpinia galanga (L) Sw*	1.6
12	*Curcuma mango val.*	1.6
13	*Boesenbergia pandurata Roxb*	1.6

14	*Curcuma heyneana Val.*	1.4
15	*Curcuma Aeroginosa Roxb*	1.4
16	*Curcuma soloensis*	1.3
17	*Zingiber aromaticum Val*	1.2
18	*Curcuma petiolata Roxb*	1.1
19	*Zingiber officinale var Officinarum*	0.8
20	*Curcuma domestica Val*	0.6

The results of phytochemical screening of zingiberaceae ethanol extract are shown in Table 2. Most of the zingiberaceae rhizome extracts contain flavonoids. Flavonoid compounds play a role in various pharmacological effects. Flavonoid compounds are effective in combination therapy with antidiabetic drugs to prevent diabetic complications of nephropathy, retinopathy and cardiovascular.[22, 23]

Table 2: Phytochemical screening of zingiberaceae family obtained by macerated-extraction.

No.	Zingiberaceae	Phytochemical screening				
		Alkaloids	Flavonoids	Saponin	Steroid	Tanin
1	*Zingiber cassmunar Roxb.*	-	+	-	-	+
2	*Zingiber ottensi Val.*	-	+	-	+	+
3	*Zingiber officinale Var. Officinarum*	+	+	-	-	+
4	*Zingiber officinale Var. Amarum*	-	+	-	+	-
5	*Zingiber officinale Var. Rubrum.*	+	+	-	-	+
6	*Zingiber littorale Nor.*	+	-	+	-	+
7	*Zingiber aromaticum Val*	-	+	+	-	+
8	*Zingiber zerumbet (L) J.E. Smith*	-	+	+	+	-
9	*Kaempferia galanga L*	-	-	-	+	+
10	*Alpinia galanga (L) Sw*	-	-	-	-	+
11	*Curcuma domestica Val*	+	+	-	+	+
12	*Curcuma zedoaria*	-	+	+	-	+
13	*Curcuma Xanthorrhiza Roxb*	+	+	+	+	+
14	*Curcuma mangga Val*	+	-	-	-	-
15	*Boesenbergia pandurata Roxb*	+	-	-	-	+
16	*Curcuma aeroginosa Roxb*	-	+	+	-	+
17	*Curcuma petiolata Roxb.*	-	-	-	-	-
18	*Curcuma heyneana*	-	+	-	+	+
19	*Curcuma purpurascens Val*	-	-	-	-	+
20	*Curcuma soloensis*	-	-	-	-	+

(+) identified, (-) not identified

Diuretics activity of zingiberaceae

Diuretic drug classes are compounds that can increase urinary expenditure (diuresis) through the direct action of the kidneys. This study was conducted to determine the diuretics effect of rhizomes of zingiberaceae at a dose of 50 mg/kg, in male Wistar rats. In a diuretic study, all

animals receive warm water to the uniformity of hydrated rats, making it easier to collect urine.[24]

Results of measurements of urine volume cumulatively for 5 hours, the group receiving an extract of zingiberaceae, showed increased urine volume compared to the control group (Fig. 1). The results of statistical tests showed that the volume of urine in the group of animals receiving zingiberaceae extract showed no significant differences compared to the control group ($p < 0.05$), except for the extract of *Alpinia galanga* (L) Sw ($p > 0.05$). This showed that the extract of zingiberaceae rhizomes has a diuretic effect.

The volume of urine in the group receiving the extract: *Zingiber aromaticum* Val., *Zingiber cassumunar* Roxb., *Zingiber officinale* var. Amarum, *Zingiber officinale* var Rubrum, *Zingiber officinale* var officinarum, *Kaempferia galanga* L., *Curcuma heyneana* Val., *Boesenbergia pandurata* Roxb, *Curcuma zedoaria*, and *Curcuma domestica* Val, showed no significant difference compared to the group receiving furosemide 3.6 mg/kg ($p > 0.05$).

Five species of zingiberaceae showed the highest activity as a diuretic (*Zingiber ottensi* Val, *Zingiber officinale* var Officinarum, *Zingiber officinale* var. Rubrum, *Kaempferia galanga* L, and *Boesenbergia pandurata* Roxb followed by an examination of the levels of sodium and potassium ions in the urine. This was done to predict the risk of hypokalemia and hyponatremia in use zingiberaceae rhizome extract. It is known that side effects of the use of diuretics are hypokalemia and hyponatremia. This may lead to a fatal complication such as ventricular arrhythmias, coronary artery vasospasm or sudden death especially in cardiac patients.[25]

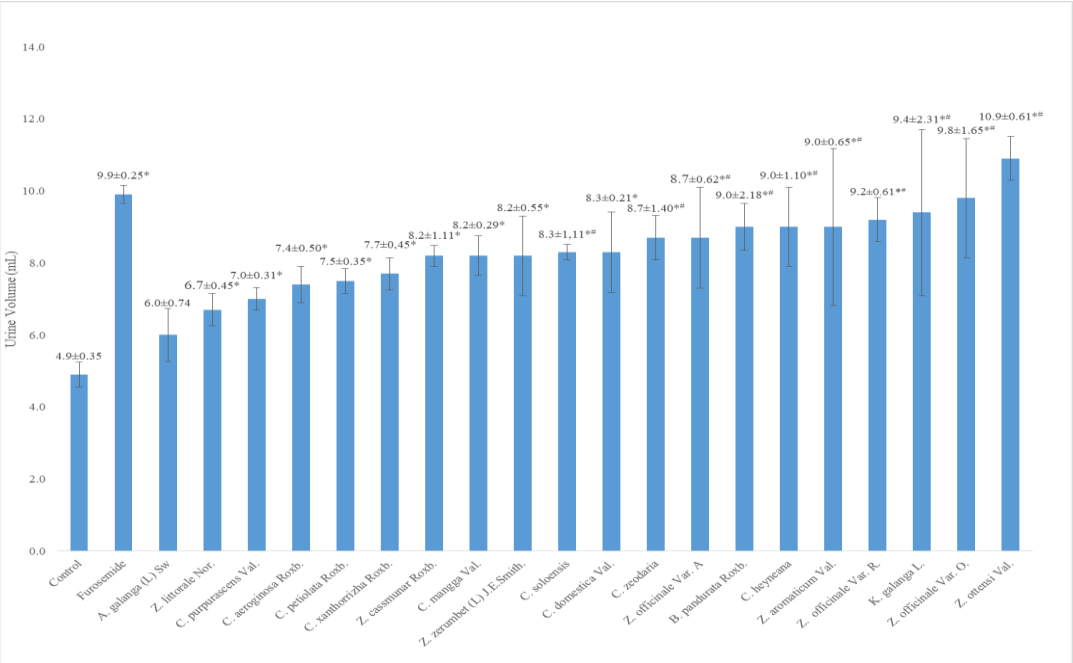

Figure 1: Cumulative of urine volume (mL) for 5 hours for all treatment groups. All groups of treatment received 5 ml of warm water. Control group received drug vehicle, furosemide group received 3.6 mg/kg; test group received an extract of zingiberaceae 50 mg/kg. * There was a significant difference compared to the control group ($p<0.05$). #There was not significant difference when compared to the furosemide group ($p> 0.05$).

Diuretic activity of *Zingiber ottensi* Val, *Zingiber officinale* var.*officinarum*, *Zingiber officinale* var. Rubrum, *Kaempferia galanga* L., and *Boesenbergia pandurata* Roxb. different from furosemide. Furosemide showed at risk of hypokalemia and hyponatremia. Five extracts of zingiberaceae can save the expenditure of potassium and sodium ions in the urine (Fig. 2 and 3).

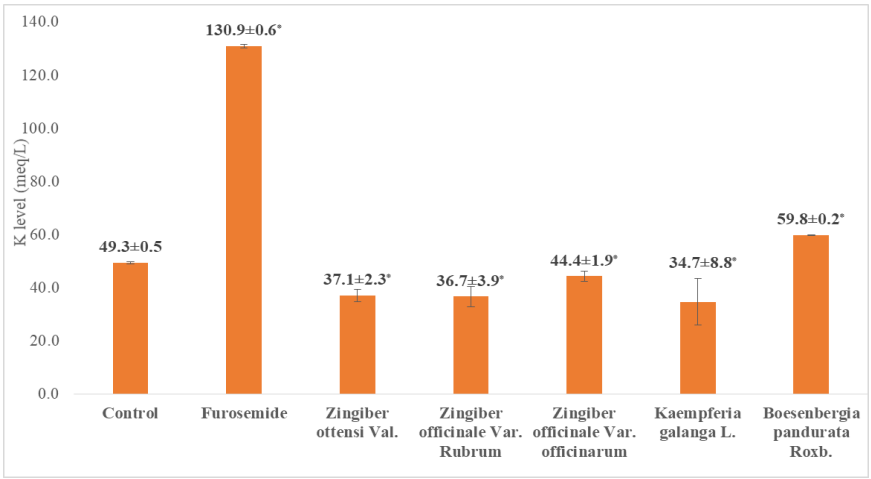

Figure 2: Potassium ion levels in the urine for 5 hours (mEq/L) for all groups of treatments. Control group received drug vehicle, furosemide group received 3.6 mg/kg; test

group received an extract of zingiberaceae 50 mg/kg. *There was a significant difference compared to the control group (p <0.05). #There was no significant difference compared to the furosemide group (p> 0.05)

Statistical test results showed that the levels of potassium in the urine of a group of animals receiving furosemide, *Zingiber ottensi* Val, *Zingiber officinale* var. Rubrum, *Kaempferia galanga* L., and *Boesenbergia pandurata* Roxb significantly different compared to the control group (p<0.05). A group of animals that received furosemide showed the highest levels of potassium in the urine (Fig. 2). Urinary potassium levels in the group receiving the extract *of Zingiber officinale* var *officinarum* showed no significant difference compared to the control group (p>0.05). It suggested that the diuretic activity of zingiberaceae species prevent hypokalemia.

The group receiving the 5 species of zingiberaceae showed higher levels of sodium in urine compared to the normal group (p <0.05). Sodium levels were highest in the group receiving furosemide. Levels of sodium in the urine in the group receiving 5 zingiberaceae extracts can be sorted from highest to lowest were *Zingiber officinale* var Rubrum, *Kaempferia galanga* L, *Boesenbergia pandurata* Roxb, *Zingiber officinale* var officinarum, and *Zingiber ottensi* Val. Sodium levels in the urine of the group receiving the extract of *Zingiber ottensi* Val lower than the control group (p<0.05). It suggested that *Zingiber ottensi* Val was the most potent in inhibiting sodium expenditure (Fig. 3).

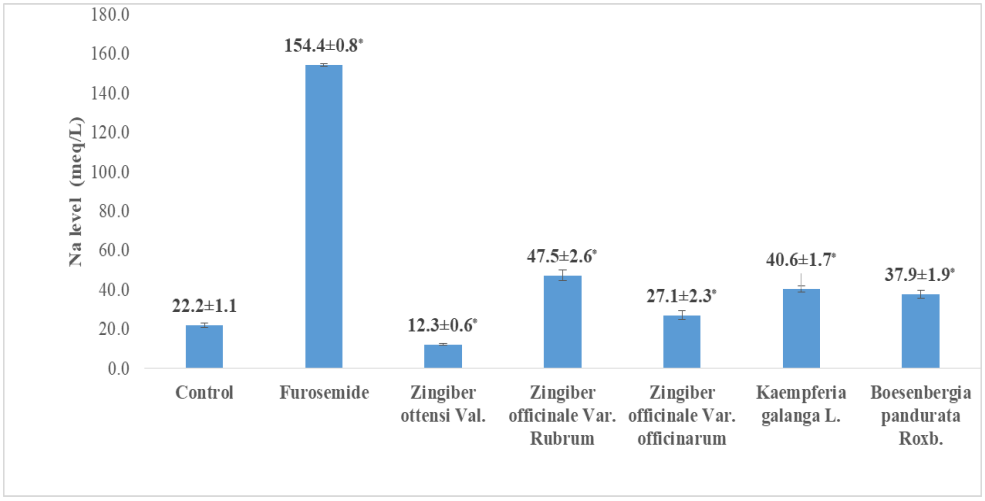

Figure 3: Sodium ion levels in the urine for 5 hours (mEq/L) for all groups of treatments. Control group received drug vehicle, furosemide group received furosemide 3.6 mg/kg; test group received an extract of zingiberaceae 50 mg/kg. *There was a significant

difference Compared to the control group (P <0.05). #There was no significant difference Compared to the group receiving furosemide (P> 0.05).

These results are in line with research conducted by Mohammad, et al. 2016 that *Kaempferia galanga* L had diuretic activity at doses of 200 mg/kg with Na and K levels in urine was 2436.16 ppm (106.4 meq/L) and 677 (17.3 meq/L) whereas the dose of 400 mg/kg was 2234.50 (97, 6 meq/L) and 699.50 (17.9 meq/L) respectively.[20]

The rhizomes of *Zingiber ottensi* Val, *Zingiber officinale* var. Rubrum, *Zingiber officinale* var officinarum and *Boesenbergia pandurata* Roxb, there was no previous studies have reported the effects of diuretics. This study is the first report on the effects of zingiberaceae as a diuretic.

CONCLUSION

Based on these results, it can be concluded that the ethanol extract of the rhizome *of a* zingiberaceae dose of 50 mg/kg (except *for Alpinia galanga* L.) has a diuretic activity. Our study suggested that, *Zingiber ottensi* Val, *Zingiber officinale* var. *Officinarum, Zingiber officinale* var. Rubrum, *Kaempferia galanga* L, and *Boesenbergia pandurata* Roxb, as potassium-sparing diuretics. Further research is needed to determine the potential active compounds as diuretics.

CONFLICT OF INTEREST

Authors declared no conflict of interest.

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