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Research Article

Preliminary Study of Blood Pressure Lowering Effect of *Anredera cordifolia* (Ten.) Steenis) on Wistar Rats

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ABSTRACT

This research was conducted to verify the antihypertensive effect of *Anredera cordifolia* leaves.The antihypertensive effect was examined in adrenaline-induced rats. Administration of adrenaline increased the heart rate. Heart rate were measured by non-invasive tail cuff. Diuretic effect was also examined by modified Lipschitz method. Extract was tested at doses of 50, 100, and 200 mg/kg body weight. *Anredera cordifolia* leaves extract of 50 mg/kg bw reduced the heart rate which was induced by adrenaline (significant difference at $p < 0.05$). It showed weak diuretic effect compared to furosemide. *Anredera cordifolia* leaves extract at dose of 50 mg/kg bw had antihypertensive activity on Wistar rats.

Key words: *Anredera cordifolia*, antihypertensive, adrenaline-induced hypertensive rat, heart rate, diuretic effect

INTRODUCTION

Hypertension is the most common cardiovascular disease. The prevalence of hypertension increases with advancing age; for example, about 50% of people ranged from 60 to 69 years old suffered from hypertension, and the prevalence is further increased above age 70. Elevated arterial pressure causes pathological changes in the vascular and hypertrophy of the left ventricle. As a consequence, hypertension is the principal cause of stroke, it is a major risk factor for coronary artery disease that lead to complications myocardial infarct and sudden cardiac death, and it is a major contributor to cardiac failure, renal insufficiency, and dissecting aneurysm of the aorta[1]. WHO reported that increasing in blood pressure caused 51% of stroke deaths and 45% of coronary heart disease deaths[2]. In Indonesia, the prevalence of hypertension is 26,5%[3]. Hypertension is defined conventionally as a sustained increase in blood pressure 140/90 mm Hg. At this condition, hypertension patients which was related with cardiovascular disease need a medical attention[1]. Hypertension can be treated with pharmacological (using antihypertensive drugs) and nonpharmacological therapy (lifestyle modifications). The overall goal of treating hypertension is to reduce morbidity and mortality and also achieve goal blood pressure; less than 140/90 mmHg for most patients and less than 130/80 mmHg for patients with compelling indications. If hypertension cannot be treated with only lifestyle modifications, antihypertensive drugs need to be taken[4]. Antihypertensive drugs have many side effects that can complicate the clinical problem. That is why medical professionals and even most of patient prefer to herbal medicine and preventive strategy[5]. Madeira vine (*Anredera cordifolia* (Ten.) Steenis), also known as mignonette vine, is a perennial, climbing vine grown as an ornamental species, but has naturalised to become an environmental weed. Many studies were performed to determine the best way to control its growth[6]. However, Chuang reported that ancordin from madeira vine rhizome stimulate the nitric oxide (NO) productions in RAW264.7 cells[7]. Another effect from madeira vine are as wound healing[8], increase breast milk[9], hepatoprotector[10], antimicrobial effect[11], antiobesity[12], antidiabetic[13], and improve kidney function[14]. In Indonesia, it is called binahong and used traditionally for lowering blood pressure[15]. The aim of present study was to prove antihypertensive effect of madeira vine scientifically. Further more, we can discover its mechanism in antihypertensive effect.

MATERIALS AND METHODS

Preparation of ethanolic extract

The leaves of *Anredera cordifolia* were collected from Lembang-Bandung. The plant was identified in Herbarium Bandungense, School of Life Science and Technology, Bandung Institute of Technology**.** Crude drug was extracted and repeated in three times by reflux using ethanol for 3 hours at 80**℃.** The ethanol extract was concentrated using rotary evaporator**.**

Phytochemical evaluation

Phytochemical screening was conducted to determine the presence of saponin, quinone, flavonoid, tannin, alkaloid, steroid/triterpenoid in extract.

Experimental animal

Male Wistar rat (200-300 g) were provided by School of Pharmacy, ITB. They were housed in clean and transparent polypropylene cages and maintained at 25-27℃ and relative humidity 55-75%, under a 12-hour light-dark cycle, and free access to food and water at all times. This study was performed by according to the Guideline for

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Care and Use of Animals Laboratory of School of Pharmacy – Bandung Institute of Technology.

Evaluation of antihypertensive effect

Evaluation of acute antihypertensive effect of *Anredera cordifolia* leaves extract used 30 Wistar rats. The animals were devided in six groups (n=5). Group 1: rats with no treatment (negative control); group 2: rats treated with adrenaline 1.2 µg/kg bw,without drug/extract (positive control); group 3: rats treated with adrenaline and atenolol 9 mg/kg bw and group 4-6: treated with adrenaline and extract. Heart rate was recorded through tail cuff (ML125 NIBP Controller, ADInstrument). Heart rate was recorded before drug administration (t0/baseline), after drug administration (t1), and after adrenaline induction (t2)[16-18].

Evaluation of diuretic activity

Evaluation of diuretic activity of *Anredera cordifolia* leaves extract used 30 Wistar rats. The animals were devided in six groups (n=5). Group 1: rats with no treatment (negative control); group 2: rats treated with furosemide 20 mg/kg bw (standard group); group 3-5: rats treated with extract. The urine was collected in metabolite cages every hour up to 5 hours after drug / extract administration. During this period, no food or water for the animals. Total volume of urine was measured. The concentration of Na^+ and K^+ were determined by flame emission spectrophotometer[19-21].

RESULTS

Percentage yield of etanolic extract of binahong leaves (EEBL) were 12.86 % w/w. Preliminary phytochemical screening of EEBL revealed that the presence of secondary metabolite like saponin, flavonoid, tannin, steroid/terpenoid. The heart rate of 6 groups were presented in Figure 1. The positive control showed increasing of heart rate after adrenaline administration (t2). In contrast, extract could prevent increasing in heart rate, which can be seen its no significant changes between baseline values and t2 values. Volume of urine excretion (ml/24h) of 6 groups were exposed in Figure 2. Only the standard group revealed significant difference in volume of urine excretion compared to negative control group ($p<0.05$). The EEBL groups gave a slightly increasing involume of urine excretion. However, the EEBL 200 mg/kg bw had significant difference compared to negative control group ($p<0.05$) at hour 24. Figure 3 showed the effect of oral administration of EEBL in urinary electrolyte excretion**.** EEBL 50 mg/kg bw and furosemide group expressed significantly sodium ion excretion compared with negative control group **(**$p<0.05$**).** In furosemide group, increasing in urinary electrolyte not only in sodium ion, but also for potassium ion**.**

DISCUSSION

Cardiovascular system is included heart, blood, and blood vessel. The heart pumps blood so that blood flows through the body within blood vessel. Contraction of heart ventricles generates blood pressure **(**BP**)**, the hydrostatic pressure was given by blood on the walls of a blood vessel. BP is determined by cardiac output, blood volume, and vascular resistance. The cardiac output depends on heart rate and stroke volume[22]. Drugs which can decrease myocardial contractility, heart rate, and cardiac output can be used for lowering blood pressure and treat hypertension[1].

In the body, epinephrine and norepinephrine release by adrenal medulla to increase cardiac output by increasing heart rate and force of heart contraction[22]. In general, stimuli which can increase the heart rate also increase blood pressure, whereas decreasing in heart rate will give lower blood pressure[23]. In this experiment, adrenaline used to increase the heart rate. Adrenaline have positive chronotropic and inotropic actions. Atenolol is one of β**-**adrenergic receptor antagonists**.** It slows the heart rate and decrease myocardial contractility**.** Short**-**term administration of β-receptor antagonists such as propranolol will decrease cardiac output**.** β-receptor antagonists will attenuate the expected rise in heart rate during exercise or stress[1]**.** Administration of atenolol can reduce increasing in adrenalin**-**induced heart rate**.** This result similar with administration of EEBL**.** Moreover, EEBL gave lower increasing in heart rate than atenolol group **(**standard group**)** and adrenalin group **(**positive control group**).** Based on this result, it can be suggested that EEBL can reduce the heart rate by blocking the effect of adrenaline**.** EEBL may be act as β**-**adrenergic receptor antagonists and used as antihypertensive drug**.** Diuretic are drugs which can increase the rate of urine flow. Diuretic will be clinically effective, if it increases the rate of sodium ion excretion (natriuresis) and accompanying anion, usually chloride ion, but not for potassium ion[1]. Lost in potassium ion has to be avoided[19]. Furosemid is potent diuretic. It inhibits activity of $Na^+/K^+/2Cl^-$ symporter in the thick ascending limb of the loop. It is not only increases urine excretion but also sodium and potassium ions[1]. The result of diuretic test demonstrated that EEBL group at doses of 50, 100, and 200 mg/kg bw have a weak diuretic activity compared to furosemide group. The volume urine excretion were slightly increased compared to negative control (normal group). EEBL at dose of 200 mg/kg bw showed diuretic effect at hour 24 after administration. However, there was significantly increased in level of sodium ion for EEBL 50 mg/kg bw group compared to negative control but not in potassium ion. The potassium ion was only slightly increased. These result showed that EEBL 50 mg/kg bw had similarity profile with thiazide diuretic. Thiazide administration produce less in urin volume (concentrated urine) but there is increasing in sodium, chloride, and potassium ion[24]. Thiazide diuretic is one drug of choice in hypertension treatment. The Eighth Joint National Committee 8 (JNC 8) recommend four class of antihypertensive agent which are thiazide-type diuretic, ACEI (angiotensin-converting enzyme inhibitor), ARB (angiotensin receptor blocker) or CCB (calcium channel blocker) for general non-black population, aged < 60 years[25]. The mechanism by which diuretic reduce arterial blood pressure is not known. Initially, blood pressure will be reduced because of decreasing in blood volume, venous return and cardiac output. Gradually, the cardiac output returns to normal, but the antihypertension effect remains because of the peripheral resistance decrease. Diuretic

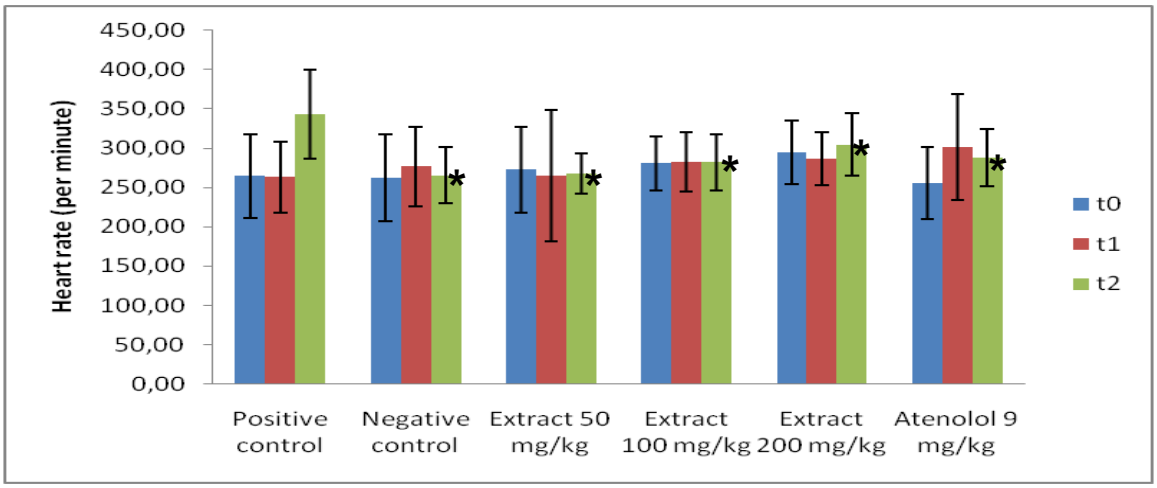

Figure 1: Heart rate of each group before drug administration (t0), after drug administration (t1), and after adrenaline induction (t2). All of data expressed as mean±SD, n = 5. *Significant difference compared to positive control group ($p<0.05$).

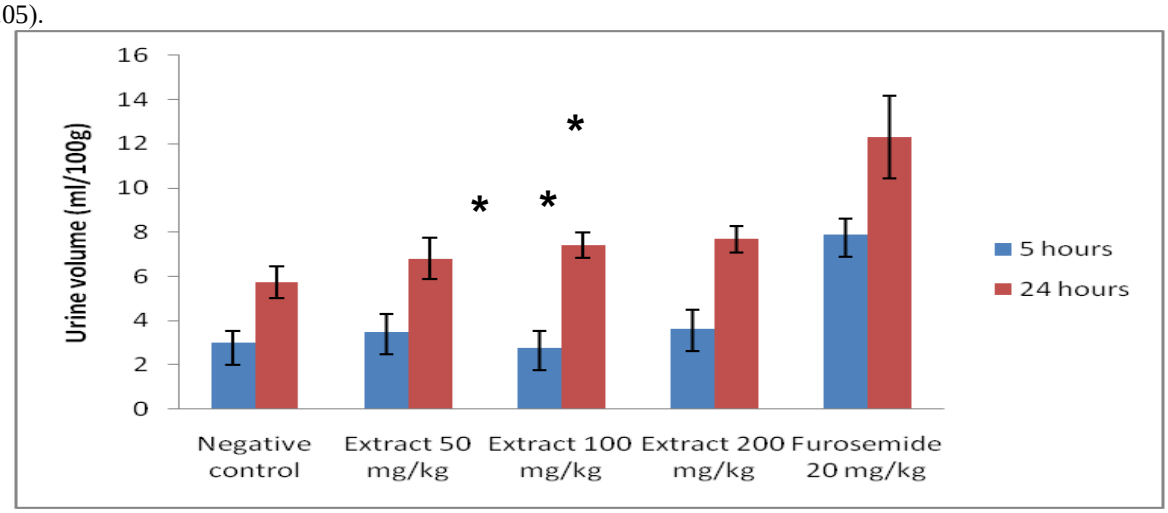

Figure 2: Volume of urine excretion after sample administration. All of data expressed as mean±SD, n = 5. *Significant difference compared to negative control group ($p<0.05$).

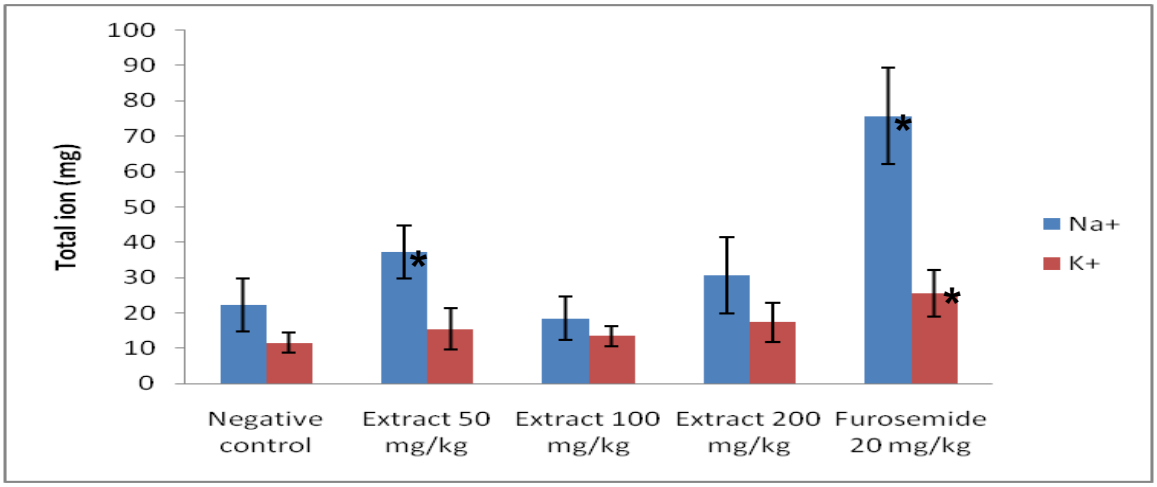

Figure 3: Total electrolyte after sample administration. All of data expressed as mean±SD, n = 5.*Significant difference compared to negative control group($p<0.05$).

have no direct effect on vascular smooth muscle. The vasodilatation effect seem associated with small reduction of Na^+ in the body. One possible mechanism is decreasing Na^+ in smooth muscle will cause secondary reduction in intracellular Ca^{2+}, so that the muscle becomes less responsive to endogenous vasoconstrictors. Thiazide

diuretics may cause hypokalemia, diabetes mellitus and gout, but it is now demonstrated that they have a flat dose–response curve and the low doses of thiazides currently used for lowering blood pressure which can cause insignificant metabolic effect. Thiazides seem to be particularly effective in older patients (over 55 years)[26]. According to phytochemical screening result, EEBL contains saponin, flavonoid, tannin, and steroid/terpenoid. This result was consistent with other studies. Astuti[27] and Ekaviantiwi[28] showed that saponins and phenolic acids were found in the EEBL. Lemmens[29] reported that triterpenoids saponins, such as boussingoside A1, several triterpenoids like larreagenin A, oleanolic acid derivatives and ursolic acid has been isolated from *Anredera cordifolia*. Yuliani[30] reported that optimum condition for extracting ursolic acid from *Anredera cordifolia* leaves was using ethanol 95% at 50°C. Yang[31] reported that quercetin was isolated from *Anredera cordifolia* shoot. Chuang[7] reported that *Anredera cordifolia* contained ancordin, a peptide. It was found in rhizomes and aerial tubers, but only a little in fresh leaves of *Anredera cordifolia*. It stimulates the nitric oxide (NO) productions (expressed as nitrite concentrations) in RAW264.7 cells without significant cytotoxicity. NO production is important in hypertension treatment since it can cause blood vessel dilatation then decrease blood pressure. Interaction of the chemical compounds contained in *Anredera cordifolia* could generate antihypertensive effect. Oleanolic[32,33] and ursolic acid[34-37], quercetin[38-42], and apigenin[42-44] were reported to have antihypertensive effect.

CONCLUSION

Etanolic extract of binahong leaves had potency for lowering blood pressure. Therefore, it can be used as antihypertensive agent. Its antihypertensive effect might be produced by inhibition of β-adrenergic receptor and natriuretic effect.

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