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SURAT TUGAS
MELAKUKAN KEGIATAN PENELITIAN DAN PUBLIKASI
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1.	Effect of the ethanol extract of Pereskia bleo (Kunth) DC. on the blood pressure and electrolyte levels of hypertensive rats

Demikian surat tugas ini diberikan kepada yang bersangkutan untuk dilaksanakan dengan penuh amanah dan tanggung jawab

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Effect of the ethanol extract of *Pereskia bleo* (Kunth) DC. on the blood pressure and electrolyte levels of hypertensive rats

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ABSTRACT

Introduction: The green cactus *Pereskia bleo* is thought to have anti-cancer, anti-tumor, anti-inflammatory, and anti-rheumatic properties. Additionally, it treats hypertension and diabetes; However, no scientific evaluation of its antihypertensive activity has been conducted. The purpose of this study was to investigate the effects of oral administration of *P. bleo* extract (PBE) on male rats' blood pressure, urine volume, and sodium and potassium levels.
Methods: Sodium chloride (NaCl) solution (4%) was administered orally to induce hypertension. A non-invasive tail method was used to measure blood pressure. The sodium and potassium concentrations as well as the total volume of urine were measured from the collected urine.
Results: Hypertensive rats' blood pressure was reduced by 250, 500, and 1000 mg/kg of PBE. Similar to the positive control group (captopril dose of 1.25 mg/kg BW), the most significant drop in blood pressure was occurred at the dose of 1000 mg/kg BW ($P>0.05$). All treatment groups saw an increase in urinary sodium and potassium levels.
Conclusion: In NaCl-induced hypertensive rats, oral administration of *P. bleo* ethanolic extract decreased blood pressure to the standard value by increasing urinary sodium and potassium levels. Hence, it might be used as an anti-hypertensive agent.

Implication for health policy/practice/research/medical education:
This paper supports the traditional medicine that *Pereskia bleo* extract has diuretic effect and effectively reduces blood pressure.
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Introduction

Premature death and rising healthcare costs continue to be significant outcomes of cardiovascular disease (CVD) (1). Worldwide, hypertension is the leading cause of CVD and sudden death. Herbal treatments for CVD are becoming more popular (2,3), because it is assumed that herbs are safer and simpler to use (4).

Green cactus (*Pereskia bleo*) is one of these medicinal plants, which is used to treat diabetes and hypertension and is thought to have anticancer, antitumor, antirheumatic, and anti-inflammatory properties (5). Alkaloids, fatty acids, flavonoids, phytosterol glycosides, lactones, phenols like alpha-tocopherol, lactones, sterols like beta-carotene, and terpenoids have all been found in the leaves of *P. bleo* (6). The leaves of the plant are used to revitalize the body and are effective against cancer, high blood pressure, diabetes, stomach pain, ulcers, rheumatological conditions, and inflammation (7). The leaves of this plant are also used to reenergize the body in China and Malaysia (8).

The utilization of the seven-bladed needle plant (*P. bleo* (Kunth) DC) has been the subject of numerous studies, as a medication for pain relief and diabetes management (9). At a concentration of 500 mg/kg BW, the roots, stems, and leaves of *P. bleo* were found to significantly lower glucose levels in diabetic rats in an earlier study (10). *P. bleo*'s phenolics have antioxidant properties. Diabetes mellitus patients may experience elevated body fluid

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volume and insulin resistance-induced hyperinsulinemia and hyperglycemia, as well as elevated peripheral artery resistance as a result of vascular remodeling. Systemic blood pressure is raised by these two mechanisms (11). *P. bleo* may also lower blood pressure due to its ability to lower glucose levels. Despite its empirical use as a treatment for hypertension, no scientific studies have been conducted on *P. bleo*. As a result, the purpose of this study was to scientifically test the effectiveness of *P. bleo* as an antihypertensive agent by focusing on systolic blood pressure (SBP) and diastolic blood pressure (DBP), heart rate, and diuretic effects.

Materials and Methods

Materials

In January 2021, fresh *P. bleo* flowers were harvested from the Universitas Muhammadiyah Prof. Dr. HAMKA in East Jakarta, Indonesia. Herbarium Bogoriense, Bogor, Indonesia, identified and verified the leaves' taxonomy. A voucher specimen (B-2925) was deposited at the Universitas Muhammadiyah Prof. Dr. HAMKA pharmacognosy laboratory as a record. The plant material was ground into a coarse powder and shade-dried. The Coda (Kent Scientific) non-invasive blood pressure system was used to keep track of the rats' heart rate and blood pressure.

Preparation of ethanol extract

For a total of 24 hours, the dried plant powder (1 kg) was macerated at room temperature with ethanol as the solvent for multiple extractions. Filtration was used to separate the plant material. A vacuum evaporator was used to concentrate the 70% ethanol extracts at lower pressure (12). The yield of the ethanol extract was 23.34 % w/w. The antihypertensive activity of the final 70% ethanol *Pereskia bleo* extract (PBE) was evaluated.

Animals

Healthy male albino Sprague Dawley rats aged around 8–9 weeks, weighing 180–250 g, were obtained from the animal house, Karanganyar, Central Java. Before the studies, they were kept for an average of ten days in the laboratory, fed standard pellets, and given water on demand. The experimental plan submitted by Universitas Prof. Dr. HAMKA, registration was approved by the institution's Animal Ethics Committee. no. 02/21.03/0923. All pharmacological tests (blood pressure and diuretic effects) were conducted on rats. Six groups of five rats were separated. The standard group was group I; the negative control group was group II; and the positive control group was group III, which received captopril 12.5 mg/kg BW. PBE was taken orally at doses of 250, 500, and 1000 mg/kg BW for groups IV, V, and VI, respectively.

Hypertension induction and antihypertensive test

Hypertension was induced in acclimatized rats by orally administering 4% NaCl (1% of body weight) daily for 2–4 weeks and continued during the study (13). The rats in the study were divided into six groups of four rats each. Group I was the normal control given a standard diet and distilled water. Rats in groups II to VI were induced hypertension with 4% NaCl for two weeks; the induction was continued during the study. The administration of captopril and *P. bleo* ethanol extract was started on day 15 and continued until day 45. Blood pressure measurements were carried out three times, namely before treatment (day 0), after induction with 4% NaCl (day 15), and after administration of captopril and PBE (day 46) (13). The measured blood pressure parameters included SBP, DBP, and heart rate, which were measured using the Coda® Non-Invasive Blood Pressure System (Kent Scientific).

Urine sampling and measurement of potassium and sodium levels

Urine sampling was carried out on day 46. Rats were placed in metabolic cages for 24 hours after the administration of the test preparation. The collected urine samples' volume and potassium and sodium levels were measured. A Microlab 300® spectrophotometer and the Potassium Liquid Rapid Test Human® (Human, Magdeburg, Germany) were used to measure the potassium level. A volume of 50 µL of urine was added to 500 µL of trichloroacetic acid and centrifuged at 6000 rpm for 5 minutes, following which the supernatant was collected. The test was carried out by reacting the supernatant with a mixture of sodium tetraphenyl boron and sodium hydroxide, vortexing the samples and allowing them to stand for 5 minutes, then measuring the samples at a wavelength of 578 nm.

Sodium levels were measured using a Microlab 300® spectrophotometer (ELITechGroup, Logan, USA) employing the Sodium Rapid Test Human® (Human, Magdeburg, Germany). A volume of 20 µL of urine was added to a mixture of uranyl acetate and magnesium acetate (Prec), left for 5 minutes, then vortexed for 30 seconds and left for 30 minutes, then centrifuged at 6000 rpm for 5 minutes to obtain the supernatant. The test was carried out by reacting the supernatant with a mixture of ammonium thioglycolate and ammonia (RGT) at 1000 µL. Measurements were made after 5 minutes at a wavelength of 405 nm.

Statistical analysis

The experimental data were expressed as the mean ± SEM. Data were analyzed by one-way analysis of variance (ANOVA) followed by Tukey's test. The significance of the difference between means was determined, where a P value < 0.05 was considered significant.

Results

Pereskia bleo extraction

The extraction results were obtained through organoleptic,

physicochemical, and phytochemical tests (14,15). The organoleptic products of the extract were blackish-brown, aromatic, and thick in texture. The results of the physicochemical test revealed a water content of 6.46% (v/b) and a total ash content of 7.18% (w/b). The phytochemical test results of PBE showed the presence of alkaloids, phenols, flavonoids, saponins, tannins, and steroids.

Hypertension results of the extract

The induction method used in this study involved the oral administration of 4% b/v NaCl every day for 2–3 weeks. As a result, SBP increased from an average of 115.75 ± 3.36 mm Hg to 141.40 ± 3.70 mm Hg and DBP increased from an average of 90.10 ± 4.77 mm Hg to 115.35 ± 5.26 mm Hg.

Antihypertensive testing of PBE at doses of 250, 500, and 1000 mg/kg BW showed that PBE could reduce the blood pressure of hypertensive rats induced with 4% NaCl. The most significant percent reductions in SBP and DBP and heart rate at a dose of 1000 mg/kg BW (group VI) were 59.38% ± 6.70%, 22.67% ± 8.95%, and 24.20% ± 8.98%, respectively (Table 1).

Urine volume and potassium and sodium levels

The treatment group showed significant differences in urine volume, potassium, and sodium levels from the other groups ($P < 0.05$). The average urine volume, potassium, and sodium levels in group VI were higher than in other groups and similar to the positive control group (group III; $P > 0.05$) (Table 2).

Discussion

The physicochemical parameters of plant extracts are related to the quality standards of the section. The extract quality standard parameters consist of specific and non-specific parameters. Typical parameters include the qualitative chemical content and quantitative levels of the chemical compounds responsible for pharmacological activity. The parameters are assessed by organoleptic and chemical content testing of the extract. Based on the color test, chemical content testing of the extract found that the 70% ethanol extract of *P. bleo* contained alkaloids, phenols, flavonoids, saponins, tannins, and steroids. These results correspond to previous studies using ethanol and methanol extracts (5).

White male rats aged 3–4 months with a body weight range of 180–250 g were used in this research. The used rats exhibited normal behavior and had a blood pressure ranging from 100 mm Hg to 129 mm Hg. Statistical analysis showed that hypertension induction with orally administered 4% NaCl for two weeks could increase blood pressure significantly compared to the group of non-induced rats. Previous studies reported that the administration of 4% NaCl for 14–17 days to male rats of the Sprague-Dawley strain could increase blood pressure by affecting the sympathetic nervous system (16).

Using animal models is expected to provide an

Table 1. The percentage of reduction in systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate in hypertensive rats after treatment according to group division (day 46)

Group	% Decrease in SBP	% Decrease in DBP	% Decrease in heart rate
I	−1.87 ± 7.87	26.01 ± 34.79	5.14 ± 10.84
II	24.87 ± 6.69	13.57 ± 6.11	0.32 ± 7.51
III	56.47 ± 4.09[a]	42.23 ± 6.81[a]	33.01 ± 6.35[a]
IV	44.91 ± 6.44[a]	24.79 ± 24.24[a]	3.47 ± 15.35
V	46.72 ± 7.63[a]	24.54 ± 27.22[a]	5.01 ± 9.94
VI	59.38 ± 6.70[a]	22.67 ± 8.95[a]	24.02 ± 8.98[a]

Group I represented the standard group, group II was the negative control, and group III was the positive control group treated with captopril 12.5 mg/kg. Groups IV, V, and VI were orally treated with *Pereskia bleo* extract (PBE) at 250, 500, and 1000 mg/kg, respectively. The data were expressed as mean ± SEM, (n=5). [a] Similar to group III (Captopril dose 1.25 mg/kg BW; $P > 0.05$).

Table 2. Urine volume, potassium, and sodium levels in hypertensive rats after treatment according to group division (day 46)

Group	Urine volume (mL)	Potassium (mEq/L)	Sodium (mEq/L)
I	3.28 ± 0.15	17.13 ± 1.26	80.63 ± 5.76
II	3.93 ± 0.15	43.85 ± 2.24	106.68 ± 4.75
III	6.7 ± 0.22[a]	23.7 ± 1.76[a]	15.25 ± 7.0[a]
IV	4.4 ± 0.24	27.95 ± 1.48	117.73 ± 4.0
V	5.13 ± 0.22	31.53 ± 1.20	128.6 ± 2.6
VI	6.3 ± 0.22[a]	36.85 ± 1.79[a]	143.6 ± 2.99[a]

Group I represented the standard group, group II was the negative control, and group III was the positive control group treated with captopril 12.5 mg/kg. Groups IV, V, and VI were orally treated with *Pereskia bleo* extract (PBE) at 250, 500, and 1000 mg/kg, respectively. The data were expressed as mean ± SEM, (n=5). [a] Similar to group III (Captopril dose 1.25 mg/kg BW; $P > 0.05$).

understanding of various aspects of a disease, such as etiology, pathophysiology, complications, and treatment. Several animal models have been developed to understand the aetiological factors that play a role in the occurrence of hypertension in humans. The limitation of using animal models of hypertension is the need for more evidence to support that the model describes the incidence of hypertension in humans. Factors that can influence the results in animal models include the dosage, species differences, sex, and age of the animal at the beginning of exposure, and the methods used for measuring blood pressure (17). Hypertension due to salt induction is associated with oxidative stress (renal expression increases upon the oxidation of nicotinamide adenine dinucleotide phosphate oxidase reduction in the antioxidant activity of superoxide dismutase (SOD). A high-salt diet also induces endothelial dysfunction through mechanisms associated with oxidative stress (18).

The blood pressure measurements showed that all treatment groups, except the standard group (group I) and the negative control group (group II), could decrease SBP, DBP, and heart rate. The SBP and DBP and heart rate of Group VI fell by 59.38% ± 6.70%, 22.67% ± 8.95%, and 24.20% ± 8.98%, respectively, after induction (day 15). These results showed that administering captopril and PBE could lower the blood pressure of hypertensive rats induced with 4% NaCl. The most significant decrease in blood pressure was in group VI, comparable to the positive control group (captopril dose 1.25 mg/kg BW; $P > 0.05$).

Captopril is the first angiotensin-converting enzyme inhibitor discovered and widely used in clinics to treat mild-to-severe hypertension and is effective for dealing with hypertensive crises (19). The angiotensin-converting enzyme plays a role in converting angiotensin I into angiotensin II. Angiotensin II is a potent vasoconstrictor that can increase blood pressure and cause the release of superoxide free radicals through the NADH/NADP oxidase system to reduce nitric oxide (NO) concentrations, resulting in a decrease in the relaxation response of the endothelium (20). The administration of supplements containing flavonoids is likely to increase the synthesis of endothelial nitric oxide (eNOS) to increase the bioavailability of NO (20).

Pereskia bleo is a source of flavonoids and phenolics. Flavonoid and phenolic compounds are reported to have the ability to increase the production of NO by activating eNOS mRNA expression so that they can relax the blood vessels (20).

The sodium excretion in group II decreased compared to the other groups in this study. According to Fujita and Ando, the response to changes in blood pressure due to salt intake can be grouped into salt-sensitive and non-salt-sensitive groups. Increased salt intake decreased the excretion of urinary sodium in the salt-sensitive group (21). The sodium excretion in all treatment groups increased compared to the standard group. Increased excretion of sodium (natriuresis) is a mechanism to lower arterial blood pressure back to normal. Natriuresis can cause a decrease in the volume of extracellular fluid so that blood pressure is reduced (21). These results align with previous studies reporting that increased urine excretion was followed by increased sodium excretion (13).

Potassium excretion in group VI tended to increase compared to the captopril group (group III). The decrease in potassium excretion in the positive control group (captopril group) may have been caused by a reduction in aldosterone (22), which regulates the potassium concentration in the body. The decrease in aldosterone is due to inhibiting the enzyme conversion of angiotensin, which can lead to hyperkalemia (23). The tendency to increase potassium excretion could be due to PBE's function as a diuretic (13,24), which can reduce the risk of hyperkalemia.

The 70% ethanol extract of *P. bleo* could lower SBP and DBP by 59.38% ± 6.70% and 22.67% ± 8.95%, respectively, comparable to captopril dose of 1.25 mg/kg BW.

Conclusion

This study's results showed that PBE as an antihypertensive agent could lower blood pressure by decreasing the heart rate, diuresis, natriuresis, and vasodilation of blood vessels.

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Authors' contributions

SS, TB, and EH revised the initial manuscript before submission to the journal website. BF, ADAPP, NNY, and NAF managed the experiment in the laboratory during the research. All authors read, reviewed, and approved the manuscript and English language.

Conflict of interests

The authors declare that they have no competing interests.

Ethical considerations

The institutional Animal Ethics Committee approved the experimental protocol of Universitas Prof. Dr. HAMKA, Reg. no. 02/21.03/0923. The authors have observed ethical issues, including plagiarism, data fabrication, double publication, etc.

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