Trop J Nat Prod Res, April 2021; 5(4):692-697

ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

Tropical Journal of Natural Product Research

Available online at https://www.tjnpr.org

Original Research Article

Investigation of Angiotensin-Converting Enzyme Inhibitory Effects of Indonesian Traditional Medicine (Jamu)

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ARTICLE INFO

Article history:
Received 15 February 2021
Revised 11 March 2021
Accepted 07 April 2021
Published online 03 May 2021

ABSTRACT

The renin-angiotensin-aldosterone system (RAAS) is a significant factor in maintaining blood pressure. Several Indonesian plants in herbal medicine (jamu) have been proven in vitro to be ACE inhibitors. This study assessed the angiotensin-converting enzyme inhibitory effects of antihypertensive jamu in Wistar rats. Thirty rats were divided into six groups. Group I represented the standard controls (SC), which was administered standard diet, and aqua dest drinks. Groups II to VI were made hypertensive by administering 10% fructose drink for ten weeks. Group II was the negative control (NC), and was administered standard diet and 10% fructose solution. Captopril (0.5 mg/kg BW) was administered to group III, while groups IV – VI were administered jamu at doses of 120 mg/kg BW (D1), 240 mg/kg BW (D2), and 360 mg/kg BW (D3), respectively from day 57 to 71. Blood pressure was measured every week before giving fructose until the last day of treatment. On day 72, rats were sacrificed, and plasma was taken to measure angiotensin-converting enzyme activity using an ELISA reader. The blood pressure rise started at week 3 of fructose administration. In the groups: Captopril, D1, D2, and D3, there was a significant decrease in systolic and diastolic blood pressure compared to the negative control ($p < 0.05$). Plasma angiotensin-converting enzyme levels was significantly different between the negative control and the normal control, D1, D2, D3, and the captopril groups ($p < 0.05$). There was no significant difference between D3 compared to the standard controls ($p > 0.05$). Antihypertensive jamu has angiotensin-converting enzyme inhibitory activity *in-vivo*.

Keywords: Antihypertensive, Blood pressure, ACE inhibitor, Jamu

Introduction

Hypertension represents a condition when blood pressure increase chronically.[1] It can occur because the heart works harder to adequately pump blood to meet the body's oxygen and nutritional needs. If allowed, this disease can interfere with other organs' function, especially vital organs like the heart and kidneys.[1] The prevalence of high blood pressure in Indonesia for people aged ≥ 18 years is 34.1%; the highest is in South Kalimantan (44.1%), while the lowest is in Papua (22.2%). The mortality rate due to hypertension in Indonesia is 427,218 of the 63,309,620 predicted number of cases. The percentage of hypertension based on the age group is 31.6% in the 31-44 years age group, 45.3% at the age 45-54 years, and 55.2% at the age 55-64 years. From 34.1% of hypertension sufferers, it is identified that 8.8% were diagnosed, 13.3% of hypertensive patients did not receive treatment, and 32.3% did not regularly take medicine. Many hypertensive patients do not get proper treatment because they do not know that they have hypertension. They do not take medication for several reasons; namely, the patient felt healthful (59.8%), did not regularly visit health care facilities (31.3%), used conventional medication (14.5%), handled another therapy (12.5%), skipped to receive medicine (11.5%), could not afford to buy medicine (8.1%), there were drug side effects (4.5%). Antihypertensive medicines were not obtainable in health care facilities (2%).[2,3]

The renin-angiotensin-aldosterone system remains a significant factor in maintaining arterial blood pressure. One of the target components is an Angiotensin-Converting Enzyme (ACE), α-dipeptidyl-carboxypeptidase glycolyzed zinc. ACE breaks down angiotensin 1 to angiotensin 2, and in turn, aldosterone is formed. Aldosterone's primary function is to regulate arterial blood pressure and electrolyte balance. Most guidelines for managing patients with cardiovascular disorders recommend ACE inhibitors as the first-choice treatment. In contrast, angiotensin receptor blockers (ARBs) are recognized as possible options for patients who are intolerant to ACE inhibitors.[4]

In addition to using conventional medicine, the management of hypertension is often treated with medicinal herbs. In Indonesia itself, herbal medicine (jamu) has become part of Indonesia's culture and natural wealth. The results of Basic Health Research in 2013 showed that 30.4% of the people had used traditional health services 49.0% used herbal ingredients.[5] Traditional medicine using several herbs is considered safer than conventional medicine due to the relatively few side effects. Herbal ingredients consisting of several plants have synergistic and complementary effects that can strengthen the therapeutic effect.[6]

ACE inhibitor drugs obtain the first line for the treatment of hypertension recent. Captopril, Lisinopril, Enalapril, and Ramipril represent any typical effective remedies that target ACE inhibitors. Extended treatment of these drugs can cause disadvantageous effects like dizziness, cough, and angioneurotic edema.[7] Extensive research has been done to look for an alternative to these drugs. Most of the extensive research has precisely targeted bioactive compounds from nature. Some examples include peptides, anthocyanins, flavonols, and triterpene number of extracts and compounds derived from plants proven in-vitro as ACE inhibitors. ACE inhibitors derived from nature have safety economic value.[8,9,10]

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Citation: Eff ARY, Hurit HE, Rahayu ST, Lena AP. Investigation of Angiotensin-Converting Enzyme Inhibitory Effects of Indonesian Traditional Medicine (Jamu). Trop J Nat Prod Res. 2021; 5(4):692-697. doi.org/10.26538/tjnpr/v5i4.17

Official Journal of Natural Product Research Group, Faculty of Pharmacy, University of Benin, Benin City, Nigeria.

ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

Our previous study regarding the standardization and screening of nine antihypertensives jamu that had activity as ACE inhibitors showed that the herbal extracts met specific and non-specific parameters and had ACE inhibitor activity with varying IC_{50} values, i.e., 18.37 - 740.8 ppm.[10] The study assessed antihypertensive herbal medicine activity, which has the smallest IC_{50} in vivo using the fructose-fed rat method.[10] Fructose in common is a potential mediator of hypertension and hyperuricemia. Various published studies have sufficiently shown that giving rats a high-fructose diet causes metabolic syndrome, including hypertension, hyperglycemia, insulin resistance, obesity, and hyperuricemia.[11,12,13] Hypertension naturally happens in the second week later fructose 10% administration in drinks or 60% in food.[14]

Materials and Methods

Material

Antihypertensive jamu was purchased from herbal medicine shops in North Jakarta, aqua dest, alcohol (Bratachem), fructose (Sigma), Wistar rat purchased from Bogor, Rat Angiotensin Converting Enzyme (Cusabio Elisa Kit NO CSB-E04490r, Wuhan China), Captopril (Indofarma), Sodium Pentothal injection (Abbot), disposable syringes, analytical balance (Sartorius), non-invasive blood pressure (Life Science), rat restrainer, Spectrophotometer (TECAN Nanoquant Infinite 200 Pro multimode microplate reader), animal scales.

Methods

After acclimatization for two weeks, 30 Wistar rats were divided into six groups, namely the captopril group with a dose of 0.5 mg/kg BW, negative control (NC), jamu with a dose of 120 mg/kg BW (D1), 240 mg/kg BW (D2), 360 mg/kg BW (D3) and the standard control group (SC). In the first week, all groups except the standard control group were given fructose 10% in standard drinks and food, while the standard control group was assigned aquadest and standard fares. According to the group's division, rats were given treatment for two weeks at weeks 9 and 10 unless the standard control group did not receive any treatment. Bodyweight and blood pressure were measured weekly, and at the end of week 10 (day 71), the rats were anesthetized using Sodium Pentothal at a dose of 2 mg/kg BW.[15] Blood was collected, handling a tube containing heparin. Then it was centrifuged for 15 minutes at 1000 x g at 8^0C for 30 minutes. Furthermore, rat angiotensin-converting enzyme (ACE) concentrations in plasma were estimated using Cusabio Elisa Kit NO CSB-E04490r (Wuhan, China). ACE activity measurements follow the manufacturer's recommendations using a microplate reader at a wavelength of 450 nm.[16]

Ethical Consideration

The research received approval from the Esa Unggul University health research ethics committee with approval number 0161-20.152/ DPKE-KEP/FINAL-ENUEUN/2020.

Statistical analysis

Data from the measurement of body weight, systolic and diastolic blood pressure, and plasma ACE activity were analyzed using the one-way ANOVA test and followed by multiple comparison analyses utilizing the Tukey method.

Results and Discussion

The body weight measurements are presented in Figure 1. Figure 1 shows that the mean body weight at the first week was 209.5 grams and increased to 268.8 at week 8, or an increase in body weight of 29.5% in all groups except in the standard control group (SC), rise from the first week to week eight only by 18%. Giving treatment for two weeks did not decrease body weight significantly ($p > 0.05$). Nowadays, the increasing consumption of fructose in the recent diet has become a health problem worldwide. Excessive fructose consumption has been shown to have disadvantageous effects such as obesity, cardiovascular and metabolic complications.[17] A study conducted by Sandeva *et al*. on rats showed that fructose consumption in drinks increased body weight, body length and measured body fat, significantly different from the control group. Excessive fructose consumption increases body weight, changes dietary patterns and lipid profiles. It has contributed to the increasing epidemic of obesity and metabolic syndrome.[18] A high-fructose diet interferes with the secretion and production of neuropeptides such as ghrelin and leptin, associated with appetite control. It may stimulate the compensation system in the hypothalamus.[18]

The systolic and diastolic blood pressure measurements are shown in Table 1. The mean systolic and diastolic blood pressure measurements of whole therapy groups at week 1 were similar. Giving 10% fructose in drinks beginning at week 1 to week eight enhanced systolic and diastolic blood pressure. The blood pressure rise started at week 3 of fructose administration. In the negative control group (NC), blood pressure increased until the end of fructose administration. In the group administered treatment at week 9 to week 10, i.e., the Captopril, D1, D2, and D3 groups, a reduction in systolic and diastolic blood pressure was significantly different when opposed to the negative control ($p < 0.05$).

Essential hypertension is caused by multifactor that is unknown with certainty. Various aspects of the disease, like etiology, pathophysiology, complications, and treatment, can be explained using animal models. Several animal models were developed to recognize the etiological factors that play a role in hypertension in humans. Several animal illustrations were developed to understand the etiological factors that represent a part of hypertension in humans.[14] A limitation of using animal models for hypertension is the absence of evidence to support that any animal model in the hypertension experiment describes humans' incidence. Some of the factors that can affect the results in using animal models are dose, differences in animal species, sex, age of the animal at initial exposure, and the method used to measure blood pressure.[14]

Diets high in fructose should be done for decades to create hypertension criteria and insulin resistance in animals.[12] Several studies reported the mechanism underlying fructose-induced insulin resistance, including Hwang's research showing that mice given 66% fructose for two weeks experienced increased blood pressure from 124 mm Hg to 145 mm Hg.[19] Likewise, the study conducted by Dupaz *et al*. demonstrated that administering 25% fructose in a drink for 21 weeks in Wistar rat with a mean age of 7 weeks raised systolic blood pressure at week 4 to 136.3 versus 122.7 in the standard control group. The study similarly demonstrated a progressive increase in fasting glucose levels in the third week after 25% fructose administration. Fructose causes insulin resistance and decreased insulin sensitivity, with the HOMA 2-IR value increasing 86% compared to controls and ISI-gly reducing by 33% compared to controls.[20] Glushakova *et al*. also proved that a 20% fructose intake significantly raised SBP in used mice following 33 weeks.[21] Another possible mechanism for fructose to induce uncontrolled hypertension in exposed rats by force fraudulently occurs through the used formation of the aldehyde conjugate level, which results from fructose metabolism. The aldehyde preferentially binds to the sulfhydryl group protein-membrane to cause calcium channel interference, improving free calcium levels, peripheral resistance, and raising blood pressure.[22]

The results about the angiotensin-converting enzyme activity inhibition are shown in Table 2. The results showed a significant difference between the negative control (NC) with a standard control, D1, D2, D3, and the captopril group ($p < 0.05$). There was no significant differentiation among the standard control group with D3 ($p > 0.05$).

Animals and humane investigations have adequately demonstrated a direct connection positively linking the Renin-Angiotensin-Aldosterone System (RAAS) and insulin resistance pathogenesis. Angiotensin II affects glucose metabolism in its direct effects against insulin signaling pathways, reduced tissue blood flow, oxidative stress, enhanced sympathetic activity, and adipogenesis. The increase in sympathetic nerve activity produces an increment toward catecholamines, blood pressure, and endothelial dysfunction.[23] Inhibition of RAAS with selective ACE inhibitors or angiotensin receptor blockers may naturally increase glucose metabolism by

avoiding angiotensin II generation or blocking AII receptor activation.[24]

Renin-Angiotensin-Aldosterone System (RAAS) represents a physiological function in the heart, kidney, and endocrine and is pathological in several diseases. Inhibition RAAS can be carried out at five main points, particularly the release of renin from juxtaglomerular cells, the breakdown of angiotensinogen activated by renin, ACE, which transforms angiotensin I to angiotensin II, angiotensin II preferentially attaches to AT1 receptors, and aldosterone action on mineralocorticoid receptors.[25] Angiotensin Conversion Enzyme (ACE) represents a function in regenerating angiotensin I to angiotensin II, a great vasoconstrictor.[4]

The interaction between the ET-1 system, vasoactive peptides produced by endothelial cells, and the renin-angiotensin system play a role in developing hypertension due to chronic fructose administration. ET-1 is an endogenous vasoconstrictor and growth factor for vascular smooth muscle cells. Insulin can induce the release of ET-1 in conditions of hyperinsulinemia and insulin resistance, thereby increasing blood pressure and vascular dysfunction.[26] A study conducted by Tran *et al*., 2009 in mice given fructose and chronically given the ET-1 receptor antagonist can normalize angiotensin II levels.[27] The renin-angiotensin system is a mediator in maintaining blood pressure. Hypertension and insulin resistance occurs when the system is activated excessively, causing an increase in angiotensin II. The vasoconstrictor effect of angiotensin 2 mediates insulin resistance development by reducing blood flow and glucose absorption to insulin-sensitive tissues.[27]

Epidemiological studies adequately prove that the renin-angiotensin system (RAS) is nearly correlated to glucose homeostasis. Drugs that work by interfering with the overall RAS have a beneficial effect on glucose homeostasis. In-vivo studies in animals and metaanalytic studies in humans show that ACE inhibitors or ARBs induce metabolic improvement in patients with insulin resistance. ACE inhibitors and ARB have a tremendous effect in lowering blood pressure without affecting glucose and fat metabolism.[28] ACE inhibitor drugs represent the first choice for the prescription of hypertension in recent decades. Captopril, Lisinopril, Enalapril, and Rampiril in common are some prime examples of effective drugs that precisely target ACE inhibitors. Lengthened usage of these medications can cause side effects such as dizziness, coughing, and angioneurotic edema. Therefore, there has been an extensive search for the sources of bioactive compounds from natural ingredients. Some examples include peptides, anthocyanins, flavonols, and triterpenes.[9]

Data from the Ministry of Health, the Republic of Indonesia, shows that 8.8% population in this country is diagnosed with hypertension. Hypertension sufferers experienced an increase of 8.3% from 2007-2018. One way to control blood pressure can be made with modern and traditional remedies, using herbal medicine / jamu. Herbal medication can be practiced for complementary therapy in health care facilities to prevent, promote, cure, rehabilitation, and palliative.[29] The evaluation conducted by Lalistra on hypertensive cases at the Sibella Surakarta Public Health Center revealed several factors behind the patient's use of herbal medicine as a complementary therapy. These factors represent hereditary confidence (16.13%), cheap and easy to get prices (6.45%), likes to drink herbal medicine (51.61%), the influence of doctors (3.23%), and trust in its safety because it has been officially registered at the Food and Drug Inspection Agency (3.23%), and believes in its usefulness (19.36%). Jamu is the most widely used herbal medicine.[30]

Our previous research showed that antihypertensive herbal medicine had ACE inhibitory activity in-vitro with an IC_{50} value of 18.37 ppm. These herbs consist of *Phaleria macrocarpa*, *Gynura procumbens*, *Imperata cylindrica*, *Centella asiatica*, and *Syzygium polyanthum*. The Jamu meets standard parameters according to the criteria set by the Indonesian Ministry of Health.[10,31] Table 2 shows that plasma ACE activity in the hypertensive rats treated at doses of 120 mg/kg, 240 mg/kg, and 360 mg/kg obtained significantly different from negative controls ($p < 0.05$). Whereas in the group treated with jamu at a used dose of 360 mg/kg BW, there denoted no meaningful differentiation between standard controls ($p > 0.05$).

Phalera macrocarpa (Mahkota Dewa) has several pharmacological activities: antihypertensive, antidiabetic, anticancer, anti-inflammatory, and antioxidant. This plant comprises bioactive compounds such as phenolic compounds, terpenes (isoprenoid), alkaloids, and benzophenones.[29] An investigation carried by Rinayanti *et al*., 2013 proved that the Mahkota Dewa leaves and fruit had activity as an ACE inhibitor with an IC_{50} value of 189.13 ppm in petroleum ether extract 157.74 ppm in ethyl acetate extract, and 101.52 ppm in methanol extract. While the fruit's IC_{50} values were 161.7 ppm in petroleum ether extract, 139.11 ppm in ethyl acetate extract, and 122.38 ppm in methanol extract, respectively.[32] A study conveyed by Ali *et al*. on hyperglycemic rats confirmed that the butanol extract of Mahkota Dewa had an antidiabetic effect. The extract was effective in reducing plasma glucose levels by 66.67% ($p < 0.05$), which was similar to metformin (51.1%), glibenclamide (66.67%), and insulin (71.43%) following 12 days of medication.[33]

Gynura procumbens contains bioactive compounds and has various therapeutic effects in multiple diseases such as rheumatism, diabetes mellitus, constipation, and hypertension. The leaves contain flavonoids, saponins, tannins, terpenoids, and sterol glycosides.[34] Hoe *et al*. demonstrated that *G. procumbens* reduces systolic and diastolic blood pressure in hypertensive rats. This plant inhibits the activity of angiotensin-converting enzymes and dilates blood vessels by releasing nitric oxide and prostaglandins. *G. procumbens* extract has negative inotropic and chronotropic effects on the atria. It reduces heart rate. The bioactive compounds in this plant can repress calcium ions into the blood vessel muscles, causing vasodilation and lowering blood pressure.[35] The leaves *Gynura procumbens* ethanol extract had an antidiabetic effect in streptozotocin-induced rats comparable to metformin. The antidiabetic mechanism within the stimulation of glycolysis and interference of gluconeogenesis in the liver. The flavonoids contained in *G procumbens* have an insulin-mimetic effect.[36]

Imperata cylindrica (L.) Beauv (Alang-alang) is a type of grass that grows popular throughout the world's tropics and subtropics. *Imperata* leaf extract contains tannins, saponins, flavonoids, terpenoids, alkaloids, phenols, and cardiac glycosides. In contrast, the roots contain flavonoids, potassium, cylindrene, and graminone B.[37] The methanol extract of Alang-alang root had an antihypertensive effect on NaCl-induced rats. This extract at proper doses of 60 and 90 mg / kg-BW progressively reduced the proportional amplitude of heart stroke volume and heart rate, which were comparable to amlodipine and Captopril.[38]

Centella asiatica contains chemical compounds like asiatic acid, asiaticoside, madecassoside, terpenoids, and flavonoids. These compounds serve a role in pharmacological activities, including antihypertensive, antioxidant, anti-fibrotic, and cardio-renal protectors. Manesai *et al*. properly investigated the beneficial effect of asiatic acid on the Ang II-AT1R-NADPH oxidase-NF-κB pathway against renovascular hypertensive rats. This comprehensive study objectively evaluated the potential effect of asiatic acid on hemodynamic alterations, renin-angiotensin system (RAS), oxidative stress, and inflammation in hypertensive rats. Male Sprague-Dawley rats made hypertension using the Goldblatt model (2K-1C). This model is commonly used for renovascular hypertension studies. The administration of asiticoside at a dose of 30 mg/kg/day or captopril 5 mg/kg/day during four intensive weeks improves cardiac hemodynamics, significantly lowering blood pressure, reducing oxidative stress and active inflammation. Asiatic acid naturally has an ACE inhibitor effect by inhibiting the Ang II-AT1R-NADPH oxidase-NF-κB specific pathway.[39] Giving asiastic acid 30 mg/kg BW for three weeks to rats fed a high-fat, and high-fructose diet had an antihypertensive effect. Asiatic acid reduces excessive RAS activity, improves vascular function, and decreases sympathetic activity.[40]

The leaves of *Syzygium polyanthum* are traditionally used to manage diseases like hypertension, diabetes mellitus, ulcers, diarrhea, and infectious skin diseases. This plant leaves extract contains phenolic compounds, i.e., caffeic acid, gallic acid, and 4-allyl-1,2-dihydroxybenzene (hydroxychavicol).[41] Several comprehensive studies have sufficiently shown the potential impact of *S. polyanthum* on lowering blood pressure. Intravenous administration of ethanol and

ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

water extract of *S. polyanthum* leaves at a typical dose of 20-100 mg/kg BW can significantly reduce the elevated blood pressure of normal Wistar Kyoto (WKY) and spontaneous hypertensive rats (SHR). The effect of reducing blood pressure was only seen in SHR rats when the extract was administered orally.[42] Giving methanol extract and water extract of *S polyanthum* leaves at a dose of 2.5 g / kg once daily decreased blood pressure in SHR rats. Blood pressure-lowering effects were seen following two weeks of treatment administration. In contrast, the water extract was seen after three weeks of administration. *S. polyanthum* leaves extract had an antihypertensive effect through vasorelaxation and inhibition of the angiotensin-converting enzyme (ACE).[43] In-vitro studies conducted by Muthia *et al*. explained that *S. polyanthum* leaves extract at a concentration of 100 ppm had ACE inhibitory activity of 53.37 ± 0.95%. At the same time, Captopril was 88.17 ± 2.89%.[44]

The study was an initial verification of antihypertensive herbal medicine's claim with an ACE inhibitor's mechanism. The study results indicate that giving antihypertensives herbal medicine (jamu) at doses of 120 mg/kg, 240 mg/kg, and 360 mg/kg BW lowered blood pressure in rats induced by 10% fructose. The jamu at a 360 mg/kg BW dose reduced the plasma's ACE activity, which was not significantly different from the standard control ($p > 0.05$). However, further studies are still needed using other models, such as the Goldblatt model (2K-1C). The use of this model is analogous to the clinical state of renal hypertension in humans. The response to decreased blood pressure due to drug administration will be more clearly examined using this model.

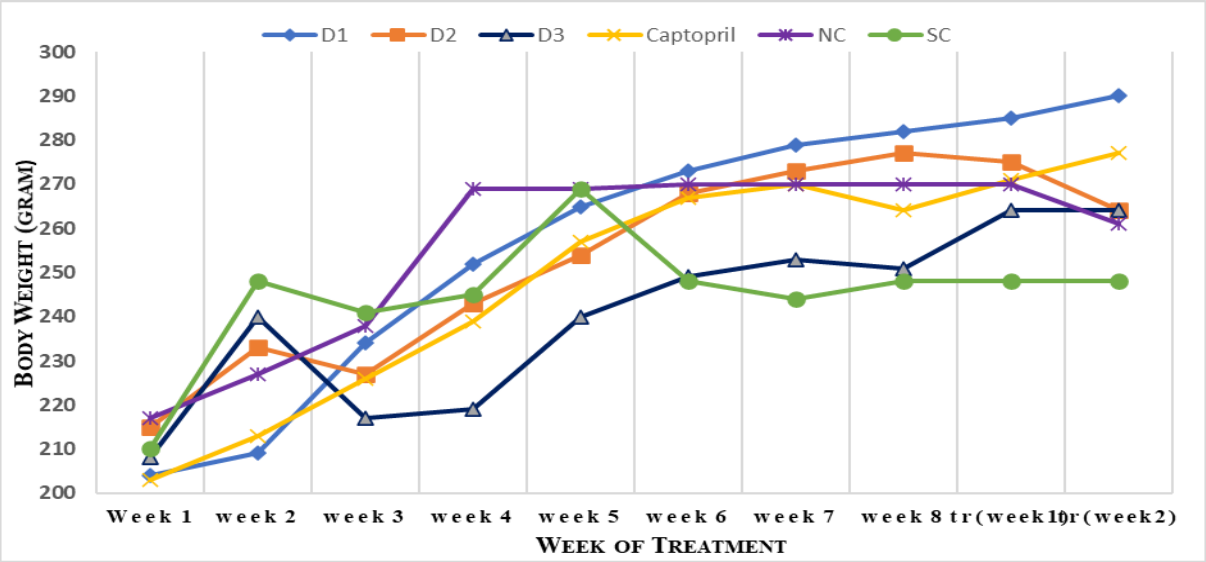

Figure 1: The average body weight according to the treatment group each week (grams).
D1: standard diet, 10% fructose solution and jamu dose of 120 mg/kg BW; D2: standard diet, 10% fructose solution and jamu dose of 240 mg/kg BW; D3: standard diet, 10% fructose solution and jamu dose of 360 mg/kg BW; Captopril: standard diet, 10% fructose solution and Captopril dose of 0.5 mg/kg BW; NC: standard diet and 10% fructose solution; SC: standard diet, and aqua dest drinks. There were significant differences between D1, D2, D3, Captopril, and NC with the standard control (SC) ($p<0.05$)

Table 1: Effect of jamu on blood pressure in fructose 10% induced hypertensive rats

Group	BP (mm Hg)	Week 1	week 2	week 3	week 4	week 5	week 6	week 7	week 8	Week 9	Week 10
D1	SBP	113.3 ± 1.9	120.2 ± 1.1	122.6 ± 1.5	126.7 ± 2.2	126.6 ± 1.3	146.3 ±1.8	142 ± 3.4	132.4 ± 4.0	126.3 ± 5.1	125.3 ± 3.6*
	DBP	85.7 ± 2.5	87.2 ± 1.8	89.5 ± 3.1	90.7 ± 1.4	99.8 ± 1.2	115.5 ± 1.2	108.6 ± 1.8	108 ± 1.7	104 ± 2.1	99.4 ± 1.6*
D2	SBP	119.8 ± 1.1	119.8 ± 1.1	124.2 ± 1.3	116.3 ± 1.3	127.6 ± 1.6	131.3 ± 4.7	131.8 ± 1.6	138.2 ± 1.3	133.3 ± 2.9	115.4 ± 2.8*
	DBP	91.3 ± 2.8	94.3 ± 1.9	95.8 ± 3.4	97.7 ± 1.1	101.5 ± 1.7	103.1 ± 1.9	104.1 ± 2.4	108.8± 1.2	107 ± 2.5	95.6 ± 2.5*
D3	SBP	119 ± 0.5	108.7 ± 3.6	118.9 ± 1.4	125.6 ± 2.1	123.2 ± 1.8	136.9 ± 2.8	133.2 ±4.1	135.6 ± 3.7	134.8 ± 4.1	133. ± 3.1*
	DBP	82.5 ± 2.3	83 ± 3.6	89.9 ± 1.5	94.9 ± 2.9	97.7 ± 2.9	108.6 ± 2.4	104.2± 1.2	109.7 ± 1.3	106. ± 1.3	105.4 ± 1.6*
Captopril	SBP	114.3 ± 0.6	117.8 ± 1.9	130 ± 4.4	128.4 ± 3.3	126.2 ± 2.2	135 ± 1.8	146.5 ±2.3	146.8 ± 2.8	144.6 ± 2.7	126.3 ± 3.8*
	DBP	84.6 ± 4.3	87.6 ± 2.3	100.2 ± 1.1	99.3 ± 1.8	101.8 ± 1.8	107.6 ± 1.8	116.8 ± 1.1	114.3± 1.2	106.7± 2.0	92.7 ± 1.3*
NC	SBP	112.2 ± 1.6	122.8 ± 1.6	125.3 ± 1.2	125.5 ±1.6	129.8 ± 1.9	130.4 ± 2.4	137.9 ± 3.9	151.7 ± 2.3	151.7 ± 2.3	151.7 ± 2.3
	DBP	82.6 ± 2.3	94.3 ± 4.1	99.1 ± 2.9	100.5 ± 1.4	105.8 ± 2.1	98.5 ± 2.3	115.8 ± 2.3	115 ± 1.9	115.1 ± 2.4	115 ± 2.0
SC	SBP	113.5 ± 0.6	116 ± 1.8	116.2 ± 1.7	112.7 ± 4.5	110.7 ±1.2	114.1 ± 2.6	114 ±2.6	114 ±2.6	114.1 ± 2.6	114 ± 2.6*
	DBP	91.4 ± 4.1	96.4 ± 2.9	97.2 ± 3.4	89 ± 3.4	85 ± 1.1	88.7 ± 2.7	88.7 ± 1.8	88.7 ± 2.1	88.7 ± 1.8	88.7 ± 2.2*

Data presented as mean ± SD, * significant difference in decreasing SBP and DBP with the negative control (NC) ($p < 0.05$).

Table 2: Plasma ACE activity

No	Group	ACE activity(pg/ml) ± SD
1	D1	50.29 ± 4.99*
2	D2	31.67 ± 2.35*
3	D3	21.73 ± 1.11*, **
4	Captopril	13.65 ± 4.07*
5	NC	132.50 ± 6.9
6	SC	21.90 ± 4.43

* a significant difference with negative control (NC) ($p < 0.05$); ** no significant difference with the standard control ($p > 0.05$).

Conclusion

Antihypertensive jamu at the dose 120 mg/kg BW, 240 mg/kg BW, and 360 mg/kg BW decrease both systolic and diastolic blood pressure and have ACE inhibitor activity *in-vivo*

Conflict of interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

Acknowledgements

The authors express their gratitude to the Indonesia Ministry of Education and Culture for this research's funding.

References

1. Drozdz D and Kawecka-Jaszcz K. Cardiovascular changes during chronic hypertensive states. Pediatr Nephrol. 2014; 29(9):1507-1516.
2. Tirtasari S and Kodim N. Prevalensi dan Karakteristik Hipertensi Pada Usia Dewasa Muda di Indonesia. Tarumanagara Med J. 2019; 1(2):395-402.
3. Ministry of Health of the Republic of Indonesia at: https: // www. Ministry of Health. go. id / article / view / 19093000001 / heart disease-causes-death-most-k.-2-in-Indonesia. html. accessed on February 1, 2021.
4. Messerli FH, Bangalore S, Bavishi C, Rimoldi SF. Angiotensin-Converting Enzyme Inhibitors in Hypertension: To Use or Not to Use? J Am Coll Cardiol. 2018; 71(13):1474-1482.
5. Indonesia Ministry of Health. Basic Health Research 2013. Heal Res Dev Agency, Indones Minist Heal. 2013; 72-77 p.
6. Dewi TF. Analysis of antihypertensive herbs at the Tawangmangu Hortus Medicus Research House for the Period of January-June 2017. J Jamu Indones. 2020; 4(2):42-47.
7. Herman L, Padala S, Bashir K. Angiotensin Converting Enzyme Inhibitors (ACEI) – StatPearls - NCBI Bookshelf [Internet]. 2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK431051/
8. Rinayanti A, Radji M, Mun'im A, Suyatna FD. Screening Angiotensin Converting Enzyme (ACE) Inhibitor Activity of Antihypertensive Medicinal Plants from Indonesia. Int J Pharm Teach Pract. 2013; 4(1):527-532.
9. Lettre DP, Kumar R, Kumar A, Sharma R, Baruwa A. Pharmacological review on Natural ACE inhibitors. Der Pharm Lett. 2010; 2(2):273-293.
10. Eff ARY, Rahayu ST, Mahayasih PG, Januarko MU. Standardization of Indonesian traditional antihypertensive medicines (JAMU) through the ACE inhibitor mechanism. Pharmacogn J. 2020; 12(3):422-429.
11. Yanti AR, Radji M, Mun'im A, Suyatna FD. Effects of the Methanol extracts *Phaleria macrocarpa* (Scheff Boerl fruits on Angiotensin Converting Enzyme (ACE) activity. Int J Adv Pharm Biol Chem. 2014; 3(4):912-918.
12. Jalal DI, Smits G, Johnson RJ, Chonchol M. Increased Fructose Associates with Elevated Blood Pressure. J Am Soc Nephrol. 2010; 21:1-7.
13. Jadhav GB and Upasani CD. Antihypertensive Effect of Silymarin on Fructose Induced Hypertensive Rats. Blood. 2012; 46(1):101-106.
14. Dornas CW and Silva EM. Review Animal models for the study of arterial hypertension. Biosci. 2011; 36(4):731-737.
15. Isbagio WD. Euthanasia pada hewan percobaan. Media Litbangkes. 1992; 11(01):18-24.
16. Nurfadila SA, Saputri SC, Harahap Y. Effects of *Hibiscus sabdariffa* callices aqueous extract on the hypertensive potensy of Captopril in the two-kidney- one clip rat hypertensive model. Evid-Based Compl Altern Med. 2019; 2019:1-7.
17. Senador D, Shewale S, Irigoyen MC, Elased KM, Morris M. Effects of restricted fructose access on body weight and blood pressure circadian rhythms. Exp Diabet Res. 2012; 2012:1-7.
18. Sandeva RV, Mihaylova SM, Sandeva GN, Trifonova KY, Popova-Katsarova RD. Effect Of High-Fructose Solution On Body Weight, Body Fat, Blood Glucose And Triglyceride Levels In Rats. J Biomed Clin Res. 2015; 8(1):5-8.
19. Hwang IS, Ho H, Hoffman BB, Reaven GM. Fructose-induced insulin resistance and hypertension in rats. Hypertension. 1987; 10(5):512-516.
20. Dupas J, Feray A, Goanvec C, Guernec A, Samson N, Bougaran P, Guerrero F, Mansourrati J. Metabolic Syndrome and Hypertension Resulting from Fructose Enriched Diet in Wistar Rats. Biomed Res Int. 2017; 2017:1-10.
21. Glushakova O, Kosugi T, Roncal C, Mu W, Heinig M, Cirillo P, Sanchez-Lozada GL, Johnson JR, and Nakagawa T. Fructose induces the inflammatory molecule ICAM-1 in endothelial cells. J Am Soc Nephrol. 2008; 19(9):1712-1720.
22. Vasdef S, Ford CA, Longerich L, Gadag V, Wadhawan S. Role of aldehydes in fructose induced hypertension. Mol Cell Biochem. 1998; 181:1-9.
23. Tran LT, Macleod KH, McNeill JH. Endothelin-1 modulates angiotensin II in the development of hypertension in fructose-fed rats. Mol Cell Biochem. 2009; 325:89-97.
24. Kurtz TW and Pravenec M. Antidiabetic mechanisms of angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists: beyond the renin – angiotensin system. J Hypertens. 2004; 22(12):2253-2261.
25. Atlas SA. The renin-angiotensin aldosterone system: pathophysiological role and pharmacologic inhibition. J Manag Care Pharm. 2007; 13(8 Suppl B):9-20.
26. Kang DG, Moon MK, Sohn EJ, Lee DH, Lee HS. Effects of morin on blood pressure and metabolic changes in fructose-induced hypertensive rats. Biol Pharm Bull. 2004; 27(11):1779-1783.
27. Tran LT, MacLeod KM, McNeill JH. Endothelin-1 modulates angiotensin II in the development of hypertension in fructose-fed rats. Mol Cell Biochem. 2009; 325(1-2):89-97.

28. Yao J, Gong X, Shi X, Fan S, Chen J, Chen Q. The efficacy of angiotensin converting enzyme inhibitors versus angiotensin II receptor blockers on insulin resistance in hypertensive patients: A protocol for a systematic review and meta-analysis. Med (Baltimore). 2020; 99(24):e20674.
29. Ministry of Health the Republic of Indonesia. Hipertensi Penyakit Paling Banyak Diidap Masyarakat - Direktorat P2PTM [Internet]. Kemenkes RI. 2019. Available from: https://www.kemkes.go.id/article/view/19051700002/hipertensi-penyakit-paling-banyak - diidap-masyarakat.html
30. Laristra T and Farida Y. Herbal Medicine Use of Hypertension Patient in Sibela Primary Care Surakarta. Pros APC Annu Pharm Conf. 2019; 79-91p.
31. Eff ARY, Hurit HE, Rahayu ST, Januarko MU, Maya WMPG. Antihypertensive, Antidiabetic, Antioxidant and Cytotoxic Activities of Indonesian Traditional Medicine. Pharmacogn J. 2020; 12(6):1623-1629.
32. Rinayanti A, Radji M, Mun A, Suyatna FD. Screening Angiotensin Converting Enzyme (ACE) Inhibitor activity of antihypertensive medicinal plants from Indonesia. Int J Pharm Teach Pract. 2013; 4(1):527-532.
33. Ali RB, Atangwho IJ, Kaur N, Abraika OS. Bioassay-Guided Antidiabetic Study of *Phaleria macrocarpa* Fruit Extract. Molecules. 2012; 17:4986-5002.
34. Kamran A. an Updated Phytochemical and Pharmacological Review on *Gynura procumbens*. Asian J Pharm Clin Res. 2019; 12(4):9-14.
35. Hoe SZ, Lee CN, Mok SL, Kamaruddin MY, Lam SK. *Gynura procumbens* Merr. decreases blood pressure in rats by vasodilatation via inhibition of calcium channels. Clin. 2011; 66(1):143-150.
36. Hui-Wen Lee. Antidiabetic effect of *Gynura procumbens* leaves extracts involve modulation of hepatic carbohydrate metabolism in streptozotocin-induced diabetic rats. J Med Plants Res. 2012; 6(5):796-812.
37. Liu R, Chen S, Ren G, Shao F, Huang H. Phenolic Compounds from roots of *Imperata cylindrica* var. major. Chinese Herb Med. 2013; 5(3):240-243.
38. Ruslin, Asmawi MZ, Rianse U, Sahidin I, Dhianawaty D, Soemardji AA, Amalia L. Antihypertensive activity of Alang-alang (*Imperata cylindrica* (L.) Beauv. root methanolic extract on male Wistar rat. Int J Res Pharm Sci. 2013; 4(4):537-542.
39. Maneesai P, Bunbupha S, Kukongviriyapan U, Senggunprai L, Kukongviriyapan V, Prachaney P, Pakdeechote P. Effect of asiatic acid on the Ang II-AT1R-NADPH oxidase-NF-κB. Naunyn-Schmiedeberg's Arch Pharmacol. 2017;390(10):1073-1083.
40. Maneesai P, Bunbupha S, Kukongviriyapan U, Prachaney P, Tangsucharit P. Asiatic acid attenuates renin-angiotensin system activation and improves vascular function in high-carbohydrate , high-fat diet fed rats. BMC Compl Altern Med. 2016; 2016:1-11.
41. Ismail A and Wan Ahmad WAN. *Syzygium polyanthum* (Wight) Walp: A potential phytomedicine. Pharmacogn J. 2019; 11(2):429-438.
42. Ismail A, Mohamed M, Sulaiman SA, Wan Ahmad WAN. Autonomic nervous system mediates the hypotensive effects of aqueous and residual methanolic extracts of *Syzygium polyanthum* (Wight) Walp. var. polyanthum leaves in anaesthetized rats. Evid-Based Compl Altern Med. 2013; 2013:1-16.
43. Ismail A, Ramli NS, Mohamed M, Wan Ahmad WAN. Acute and sub-acute antihypertensive effects of *Syzygium polyanthum* leaf extracts with determination of gallic acid using HPLC analysis. Pharmacogn J. 2018; 10(4):663-671.
44. Muthia R, Suganda AG, Sukandar EY. Angiotensin-I Converting Enzyme (ACE) Inhibitory Activity Of Several Indonesian Medicinal Plants. Res J Pharm Biol Chem Sci. 2017; 8(1):192-199.