INTRODUCTION

Many traditional medications from herbal preparations are used in the mixture formulation. When it is in single herbal preparation, it often loses its expected pharmacological effect. Therefore, instead of investigating every single compound of the traditional herbal preparation pharmacological effect, using the original formula of herbal preparation which already proven its effectiveness for many decades will be far more promising.

Allium sativum, Belericae fructus, Curcuma aeruginosa, and Amomi fructus are kind of spice which often use for cooking whether alone or as a mixture with other spices. The mixture of A. sativum, B. fructus, C. aeruginosa, and A. fructus is preparation which has been used for hypertension treatment for years in Indonesia.

A. sativum or garlic bulb, B. fructus or jelawe, C. aeruginosa or temu ireng rhizome, and A. fructus or kapulaga have been widely used by people in Indonesia. Garlic bulb (A. sativum) is an herb that has been used to treat cardiovascular problems. Results of a meta-analysis study showed that the A. sativum lower blood pressure in hypertensive patients but not in people with normal blood pressure [1]. The clinical study also indicates that A. sativum can lower blood pressure when compared with placebo [2]. Meanwhile, B. fructus or Terminalia bellerica or known as jelawe in Indonesia is also proved to have antioxidant and antihypertensive effects [3,4]. C. aeruginosa rhizome or locally known as temu ireng has demonstrated activity as an antioxidant [5,6]. The other ingredient, A. fructus, also has many therapeutic effects such as anti-inflammatory, analgesics, and gastrointestinal protections [7].

Despite the long history of the polyherbal preparation as blood pressure lowering medicine, its activity toward blood pressure has not been proven scientifically. As a single preparation, A. sativum has been found to be effective to reduce blood pressure in hypertension patient [1]. However, combination of A. sativum with other herbs which also known to have either antihypertension or antioxidant activity such the polyherbal that had long been used in Indonesia is not yet known. Therefore, our study aims to investigate polyherbal preparation containing A. sativum, B. fructus, C. aeruginosa, and A. fructus blood pressure lowering effects on a hypertensive rat model.

MATERIALS AND METHODS

The protocol of this study has been reviewed and approved by Faculty of Medicine Universitas Gadjah Mada Ethical Committee with approval number KE/PP/58/EC/2016.

Polyherbal preparation

The polyherbal preparation was prepared by PT Marguna Tarulata APK Farma, Tegal, Indonesia. The polyherbal contains powder of A. sativum bulbus 180 mg, B. fructus 60 mg, C. aeruginosa rhizome 60 mg, and A. fructus 35 mg.

Animal experiment

The experiment was conducted using 12–16-week-old Wistar rat. The rats were kept in an individual cage and housed under maintained temperature and humidity house with 12:12-h light-dark cycle and free access to food and drink. The increase of the blood pressure is induced by unilateral nephrectomy followed by deoxycorticosterone acetate (DOCA)-salt administration. The left unilateral nephrectomy was done to all rats. 1 week after the unilateral nephrectomy surgery, DOCA was given twice a week at 25 mg/kg BW and the drink was changed into NaCl 0.9% and KCl 0.2%. Observation of the condition was performed every day during the study. At week 6 of DOCA administration, the rats were divided into five groups which are negative control group (NEG) that received aquadest 4 mL/kg BW, results:
positive control group (hydrochlorothiazide treatment [HCT]) that received hydrochlorothiazide 3 mg/kg BW, polyherbal extract 63 mg/kg BW group (DOSE 1), polyherbal extract 126 mg/kg BW group (DOSE 2), and polyherbal extract 252 mg/kg BW group (DOSE 3). The dose used is chosen based on the dose conversion from the human recommended dose of the polyherbal preparation. The treatment was given orally every day for 3 weeks. The blood pressure was measured weekly using CODA tail cuff blood pressure machine.

Data analysis
The data are presented as mean ± standard error of mean. The analysis was performed by one-way ANOVA followed by post hoc analysis using GraphPad Prism software. p<0.05 was considered as statistically significant.

RESULTS AND DISCUSSION

Results
The treatment given for 3 weeks did not change the body weight of the rats. The body weight measurement result at 3 weeks after treatment is shown in Fig. 1.

The heart rate and blood pressure measurement were measured by indirect methods using tail cuff blood pressure measurement machine. The heart rate measurement is shown in Fig. 2. The heart rate was the same among all groups of treatment.

The systolic blood pressure measured after 3 weeks of treatment is shown in Fig. 3. The mean of systolic blood pressure on the HCT group and DOSE 2 group was lower compared with those on the NEG group. Interestingly, the difference in systolic blood pressure between DOSE 3 group and NEG group was not statistically significant (n=5).

We also calculate the systolic blood pressure change by subtracting the systolic blood pressure after treatment (week 8) with the systolic blood pressure before treatment (week 6). Systolic blood pressure change is showed in Fig. 4.

The result shows that the systolic blood pressure change was positive in the HCT group, DOSE 1 group, and DOSE 2 group. Meanwhile, NEG group and DOSE 3 group show negative systolic blood pressure change. Positive blood pressure change indicates that the blood pressure after treatment is lower compared to those before treatment. Meanwhile, negative systolic blood pressure change shows that the blood pressure before treatment is higher compared to those before treatment. The systolic blood pressure change is significantly higher in HCT group and DOSE 2 group. Meanwhile, the systolic blood pressure change is not different between DOSE 1 group, DOSE 3 group, and NEG group.

Discussion
The administration of DOCA, a synthetic mineralocorticoid, with NaCl 0.9% and KCl 0.2% to uninephrectomized Wistar rat is one of the animal models for hypertension. The blood pressure increased in this model is suggested to be the result of excess body fluid volume [8].

After 3 weeks of therapy, it appears that systolic blood pressure in the HCT group was the lowest compared to those on the other groups. We suggest that it caused by the diuretic effect of hydrochlorothiazide. Hydrochlorothiazide is known as one of the first-line drugs for uncomplicated hypertension [9]. The mechanism of the action of hydrochlorothiazide in lowering blood pressure is not known clearly. The blood pressure lowering effect of hydrochlorothiazide is known to be the result of two mechanisms which are direct action on the endothelial and smooth muscle of blood vessels causing vasodilatation and indirect effects by decreasing cardiac output which occurs due to the mechanism of the action of hydrochlorothiazide in Na+/Cl cotransporter in distal convoluted tubule that regulates Na absorption which causes diuresis [10].

The systolic blood pressure in the polyherbal preparation group was lower compared with those on the NEG group. However, only systolic blood pressure in DOSE 2 group was lower statistically compared to those on the NEG group. This is probably due to the difference in the mechanism of the action of polyherbal preparation with hydrochlorothiazide.

Polyherbal preparation tablets contain garlic bulbs (A. sativum), jelawe (T. bellerica), temu ireng rhizome (C. aeruginosa), and cardamom (A. fructus). Garlic bulb (A. sativum) is an herb that has been widely used empirically to treat hypertension. A clinical study showed that A. sativum...
not only has an effect on blood pressure but also has antioxidant activity [5,6]. Based on those studies, we suggest that the mechanism of the action of polyherbal preparation on blood pressure could be through the antioxidant effect of the polyherbal compound.

The buildup of reactive oxygen species (ROS) is one of the mechanisms that play a role in the rise in blood pressure [15]. Some sources of oxidant are known to be present in hypertension such as NADPH oxidase, mitochondria, xanthine oxidase, endothelium nitric oxide synthase, cyclooxygenase, and cytochrome P450 epoxygenase [16]. The previous research has shown that administration of antioxidants rich diets has been shown to lower blood pressure in both animal and human models [16-18]. Antioxidant not only can improve blood pressure control but also can prevent the development of endothelial dysfunction and improve cardiovascular risk in the hypertensive patient. Ramipril, an angiotensin-converting enzymes inhibitor, shows its antioxidant effect on the patient with hypertension [16,19].

Antioxidants are needed to counteract oxidative stress in the body. However, high dose antioxidants can cause body function disorders because they provide pro-oxidant effects and disturb the balance of ROS in the body that actually is still needed to maintain the balance of body function [20]. The previous studies have shown that administration of antioxidants in high doses actually has a pro-oxidant effect [21]. Some antioxidant agent also has potential as pro-oxidant [16]. Those may be the reasons why in the highest dose of polyherbal preparation, the blood pressure did not decrease the blood pressure.

CONCLUSION

Polyherbal preparation contains garlic bulbs (A. sativum), jelawe (T. bellerica), temu ireng rhizome (C. aeruginosa), and cardamom (A. fructus) and shows the potential to be developed as a blood pressure lowering agent.

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AUTHORS’ CONTRIBUTIONS

Fara Siviu Yuliani and Setyo Purwono were supporting the design of the study and conducting the study along with Dwi Aris Agung Nugrahaningsih. Eti Nurwening Sholikhah, Mustofa, and Ngatidjan have of the study and conducting the study along with Dwi Aris Agung Fara Silvia Yuliani and Setyo Purwono were supporting the design of the study and conducting the study along with Dwi Aris Agung Nugrahaningsih. Eti Nurwening Sholikhah, Mustofa, and Ngatidjan have proofread the manuscript and recommend the critical revision to the manuscript drafted by Dwi Aris Agung Nugrahaningsih.

CONFLICTS OF INTEREST

There are no conflicts of interest regarding the publication of the manuscript.

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