

## Effects of Polyherbal Tablet for Hypertensive Patients

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### ABSTRACT

Hypertension is a degenerative disease whose prevalence is high and continues to increase over time. Polyherbal tablet have long been used by Indonesian people for hypertension drugs containing garlic (*Alium sativum*), jelawe (*Belericacae fructus*), temu ireng rhizomes (*Curcumae aeruginosae*) and kapulaga (*Amomi fructus*) extracts. This study aims to determine the effect of polyherbal tablet on hypertensive patients. The subjects of 29 hypertensive patients participated in an open-randomized-without comparison-study for 6 weeks. Subjects were divided into 3 groups, each subject received polyherbal tablet with a dose of 2x600 mg (group 1), 2x1200 mg (group 2) and 2x2400 mg (group 3). Blood pressure was monitored on D-0, D-3, D-5, D-7, W-2, W-3, W-4, W-5 and W-6. There was a significant decrease in systolic and diastolic blood pressure at the sixth week in all three treatment groups. The highest decrease in systolic blood pressure was in group 1 while diastolic blood pressure was in group 2 ( $-22.94 \pm 5.871$  and  $13.13 \pm 4.324$  respectively). The lowest reduction in systolic and diastolic blood pressure occurred in the third group ( $-15.07 \pm 3,519$  and  $8.98 \pm 3,394$  respectively). This study suggests that polyherbal tablet contains garlic (*Alii sativi*), jelawe (*Belericacae Fructus*), temu ireng rhizome (*Curcumae aeruginosae*) and cardamom (*Amomi Fructus*) can reduce blood pressure in patients with hypertension.

**Keywords:** Garlic; *Belericacae fructus*; *Curcumae aeruginosae*; *Amomi fructus*; hypertension

### INTRODUCTION

Hypertension is one of the global burdens of disease, with patients diagnosed with hypertension worldwide reaching 1 billion people in 2008 and it is estimated that it will continue to increase every year (WHO, 2013). Uncontrolled hypertension will cause several serious complications, namely myocardial infarction, stroke, renal failure and death (James *et al.*, 2104). In addition to controlling risk factors such as obesity, physical inactivity and low salt diets, hypertension control strategies are focused on the administration of antihypertensive therapy (Rahimi *et al.*, 2015)

One of several herbal medicines to treat hypertension in Indonesia is polyherbal tablet. Polyherbal tablet contain garlic (*Alii sativi*), jelawe (*Belericacae fructus*), temu ireng (*Curcumae aeruginosae*) and cardamom (*Amomi fructus*) extracts. Garlic (*Alii sativi*) has been widely used to treat various cardiovascular disorders. The results showed that garlic can reduce the blood pressure of hypertensive patients better than placebo (Ried *et al.*, 2016; Wang *et al.*, 2015). *Belericacae fructus* (*Terminalia bellerica*) has antioxidant and antihypertensive effects (Khan AU and Gilani AH, 2008; Chavan *et al.*, 2010). Antioxidant activity is also possessed by *Curcumae aeruginosae* and

*Amomi fructus* (Choudhury *et al.*, 2013; Nurcholis *et al.*, 2015; Guo *et al.*, 2008). Oxidative stress is the main mechanism in endothelial dysfunction and vascular damage, which has been known to play an important role in the pathogenesis of hypertension (Baradaran *et al.*, 2014; Guzik and Touyz, 2017). Research has been conducted on the effectiveness of polyherbal tablet and the results show that polyherbal tablet a dose of 252 mg/kgBB (equivalent to the dose in humans) can reduce the blood pressure of mice in the hypertension model (Ngatidjan and Nugrahaningsih, 2016). So the purpose of this study is to determine the effect of polyherbal tablet in hypertensive patients.

### METHODOLOGY

This study has received appropriate ethical approval (Number: KE/FK/0234/EC/2018) from the Medical and Health Research Ethics Commission of the Faculty of Medicine, Public Health and Nursing, Gadjah Mada University. The subjects of this study were hypertensive patients who had never been treated or who had been treated but had not taken medicine for 2 weeks or more with the inclusion criterias are adult, male and female, aged between 20-60 years; meet criteria for diagnosing hypertension stage 1 according to JNC 8 (TDS 140-159 or TDD 90-99 mmHg); new or stage 1 hypertensive patients which within 14 days before recruitment do not

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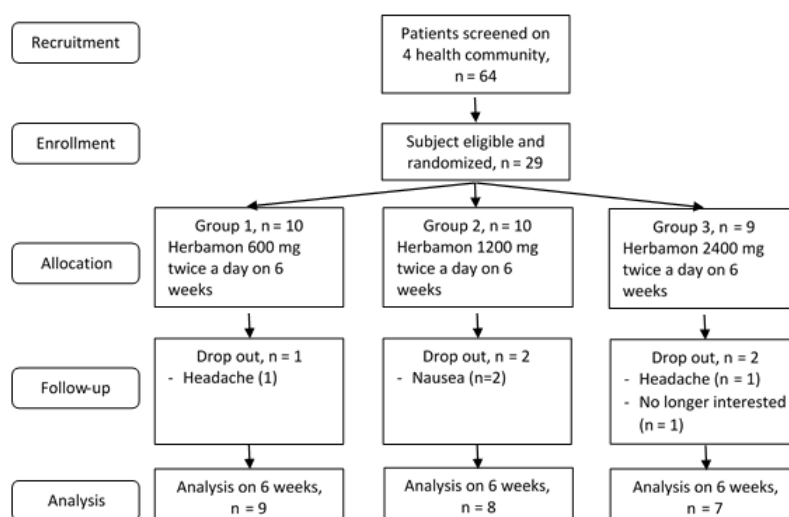


Figure 1. Trial flow chart

take antihypertensive drugs or herbs intended to reduce blood pressure; willing to take part in the study by signing an informed consent. Patients who are pregnant / lactating women, have a history of diabetes, a history of heart disease, liver function abnormalities (SGOT and / or SGPT > 3 times the upper limit of normal values), abnormal kidney function (urea and / or creatinine > 3 mg/dl), Polyherbal tablet hypersensitivity / intolerance was excluded.

This study is randomized, open-trial, without comparison. Subjects were divided into 3 groups, each subject received polyherbal tablet 2 times a day with polyherbal tablet doses of 2 x 600mg (group 1), 2 x 1200mg (group 2) and 2 x 2400mg (group 3) for 6 weeks. Doses can be titrated according to blood pressure when monitoring measurements in D1, D3, D5, D7, W2, W3, W4, W5 and W6. The daily dose range of polyherbal tablet are 1200 - 4800 mg/d. Polyherbal tablets preparations in tablet form were prepared by PT Marguna Tarulata APK Farma with 600 mg strength. The subjects would get the tablets gradually along with blood pressure measurement. polyherbal tablet is taken twice with an interval of 12 h. The tablets taken at the same time which is between 07.00-09.00 and 19.00-21.00, before or after meals. Subjects who meet the criteria to respond to therapy, they would receive a tablet of 7 d to week 6. During the study, subjects were required to consult other drugs (including OTC) consumed to the researcher. Other drugs that can be consumed were drugs that do not affect the subject's blood pressure. All drugs consumed by the subjects were recorded and reported.

Examinations were carried out include vital sign examinations, basic physical examinations, ECG and laboratory examinations. Vital sign examination was carried out by paramedics in 9 times on D-0 (day 0), D-3, D-5, D-7, W-2, W-3, W-4, W-5 and W-6. Vital sign examination included examination of blood pressure, body temperature, pulse rate and respiratory rate. Blood pressure examination used a calibrated Standard adult size nylon aneroid sphygmomanometer. Measurements were performed at the position after the subject has sat quiet for at least 5 minutes in the chair and performed 2 measurements on the left arm that is parallel to the heart. The value obtained was the average of 2 measurements. The basic physical examination was carried out by the doctor, each subject was examined twice, at D-0 and W-6. Physical examinations included examination of the cardiovascular, respiratory, gastrointestinal, dermatological, musculoskeletal and nervous systems; examination of height and weight. Each subject received an ECG examination twice on D-0 and W-6. Laboratory tests included routine blood test, SGOT, SGPT, ureum and creatinine which were also carried out twice on D-0 and W-6.

## RESULT AND DISCUSSION

The study was conducted in Plosokuning, Kayen, Kancilan, and Babadan DI Yogyakarta. Of the 64 people with hypertension during screening, 29 subjects met the inclusion criteria (Figure 1). Ten subjects were allocated in group 1 and group 2. Only 9 subjects is randomized into group 3. One subject from group 1 dropped out (DO) at the beginning of taking the drug because of headache

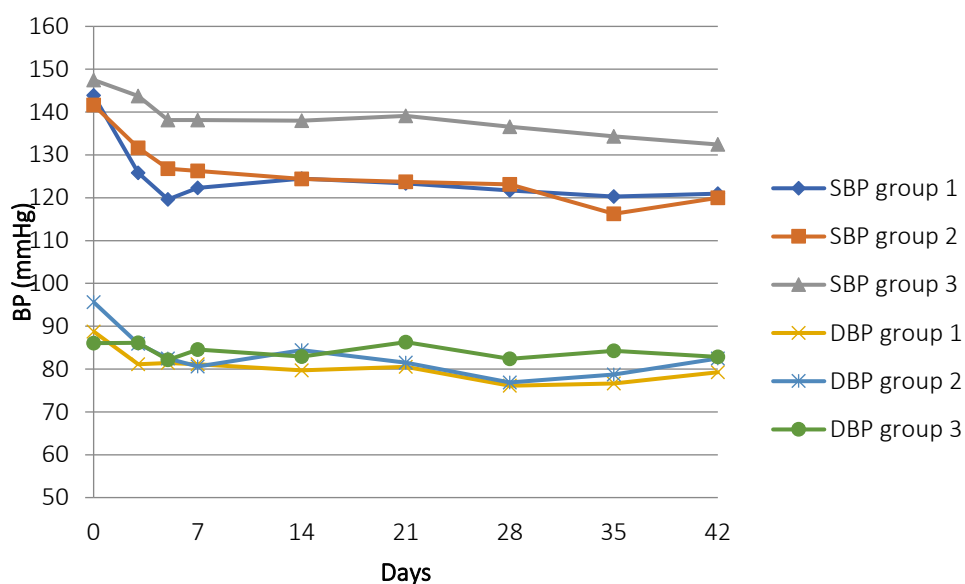


Figure 2. Effect polyherbal tablet on blood pressure by days.

complaint, 2 subjects from group 2 dropped out at the beginning of drug consumption and at day 5 because they complained of nausea, and 2 subjects from group 3 dropped out at the beginning of drug consumption and during the third week because they complained of nausea and decided not to continue the study. So that the number of subjects analyzed at the end of the study were 24 subjects.

Baseline characteristics did not differ significantly between treatment groups, including age, BMI and blood test parameters. Based on the BMI value of the participants, most of the participant was included in the overweight category with BMI average of  $24.96 \pm 4.21$ . The average of total cholesterol, LDL and HDL in groups 1, grup 2 and grup 3 were  $206.58 \pm 26.02$ ,  $55.71 \pm 11.89$ , and  $136.75 \pm 23.99$  respectively (Table I). These data shows that most of the participant has dyslipidemia.

The mean blood pressure reduction from baseline compared to the end of the study (week 6) is presented in Table II. All groups showed a significant decrease in systolic blood pressure. The highest Systolic Blood Pressure decrease was seen in the group 1. Diastolic blood pressure decreased significantly only in the group 1 and 2. The highest reduction in diastolic blood pressure was found in group 2. Figure 2 shows the mean blood pressure for each measurement. Eventhough the systolic blood pressure decreased in all three groups, systolic blood pressure in the third group did not reach the normal blood pressure value until the end of the study.

Our study showed that polyherbal tablet containing *Alium sativum*, *Belericæ fructus*, *Curcuma aeruginosa*, dan *Amomi fructus* can reduce systolic blood pressure by an average of 20 mmHg and diastolic blood pressure by 10 mmHg. There was a significant decrease in systole blood pressure in the all groups and diastolic blood pressure in group 1 and 2. The difference of mean systolic and diastolic blood pressure reduction were not statistically significant among the three groups ( $p = .632$  and  $p = .231$  respectively). Grup 1 that received 2 x 600 mg tablet showed the highest decrease in systolic blood pressure. During the study, the subjects in the group 1 whom blood pressure fail to reach the normal value, the polyherbal dose was increased to a dose of 2 x1200 mg. This shows that the group 2 dose actually has a better blood pressure reduction effect than dose 1. This result is in accordance with the results of preclinical study on hypertensive animal models (Ngatidjan and Nugrahaningsih, 2016). In preclinical study, blood pressure was the lowest at the group treated with the dose that equal to the dose used in group 2 of the present study.

Polyherbal tablet used in this study contains garlic (*Alii sativi*), jelawe (*Belericæ Fructus*), temu ireng rhizome (*Curcumæ aeruginosæ*) and cardamom (*Amomi Fructus*) extracts. Several meta-analyzes showed that garlic can reduce blood pressure in patients with hypertension (Ried, 2014; Xiong *et al.*, 2015). Effects of blood pressure reduction by garlic with a dose range of 240-2400 mg can reduce systolic blood pressure by

Table I. Baseline characteristics

Characteristics	All Subjects* (n = 24)	Group 1 (n = 9)	Group 2 (n = 8)	Group 3 (n = 7)
Gender (m/f)	1/23	0/9	0/8	1/6
History of smoking (n/%)	1/4	0/0	0/0	1/14
	<b>mean±SD (range)</b>		<b>mean±SD</b>	
Age (years)	51.50±6.56 (39-60)	49.22±6.18	51.63±6.55	54.29±6.87
BMI (kg/m <sup>2</sup> )	24.96±4.21 (19.55-32.70)	23.83±4.67	25.49±3.39	25.79±4.71
Hb (g/dL)	12.74±1.04 (10.20-14.70)	12.62±.92	13.14±.81	12.44±1.39
RBC (10 <sup>6</sup> /μL)	4.64±.38 (3.75-5.43)	4.48±.35	4.78±.37	4.67±.39
Hematocrite (%)	39.44±2.74 (35.70-44.00)	39.07±3.12	40.50±2.20	38.70±2.81
WBC (/μL)	7238.33±1202.5 (5230-10150)	7228.89±1252.1	7438.75±1505.8	7021.43±835.9
Trombocyte (/μL)	293250±67242 (179000-466000)	289333±68167	269875±38394	325000±86540
SGOT (U/L)	18.58±4.58 (12-27)	17.33±4.95	19.38±4.50	19.29±4.50
SGPT (U/L)	16.13±7.66 (7-45)	16.00±11.31	15.75±3.20	16.71±6.45
TC (mg/dL)	206.58±26.02 (164-281)	201.78±23.06	208.13±20.56	211.00±36.50
TG (mg/dL)	116.92±47.88 (72-241)	102.33±24.76	127.38±53.73	123.71±63.92
HDL (mg/dL)	55.71±11.89 (35-79)	58.56±9.28	54.38±16.92	53.57±8.54
LDL (mg/dL)	136.75±23.99 (100-197)	132.33±25.52	138.00±17.28	141.00±30.62
Ureum (mg/dL)	25.53±9.25 (14.0-50.5)	23.12±5.40	29.29±14.53	24.34±3.64
Creatinine (mg/dL)	.74±.14 (.47-1.00)	.67±.11	.78±.15	.80±.11

Abbreviations: BMI, body mass index; f, female; Hb, hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; m, male; RBC, red blood cells count, SD, standard deviation; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; TC, total cholesterol; TG, triglycerides; WBC, white blood cells count.

\* no significant differences between groups

8.35 mmHg and diastolic pressure by 6.1 mmHg (Ried, 2014). The garlic active compound which is suggested to have antihypertensive effects are s-allylcysteine, allicin, allyl methyl sulfide (AMS) and diallyl sulfide (DAS). The garlic antihypertensive action is suggested due to its antioxidant activity by trapping reactive oxygen species such as O<sub>2</sub><sup>-</sup> and H<sub>2</sub>O; inhibiting the activity of NADPH oxidase; and increasing the activity of superoxide dismutase (potent antioxidant). Besides the hypotensive

effect of garlic also through inhibiting of Na<sup>+</sup> channel activity, suppressing NFκB expression thereby reducing atherosclerosis, triggering the production of H<sub>2</sub>S which functions as a vasodilator, inhibiting ACE, and inhibiting Angiotensin II-induced cell cycle production from vascular smooth muscle cells (Hosseini and Hosseinzadeh, 2015; Ried and Fakler, 2014; Shouk *et al.*, 2014). *Belericæ fructus* or jelawe is thought to have antihypertensive effects through inhibition of

Table II. Mean changes of sitting blood pressure from baseline compared with the end of study

Treatment	N	Mean change (SE)	95% CI	p-value
<b>Systolic blood pressure</b>				
Polyherbal tablet 2x 600 mg	9	-22.94 (5.871)	(-36.483, -9.406)	.004
Polyherbal tablet 2x1200 mg	8	-21.63 (6.279)	(-36.473, -6.777)	.011
Polyherbal tablet 2x2400 mg	7	-15.07 (3.519)	(-23.683, -6.460)	.005
<b>Diastolic blood pressure</b>				
Polyherbal tablet 2x600 mg	9	-9.56 (3.648)	(-17.968, -1.143)	.031
Polyherbal tablet 2x1200 mg	8	-13.13 (4.324)	(-23.349, -2.901)	.019
Polyherbal tablet 2x2400 mg	7	-8.98 (3.394)	(-11.520, 5.092)	.380

Ca<sup>2+</sup> influx on calcium channels and through its antioxidant effects. Research conducted by Namphootiri *et al* (2011) showed that *Belericacae fructus* has antioxidant activity and radical scavenging in DPPH, superoxide and hydroxy radical due to its gallic acid and ferulic acid content. *Curcuma aeruginosa* and *Amomi fructus* also have antioxidant effects (Nurcholis *et al.*, 2015; Guo *et al.*, 2008). Study conducted by Moon-ai *et al* (2012) of 15 *Zingiberaceae* plants showed that *Curcuma aeruginosa* had a significant superoxide dismutase activity. Whereas *Amomi fructus* has DPPH radical scavenging activity and ferric reducing antioxidant power (FRAP) which can scavenging free radical and reduces prooxidants (Guo *et al.*, 2008). Oxidative stress is the main mechanism in endothelial dysfunction and impaired vascular relaxation, which has been known to play an important role in the pathogenesis of hypertension. So that antioxidants administration is hypothesized to function as a vascular protector (Siti *et al.*, 2015).

The treatment with highest dose of the polihherbal (Polyherbal tablet 2x2400 mg) showed the lowest reduction in blood pressure. This result is also in accordance with studies in rat, that showed that at the highest doses the decrease of the blood pressure was not better than lower dose. It might be caused by the antioxidant effect of the compound in the polyherbal. In the high dose, the antioxidant can be converted into prooxidant and loss its protective effect (Bouayed and Bohn, 2010; Suru and Ugwu 2015).

## CONCLUSION

The polyherbal tablet contains garlic (*Alii sativi*), jelawe (*Belericacae Fructus*), temu ireng rhizome (*Curcuma aeruginosae*) and cardamom (*Amomi Fructus*) can reduce blood pressure in patients with hypertension.

## ACKNOWLEDGEMENT

We thank to all patients, village head and health cadres for their involvement and helping in

this study. This research was funded by Ministry of Research, Technology and Higher Education grant, Republic of Indonesia. Thank you to Prof. Dr. Mae Sri Hartati W, Apt, M.Si and Prof. dr. Ngatidjan, MSc, SpFK for her support for this research. Polyherbal tablet procurement is provided by PT Marguna Tarulata APK Farma which is not involved in the design preparation, data collection, analysis and research publication.

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