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ORIGINAL ARTICLE

Antihypertensive Activities of *Peronema Canescens* Jack Extract: An *In Vivo* Study

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Abstract

Background/Aim: Hypertension commonly known as high blood pressure is characterised by a systolic readings of 140 mm Hg or higher and/or a diastolic readings of 90 mm Hg or above. Elevated blood pressure can lead to a heightened release of nitric oxide, a crucial factor in vascular relaxation. *Peronema canescens* Jack, commonly referred to as Sungkai, is known to contain flavonoids with antihypertensive properties and antioxidants that may help prevent cellular oxidation. This research aimed to evaluate the antihypertensive effects of ethanol extract from *Peronema canescens* Jack leaves and its impact on nitric oxide levels in hypertensive rats.

Methods: This study used hypertensive male Wistar rats induced by NaCl (3.75 g/kg BW) and prednisone (1.5 mg/kg BW) administered orally. Blood pressure measurements were conducted using the non-invasive tail-cuff method and nitric oxide levels were analysed by reacting the sample with the Griess Reagent Assay.

Results: The study's findings demonstrated a decrease in systolic, diastolic and mean arterial blood pressure, along with an increase in nitric oxide levels after administering ethanol extract of *Peronema canescens* Jack leaves (EEPC) at dosages of 50, 100 and 200 mg/kg BW. The most significant reduction in blood pressure was noted at the 100 and 200 mg/kg BW dosages ($p < 0.05$), while the highest elevation in nitric oxide levels was observed at the 200 mg/kg BW dosage ($p < 0.05$).

Conclusion: The study concludes that administering the EEPC to hypertensive rats, induced by NaCl and prednisone, can lower blood pressure and elevate nitric oxide levels. These findings suggest that *Peronema canescens* Jack leaves hold potential as an antihypertensive agent.

Key words: *Peronema canescens* Jack, Antihypertensive agents; Nitric oxide; Hypertension; Rats.

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Introduction

Hypertension is a multifactorial chronic condition arising from a combination of environmental, lifestyle and genetic factors. Additionally, it is affected by elements such as obesity, high levels of stress, insufficient physical activity and excessive salt intake.[1] Hypertension is often referred to as a silent killer because it has a significant impact on heart failure, stroke and death.[2] A notable rise in blood pressure will result in an elevated release of nitric oxide.

Nitric oxide is an essential component and functions as a vascular relaxant. Synthesised nitric oxide is released by the vascular endothelium, acting as a potent vasodilator. Consequently, oxidative stress that occurs in hypertension can be mitigated with antioxidants, as they have a beneficial effect on hypertension.[3]

Captopril ranks as one of the most commonly prescribed antihypertensive drugs, comprising 47.46 % of all such prescriptions, with amlodipine at 34.75 %, hydrochlorothiazide at 16.10 % and both furosemide and spironolactone each at 0.85 %.[4] Captopril functions by blocking the production of angiotensin II, a hormone responsible for constricting blood vessels. Nonetheless, the administration of captopril, an angiotensin converting enzyme (ACE) inhibitor, may lead to a persistent dry cough as a result of bradykinin accumulation, an active metabolite.[5] This side effect can lead to a loss of motivation, decreased awareness and reluctance among patients to adhere to their medication therapy, resulting in a high rate of non-compliance.[6] Consequently, people are more inclined to use herbal remedies, which are considered safer.

In Indonesia, the use of traditional medicine is still believed by some groups to be an alternative complementary therapy for maintaining health. One of the plants originating from the Dayak tribe of Kalimantan and used empirically to reduce high blood pressure is Sungkai (*Peronema canescens* Jack). Sungkai leaves contain flavonoids, which can prevent hypertension. Flavonoids and tannins act as antioxidants, preventing the oxidation of body cells. In addition, substances including flavonoids, saponins, alkaloids and phenols demonstrate anti-inflammatory effects.[7] The antioxidant activity observed in *Peronema canescens* Jack leaves is linked to their phenolic and flavonoid compound concentrations. Therefore, higher levels of flavonoids and phenolics are associated with improved antioxidant performance in the plant.[8]

Therefore, this research was conducted using hypertensive rats to assess the antihypertensive activity by measuring reductions in blood pressure and increases in nitric oxide levels after administering ethanol extract of *Peronema canescens* Jack leaves (EEPC) at a specific dose, compared to synthetic antihypertensive drugs like captopril. This research is innovative in exploring the potential application of *Peronema canescens* Jack leaves as a novel approach for preventing and treating hypertension, with the aim of improving therapeutic outcomes for this condition in the future.

Methods

The Sungkai (*Peronema canescens* Jack) leaves were obtained directly from the Palaran District, Samarinda City, East Kalimantan, Ethanol 96 % (*CV. Surya Artathama*), NaCl (*CV. Surya Artathama*), NaCMC (*CV. Sentra Chemicals,* Indonesia), Prednisone®, Captopril®, N-(1-naphthyl)-ethylene diamine-hydrochloride (*Sigma-Aldrich*), sulphanilamide (*Merck*) and sodium nitrate (*Merck*). Glassware (*Iwaki*), The Coda (*Kent Scientific*) non-invasive blood pressure system and a 96-well plate were used to determine nitric oxide.

Preparation extract

The preparation of ethanol extract from the leaves of *Peronema canescens* Jack was prepared by macerating 1 kg of dried leaves in 96 % ethanol at a 1:10 ratio for 3 days. After maceration, the mixture was concentrated via evaporation with a rotary evaporator to obtain the EEPC.[9]

Animals

The study was approved by the Research Ethics Commission of Universitas Ahmad Dahlan under approval number 012307118. The research utilised 30 male Wistar rats, allocated into six groups of five animals each: one normal group treated with a 0.5 % NaCMC solution, a negative control group administered 3.75 g/kg BW NaCl and 1.5 mg/kg BW prednisone, a positive control group receiving 4.5 mg/kg BW captopril for comparison and three experimental groups treated with varying doses of EEPC at 50 mg/kg BW, 100 mg/kg BW and 200 mg/kg BW. All treatments were given orally.[10] The rats were maintained at a stable temperature of 22 ± 2 ºC and a relative humidity of 55 ± 10 %, under typical laboratory conditions featuring a 12 h light/dark cycle (with light from 07:00 AM to 07:00 PM) and had unrestricted access to food and water.[11]

In vivo antihypertensive activity

The test animals were made hypertensive through the administration of a combination of NaCl (3.75 g/kg BW) and prednisone (1.5 mg/kg BW) given orally every day for 14 days. This was

followed by the oral administration of EEPC for an additional 7 days. On days 14 and 21, the rats' systolic, diastolic and mean arterial pressures were measured using a non-invasive blood pressure method with the CODA device. This method employs a tail cuff placed on the rats' tails to monitor blood pressure. The CODA device features a volume pressure recording (VPR) sensor that uses a differential pressure transducer specifically designed for non-invasive measurement of blood volume in the rats' tails.[12]

In vivo nitric oxide levels

The measurement of nitric oxide levels with ELISA Reader (*Asys*) and uses the method with several modifications.[13] Nitric oxide was measured using blood samples from male Wistar rats obtained on the 14th and 21st days. The blood obtained was then centrifuged at 3.000 rpm for 15 minutes.[14] The results of centrifugation will produce a serum ready to examine nitric oxide levels. Nitrite concentrations were determined using a serum sample analysed by the Griess Reaction Assay. For this, Griess A solution was prepared by dissolving 0.1 grams of N-(1-naphthyl) ethylenediamine hydrochloride in 100 mL of distilled water, while Griess B solution was made by dissolving 1 gram of sulphanilamide in 100 mL of 5 % (v/v) orthophosphoric acid. A standard nitrite solution was created by dissolving 69.0 mg of sodium nitrate in 100 mL of distilled water. In a 96-well microtiter plate, 100 µL of both the sample and the standard nitrite solution were added. Subsequently, 100 µL of Griess A and Griess B solutions were added to each well and the mixture was allowed to react until a colour change was observed. Absorbance was measured using an ELISA reader set at a wavelength of 550 nm.[15]

Statistical analysis

The data were presented as the mean ± standard deviation (SD). For assessing multiple comparisons, a one-way analysis of variance (ANOVA) was conducted using IBM SPSS Statistics 25.0, followed by the Tukey post-hoc test. Statistical significance was evaluated based on group differences, with a significance threshold set at $p < 0.05$.

Results

In vivo antihypertensive activity

The systolic, diastolic and mean arterial blood pressure measurements were carried out using the CODA® device. On day 14, measurements were taken to observe the effect of administering NaCl and prednisone solutions, which resulted in an increase in blood pressure. On day 21, measurements were again carried out to assess the impact of administering the EEPC as an antihypertensive. The results of these measurements can be seen in Tables 1, 2 and 3.

The systolic blood pressure measurements on day 14 showed that systolic blood pressure measurements revealed elevated levels compared to the normal group, with statistical analysis demon-

Table 1: The results of systolic blood pressure measurement on the 14th and 21st day

Groups	Dose (mg/kg BW)	Systolic blood pressure (mm Hg) (mean ± SD)		
		Day 14 (NaCl and prednisone)	Day 21 (Treatment)	Difference (mm Hg)
Normal	-	120.6 ± 4.72	121.4 ± 2.51[b]	+0.80
Control	-	145.4 ± 8.20[a]	143.8 ± 4.08	-1.60
EEPC				
	50	144.4 ± 3.97[a]	135.8 ± 6.09[c]	-8.60
	100	145.8 ± 5.35[a]	132.4 ± 3.78[b]	-13.40
	200	144.2 ± 4.97[a]	128.0 ± 5.00[b]	-16.20
Captopril	4.5	145.6 ± 7.98[a]	125.4 ± 3.36[b]	-20.20

EEPC: ethanol extract of Peronema canescens Jack leaves; The results are presented as mean ± standard deviation (SD) (n = 5); (a) significant difference from the normal group ($p < 0.05$); (b) significant difference from the control group ($p < 0.05$); (c) significant difference from the captopril group ($p < 0.05$);

strating a significant difference ($p < 0.05$). This finding suggests that male Wistar rats exhibited a substantial increase in systolic pressure after a 14-day administration of NaCl at 3.75 g/kg BW and prednisone at 1.5 mg/kg BW.

The systolic blood pressure measurements were repeated on day 21, revealing a significant variation in systolic blood pressure levels. The control group exhibited a notable difference compared to the EEPC 50, 100 and 200 mg/kg BW groups, as well as the captopril 4.5 mg/kg BW group. However, no significant differences were observed among the EEPC 100 and 200 mg/kg BW groups and the captopril 4.5 mg/kg BW group. These findings suggest that the administration of EEPC 100 mg/kg BW and EEPC 200 mg/kg BW effectively reduces systolic blood pressure to a level comparable to that of captopril.

The diastolic blood pressure measurements on day 14 showed that diastolic blood pressure was higher in the test group compared to the normal group, with statistical results indicating a significant difference ($p < 0.05$). This suggests that male Wistar rats experienced a significant increase in diastolic pressure after being administered a solution of NaCl 3.75 g/kg BW and prednisone 1.5 mg/kg BW for 14 days.

The diastolic blood pressure measurements were taken again on day 21, revealing a notable variation in diastolic blood pressure levels. Significant differences were observed between the control group and the EEPC 50, 100 and 200 mg/kg BW groups, as well as the captopril 4.5 mg/kg BW group. No significant differences were found among the EEPC 100 mg/kg BW, EEPC 200 mg/kg BW and captopril 4.5 mg/kg BW groups. There-

Table 2: The results of diastolic blood pressure measurement on the 14th and 21st day

Groups	Dose (mg/kg BW)	Diastolic blood pressure (mm Hg) (mean ± SD)		
		Day 14 (NaCl and prednisone)	Day 21 (Treatment)	Difference (mm Hg)
Normal	-	87.4 ± 4.56	86.2 ± 5.76[b]	-1.20
Control	-	111.8 ± 3.42[a]	109.6 ± 3.70	-2.20
EEPC				
	50	105.6 ± 6.34[a]	95.6 ± 3.84[c]	-10.00
	100	106.8 ± 5.45[a]	92.0 ± 4.52[b]	-14.80
	200	109.0 ± 5.33[a]	90.4 ± 7.16[b]	-18.60
Captopril	4.5	108.8 ± 5.84[a]	87.4 ± 2.40[b]	-21.40

EEPC: ethanol extract of Peronema canescens Jack leaves; The results are presented as mean ± standard deviation (SD) (n = 5); (a) significant difference from the normal group ($p < 0.05$); (b) significant difference from the control group ($p < 0.05$); (c) significant difference from the captopril group ($p < 0.05$);

Table 3: The results of mean arterial blood pressure measurement on the 14th and 21st days

Groups	Dose (mg/kg BW)	Mean arterial blood pressure (mm Hg) (mean ± SD)		
		Day 14 (NaCl and prednisone)	Day 21 (Treatment)	Difference (mm Hg)
Normal	-	98.4 ± 4.14	97.9 ± 3.66[b]	-0.53
Control	-	123.2 ± 4.60[a]	121.0 ± 3.74	-2.00
EEPC				
	50	118.5 ± 5.49[a]	109.0 ± 4.42[c]	-9.53
	100	119.8 ± 5.05[a]	105.4 ± 4.22[b]	-14.33
	200	120.7 ± 5.16[a]	102.9 ± 6.34[b]	-17.80
Captopril	4.5	121.0 ± 6.50[a]	100.0 ± 2.29[b]	-21.00

EEPC: ethanol extract of Peronema canescens Jack leaves; The results are presented as mean ± standard deviation (SD) (n = 5); (a) significant difference from the normal group ($p < 0.05$); (b) significant difference from the control group ($p < 0.05$); (c) significant difference from the captopril group ($p < 0.05$);

Table 4: The results of nitric oxide pressure measurement on the 14th and 21st days

Groups	Dose (mg/kg BW)	Nitric oxide levels (µM/L)		
		Day 14 (NaCl and prednisone)	Day 21 (Treatment)	Difference (µM/L)
Normal	-	25.82 ± 0.86	25.02 ± 0.39[b]	-0.80
Control	-	13.00 ± 1.96[a]	13.21 ± 0.94	-0.21
EEPC				
	50	12.09 ± 0.30[a]	14.94 ± 0.65[c]	+2.85
	100	13.01 ± 1.08[a]	16.95 ± 0.98[c]	+3.94
	200	13.92 ± 1.50[a]	18.95 ± 1.92[b]	+5.03
Captopril	4.5	12.94 ± 1.12[a]	20.35 ± 1.67[b]	+7.41

EEPC: ethanol extract of Peronema canescens Jack leaves; The results are presented as mean ± standard deviation (SD) (n = 5); (a) significant difference from the normal group (p < 0.05); (b) significant difference from the control group (p < 0.05); (c) significant difference from the captopril group (p < 0.05);

fore, it can be concluded that administering EEPC at doses of 100 mg/kg BW and 200 mg/kg BW effectively reduces diastolic blood pressure to a level comparable with captopril.

The mean arterial blood pressure measurement on day 14 showed that mean arterial blood pressure was higher in the test group compared to the normal group, with statistical results indicating a significant difference ($p < 0.05$). This suggests that male Wistar rats experienced a significant increase in mean arterial blood pressure after being administered a solution of NaCl 3.75 g/kg BW and prednisone 1.5 mg/kg BW for 14 days.

The mean arterial blood pressure measurements were taken again on day 21, revealing a notable variation in mean arterial blood pressure levels. Significant differences were observed between the control group and the EEPC 50, 100 and 200 mg/kg BW groups, as well as the Captopril 4.5 mg/kg BW group. No significant differences were found among the EEPC 100 mg/kg BW, EEPC 200 mg/kg BW and captopril 4.5 mg/kg BW groups. Therefore, it can be concluded that administering EEPC at doses of 100 mg/kg BW and 200 mg/kg BW effectively reduced mean arterial blood pressure to a level comparable with captopril.

In vivo experiment of nitric oxide serum test

In the subsequent study, nitric oxide levels were measured in hypertensive rats. Nitric oxide levels were assessed using serum reacted with the Griess Reaction Assay. The samples were then analysed with an ELISA Reader at a wavelength of 550 nm. The mean nitric oxide levels in male Wistar rats on days 14 and 21 are shown in Table 4.

Nitric oxide levels were measured on the 21st day. The results of statistical analysis showed significant differences after all groups (except the normal group) were given the test preparation for 7 days ($p < 0.05$). Further statistical analysis with the Tukey test revealed fundamental differences in nitric oxide levels. The normal group differed significantly from the NaCMC 0.5 group, EEPC 50, EEPC 100, EEPC 200 and captopril 4.5. However, there was no significant difference between the EEPC 200 and captopril 4.5 groups. It can be concluded that the administration of EEPC 200 can increase nitric oxide levels to (18.95 ± 1.92 µM/L), which is comparable to captopril 4.5 at (20.35 ± 1.67 µM/L).

Discussion

Sungkai (*Peronema canescens* Jack) leaves contain alkaloids, flavonoids, phenolics and saponins compounds, which are thought to have antioxidant properties.[16] Sungkai leaves sourced from Samarinda City are reported to contain 33.67 mg of GAE/g of sample for total phenolic content and 18.21 mg of QE/g of sample for total flavonoid content.[17] Antioxidant compounds are beneficial as bioactive substances, believed to have anti-inflammatory properties and actively inhibit nitric oxide, a type of free radical in gas form.[7]

This research sought to evaluate the impact of administering EEPC on lowering systolic, diastol-

ic and mean arterial blood pressure, alongside nitric oxide levels, in hypertensive rats induced by NaCl (3.75 g/kg BW) and prednisone (1.5 mg/kg BW). This induction is known to increase blood pressure in male Wistar rats, as evidenced by elevated blood pressure readings. High doses of mineralocorticoids from prednisone can lead to hypertension with a prevalence of up to 20 %. This effect may be due to prednisone stimulating the adrenal cortex to produce more cortisol, which in turn increases blood pressure and causes sodium and water retention.[10]

This study used a comparison group by administering captopril. Captopril was chosen because it is commonly used as a comparator in research on antihypertensive activity.[18] Captopril, an early antihypertensive medication, is classified as an ACE inhibitor. It functions by blocking the conversion of angiotensin I to angiotensin II, which promotes vasodilation and reduces aldosterone release. Consequently, this reduction in aldosterone levels lowers blood pressure and may lead to the retention of potassium and water.[19]

The EEPC reduces systolic, diastolic and mean arterial blood pressure due to the presence of flavonoids. Flavonoids have a hypotensive effect by inhibiting ACE activity. ACE is responsible for the formation of angiotensin II, which is a factor in causing hypertension by narrowing blood vessels (vasoconstriction) and ultimately increasing blood pressure. Additionally, ACE affects vasodilation, leading to increased blood flow to the heart and a subsequent decrease in blood pressure.[5]

In the methanol extract of *A viridiflora*, which is rich in flavonoids, it has been proven that the extract can inhibit ACE activity inhibition *in vitro.*[20] A study examining the potential inhibitory effects of 11 crude extracts from *Cuphea* spp and their pure compounds revealed that the polyphenol miquelianin demonstrated inhibitory activity similar to that of captopril, a well-known ACE inhibitor, which was also observed in presented research.[21]

Sungkai (*Peronema canescens* Jack) leaves contain active compounds such as flavonoids and phenolics, which can help regulate blood pressure and enhance the function of the blood vessel endothelium by modulating the expression of endothelial nitric oxide synthase (eNOS) and increasing nitric oxide production. Thus, flavonoids influence the ACE process, which can promote vasodilation and reduce peripheral resistance.[22]

In this study, the mean nitric oxide levels in the hypertension group induced by NaCl and prednisone, before and after treatment, were 13.00 µmol/L and 13.21 µmol/L, respectively. In the normotensive group, the levels were 25.82 µmol/L and 25.02 µmol/L. The nitric oxide levels in the normal group are consistent with the normal plasma nitric oxide levels, which are determined to be between 25 and 45 µmol/L.[23] The nitric oxide levels measured on day 14 were lower than those in the normal group, with statistical analysis indicating a significant difference ($p < 0.05$). This indicates that the administration of NaCl and prednisone for 14 days substantially decreases nitric oxide levels in male Wistar rats.

Reduced levels of blood nitric oxide are associated with elevated systolic and diastolic blood pressure, as nitric oxide functions as a vasodilator. Increased endothelial damage from excessive oxidative stress leads to decreased nitric oxide production, which in turn results in higher blood pressure and more pronounced hypertension. Consequently, individuals with hypertension exhibit diminished endothelium-dependent vasodilation due to the reduced availability of nitric oxide.[24]

Nitric oxide is a highly reactive free radical gas known for its strong oxidising capabilities and rapid diffusion. It is synthesised by three distinct nitric oxide synthase (NOS) enzymes: neuronal NOS (nNOS, NOS_1), inducible NOS (iNOS, NOS_2) and endothelial NOS (eNOS, NOS_3). As a potent anti-inflammatory and antioxidant agent, nitric oxide acts as an endogenous vasodilator and is crucial for intercellular signalling, regulating both cerebral and peripheral blood flow. Its role in maintaining vascular homeostasis is widely acknowledged.[25]

Oxidative stress occurs when there is a disruption between oxidants and antioxidants in the body, with nitric oxide, a reactive free radical gas, potentially triggering pathological oxidation. Nitric oxide may interact with superoxide anions (O_2^-) to produce the highly reactive oxidant peroxynitrite ($ONOO^-$). This oxidative stress leads to cellular damage, including protein inactivation and degeneration, lipid peroxidation and DNA damage.[26]

The plants that are rich in flavonoids and phenolic compounds have the potential to lower blood pressure and elevate nitric oxide levels. The observed reduction in blood pressure and the rise in nitric oxide levels could primarily be attributed to the vasorelaxant properties of these compounds.[9] The administration of parasite leaf extract tea can increase nitric oxide levels in hypertensive rats. This effect is due to the flavonoid content, which diffuses directly into the endothelial cells, thereby enhancing the production of nitric oxide.[27]

The most flavonoids, including apigenin, quercetin and luteolin, have been found to function as vasorelaxants. They have the potential to enhance endothelial function and lower superoxide concentrations in the vascular endothelium during oxidative stress, both of which are crucial for managing cardiovascular disease.[28]

Conclusion

The study concludes that administering the ethanol extract of *Peronema canescens* Jack leaves to hypertensive rats, induced by NaCl and prednisone, can lower blood pressure and elevate nitric oxide levels. These findings suggest that *Peronema canescens* Jack leaves hold potential as an antihypertensive agent.

Ethics

The study was approved by the Ethic Committee of the Universitas Ahmad Dahlan, decision No 012307118, dated 31 July 2023.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

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