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Research Article

Antihypertensive Effect of Combination Extract of Anredera Cordifolia (ten.) Steenis and Sonchus Arvensis l. on Dexamethasone-Induced Hypertensive Male Wistar Rat

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Abstract

Hypertension is an asymptomatic chronic disease. Uncontrolled blood pressure can cause complications that lead to death. Anredera cordifolia (Ten.) Steenis (AC) and Sonchus arvensis L. (SA) are traditionally used for the treatment of various diseases in Indonesia and one of them is to reduce blood pressure. This study aimed to determine the antihypertensive effect of a combination of SA and AC aqueous extracts (SAAE) in a rat model of hypertension induced by dexamethasone 1.5 mg/kg body weight (bw). The antihypertensive effect test was carried out on 8 groups of rats, namely the normal group, the control group, the combination of SA and AC at a dose of 25 mg/kg body weight each (SAAE 25-25), SAAE 50-50, SAAE 100-100, SA 100 and AC 100 and captopril 13.5 mg/kg bw. The results showed that all groups significantly lowered blood pressure after seven days of treatment compared to the control group ($p<0.05$). The combination of SA and AC extracts at a dose of 50-50 mg/kg bw. showed the highest decrease in blood pressure compared to the other groups, i.e. 49.1 mmHg for systole and 39.4 mmHg for diastole but was statistically not different from a single extract at a dose of 100 mg/kg bw showing an additive effect of the combination.

Keywords: anredera cordifolia; sonchus arvensis; antihypertensive; dexamethasone

Introduction

Hypertension is a chronic disease with high prevalence globally; about 1.39 billion people have hypertension as in 2010 [1]. Hypertension is such a preventable disease, but uncontrolled persistent hypertension could lead to severe and fatal complications which lead to death, such as stroke, myocardial infarction, and heart failure [2]. Thus, it is crucial to maintain the blood pressure in a desirable range according to the therapy goal (<140/90 mmHg). Traditional medicines are often chosen to cure some health problems, including hypertension. More than 60% population in the world consumes traditional medicines for health problems. In Indonesia, 14.5% of the population choose to lower hypertension with traditional medicine rather than consuming conventional medicines

Anredera cordifolia (Ten.) Steenis and Sonchus arvensis L. are two plants that have been traditionally used for various health purposes such as analgesic, wound healing, fever, and often used to reduce high blood pressure in Indonesia. A. cordifolia (AC) is an evergreen succulent plant in the Basellaceae family originating from South America; it has a particular morphology with heart-shaped leaves. Meanwhile, S.arvensis (SC) is a herb from the Asteraceae family native to Europe worldwide. Furthermore, proving the traditional claims, both plants show several potential pharmacological activities in both in vitro and in vivo studies. Previous studies has shown that the ethanol extract of A.cordifolia leaves has wound healing, antibacterial, and antihypertensive activities [3-5]. Meanwhile, S.arvensis ethanolic extract showed several activity including hepatoprotective, cardioprotective, nephroprotective, and antihypertensive [6-9].

Previous study has shown that the combination of A.cordifolia and S.arvensis is contraindicated for pregnant women and those planning to become pregnant [10]. In a study with a rat model of adrenaline-induced acute hypertension, administration of ethanolic extracts of A.cordifolia and S.arvensis (SAEE) showed potential as an antihypertensive by inhibiting the increase in blood pressure at a dose of 50-50 mg/kg body weight [11]. The previous study showed that an aqueous fraction of A.cordifolia was better in lowering blood pressure than ethanolic extract. Thus, aqueous extract was predicted to have the same potential in lowering blood pressure as the ethanolic extract. This research focuses on understanding the antihypertensive effect of A.cordifolia aqueous extract (AAE), S.arvensis's

aqueous extract (SAE), and its combination (SAAE) on a chronic-induced hypertension rat model with dexamethasone.

Methods and Materials

Dexamethasone injection (PT Pahpros), sodium chloride 0.9%, dry aqueous extract of A.cordifolia leaves (PT Phytochemindo), dry aqueous extract of S.arvensis leaves (PT Phytochemindo), captopril tablet (OGB PT Deksa), Na-CMC, chloroform, methanol, formic acid, hydrogen sulfide, amylum, lactose, and aerosil.

Apparatus

Moisture balance (Mettler Toledo), disintegration tester (Erweka), analytical balance (Mettler Toledo), CODA tail-cuff blood pressure system (Kent Scientific).

Animal

Male Wistar rats weighing 200-250 g were obtained from Biofarma. Rats were housed in polypropylene cages and maintained at 25-27ºC at relative humidity around 55-75% under a 12h light-dark cycle. Rats have free access to food and water all day. All the procedures in this experiment have been approved by The Institutional Animal Ethics Committee (No. 15/KEPHP-ITB/12-2019).

Identification of secondary metabolites (Thin Layer Chromatography)

Identification of secondary metabolites of both extracts were done by Thin Layer Chromatography (TLC). Marker compund for AAE was vitexin, and SAE was luteolin and luteolin 7-O-glycoside. Silica gel plate used as stationary phase, and solvent mixture consists of chloroform:methanol:formic acid (7:2:0.5) was used as mobile phase. The plate was observed under UV 254 nm and 366 nm.

Preparation of test substances

The test preparation and captopril as comparator drug were suspended in 0.5% Na-CMC, SAAE was made in a concentration of 5, 10, and 20 mg/ml, SAE and AAE respectively in 10 mg/ml, captopril in 1.35 mg/ml, and dexamethasone diluted with 0.9% NaCl to form concentration of 0.15 mg/ml.

Antihypertensive activity assay

Rats were habituated in the CODA tail-cuff blood pressure system. Total 24 rats were divided into eight groups which consist of normal group (non-induced and non-therapeutic groups), control group (induced and non-therapeutic group), comparator group captopril 13.5 mg/kg body weight, SAE 100 mg/kg body weight (bw) , AAE 100 mg/kg body weight, and SAAE respectively at 25-25, 50-50 and 100-100 mg/kg bw. For ten days, rats were induced with dexamethasone 1.5 mg/kg bw subcutaneously. If the rats were successfully induced, the extracts were given orally every day for seven days.

Data Analysis

Analysis of hygroscopic test data, the significance of hypertension induction, and the significance of therapy were carried out using the statistical method One Way ANOVA post-hoc LSD test with a 95% confidence interval.

Results And Discussion

The extract of Anredera cordifolia and Sonchus arvensis were dry extract and obtained from PT Phytochemindo. Characteristics of extract of Anredera cordifolia and Sonchus arvensis leaves have been proven in the previous study, Anredera cordifolia's extract contained alkaloids, flavonoids, saponins, triterpenoids, hydrolysate tannins, coumarine, and Sonchus arvensis's extract contained alkaloids, flavonoids, saponins, hydrolysate tannins, condensed tannins and coumarine [11].

SAAE Antihypertensive assay

SAAE was tested in chronic-induced hypertension rat model, this method is the closest to hypertension's pathology and it could avoid the bias when interpret the result because blood pressure doesn't fall quickly unlike in the acute-induced model. At the day 0 before the induction, rat blood pressure was measured by the invasive tail-cuff method and marked as T0, on the tenth day after being induced, blood pressure was measured again (T1). An analysis was carried out to observe the success of induction by comparing the rat's blood pressure at T1 compared to the normal group with One Way ANOVA. The analysis results showed a significant difference in systolic and diastolic blood pressure before and after induction in the dexamethasone-induced groups compared to the normal group ($p<0.05$).

Therefore, we conclude that rats were successfully induced by dexamethasone after ten days (T1) with an average increase in systolic and diastolic blood in rats of 38.1 mmHg and 28.6 mmHg (**Figure 1 and 2**). The increase in blood pressure during induction period caused by Dexamethasone is related to the glucocorticoid receptors that concentrated in the kidney and their effect on blood vessels. Dexamethasone increases the reabsorption of Na+ salt in the kidney and increase the expression of Angiotensin II receptors in the blood vessels. Also, dexamethasone can reduce the expression of eNOS or endothelial nitric oxide synthase, causing peripheral blood vessels to constrict [12].

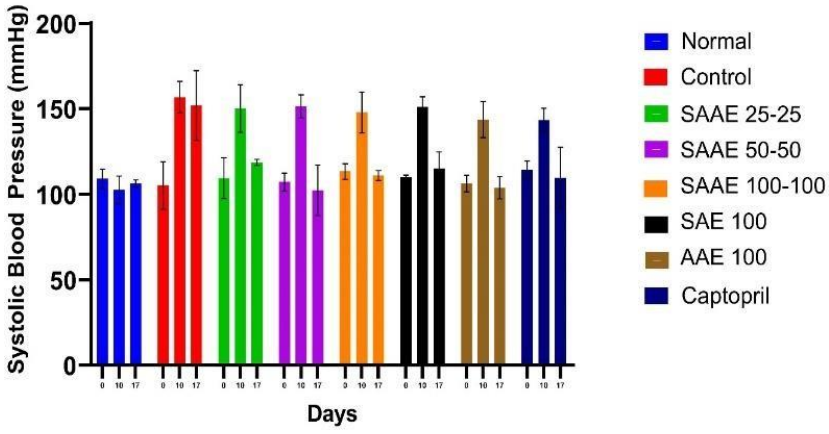

Figure 1. Systolic blood pressure (SBP) of all groups before the induction of hypertension (T0), after the induction is carried out (T1), and after the therapy (T2). (*) Significantly different compared to normal groups at T1 ($p<0.05$); (**) significantly different compared to control group at T2 ($p<0.05$).

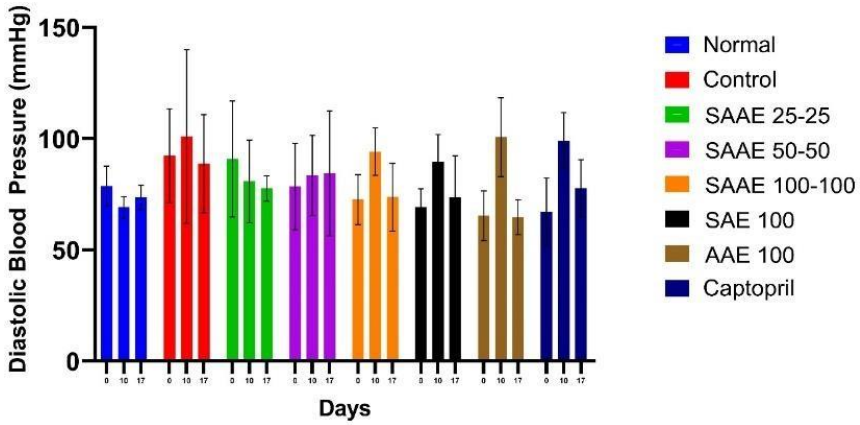

Figure 2. Diastolic blood pressure (DBP) of all groups before the induction of hypertension (T0), after the induction is carried out (T1), and after the therapy (T2). (*) Significantly different compared to Normal groups at T1 ($p<0.05$); (**) different compared to Control group at T2 ($p<0.05$).

After the induction was successful, therapy was given for seven days by administering extracts suspended in Na-CMC orally; Captopril was given as a comparison drug. Blood pressure was again measured on the last day of therapy (T2). The analysis of the therapeutic significance was carried out using the One-Way ANOVA statistical method with a follow-up post hoc LSD, compared to the mean systolic and diastolic blood pressure of each group against the Control group. On the last day of therapy, there was a significant difference between systolic and diastolic blood pressure in the Normal group; SAAE 25-25, 50-50, and 100-100 mg/kg BW; SAE 100 mg/kg bw; AAE 100 mg/kg bw; and Captopril 13.5 mg/kg bw compared to control group ($p<0.05$).

Antihypertensive therapy can be said to be potential if it can reduce systolic blood pressure by at least 20 mmHg and diastolic blood pressure by at least 10 mmHg. [13]. The reduction in blood pressure after seven days of therapy can be seen in **Table 1**. These three doses showed a large decrease in blood pressure in rats, even doses of 50-50 mg/kg bb provided the best reduction profile, i.e. 49.13 mmHg for systolic blood pressure and 39.40 mmHg for diastolic blood pressure, doses of 50- 50 mg/kg bb can be the best recommendation for lowering blood pressure compared to the other two combined doses if the research is to be continued into clinical trials.

However, after statistical analysis, there was no significant difference among the three doses in lowering blood pressure ($p>0.05$). Compared to its single administration for each extract at a dose of 100 mg/kg bw, the administration of the extracts combination (SAAE) at a half dose (50-50 mg/kg bw) showed a better reduction in blood pressure but statistically not different ($p>0.05$), indicating an additive effect after the two extracts were combined.

From the systolic and diastolic pressure data, arterial pressure can be determined. Mean arterial pressure could explain more about how extracts work on lowering blood pressure. Mean arterial pressure (MAP) is the pressure between systolic and diastolic, which can be determined by the following calculation:

MAP = Diastolic Pressure + 1/3(Systolic Pressure - Diastolic Pressure)

Mean arterial pressure is also the product of cardiac output (CO) and total peripheral resistance (TPR). MAP value is often associated with CO and TPR conditions on hypertension therapy. During hypertension, the increased MAP value can describe an increase in total peripheral resistance or CO, an increased TPR usually caused by decreased vasodilator activity on the endothelium.

Groups	Systolic (mmHg)	Diastolic (mmHg)
	ΔT2-T1	ΔT2-T1
Normal	-3.73	-4.40
Control	4.87	5.60
SAAE 25-25 mg/kg BB	31.47	22.73
SAAE 50-50 mg/kg BB	49.13	39.40
SAAE 100-100 mg/kg BB	36.87	29.20
SAE 100 mg/kg BB	36.87	15.93
AAE 100 mg/kg BB	39.93	36.00
Captopril 13.5 mg/kg BB	33.67	21.40

Table 1: Blood pressure reduction in tested groups by measuring the delta from mean systolic and diastolic blood pressure respectively after and before therapy (T2 with T1).

During the induction period compared to Day 0, mean arterial pressure was increased by mean value 120 mmHg on the T1 for every group (**Figure 3**), it reflects an increase in TPR values due to dexamethasone induction. Reduction in mean arterial pressure after administration of SAAE could reflecting a decrease in total peripheral resistance, indicating an increasing vasodilator activity during the therapy period. This proves the previous research conducted by Garmana et al. (2018), which AC was able to increase NO (Nitric Oxide) levels then SA was known to inhibit ACE and possibly inhibited degradation of Bradykinin [2,11]. Nitric Oxide acts as a vasodilator by inhibiting the influx of Ca2+ ions causing relaxation of blood vessels [14]. The antihypertensive effect of the SAAE also can be explained by the combination of effects of its secondary.

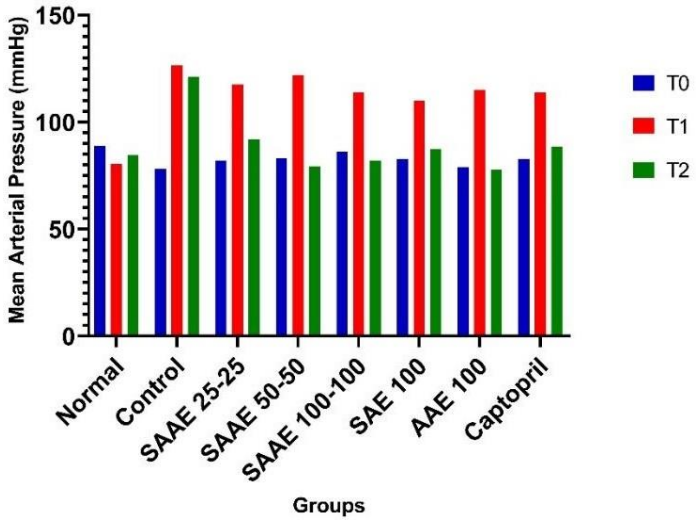

Figure 3: Mean Arterial Pressure at T0, T1, T2.

Based on TLC results and some previous studies, it was known that the marker compounds in AC were vitexin (Rf=0.52) and in SA were luteolin (Rf=0.71) and luteolin 7-O-glycosides (Rf=0.32) [11,15-17]. It is known that vitexin has vasodilating effects mediated by β1-adrenoreceptor inhibition; Luteolin lowers blood pressure by inhibiting Angiotensin II. In general, flavonoids can increase NO production in endothelial cells that act as vasodilators. The ability of flavonoid compounds to bind superoxide free radicals causes inhibition of peroxynitrite formation, which is associated with the pathology of hypertension [18].

Conclusion

The combination of aqueous extracts of Anredera cordifolia and Sonchus arvensis showed an antihypertensive effect at all doses, namely 25-25 mg/kg bw, 50-50 mg/kg bw and 100-100 mg/kg bw, which was statistically significant to the control ($p<0.05$) . The greatest decrease in blood pressure was shown by the combination of 50-50 mg/kg bw, but statistically not different from the combination of other doses and a single extract ($p>0.05$). The reduction in blood pressure of single extracts of Anredera cordifolia and Sonchus arvensis at a dose of 100 mg/kg bw was not statistically different from the combination with half the dose of each showing an additive combination.

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