JoP Journal of Pharmacopuncture
Journal of Pharmacopuncture 2023;26(4):298-306
pISSN: 2093-6966 • eISSN: 2234-6856
https://doi.org/10.3831/KPI.2023.26.4.298
Original Article
Check for updates

Cucumber (*Cucumis sativus* L.) Fruit and Combination with Losartan Attenuate the Elevation of Blood Pressure in Hypertensive Rats Induced by Angiotensin II

Tomi Hendrayana[1]*, Klaudia Yoana[1], I Ketut Adnyana[1], Elin Yulinah Sukandar[2]

[1]Pharmacology and Clinical Pharmacy Research Group, School of Pharmacy, Bandung Institute of Technology, Bandung, West Java, Indonesia
[2]Faculty of Pharmacy, General Achmad Yani University, Cimahi, West Java, Indonesia

Received May 8, 2023
Reviewed May 18, 2023
Accepted September 12, 2023

***Corresponding Author**
Tomi Hendrayana
Pharmacology and Clinical Pharmacy Research Group, School of Pharmacy, Bandung Institute of Technology, Ganesha 10, Bandung - 40132, West Java, Indonesia
Tel: +62-812-2391-0463
E-mail: tomi@itb.ac.id

Objectives: *Cucumis sativus* L. (*C. sativus*) is vegetable commonly used for managing blood pressure and often consumed in combination with standard antihypertensive therapy, despite lack of scientific evidence supporting their use. Combination of herbs and standard medication could have positive or negative effects. Therefore, this study aimed to evaluate the antihypertensive activity of *C. sativus* and the combined effect with losartan in the hypertensive rat model induced by angiotensin II. Angiotensin II is a component of the renin-angiotensin-aldosterone system that, upon binding to its receptor, constricts blood vessels leading to elevation of blood pressure.
Methods: In an antihypertensive study, rats received *C. sativus* orally at doses of 9, 18, 27, and 36 mg/kg (full dose); while in a combination study, animals received losartan 2.25 mg/kg combined by either with *C. sativus* 9 or 18 mg/kg. The standards group received losartan 2.25 mg/kg or 4.5 mg/kg (full dose).
Results: Blood pressure was measured using the tail-cuff method. *C. sativus* significantly attenuated angiotensin II-induced hypertension as observed in groups receiving *C. sativus* at 9, 18, 27, and 36 mg/kg at 30 minutes after induction showed the average change (Δ) of systolic blood pressure (SBP) and diastolic blood pressure (DBP) with respect to time zero were 28.8/18.3, 24.8/15.8, 22.8/15.5, and 11.5/9.0 mmHg, respectively. Whereas the average change (Δ) of SBP and DBP in the rats receiving the combination of half doses of *C. sativus* and losartan were 8.8/9.0 mmHg, respectively. These diminished effects were better than a full dose of *C. sativus* and comparable with a full dose of losartan (6.5/7.8 mmHg).
Conclusion: The present findings indicate that *C. sativus* dose-dependently blocks blood pressure elevation induced by angiotensin II. The combination of half dose of *C. sativus* and losartan has an additive effect in lowering blood pressure.

Keywords: antihypertensive, *Cucumis sativus* L., natural remedy, traditional medicinal plant, herb-losartan interaction

INTRODUCTION

Hypertension, a chronic condition characterized by a systolic blood pressure (SBP) of ≥ 140 mmHg and/or a diastolic blood pressure (DBP) of ≥ 90 mmHg [1], significantly increases the risk of heart attack, stroke, kidney failure, and blindness, and causes premature death [2]. Uncontrolled blood pressure is one of the most critical human health concerns worldwide, not just in high-income regions like central and Eastern Europe, but also in low-income countries of South Asia and sub-Saharan

Africa [3, 4]. Hypertension treatment follows guidelines from the Joint National Committee 8, which recommends angiotensin-converting enzyme inhibitors or angiotensin receptor blockers as first-line therapy, and diuretics or calcium channel blockers as an alternative [5].

Several traditional medicinal herbs and natural products, such as ma huang, St. John's wort, yohimbine, garlic, and licorice, are being investigated as alternatives for hypertension management [6, 7]. An elegant study by Kamyab et al. [8] found that numerous plants are used for empirical hypertension therapy worldwide, including plants from the *Asteraceae*, *Liliaceae*, *Apiaceae*, *Rosaceae*, and *Apocynaceae* families. Because of their advantages over standard antihypertensive drugs, such as fewer unwanted side effects, cost-effectiveness, and the easier availability of medicinal plants, herbal remedies are being incorporated into the clinical treatment of hypertension through evidence-based medicine [9].

Cucumber (*Cucumis sativus* L. [*C. sativus*]), which has been used empirically for cardiovascular disease therapy, belongs to the family *Cucurbitaceae* and contains cucurbitacin as the major metabolite. A previous study reported that cucurbitacin B from *Cucumis melo* L. has hypotensive effects [10]. *Lagenaria siceraria* (Molina) Standl. Fruit, which belongs to the *Cucurbitaceae* family, has also been reported to have hypotensive effects [11]. *In vitro* analysis indicates that the aqueous fraction of cucumber inhibits angiotensin II (Ang II)-induced oxidative stress, which may have hypotensive effects [12]. *Cucumis sativus* (*C. sativus*) has also been studied for its moderate diuretic activity [13]. However, evidence supporting cucumber use for hypertension management is lacking, and its effects in an Ang II-induced model of hypertension have not been evaluated. Moreover, using herbs in combination with standard antihypertensive agents may positively or negatively impact the effect of standard medication [14]. This study investigated the dose-dependent antihypertensive effects of *C. sativus* alone or when combined with losartan in an Ang II-induced rat model of hypertension.

MATERIALS AND METHODS

1. Plant material sourcing and processing

C. sativus (*CS*) plant samples were obtained from Desa Cimekar, Bandung, West Java, and identified at Herbarium Bandungense School of Life Sciences and Technology, Bandung Institute of Technology (coordinate: –6.931720432222963, 107.77177718067999). Concentrated CS fruit juice was prepared through the following steps: (a) the fruits were washed, (b) the clean fruits were juiced using a juicer without adding water, (c) the juice was filtered, (d) the filtrate was freeze-dried using an EYELA® freeze dryer FD-5N, (e) the freeze-dried juice was stored at –20℃. The plant concentrate yield was 3% (w/w).

2. Drugs and chemicals

Losartan potassium (Los) was purchased from PT Kalbe Farma. The human Ang II used to induce hypertension was purchased from Sigma–Aldrich (product no. A9525, CAS no. 4474-91-3). All other chemicals used for experimental purposes were of analytical grade.

3. Preliminary phytochemical screening

Phytochemicals are bioactive plant constituents, such as flavonoids, saponins, and terpenoids. To determine the presence of bioactive components, a preliminary phytochemical screening was performed as previously reported [15].

4. Determination of calcium, potassium, and zinc

One gram of CS was burned to ashes in a muffle furnace at 500℃. The ash was then put in a volumetric flask, mixed with 0.1 N HNO_3 to a final volume of 25 mL, and then filtered using Whatman paper no. 42 before further examination. A calibration curve for calcium, potassium, and zinc determination was generated using calcium carbonate, potassium chloride, and zinc oxide as standards, respectively, using atomic absorbance spectrometry (Agilent® Spectr-AA variant 55B, 422.7 nm). At least three readings were obtained and the results were presented as average values.

5. Ethics approval

Ethical approval for the use of laboratory animals was granted by the animal research ethics committee of Bandung Institute of Technology (ethics certificate No. 03/KEPHP-ITB/10-2019).

6. Animals

The animal facilities and protocols complied with the stan-

dards for the care and use of experimental animals. Adult male Wistar rats weighing 225 ± 25 g were housed in standard laboratory conditions under a 12:12-hour light–dark cycle, with free air circulation, at 25 ± 2℃ and 65 ± 10% humidity. Husk replacement was done every 2-3 days. The rats were fed standard animal feed with free access to water. The animals were acclimatized to laboratory conditions for seven days and fasted with free access to water for 12 hours before each experiment.

7. Evaluation of the antihypertensive activity of *CS*

The antihypertensive activity of *CS* was evaluated as previously described [16, 17]. Briefly, Ang II was used to induce blood pressure (BP) elevation in rats. For this, the animals (four per group) were randomly assigned to the following groups: 1) Group 1 (normal control), which received the vehicle (0.5% Na CMC solution), 2) Group 2, which received the vehicle and Ang II, 3) Groups 3-6, which received *CS* at 9, 18, 27, and 36 mg/kg, respectively, along with Ang II, 4) Groups 7 and 8, which received Los at 2.25 mg/kg in combination with CS at 9 and 18 mg/kg, respectively, along with Ang II, and 5) Groups 9 and 10, which were treated with Los at 2.25 and 4.5 mg/kg, respectively, along with Ang II. CS and losartan treatments lasted for four weeks. Ang II induction and BP measurements were done on the 28th day of the experiment.

All rats, except the normal control (Group 1), underwent hypertension induction via intraperitoneal Ang II (100 μg/kg)

Table 1. The result of phytochemical screening of *C. sativus*

Phytochemical components	Result	Observation
Flavonoid	+	Pink solution
Saponin	+	Foam stable for 10 minutes
Terpenoid	+	Orange solution

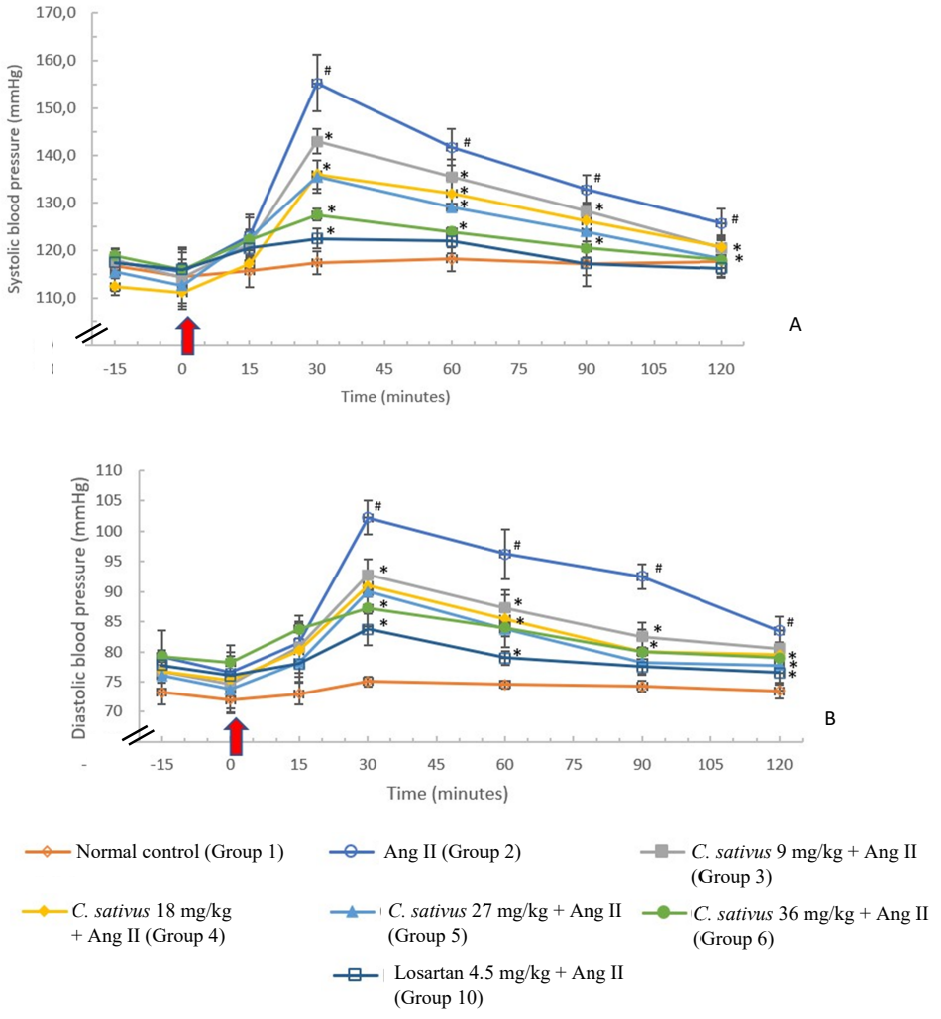

Figure 1. Effects of systemic angiotensin II injection on blood pressure. Angiotensin II was administered at 100 ug/kg i.p. at 15 minutes after administration of *C. sativus*, losartan, or sodium-CMC (vehicle). (A) systolic blood pressure; (B) diastolic blood pressure. The red arrow represents time of angiotensin II injection, the same time for recording at time zero. *$p < 0.05$ *C. sativus* or losartan + Ang II vs. Ang II. #$p < 0.05$ Ang II vs. normal control.

 https://doi.org/10.3831/KPI.2023.26.4.298

injection 15 minutes after administering CS or Los. SBP and DBP readings were taken on conscious rats 15 minutes before induction, immediately after induction (0), and 15, 30, 60, 90, and 120 minutes after induction, using a CODA® Noninvasive Blood Pressure System (Kent Scientific Corporation, USA) according to the manufacturer's instructions. Five measurements were taken per rat and expressed as average readings.

8. Statistical analyses

Data are presented as mean ± standard deviation. Differences between multiple groups were compared using one-way analysis of variance (ANOVA) followed by the LSD test, using SPSS version 27.0. $p < 0.05$ indicated statistically significant differences.

RESULTS

1. Phytochemical screening

Flavonoids, saponins, and terpenoids were detected in *CS* (Table 1).

2. Calcium, potassium, and zinc content

Calcium, potassium, and zinc levels in CS were 16.65 ± 0.09

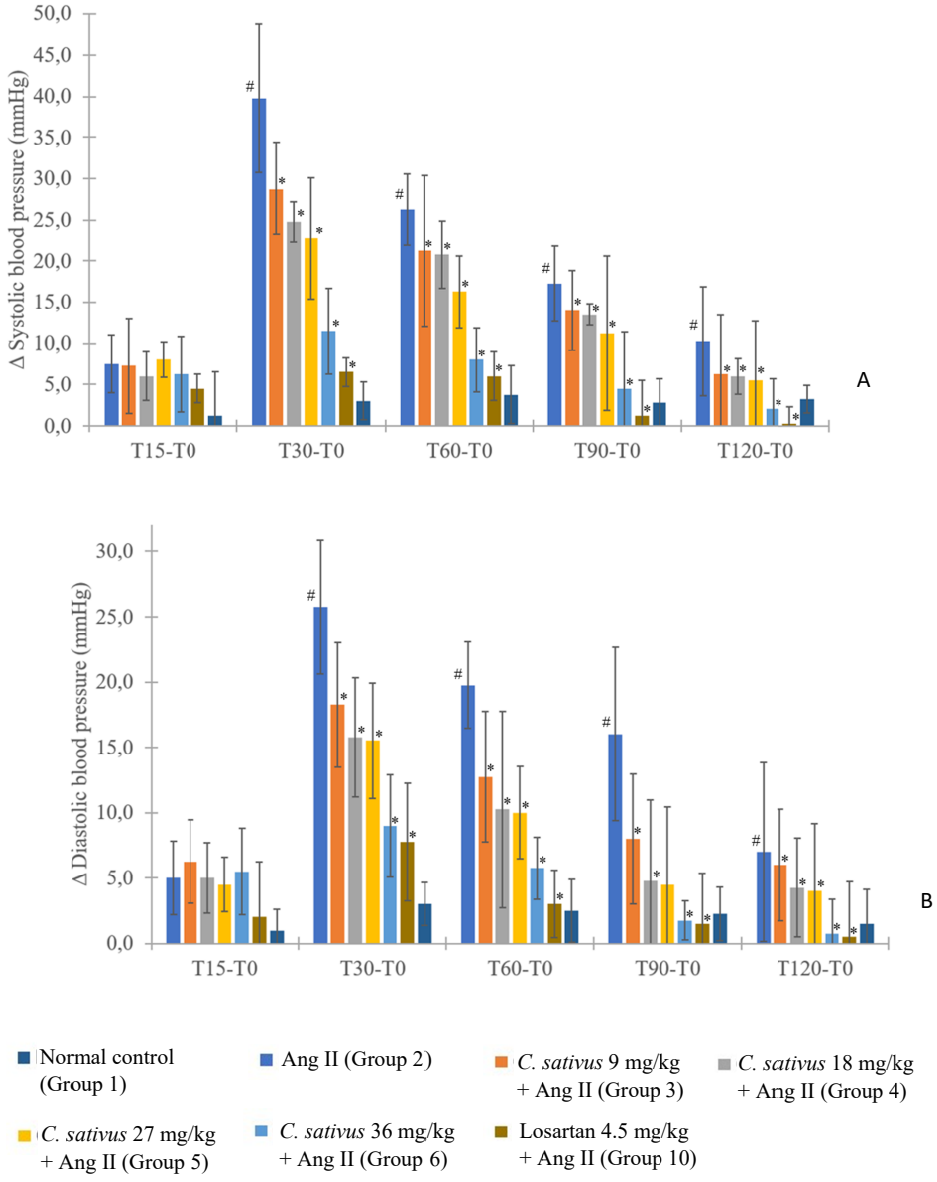

Figure 2. Attenuation effects of *C. sativus* (9, 18, 27, 36 mg/kg) and losartan on angiotensin II-induced elevation of blood pressure in rats. *C. sativus*, losartan, or sodium-CMC (vehicle) was administered 15 minutes prior to induction of angiotensin II (100 ug/kg, i.p). Time of angiotensin II injection was set for recording at time zero. (A) present change of systolic blood pressure from the time of observation to time zero; (B) present change of diastolic blood pressure from the time of observation to time zero. *$p < 0.05$ *C. sativus* or losartan + Ang II vs. Ang II. #$p < 0.05$ Ang II vs. normal control.

μg, 2.01 ± 0.17 mg, and 0.30 ± 0.03 μg per gram of dried fruit, respectively.

3. The effect of *CS* fruit on BP

Intraperitoneally injecting male Wistar rats with Ang II (100 μg/kg) increased their BP when compared with the normal controls, with the optimal increase occurring within 30 minutes of induction (SBP: 117.5 ± 2.4 vs 155.3 ± 5.9 mmHg in the normal control vs Ang II groups; DBP: 75.0 ± 0.8 vs 102.3 ± 2.8 mmHg in the normal control vs Ang II groups; $p < 0.05$, Fig. 1). The BP returned to baseline 120 minutes after induction.

BP monitoring revealed that *CS* (9, 18, 27, and 36 mg/kg) significantly lowered the Ang II-induced BP elevation (Fig. 2A, B). Thirty minutes after hypertension induction, the average SBP change (Δ), when compared with time zero in the groups that received *CS* + Ang II (*CS* doses: 9, 18, 27, and 36 mg/kg), were 28.8, 24.8, 22.8, and 11.5 mmHg, respectively (Fig. 2A), whereas the DBP changes were 18.3, 15.8, 15.5, and 9.0 mmHg, respectively (Fig. 2B). From 30 minutes after induction to the end of the treatment period, all groups treated with *CS* + Ang II exhibited a significant ($p < 0.05$) progressive, dose-dependent, SBP and DBP decline when compared with the Ang II group.

4. The effect of losartan-*CS* cotreatment on BP

The effects of various doses of *CS*, Los, and their combination on BP are shown in Figs. 3, 4. Thirty minutes after hypertension induction, the average SBP Δs when compared with time zero in the groups that received *CS* at 9 and 18 mg/kg, Los at 2.25 mg/kg, a combination of *CS* (9 mg/kg) + Los (2.25 mg/kg), and Los at 4.5 mg/kg along with Ang II, were 28.8, 24.8, 17.0, 13.8, and 6.5 mmHg, respectively. At 120 minutes of treatment, the SBP Δs were 6.3, 6.0, 0.8, 1.5, and 0.3, respectively

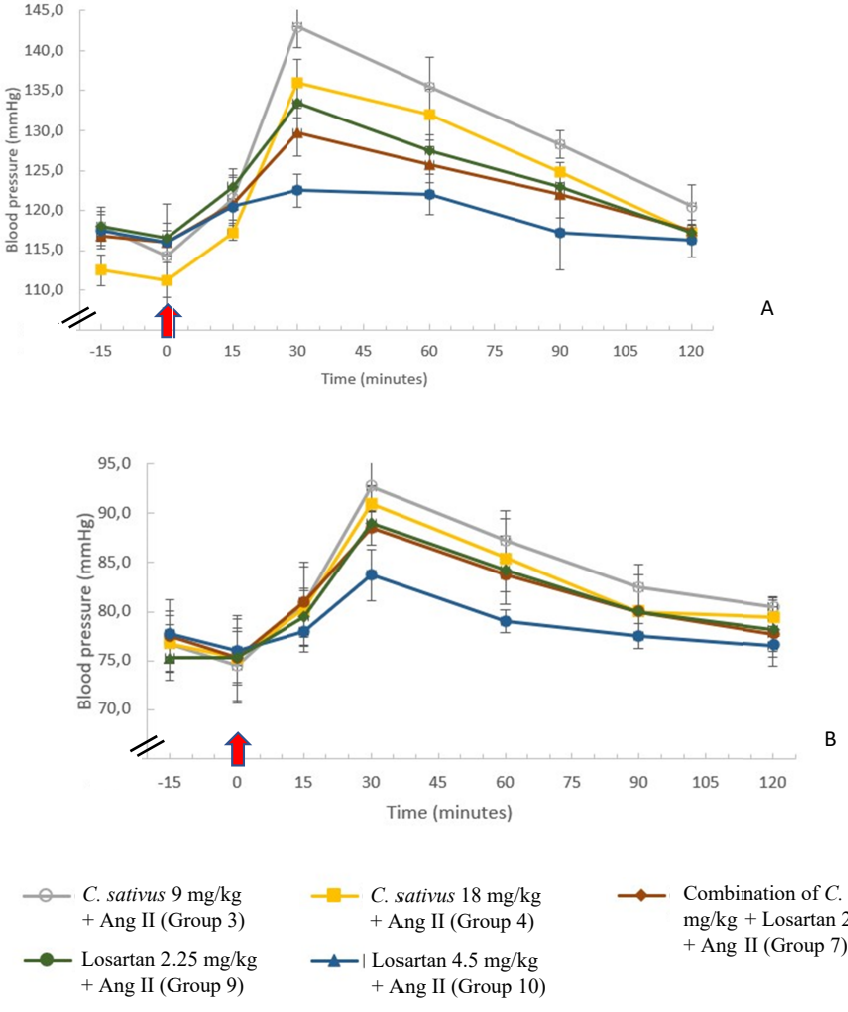

Figure 3. Effects of *C. sativus* (9 and 18 mg/kg), losartan (2.25 and 4.5 mg/kg), and combination *C. sativus* (9 mg/kg) + losartan (2.25 mg/kg) on angiotensin II-induced hypertensive rats. *C. sativus*, losartan, or their combination was administered 15 minutes prior to induction of angiotensin II (100 ug/kg, i.p). The red arrow represents time of angiotensin II injection and was set for recording at time zero. (A) systolic blood pressure; (B) diastolic blood pressure.

 https://doi.org/10.3831/KPI.2023.26.4.298

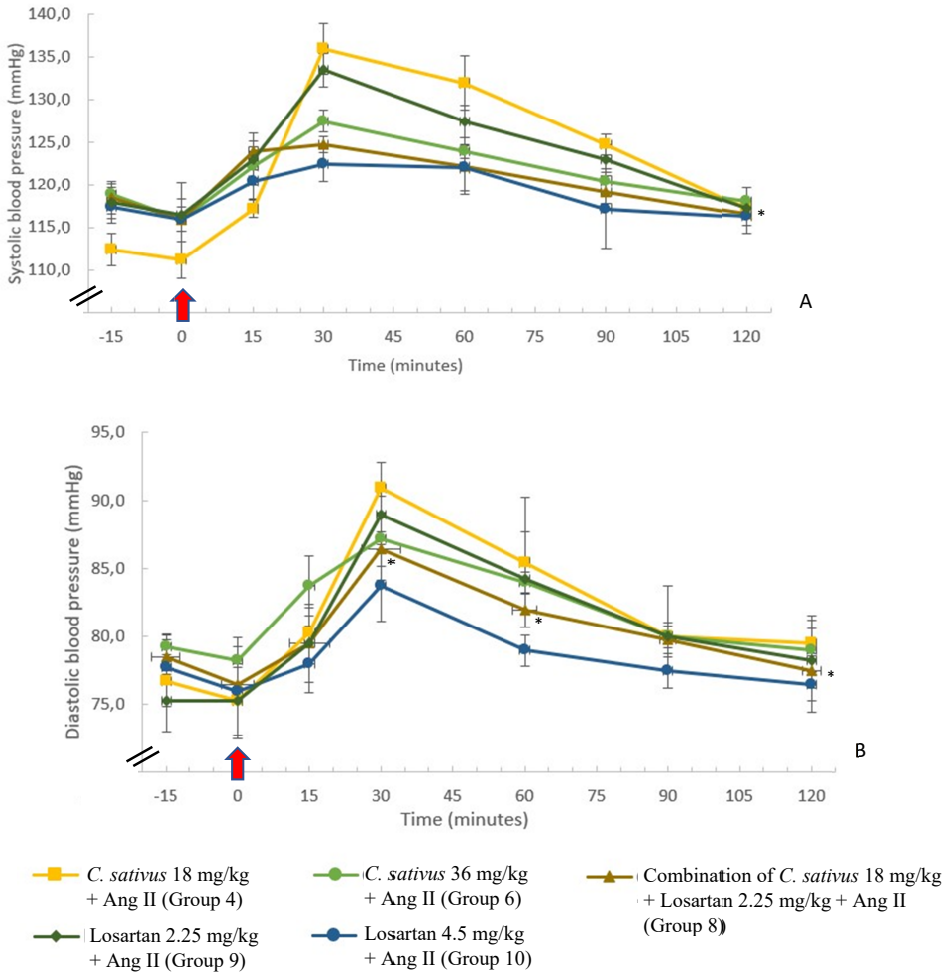

Figure 4. Effects of *C. sativus* (18 and 36 mg/kg), losartan (2.25 and 4.5 mg/kg), and combination *C. sativus* 18 mg/kg + losartan 2.25 mg/kg on angiotensin II-induced hypertensive rats. *C. sativus*, losartan, or their combination was administered 15 minutes prior to induction of angiotensin II (100 ug/kg, i.p). The red arrow represents time of angiotensin II injection and was set for recording at time zero. (A) systolic blood pressure; (B) diastolic blood pressure. *p < 0.05 combination of *C. sativus* 18 mg/kg + losartan 2.25 mg/kg + Ang II vs. *C.sativus* 36 mg/kg + Ang II.

(Fig. 3A). After the same treatments, DBP Δs were 18.3, 15.8, 13.8, 13.3, and 7.8 mmHg after 30 minutes and 6.0, 4.3, 3.0, 2.5 and 0.5 mmHg after 120 minutes (Fig. 3B). The BP Δs in the groups that received half the *CS* dose + Los was comparable to that of the full *CS* dose.

At 30 minutes after hypertension induction, the average SBP Δ when compared with time zero in the groups that received *CS* at 18 and 36 mg/kg, Los at 2.25 mg/kg, a combination of *CS* at 18 mg/kg + Los at 2.25 mg/kg, and Los at 4.5 mg/kg along with Ang II, were 24.8, 11.5, 17.0, 8.8, and 6.5 mmHg, respectively (Fig. 4). At 120 minutes, the SBP Δs were 6.0, 2.0, 0.8, 0.5, and 0.3 mmHg, respectively (Fig. 4A). In the same conditions, DBP Δs at 30 and 120 minutes after hypertension induction were 15.8, 9.0, 13.8, 9.0, and 7.8 mmHg and 4.3, 0.8, 3.0, 1.0, and 0.5 mmHg, respectively (Fig. 3B). The BP Δ in rats that received half the dose of the herb-drug combination (*CS* 18 mg/kg + Los 2.25 mg/kg along with Ang II) was significantly different when compared with treatment using the full *CS* dose (36 mg/kg) + Ang II induction ($p < 0.05$) but insignificantly different when compared with the full Los dose 4.5 mg/kg + Ang II.

DISCUSSION

In this study, we find that Ang II significantly elevates SBP and DBP in rats when compared with the normal control group ($p < 0.05$), indicating that Ang II successfully induced hypertension. Ang II plays an important role in maintaining equilibrium and the homeostatic regulation of BP. In addition to its vasoconstrictor activity, Ang II is suggested to increase peripheral vascular resistance through increased sympathetic nervous system activity, increased prostaglandin concentration (which modulates vasoconstriction), and decreased nitric oxide (NO) bioactivity via reactive oxygen species formation (which have oxidant activity and induce oxidative stress, causing vasoconstriction) [18-22].

Losartan, an anti-hypertension medication, blocks angio-

tensin II receptor type 1 in the renin–angiotensin system [23]. Here, we find that pretreatment with losartan significantly diminished the effect of Ang II on BP.

Cucumis sativus (*C. sativus*) has for a long time been widely used not only as a vegetable but also in traditional medicine. There is compelling evidence that *C. sativus* has numerous pharmacological activities, such as antibacterial, anticancer, antioxidant, and analgesic effects [24-26]. This study investigated the antihypertensive effects of *C. sativus* in a rat model of hypertension. Our findings indicate that pretreatment with *C. sativus* reduced Ang II-induced BP elevation dose-dependently. Throughout the experiments, the SBPs and DBPs of the rats that received the vehicle and Ang II (Group 2) remained significantly higher ($p < 0.05$) when compared with the *C. sativus*-treated groups (Groups 3-6). Significant differences in BPs (when compared with Group 2) were observed from 30 minutes after induction, onwards. However, longer observation was not feasible because, after two hours of induction, the BP fell to levels similar to those of the normal control group (Group 1).

The antihypertensive effects of *C. sativus* can be attributed to its possession of major compounds and its mineral content. Phytochemical analysis showed that our *C. sativus* sample contained major compounds, including flavonoids, saponins, and terpenoids, which is consistent with previous reports that flavonoids like kaempferol, quercetin, and cucurbitacin have been isolated from this plant [27]. Flavonoids are been reported to have biological effects, including antioxidant, vasorelaxant, and antihypertensive activities [28, 29]. Kaempferol mediates an antihypertensive effect by inducing endothelium-dependent vasorelaxation via the NO–cGMP–PKG signaling pathway, causing vasodilation [30]. Quercetin, the prototypical, abundant dietary flavonoid, has been shown to significantly reduce BP in clinical trials [31]. Cucurbitacin is structurally a terpene and is found in many plants of the *Cucurbitaceae* family. It exerts hypotensive effects through the suppression of Ang II-induced SBP increase and induction of acetylcholine-mediated vasodilatation in mesenteric arteries [10]. The triterpene, saponin, is suggested to exert antihypertensive activity by activating calcium-activated potassium channels in vascular smooth cells, reducing calcium influx and vasodilation [32].

C. sativus also has a high mineral content and our findings show that its fruit contains calcium, potassium, and zinc. Consistent with this finding, Niyi et al. [33] found that cucumber contains several minerals, including Ca, Cu, Fe, K, Mg, Na, and Zn. Calcium can reduce intracellular calcium by inhibiting parathormone, thereby reducing BP. Potassium can increase sodium excretion, lower renin secretion, facilitate arterial vasodilation, and decrease response to endogenous vasoconstrictors. Magnesium is reported to exert strong vasodilator activity via its ability to decrease vascular smooth muscle contractility [34]. Zinc contributes to nitric oxide synthase activity, which is critical for NO synthesis [35, 36]. NO can diffuse into adjacent smooth muscles and bind to the heme moiety of cytosolic guanylate cyclase, thereby elevating guanosine monophosphate levels, which promotes vasodilatation [37, 38]

The significantly stronger BP-lowering effect observed in the group treated with half the *C. sativus*-losartan combination dose when compared with the group treated with the full *C. sativus* dose, and its comparability with the effect of full dose losartan, suggests that the effects of the combination were additive. Additive effects occur when the combined effects of compounds are similar to the sum of the compounds' independent effects [39].

CONCLUSION

Here, we show that the *C. sativus* fruit dose-dependently prevents BP elevation. Our data indicate that when administered together with losartan, *C. sativus* can have an additive BP-lowering effect. Mechanistically, the blood pressure-lowering effect is likely to be mediated by the action of *C. sativus*' active ingredients on the renin–angiotensin–aldosterone pathway, which warrants further study.

ACKNOWLEDGEMENTS

The authors would like to thank Kusnandar Anggadiredja for critically reading the manuscript and all members of the Pharmacology lab for fruitful discussions. We highly appreciate the kind assistance of staff at the School of Pharmacy ITB in conducting the research.

CONFLICTS OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

FUNDING

This work was supported in part by the 2019 Research, Community Services and Innovation Funding Scheme (P3MI) of Bandung Institute of Technology, Grant No 048.2/11.C03/PKS/2019 and Indonesian Ministry of Research and Technology / National Research and Innovation Agency, Grant No. 2/EI/KP.PTNBH/2021.

ORCID

Tomi Hendrayana, https://orcid.org/0000-0003-2432-4416
Klaudia Yoana, https://orcid.org/0009-0005-6448-9938
I Ketut Adnyana, https://orcid.org/0000-0001-5217-2312
Elin Yulinah Sukandar, https://orcid.org/0000-0003-3540-012X

REFERENCES

1. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2018;71(6):1269-324. Erratum in: Hypertension. 2018;71(6):e136-9. Erratum in: Hypertension. 2018;72(3):e33.
2. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. Lancet. 2005;365(9455):217-23.
3. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19·1 million participants. Lancet. 2017;389(10064):37-55. Erratum in: Lancet. 2020;396(10255):886.
4. Feng XL, Pang M, Beard J. Health system strengthening and hypertension awareness, treatment and control: data from the China Health and Retirement Longitudinal Study. Bull World Health Organ. 2014;92(1):29-41.
5. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014;311(5):507-20. Erratum in: JAMA. 2014;311(17):1809.
6. Tabassum N, Ahmad F. Role of natural herbs in the treatment of hypertension. Pharmacogn Rev. 2011;5(9):30-40.
7. Mansoor GA. Herbs and alternative therapies in the hypertension clinic. Am J Hypertens. 2001;14(9 Pt 1):971-5.
8. Kamyab R, Namdar H, Torbati M, Ghojazadeh M, Araj-Khodaei M, Fazljou SMB. Medicinal plants in the treatment of hypertension: a review. Adv Pharm Bull. 2021;11(4):601-17.
9. Al Disi SS, Anwar MA, Eid AH. Anti-hypertensive herbs and their mechanisms of action: part I. Front Pharmacol. 2016;6:323.
10. Yuan RQ, Qian L, Yun WJ, Cui XH, Lv GX, Tang WQ, et al. Cucurbitacins extracted from Cucumis melo L. (CuEC) exert a hypotensive effect via regulating vascular tone. Hypertens Res. 2019;42(8):1152-61.
11. Mali VR, Mohan V, Bodhankar SL. Antihypertensive and cardioprotective effects of the Lagenaria siceraria fruit in NG-nitro-L-arginine methyl ester (L-NAME) induced hypertensive rats. Pharm Biol. 2012;50(11):1428-35.
12. Trejo-Moreno C, Méndez-Martínez M, Zamilpa A, Jiménez-Ferrer E, Perez-Garcia MD, Medina-Campos ON, et al. Cucumis sativus aqueous fraction inhibits angiotensin ii-induced inflammation and oxidative stress in vitro. Nutrients. 2018;10(3):276.
13. Palanisamy V, Shanmugam S, Balakrishnan S. Evaluation of diuretic activity of polyherbal formulation. Int J Pharm. 2015;5(1):244-7.
14. Teixeira K, dos Santos P, Citadini-Zanette V, DalBó S, de Aguiar Amaral P. Medicinal plants that can cause changes in blood pressure and interactions with antihypertensive agents. Am J Ethnomed. 2017;4(1):1-8.
15. Nana FW, Hilou A, Millogo JF, Nacoulma OG. Phytochemical composition, antioxidant and xanthine oxidase inhibitory activities of Amaranthus cruentus L. and Amaranthus hybridus L. extracts. Pharmaceuticals (Basel). 2012;5(6):613-28.
16. Kamkar-Del Y, Mohebbati R, Hosseini M, Khajavirad A, Shafei MN, Rakhshandeh H. Ethyl acetate and aqueous fractions of Ziziphus jujuba prevent acute hypertension induced by angiotensin II in rats. Cardiovasc Hematol Disord Drug Targets. 2020;20(2):108-15.
17. Kazemi F, Mohebbati R, Niazmand S, Shafei MN. Antihypertensive effects of standardized asafoetida: effect on hypertension induced by angiotensin II. Adv Biomed Res. 2020;9:77.
18. Luft FC, Wilcox CS, Unger T, Kühn R, Demmert G, Rohmeiss P, et al. Angiotensin-induced hypertension in the rat. Sympathetic nerve activity and prostaglandins. Hypertension. 1989;14(4):396-403.
19. Diz DI, Baer PG, Nasjletti A. Angiotensin II-induced hypertension in the rat. Effects on the plasma concentration, renal excretion, and tissue release of prostaglandins. J Clin Invest. 1983;72(2):466-77.
20. Loiola RA, Fernandes L, Eichler R, Passaglia Rde C, Fortes ZB, de Carvalho MH. Vascular mechanisms involved in angioten-

sin II-induced venoconstriction in hypertensive rats. Peptides. 2011;32(10):2116-21.
21. Zhang F, Tang H, Sun S, Luo Y, Ren X, Chen A, et al. Angiotensin-(1-7) induced vascular relaxation in spontaneously hypertensive rats. Nitric Oxide. 2019;88:1-9.
22. Rajagopalan S, Kurz S, Münzel T, Tarpey M, Freeman BA, Griendling KK, et al. Angiotensin II-mediated hypertension in the rat increases vascular superoxide production via membrane NADH/NADPH oxidase activation. Contribution to alterations of vasomotor tone. J Clin Invest. 1996;97(8):1916-23.
23. Lever AF. Slow pressor mechanisms in hypertension: a role for hypertrophy of resistance vessels? J Hypertens. 1986;4(5):515-24.
24. Kumar D, Kumar S, Singh J, Narender, Rashmi, Vashistha B, et al. Free radical scavenging and analgesic activities of Cucumis sativus L. fruit extract. J Young Pharm. 2010;2(4):365-8.
25. Tuama AA, Mohammed AA. Phytochemical screening and in vitro antibacterial and anticancer activities of the aqueous extract of Cucumis sativus. Saudi J Biol Sci. 2019;26(3):600-4.
26. Liang J, Chen D. Advances in research on the anticancer mechanism of the natural compound cucurbitacin from Cucurbitaceae plants: a review. Tradit Med Res. 2019;4(2):68-81.
27. Krauze-Baranowska M, Cisowski W. Flavonoids from some species of the genus Cucumis. Biochem Syst Ecol. 2001;29(3):321-4.
28. Clark JL, Zahradka P, Taylor CG. Efficacy of flavonoids in the management of high blood pressure. Nutr Rev. 2015;73(12):799-822.
29. Ciumărnean L, Milaciu MV, Runcan O, Vesa ȘC, Răchișan AL, Negrean V, et al. The effects of flavonoids in cardiovascular diseases. Molecules. 2020;25(18):4320.
30. Tettey CO, Yang IJ, Shin HM. Vasodilatory effect of kaempferol-7-O-α-L-rhamnopyranoside via NO-cGMP-PKG signaling. Arch Biochem Biophys. 2019;667:1-5.
31. Serban MC, Sahebkar A, Zanchetti A, Mikhailidis DP, Howard G, Antal D, et al. Effects of quercetin on blood pressure: a systematic review and meta-analysis of randomized controlled trials. J Am Heart Assoc. 2016;5(7):e002713.
32. Karmazyn M, Gan XT. Chemical components of ginseng, their biotransformation products and their potential as treatment of hypertension. Mol Cell Biochem. 2021;476(1):333-47.
33. Niyi O, Jonathan A, Ibukun A. Comparative assessment of the proximate, mineral composition and mineral safety index of peel, pulp and seeds of cucumber (Cucumis sativus). Open J Appl Sci. 2019;9(9):691-701.
34. Houston MC, Harper KJ. Potassium, magnesium, and calcium: their role in both the cause and treatment of hypertension. J Clin Hypertens (Greenwich). 2008;10(7 Suppl 2):3-11.
35. Mousavi SM, Mofrad MD, do Nascimento IJB, Milajerdi A, Mokhtari T, Esmaillzadeh A. The effect of zinc supplementation on blood pressure: a systematic review and dose-response meta-analysis of randomized-controlled trials. Eur J Nutr. 2020;59(5):1815-27. Erratum in: Eur J Nutr. 2020;59(5):1829.
36. Olechnowicz J, Tinkov A, Skalny A, Suliburska J. Zinc status is associated with inflammation, oxidative stress, lipid, and glucose metabolism. J Physiol Sci. 2018;68(1):19-31.
37. Förstermann U, Sessa WC. Nitric oxide synthases: regulation and function. Eur Heart J. 2012;33(7):829-37, 837a-837d.
38. Benjamin N, Vane J. Nitric oxide and hypertension. Circulation. 1996;94(6):1197-8.
39. Roell KR, Reif DM, Motsinger-Reif AA. An introduction to terminology and methodology of chemical synergy-perspectives from across disciplines. Front Pharmacol. 2017;8:158.