

Antihypertensive Activity of Combination of *Anredera cordifolia* (Ten.) V. Steenis and *Sonchus arvensis* L. Leaves on Epinephrine Induced Male Wistar Rat

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ABSTRACT

In Indonesia, hypertension is a condition that can lead to death through stroke and TB. Herbs have traditionally been used in Indonesia as an alternative medicine for lowering blood pressure. The leaves of *Anredera cordifolia* and *Sonchus arvensis* have been investigated for their antihypertensive potential. Based on the number of treatments, rats were randomized into groups. Each group consists of five rats. The test animals were grouping as follows: the positive control group (hypertension induction without treatment), *A. cordifolia* 50 mg/kg b.w. group, *A. cordifolia* 100 mg/kg b.w., *S. arvensis* 50 mg/kg b.w., *S. arvensis* 100 mg/kg b.w., *A. cordifolia* 25 mg/kg b.w. + *S. arvensis* 25 mg/kg b.w., *A. cordifolia* 50 mg/kg b.w. + *S. arvensis* 50 mg/kg b.w., and atenolol 4.5 mg/kg b.w. The rats were given 0.25 mg/kg b.w. of epinephrine intraperitoneally. The initial, after induction, and final blood pressure of the animals were measured using the CODA[®] noninvasive blood pressure device. All animal test groups at T60 showed a significant difference in systolic and diastolic blood pressures to initial blood pressure (T0), $P < 0.05$. The combination of *A. cordifolia* 50 mg/kg b.w and *S. arvensis* 50 mg/kg b.w showed the highest percent inhibition of systolic and diastolic blood pressure. The combination of *A. cordifolia* and *S. arvensis* 50–50 mg/kg b.w showed the best effect of lowering systolic and diastolic blood pressure on the pathway of inhibiting adrenergic receptors.

Key words: *Anredera cordifolia*, Antihypertension, epinephrine, *Sonchus arvensis*

INTRODUCTION

Hypertension is a disease that can cause death such as

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stroke and heart failure in Indonesia. Basic Health Research survey in 2018 reported that the prevalence of hypertension increased from 25.8% to 34.1%, and the highest majority occurred in South Kalimantan province with 44.1%.^[1] If untreated, hypertension can lead to stroke, coronary heart disease, diabetes, renal failure, and blindness.^[2]

Some Indonesian people have consumed certain herbs as an alternative or additional therapy to lower blood pressure, such as *Anredera cordifolia* and *Sonchus arvensis*. *A. cordifolia* and *S. arvensis* contain flavonoids, tannins, alkaloids,

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saponins, phenols, steroids/triterpenoids, tannins, quinones, and glycosides.^[3] *A. cordifolia* leaves have antihypertensive activity. The mechanism is vasodilators through the nitric oxide (NO) pathway and adrenergic receptor antagonists. *A. cordifolia* also has an ACE inhibitory effect (moderate), a diuretic/saluretic effect, and calcium channel inhibition.^[4] *S. arvensis* leaves are reported to have antihypertensive actions through the ACE inhibitor mechanism^[5] and have a diuretic effect.^[6]

MATERIALS AND METHODS

Plant materials

Every 3 months, leaves of *A. cordifolia* and *S. arvensis* were gathered from the Herbal Jaya Garden in Tawangmangu, Karanganyar, Central Java, and identified at the Herbarium Bandungense, School of Life Sciences and Technology, Institut Teknologi Bandung (No. 652/I1.CO2.2/PL/2018).

Chemical

The chemicals used were epinephrine (PT. Etika), propranolol (PT. Dexa Medica), sodium chloride physiological (PT. Whidatama Bhakti), sodium carboxymethyl cellulose, Dragendorff reagent, aqua dest, FeCl₃, AlCl₃, ethanol 70%, HCl, KOH, Mayer reagent, and analytical grades of weighing paper. The other chemical materials used for this research were obtained from authorized organizations.

Apparatuses

The apparatuses used were rotary evaporator, reflux apparatus, and CODA noninvasive blood pressure system (a tail-cuff Method, Kent Scientific Corporation), and high-performance liquid chromatography.

Standardization of extract of *Anredera cordifolia* and *Sonchus arvensis*

According to the Indonesian Herbal Pharmacopoeia, the determination of water-soluble content, ethanol-soluble content, and water content are all part of the standardization of *A. cordifolia* and *S. arvensis* extracts. The result of phytochemical screening shows alkaloids, flavonoids, saponins, steroids, triterpenoids, and tannins.^[7]

Total flavonoid level

The total flavonoids level was calculated using Chang *et al.*^[8] The calibration curve was made using vitexin and in various concentrations. About 0.5 mg of vitexin and luteolin were dissolved each in 80% ethanol and then diluted to 10, 20, 40, 60, 80, and 100 µg/mL. About 20 µL standard solutions were mixed with 60 µL of 95% ethanol, add 4 µL potassium acetate 1 M, 4 µL aluminum chloride 10%, and 112 µL of distilled water. The mix solution was incubated for 30 min at 25°C, the absorbance was assessed at 340, and 410 nm with a Tecan Microplate reader (Switzerland). Similarly, 20 µL of ethanol extracts (2500 ppm) was carried out with the same treatment as standard.

High-performance liquid chromatography

A. cordifolia and *S. arvensis* extracts were diluted with methanol. In the high-performance liquid chromatography system, 10 10 µL samples were injected. A column (5 m; 4.6150 mm, Agilent) with an ultraviolet-visible detector was used to separate the samples. Separation is performed using solvents A (0.05% trifluoroacetic acid) and solvent B (0.038% trifluoroacetic acid in 83% acetonitrile (v/v) with the following gradient: 0–5 min, 15% B in A, 5–10 min, 70% B in A, 10–15 min, and 70% B in A. 1 mL/min was the flow rate. Vitexin and luteolin were used as standard chemicals to measure the amount in the extract. The calibration curves were used to calculate each chemical. All samples were assayed three times.

Animal experimental design

The male Wistar rats weighed 200–250 g and were 8–10 weeks old. The animals were adapted for 7 days before the experiment was carried out and maintain under laboratory room temperature was 22°C ± 3°C, relative humidity 30%–70%, and lighting was set for 12 h bright and 12 h dark. Animals were provided with suitable laboratory animal food and drink are provided indefinitely. Animals were habituated to CODA noninvasive blood pressure system three times before being given treatment. Healthy and normal male Wistar rats have fasted for 4 h before the experiment while still drinking water. Rats were randomly assigned into eight groups that each consists of five rats.

The groups are (1) the positive control group (hypertension induction without treatment), (2) *A. cordifolia* 50 mg/kg b.w. group, (3) *A. cordifolia* 100 mg/kg b.w., (4) *S. arvensis* 50 mg/kg b.w., (5) *S. arvensis* 100 mg/kg b.w., (6) *A. cordifolia* 25 mg/kg b.w + *S. arvensis* 25 mg/kg b.w., and (7) *A. cordifolia* 50 mg/kg b.w + *S. arvensis* 50 mg/kg b.w., (8) atenolol 4.5 mg/kg b.w. Each test animal's systolic and diastole blood pressure was measured using noninvasive blood pressure apparatus and recorded as initial blood pressure. The test sample was then given to the rats orally, according to their group. The rats were given epinephrine 0.25 mg/kg b.w. intraperitoneally 30 min later. After 30 min of induction, the animals' blood pressure was remeasured using noninvasive blood pressure apparatus and recorded as final blood pressure. The Institutional Animal Ethics Committee has accepted all experimental animal procedures that comply with the Committee's recommendations for the Objective of Supervision and Control of Animal Experiments (No. 002b/SK/I1. B03/KP/2019).

The statistical analysis was done to compare systolic and diastolic blood pressure before and after induction using *pair t*-test and compare test groups against a positive control group at T60 using one-way ANOVA with lysergic acid diethylamide *posthoc* test. The data were stated to be statistically significant when $P < 0.05$.

RESULTS

Standardization and phytochemical characterization

A. cordifolia leaves' crude drug was extracted using ethanol 70%, whereas *S. arvensis* leaves were extracted using aqua dest. The distilled water content, water-soluble content, and ethanol-soluble content of *A. cordifolia* and *S. arvensis* leaves, as well as phytochemical screening extract, were used to determine the standardization of the extract. Table 1 shows the data of extract standardization and phytochemical screening.

The results of extracts' characterization showed that extracts met the Indonesian Herbal Pharmacopoeia requirements, i.e. water content was not more than 10%.

Many medicinal plants contain bioactive flavonoids. The total flavonoids content of *A. cordifolia* and *S. arvensis* extracts was shown in Table 2.

High-performance liquid chromatography quantification of vitexin and luteolin

As described in Figure 1, *A. cordifolia* was examined for the presence of flavonoid chemicals, and the presence of vitexin was revealed using integrated peak areas at 350 nm for quantification. In contrast, *S. arvensis* showed the presence of luteolin [Figure 2]. The concentration of the sample was measured from the regression equation of calibration curves. Table 3 shows the quantification of these compounds.

Antihypertensive activity

In this study, epinephrine was used to induce hypertension in test animals. Table 4 shows the systolic and diastolic blood pressures before and after administering epinephrine. All animal test groups (T60) showed a significant difference in systolic and diastolic blood pressures before induction (T0) $P < 0.05$ [Table 3].

A. cordifolia, *S. arvensis* and their combination test groups could significantly reduce systolic blood pressure than the

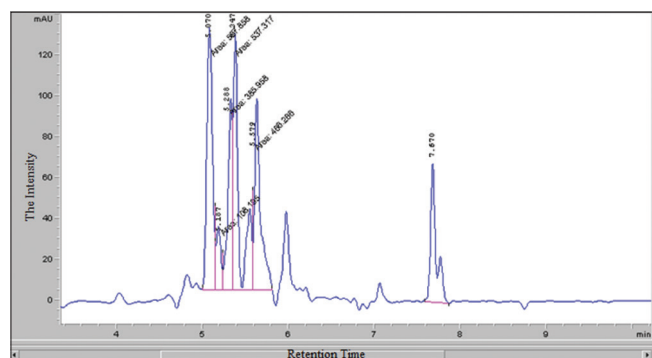


Figure 1: High performance liquid chromatography fingerprints of *Anredera cordifolia*

positive control group ($P < 0.05$). Meanwhile, *A. cordifolia* 50 mg/kg b.w and combination 50–50 mg/kg b.w could significantly reduce diastolic blood pressure to the positive control group ($P < 0.05$). Figure 3 shows that atenolol has the lowest systolic and diastolic blood pressures of all test groups.

The positive control group showed the highest blood pressure increase, which proved that epinephrine induction successfully induced hypertension in test animals. The combination of *A. cordifolia* and *S. arvensis* 50–50 mg/kg b.w group showed the smallest elevated in systolic and diastolic blood pressure than all test groups.

Table 5 shows the highest percent inhibition of systolic and diastolic blood pressure of the combination 100–100 mg/kg

Table 1: Characteristics of extract of *Anredera cordifolia* and *Sonchus arvensis* leaves

	A. <i>cordifolia</i>	S. <i>arvensis</i>
Water content (%)	5±0.0	7.5±0.54
Water soluble extract content (%)	41.47±1.53	44.96±2.19
Ethanol soluble extract (%)	35.16±1.28	16.35±3.85
Alkaloid	+	+
Flavonoid	+	+
Saponin	+	+
Steroid	–	+
Triterpenoid	+	–
Hydrolysate tannin	+	+
Condensed tannin	–	+
Coumarine	+	+

A. cordifolia: *Anredera cordifolia*, *S. arvensis*: *Sonchus arvensis*

Table 2: Total flavonoid compounds of extract of *Anredera cordifolia* and *Sonchus arvensis* leaves

Extract	Total flavonoids compounds as vitexin equivalent (µg/mg extract)	Total flavonoids compounds as luteolin equivalent (µg/mg extract)
<i>A. cordifolia</i>	165.34±1.73	-
<i>S. arvensis</i>	-	13.04±0.88

A. cordifolia: *Anredera cordifolia*, *S. arvensis*: *Sonchus arvensis*

Table 3: High performance liquid chromatography quantification of extract of *Anredera cordifolia* and *Sonchus arvensis* leaves

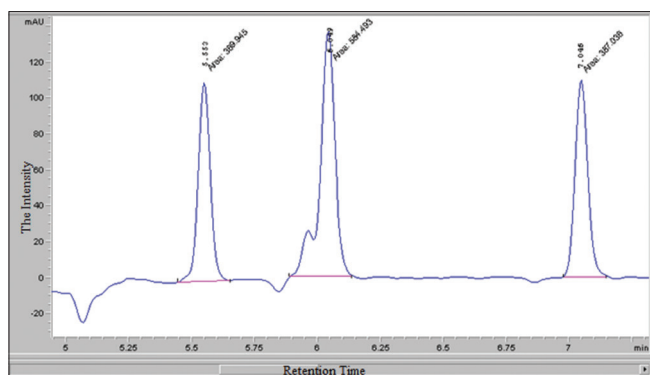
Extract	Concentration (µg/mg of extract)	Compound
<i>A. cordifolia</i>	6.56±0.15	Vitexin
<i>S. arvensis</i>	0.53±0.16	Luteolin

A. cordifolia: *Anredera cordifolia*, *S. arvensis*: *Sonchus arvensis*

Table 4: Systolic and diastolic blood pressure of rat before and after epinephrine induction

Groups	T0		T60	
	Systolic	Diastolic	Systolic	Diastolic
Positive control	102.32±7.63	72.68±3.75	152.59±10.79*	108.35±7.45*
<i>A. cordifolia</i> (50 mg/kg b.w)	110.59±2.88	75.71±4.98	139.81±7.24*	101.79±10.01*
<i>A. cordifolia</i> 100 mg/kg b.w	112.15±3.74	77.59±3.52	145.60±10.95*	108.92±8.79*
<i>S. arvensis</i> 50 mg/kg b.w	111.98±2.24	76.98±3.78	145.30±7.55*	106.30±7.68*
<i>S. arvensis</i> 100 mg/kg b.w	115.11±8.94	74.71±4.76	148.05±8.60*	108.75±7.87*
Combination 25-25 mg/kg b.w	117.89±9.12	75.33±4.47	144.82±12.53*	105.91±11.38*
Combination 50-50 mg/kg kb	115.78±4.76	79.52±5.41	138.96±5.28*	99.10±3.68*
Atenolol	112.19±6.81	72.29±2.36	123.78±5.79*	84.68±2.59*

*Means $P < 0.05$ compared to the systolic/diastolic in T0. All data is presented as mean±SD ($n=5$). *A. cordifolia*: *Anredera cordifolia*, *S. arvensis*: *Sonchus arvensis*, SD: Standard deviation

**Figure 2:** High performance liquid chromatography fingerprints of *Sonchus arvensis*

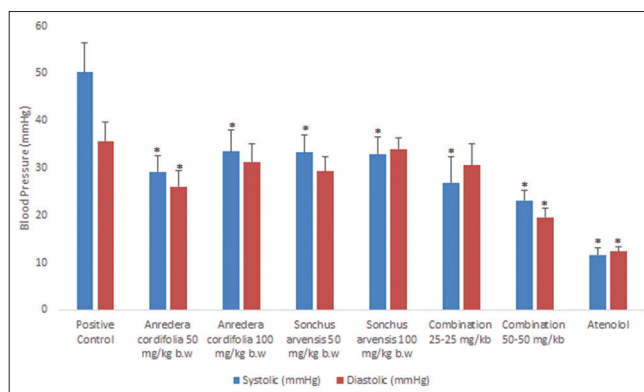
b.w group than to the *A. cordifolia* 100 mg/kg b.w, *S. arvensis* 100 mg/kg b.w, and combination 50–50 mg/kg b.w group.

DISCUSSION

Systolic blood pressure ≥ 140 mmHg and diastolic blood pressure ≥ 90 mmHg were used to classify hypertension. If the blood pressure was >150 mmHg/90 mmHg for age >60 years and >140 mmHg/90 mmHg for 60 years, pharmacological therapy for hypertension was started.^[9]

In the circulation system, cardiac output and peripheral resistance will affect blood pressure. Stroke volume and heart rate play a role in the work of cardiac output. The adrenal medulla releases epinephrine and norepinephrine, enhancing cardiac output, heart rate, and contraction force.^[10]

The alpha and beta-adrenergic receptors were the targets of epinephrine's pharmacological activities. Epinephrine causes vasoconstriction by activating the enzymes phospholipase-C and protein kinase-C. G-protein coupled binding to epinephrine induces phosphorylation and a rise in calcium influx from the endoplasmic reticulum (positive chronotropic effect).^[11-13] The activity of atenolol was slow the heart rate and decrease myocardial contractility. Atenolol is one of the β adrenergic receptor antagonists. The

**Figure 3:** Systolic and diastolic blood pressure elevation after epinephrine administration

short-term administration of atenolol will reduce cardiac output. Meanwhile, β -receptor antagonists will reduce the heart rate during exercise or stress.^[14]

A. cordifolia and *S. arvensis* have been reported to lower blood pressure. *A. cordifolia* has antihypertensive action as the vasodilator. The mechanism is the NO pathway and adrenergic receptor antagonists. *A. cordifolia* also has a moderate ACE inhibitory effect, a diuretic/saluretic effect, and calcium channel inhibition.^[4] *S. arvensis* leaves are reported to have an antihypertensive impact through the ACE inhibitor mechanism^[5] and have a diuretic effect.^[6] The combination of *A. cordifolia* and *S. arvensis* has been reported to lower systolic and diastolic blood pressure better than a single extract in the ACE inhibitor mechanism.^[15]

In this study, the combination of *A. cordifolia* and *S. arvensis* 50–50 mg/kg b.w showed the best percent inhibition of systolic and diastolic blood pressure to a combination of *A. cordifolia* and *S. arvensis* at 25–25 mg/kg b.w or a single extract in the receptor adrenergic inhibition pathway.

A. cordifolia leaves contained secondary metabolites such as flavonoids, terpenoids, steroids, glycosides, and alkaloids. Apigenin, apigethrin, and vitexin were the secondary metabolites found in the *A. cordifolia* plant.^[16] Vitexin

Table 5: Per cent inhibition of blood pressure elevation

Groups	Systolic (mmHg)	Diastolic (mmHg)
<i>A. cordifolia</i> 50 mg/kg b.w	41.88	26.91
<i>A. cordifolia</i> 100 mg/kg b.w	33.45	12.17
<i>S. arvensis</i> 50 mg/kg b.w	33.73	17.82
<i>S. arvensis</i> 100 mg/kg b.w	34.49	4.57
Combination 25-25 mg/kg	46.43	14.30
Combination 50-50 mg/kg	53.90	45.12
Atenolol	76.93	65.26

A. cordifolia: *Anredera cordifolia*, *S. arvensis*: *Sonchus arvensis*

and isovitexin have been reported to have adrenergic receptor (β -blocker) antagonistic effects.^[17] *S. arvensis* leaves contained lactone, sesquiterpenes, glycerates, triterpenoid, steroids, luteolin, and luteolin 7-O glucoside.^[18] Luteolin has been reported to lower blood pressure spontaneously in hypertensive rats.^[19,20]

CONCLUSION

The combination of *A. cordifolia* and *S. arvensis* 50–50 mg/kg b.w showed the best effect in lowering systolic and diastolic blood pressure on the pathway of inhibiting adrenergic receptors.

Acknowledgment

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Nil.

Conflicts of interest

There are no conflicts of interest.

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