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Antihypertensive Activity of Herbal Medicine (Jamu) X on Male Wistar Rats Induced with Monosodium Glutamate

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ABSTRACT: Jamu X, which is available in the market, has a simple composition consisting of noni fruit (*Morinda citrifolia* L.), celery herb (*Apium graveolens* L.), cat's whiskers leaves (*Orthosiphon aristatus*), pule bark (*Alstoniae scholaris*), meniran herb (*Phyllanthus niruri*), gotu kola herb (*Centella asiatica*), sembung leaves (*Blumea balsamifera*), plantain leaves (*Plantago major*), and andrographis herb (*Andrographis paniculata*). Jamu X is claimed to help lower blood pressure. All plants in jamu X contain flavonoids. This study aims to confirm the presence of flavonoids and prove the antihypertensive effect of jamu X on rats induced with monosodium glutamate (MSG). The presence of flavonoids was determined through test tube and thin-layer chromatography (TLC) tests. The research method employed is a randomised controlled group pretest and posttest design. Hypertensive mice were induced by administering MSG 100 mg/kg body weight/day orally for 14 days. The hypertensive rats were divided into five treatment groups: Group I rats (negative control) received CMC Na 0.5% 12.5 mL/kg body weight. Group II rats (positive control) received captopril at a dose of 2.5 mg/kg body weight/day. Group III, IV, and V rats were given jamu X at doses of 0.09, 0.18 capsules/kg body weight, once a day, and 0.18 capsules/kg body weight, twice a day, respectively. The test substance was administered orally for 14 days. The significance of the difference between systolic and diastolic blood pressure was tested using a paired t-test at a 95% confidence level. Jamu X was declared to have antihypertensive activity if there was a decrease and a significant difference in systolic and diastolic blood pressure before and after the administration of jamu X. Flavonoids were declared to be contained in jamu X. Based on the tests performed, jamu X showed antihypertensive activity at all doses.

Keywords: antihypertensive; flavonoid; traditional medicine; MSG

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INTRODUCTION

Hypertension is characterized by persistently elevated blood pressure (Schwinghammer, 2021). Hypertension leads to increased morbidity and mortality, placing a burden on healthcare costs in Indonesia (Indonesian Hypertension Doctors Association, 2021). Data from the 2013 and 2018 Basic Health Research indicate that the prevalence of hypertension increased from 25.8% to 34.11% (Ministry of Health of the Republic of Indonesia, 2013, 2019). Hypertension is described as a silent killer because it has no early clinical symptoms, yet it causes damage to internal organs (Fatima and Mahmood, 2021). The management of hypertension involves both pharmacological and non-pharmacological therapies that must be continuously undertaken by patients, potentially throughout their lifetime, unless serious adverse effects occur (van der Wardt et al., 2017).

Data presented thru the 2018 Basic Health Research shows that some patients do not regularly take antihypertensive medication because they take traditional medicine. The proportion of people over 18 years old with hypertension who regularly take antihypertensive medication by province is 54.40%. Based on data from the 2018 Basic Health Research, 31.4% of patients utilize traditional health services, one type of which is ready-made herbal remedies (Ministry of Health of the Republic of Indonesia, 2019). Several ready-made jamu aimed at helping to lower blood pressure are available in the market, one of which is branded X. The composition of the simple ingredients in this ready-made remedy consists of noni fruit (*Morinda citrifolia* L.), celery herb (*Apium graveolens* L.), cat's whiskers leaves (*Orthosiphon aristatus*), pule bark (*Alstoniae scholaris*), niruri herb (*Phyllanthus niruri*), gotu kola herb (*Centella asiatica*), sembung leaves (*Blumea balsamifera*), plantain leaves (*Plantago major*), and andrographis herb (*Andrographis paniculata*). The proportion of herbal components in the finished product is 10%, except for noni fruit and cat's whiskers leaves, which are 15%. The product is available in capsule form. The labeling on the product is "jamu." The efficacy of jamu is based on empirical evidence. Unlike phytopharmaceuticals, jamu is a type of traditional medicine whose efficacy has not been scientifically proven through preclinical and clinical trials (Head of the Indonesian Food and Drug Administration, 2023). The development of jamu into phytopharmaceuticals can be done through preclinical trials.

Preclinical testing is conducted on laboratory animals to assess the safety and efficacy of a product being tested (Directorate of Traditional Medicine, Health Supplements, and Cosmetics Registration, Food and Drug Supervisory Agency, 2022). Rats are commonly used as test animals for testing antihypertensive activity. One compound that can be given to rats to induce hypertension is MSG (Lerman et al., 2019).

The pharmacological activity of plants is mainly due to their secondary metabolite content. All the plant components in jamu X contain flavonoids (Lee et al., 2020; Al-Asmari et al., 2017; Akowuah et al., 2004; Candrasari et al., 2018; Nisar et al., 2018; Kunjumon et al., 2022; Dai et al., 2023; Adom et al., 2017; and Aminah et al., 2021). Based on the explanation above, it is necessary to conduct preclinical testing of jamu X antihypertensive activity, as well as testing the flavonoids it contains.

METHODS

Materials

The materials used in this research were jamu X obtained from the official online market of the product. Silica 60 GF 254, NH_4OH, ethanol 96%, sodium hydroxide (NaOH), methanol choloroform, and quercetin were of Mercks® and were purchased from CV. Global Sarana Instrument. MSG as the inductor of hypertension was Ajinomoto®. Captopril as the agent for positif control was obtained from PT. Phapros. The instrument used was non-invasive anti-hypertensive test CODA® High Throughput.

Flavonoid Identification

Flavonoids were identified through test tube and TLC tests. The test tube test consisted of two identifications: the phenol test and the flavonoid test. The contents of one capsule of jamu X were emptied, then placed in a large test tube, and 5 mL of 96% ethanol was added. The mixture in the test tube was gently shaken, then allowed to stand until the contents of the jamu X capsule settled. The obtained filtrate was transferred to an erlenmeyer flask, and ethanol was added in stages until a total volume of 85 mL of 96% ethanol was reached. Testing for the presence of phenolic compounds was conducted by preparing the diluted filtrate of jamu X in two test tubes. The first tube was used as a control without any reagent, and a few drops of $FeCl_3$ were added to the second tube. The formation of green, red, purple, blue, or black colors strongly indicates the presence of phenols (Harborne, 1987).

Positive results from the phenol presence test were followed by the identification of flavonoid presence through test tube and TLC analysis. The test tube test was performed using the Shinoda test, adding Pb acetate, NaOH, and NH_4OH. The jamu X filtrate was mixed with 5 mL of amyl alcohol, a sufficient amount of Mg powder, and five drops of concentrated HCl added down the side of the tube. The presence of flavonoids was confirmed by the Shinoda test, which showed a positive result with the formation of a pink to dark red color. The white precipitate formed after adding lead acetate indicates the presence of flavonoids. The addition of NaOH, which forms a bright yellow solution, confirms the presence of flavonoids in jamu X (Kumoro, 2015). The presence of flavonoids in jamu X through the addition of NH_4OH is indicated by the formation of a bright yellow solution (Saikh & Patil, 2020).

Flavonoids in jamu X were qualitatively tested using TLC with a mobile phase consisting of a mixture of methanol and chloroform in a 1:2 ratio. The mobile phase was prepared in a volume of 30 mL. The mobile phase was placed in the chamber with a filter paper hanging inside, and then saturation was performed. The chamber is considered saturated when the filter paper is thoroughly wetted with the mobile phase.

The diluted filtrate of jamu X was spotted onto a silica gel 60 F254 plate, which served as the stationary phase. Quercetin was dissolved in pro-analysis ethanol and also spotted onto a silica gel 60 F254 plate. The plate was eluted in a chamber saturated with the mobile phase. The silica gel 60 F254 plate was dried when the mobile phase reached the elution limit. The silica gel 60 F254 plate was exposed to ammonia vapour and then observed under UV light at 254 and 366 nm. Jamu X is stated to contain flavonoids, as indicated by an increase in colour intensity of the spots after exposure to ammonia vapour (Harborne, 1987). The distance from the inoculation site to the appearance of the spot was

measured. The retardation factor (Rf) is calculated by dividing the distance travelled by the spot by the distance travelled by the mobile phase.

Rat Blood Pressure Measurement

Rats were trained to enter the holder without coercion during the adaptation period. Blood pressure measurement was performed by placing the rat in a holder, which was then placed on a heating pad. The occlusion cuff and VPR cuff are each connected to blood pressure cuff connectors. The occlusion cuff and VPR cuff are placed on the rat's tail, and then blood pressure is measured. The measurement results are displayed on the laptop monitor. Blood pressure measurements were taken three times, and then the average blood pressure was calculated as research data.

Modeling Hypertensive Rats

The rats were acclimated to the laboratory environment for seven days, being fed twice a day, morning and evening. The method for creating hypertensive rat is based on research conducted by Anas and Hatimah (2018). The 40 rats used were first measured for their systolic blood pressure. The normal systolic blood pressure of a rat is ≤ 140 mmHg. For 14 days, all rats received MSG (100 mg/kg body weight/day) orally. The rat's systolic blood pressure was measured one day after MSG administration on day 14 again. A systolic blood pressure ≥ 140 mmHg and a significant increase in systolic blood pressure indicate that the rats have hypertension (Ismiyati, 2013).

Antihypertensive Activity Test of Jamu X

The antihypertensive activity of jamu X refers to the study by Anas and Hatimah (2018). A total of 25 hypertensive rats were divided into 5 treatment groups, with each group consisting of 5 rats. Rats in group I, serving as the negative control group, were treated with 0.5% CMC Na solution at a dose of 12.5 mL/kg body weight per day, while rats in group II received captopril 2.5 mg/kg body weight as a positive control. Rats in groups III and IV were administered jamu X at doses of 0.09 and 0.18 capsules/kg body weight, respectively, once daily. Jamu X administered at a dose of 0.18 capsules/kg body weight twice a day, was given to group V. The 0.5% CMC Na solution, captopril suspension, and jamu X suspension were administered for 14 consecutive days. The systolic blood pressure of the rat was measured again on day 15. A significant decrease in systolic blood pressure indicates the antihypertensive activity of jamu X.

The antihypertensive activity of jamu X was compared to captopril, as well as the comparisons between different doses of jamu X, using data on the percentage reduction in blood pressure. The percentage reduction in blood pressure was calculated by dividing the difference between blood pressure before and after the administration of jamu X by the blood pressure before administration of jamu X, and then multiplying by 100%. The significance of the differences in systolic and diastolic blood pressure reduction data was determined using a one-way ANOVA test. The significance of the differences in blood pressure reduction percentages between the two treatment groups was determined using the Tukey test. A significant difference in the percentage decrease in blood pressure is indicated by a test result with a p-value less than 0.05 ($p < 0.05$). Jamu X was found to have greater activity than captopril, as evidenced by a significantly greater percentage reduction in systolic and diastolic blood pressure after administration of jamu X compared to captopril. Increasing the dose of jamu X was found to enhance its antihypertensive activity,

resulting in a significant increase in the percentage reduction in blood pressure. The difference test was conducted at a 95% confidence level.

RESULT AND DISCUSSION

Flavonoid Identification

The diluted filtrate of jamu X with added $FeCl_3$ turned blackish-brown, indicating that jamu X contains phenolic compounds. The color formed in the filtrate after adding $FeCl_3$ is shown in Figure 1. The detection of phenol compounds in jamu X was followed by an examination for the presence of flavonoids using several types of reagents. Detection of flavonoids using the Shinoda test, lead acetate, alkali, and ammonia did not yield positive results. The results of the testing are shown in Figure 2. This result is possible because the flavonoid content in the jamu X filtrate is very low, making it undetectable through various test tube assays. The simple extraction process of flavonoids in jamu X using ethanol yielded a dark brown filtrate. If the filtrate is not diluted, it will be challenging to observe colour changes or the formation of precipitates. This dilution likely resulted in a low flavonoid content in the jamu X filtrate.

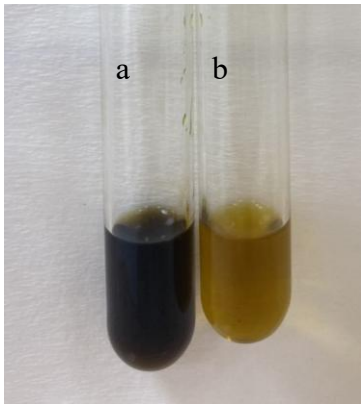


Figure 1. Results of fenolic identification of jamu X using $FeCl_3$ (a: filtrate of jamu X + $FeCl_3$; b: jamu X filtrate)

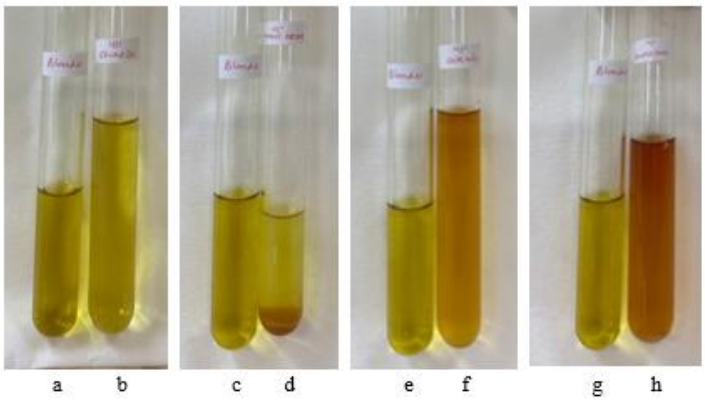


Figure 2. Results of flavonoid presence testing. Jamu X filtrate (a, c, e, g), Shinoda test (b), jamu X filtrate + Pb acetate (d), jamu X filtrate + NaOH (f), jamu X filtrate + NH_4OH (h)

The analysis of flavonoid content in jamu X was conducted employing the thin layer chromatography (TLC) technique. The analysis of the diluted filtrate of jamu X, following elution with a mobile phase composed of a methanol and chloroform mixture, revealed no visible spots. However, after exposure to ammonia vapour, one spot became apparent. The intensity of the spot color also increased for quercetin, indicating that the spots separated from the dilution of the jamu X are likely flavonoids. Spot observation employing ultraviolet light is illustrated in Figure 3.

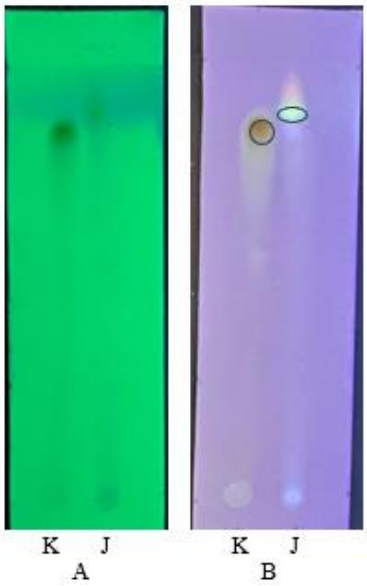


Figure 3. Spot observation using UV light

Description:
K : Quercetin
J : Jamu X
A : Observation under 254 nm UV light
B : Observation under 366 nm UV light
Stationary phase: Silica gel 60 F254
Mobile phase : Chloroform: Methanol (1:2)
Spot detection : Ammonia vapour

The Result of Animal Modelling

Male Wistar rats were used in this study, considering the stability of their hormonal system, thus minimizing blood pressure changes other than those caused by the hypertension inducer or the tested substance. Compared to female rats, male rats tend to have higher blood pressure, which is likely due to the influence of higher levels of androgen hormones (Nugroho et al., 2018). The higher blood pressure in male rats makes it easier to observe changes in blood pressure, whether due to the administration of the hypertension inducer MSG or the administration of jamu X.

The rats were acclimated to the laboratory environment and trained to enter the holder voluntarily during the adaptation period. Rtas are kept in cages with the size and number of rat adjusted to the cage area. Environmental control in the laboratory is implemented to minimize noise and light disturbances. Rat gender selection, adaptation to

the laboratory environment, and training to enter the holder are carried out to prevent rats from experiencing stress that can increase pressure (Lin et al., 2016). Additionally, rat maintenance and laboratory environmental control are also implemented to minimize stress.

The inductor used to increase the blood pressure of rat is MSG. The speed of MSG in increasing blood pressure within 2 weeks was the primary consideration for its selection as a sole hypertensive agent (Hidayati et al., 2015). Other methods that can be compared to MSG regarding the duration of causing hypertension include the use of deoxycorticosterone acetate salt (DOCA-salt), which takes 4–8 weeks; Dahl-salt, which takes 9–12 months; creating transgenic mice, which takes 5 months; the spontaneous hypertension rat model, which takes 5–6 weeks; and the stress rat model, which takes 4 months (Sjakoer and Permatasari, 2011). Additionally, the use of MSG as a hypertension inducer also considers the ease of implementation and the availability of the inducing material.

The results of this study demonstrate an elevation in the average systolic and diastolic blood pressure of rats following MSG exposure. Systolic and diastolic blood pressure values exceeded the normotensive thresholds, surpassing 140 mmHg and 90 mmHg, respectively. Statistical analysis employing the paired t-test indicated a significant difference in both systolic and diastolic blood pressure of rats prior to and following MSG administration ($p < 0.05$). The statistical analysis results indicate that following MSG administration, all rats exhibited hypertension. This study involved 40 rats; however, 13 were excluded due to mortality during induction and lack of significant blood pressure increase. Figure 4 presents the average blood pressure results prior to and following MSG administration.

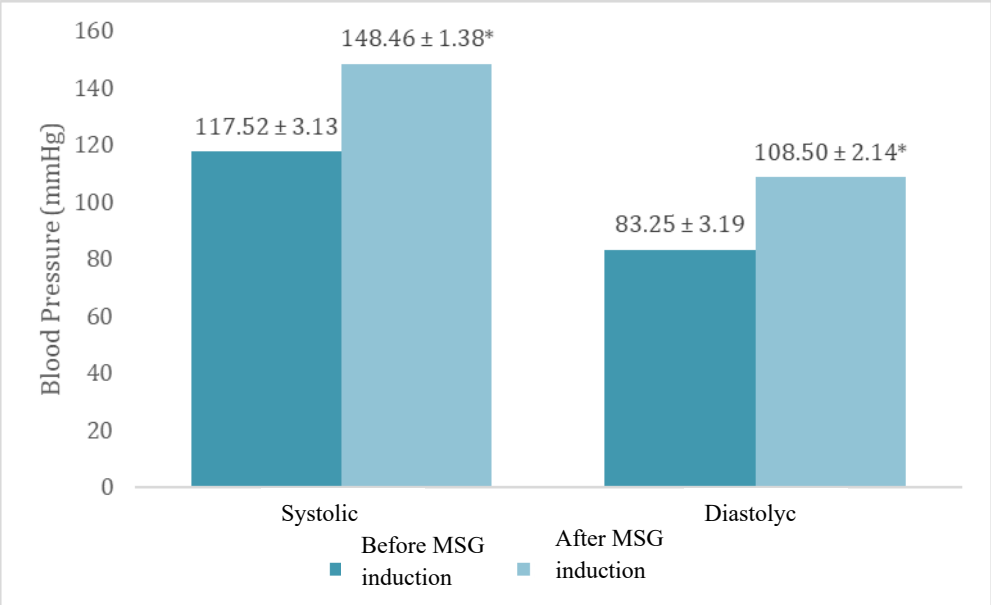


Figure 4. Mean blood pressure ± SE before and after MSG administration (n = 27).

The Result of Anti-hypertensive Test of Jamu X

The total number of hypertensive rats used in the study was 27; however, the research data for testing antihypertensive activity were only from 25 rats, with five rats in each treatment group. The number of rats decreased because two rats had unmeasurable blood pressure when it was measured.

The doses used in this study were 0.09 and 0.18 capsules/kg body weight administered once daily, and 0.18 capsules/kg body weight administered twice daily. This dosage determination is based on calculating the conversion of the jamu X dosage for humans, as stated on the packaging, into a dosage for rats. The weight of jamu X administered to the rats was determined by weighing the contents of 10 capsules of jamu X and then calculating the average. The average weight of jamu X per capsule was 700 mg.

Detailed results of systolic and diastolic blood pressure measurements are presented in Table 1.

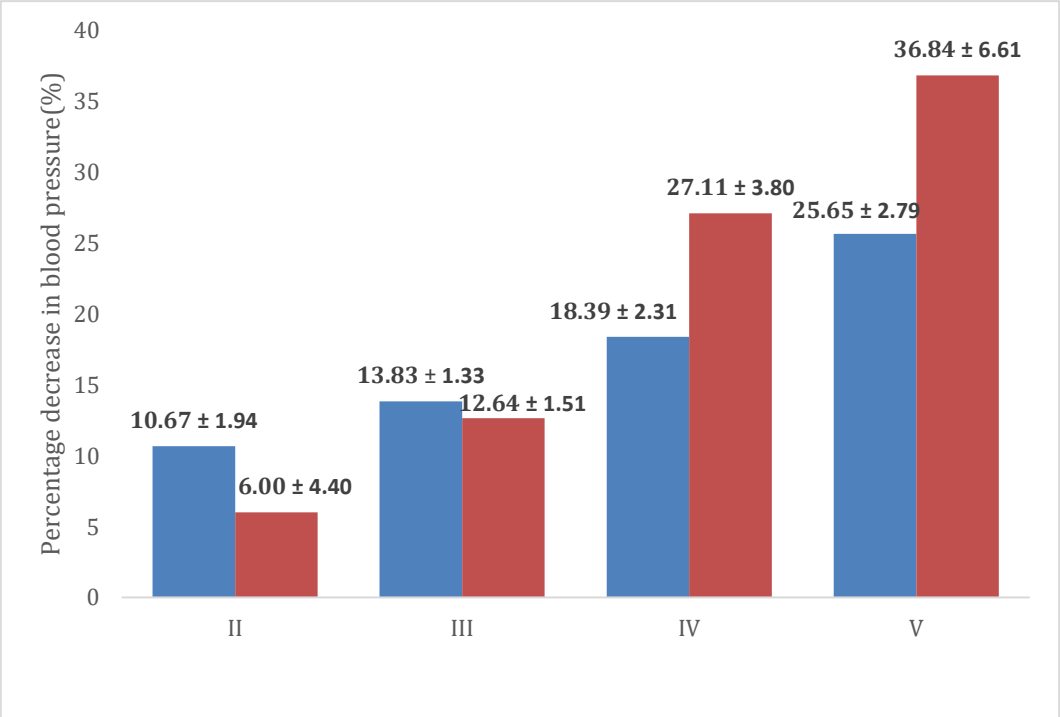
Table 1. The result of antihypertensive activity of jamu X

Group	Average of systolic blood pressure ± SE (mmHg)		Average diastolic blood pressure ± SE (mmHg)	
	Before treatment	After treatment	Before treatment	After treatment
I	147.55 ± 4.12	148.40 ± 1.65	106.10 ± 3.49	105.25 ± 3.31
II	146. 75 ± 2.52	130.95 ± 1.85*	97.90 ± 2.26	91.75 ± 3.11
III	144.70 ± 2.79	124.55 ± 0.98*	101.90 ± 2.28	88.90 ± 0.93*
IV	152.60 ± 2.87	124.35 ± 2.37*	120. 40 ± 4.26	87.15 ± 1.59*
V	147.95 ± 2.16	110.00 ± 4.31*	110.50 ± 2.78	69.80 ± 7.37*

Explanation:
I : Administered by 0.5% Na CMC 12.5 mL/kgBW/day
II : Administered by captopril at a dose of 2.5 mg/kgBW/day
III : Administered by jamu X at a dose of 0.09 capsules/kgBW/day
IV : Administered by jamu X at a dose of 0.18 capsules/kgBW/day
V : Administered by jamu X at a dose of 0.18 capsules/kgBW, twice daily
* : There is a significant difference before and after treatment

Based on the average systolic and diastolic blood pressure readings, the administration of jamu X at various doses appears to lower blood pressure. The significance of the decrease was confirmed using a paired t-test. The results of the paired t-test showed a significant decrease in systolic and diastolic blood pressure at various doses of jamu X ($p < 0.05$). The decrease in systolic and diastolic blood pressure indicates that jamu X, administered at various doses, exhibits antihypertensive activity. The magnitude of antihypertensive activity, expressed as the percentage reduction in systolic and diastolic blood pressure, was compared between jamu X at various doses and captopril. A summary of the data on the percentage reduction in systolic and diastolic blood pressure is shown in Figure 5. Based on Figure 5, the group treated with captopril showed the lowest percentage reduction in both systolic and diastolic blood pressure. The ranking of jamu X doses appears to enhance antihypertensive activity, as indicated by the percentage decrease in both systolic and diastolic blood pressure, which increases with increasing doses. Statistical analysis, in the form of a difference test, reveals a significant difference. Increasing the dose of jamu X from 0.09 capsules/kgBW/day to double that amount, 0.18 capsules/kgBW/day, did not significantly increase the percentage reduction in systolic

blood pressure ($p > 0.05$). Similarly, increasing the frequency of administration of jamu X from 0.18 capsules/kg body weight/day to twice daily did not significantly increase the data on the percentage reduction in systolic blood pressure ($p > 0.05$). In contrast to these two findings, increasing the dose from 0.09 capsules/kg body weight/day to 0.18 capsules/kg body weight twice daily was followed by an increase in the percentage reduction in blood pressure ($p < 0.05$). The increase in dose was accompanied by an increase in antihypertensive activity, possibly due to an increase in the content of active metabolites such as flavonoids, which are thot to contribute to this activity. It is necessary to determine the amount of flavonoid content in jamu X as one step toward standardizing herbal medicine.



Explanation:

Red block	: Systolic
Blue block	: Diastolyc
II	: Administered by captopril at a dose of 2.5 mg/kgBW/day
III	: Administered by jamu X at a dose of 0.09 capsules/kgBW/day
IV	: Administered by jamu X at a dose of 0.18 capsules/kgBW/day
V	: Administered by jamu X at a dose of 0.18 capsules/kgBW, twice a day

Figure 5. Average ± SE percentage decrease in blood pressure for captopril and jamu X.

The lowest average decrease in systolic blood pressure was observed in the positive control group, which received captopril. The average percentage decrease in systolic blood pressure in the positive control group was smaller than in the groups given jamu X at 0.09 and 0.18 capsules/kg body weight/day, but there was no significant difference. The results of this statistical analysis indicate that jamu X, administered at doses of 0.09 and 0.18

capsules/kg body weight/day, exhibits the same activity as captopril. Examination using statistical analysis on the percentage decrease in systolic blood pressure showed a significant difference between the group given captopril and the group given jamu X at a dose of 0.18 capsules/kgBW, twice a day, so it can be concluded that at this dose, the antihypertensive activity is greater than that of captopril. This result further strengthens the rationale for developing jamu X into a standardized herbal medicine.

Regarding the percentage decrease in systolic and diastolic blood pressure, the lowest percentage decrease was observed in the rats treated with captopril. The dose ranking of jamu X correlates with an increase in the percentage decrease in diastolic blood pressure. The difference test using the Tukey test showed that increasing the dose of jamu X from 0.09 capsules/kg body weight/day to 0.18 capsules/kg body weight/day increased the percentage reduction in diastolic blood pressure, but the increase was not significant ($p > 0.05$). Increasing the frequency of jamu X from 0.18 capsules/kg body weight/day to twice a day did not significantly increase the percentage reduction in diastolic blood pressure ($p > 0.05$). Increasing the dose and frequency of jamu X from 0.09 capsules/kg body weight/day to 0.18 capsules/kg body weight twice a day was followed by an increase in the percentage improvement in diastolic blood pressure reduction data ($p < 0.05$).

There are two blood pressure parameters: systolic and diastolic blood pressure. The percentage decrease in systolic blood pressure is more of a focus than the decrease in diastolic blood pressure in determining the increased antihypertensive activity when increasing the dose of jamu X. The blood pressure measurement that is prioritized for observation is systolic blood pressure. This priority considers the significance of systolic blood pressure in daily clinical practice, which has been identified as a target for hypertension therapy (Strandberg and Pitkala, 2003).

Systolic blood pressure is the pressure measured when the heart's ventricles contract to pump blood throughout the body and eject it from the arteries, making systolic blood pressure crucial in diagnosing hypertension. The diastolic blood pressure recorded in this study exhibited greater variability than systolic blood pressure, as seen by a higher standard error value in the data about the percentage reduction in diastolic blood pressure.

The predicted active compound in jamu X is a phenolic group, specifically flavonoids. The antihypertensive effect is possible due to the presence of flavonoids, which can lower blood pressure by increasing the relaxation of the blood vessel endothelium. Flavonoids also act as ACE inhibitors, which block the renin-angiotensin-aldosterone system, leading to a decrease in blood pressure. ACE inhibitors block the enzyme that converts angiotensin I into angiotensin II, a potent vasoconstrictor that causes hypertension (MacLaughlin and Saseen, 2020).

This study's results facilitate the advancement of jamu X from traditional to standardized herbal medicine. Besides investigating the quantification of flavonoid concentrations, the safety profile of jamu X can be examined by acute and chronic toxicity assessments.

CONCLUSION

Jamu X contains flavonoid compounds and exhibits antihypertensive activity in male white rats that have been induced with MSG.

AUTHOR CONTRIBUTION

FL: Concepts or ideas; design; definition of intellectual content; literature search; experimental studies; data analysis; manuscript preparation.
KD: Design of experimental; literature search; data analysis; manuscript editing; manuscript review

ETHICS APPROVAL

The in vivo test had been approved by the ethics commission of Faculty of Medicine Universitas Wahid Hasyim with number of 019/FK-UWH/EC/V/2024.

CONFLICT OF INTEREST

None to declare

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