

## Lowering blood pressure effect of *Apium graveolens* (*seledri*) and *Orthosiphon stamineus* benth (*kumis kucing*) in mild and moderate hypertension

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### Abstrak

Di Indonesia *Apium graveolens* (*seledri*) dan *Orthosiphon stamineus* benth (*kumis kucing*) sudah lama dikenal sebagai bahan obat tradisional yang dipercaya dapat menurunkan tekanan darah. Pada saat ini sudah beredar di pasaran Indonesia kemasan fitofarmaka yang berisi kombinasi antara dua bahan tersebut. Oleh karena itu perlu dilakukan penelitian untuk mengetahui efektifitas dan efek samping terhadap penderita hipertensi ringan dan sedang. Penelitian dilakukan di daerah Monica Jakarta di Jakarta Selatan 3 Juli sampai 29 Oktober 2001 terhadap penderita hipertensi ringan dan sedang dengan randomized double blind controlled trial. Kelompok pertama (72 subjek) mendapat fitofarmaka (*Tensigard*<sup>®</sup> yang berisi *seledri* dan *kumis kucing*) sebanyak 3 x 250 mg, sedangkan kelompok kedua (70 subjek) diberikan Amlodipine 1 x 5 mg. Pengamatan dilakukan selama 12 minggu dan parameter yang diukur adalah tekanan darah sistolik maupun diastolik, kadar lipid plasma, kadar gula darah sebelum dan sesudah perlakuan, serta kadar elektrolit tiap dua minggu perlakuan. Hasil penelitian menunjukkan bahwa pemberian fitofarmaka selama dua belas minggu menurunkan tekanan darah sistolik (TDS) maupun diastolik (TDD) setara dengan Amlodipine (TDS  $24,72 \pm 1.63$  mmHg vs  $26,27 \pm 2.18$  mmHg,  $P > 0,05$ ; TDD  $10,00 \pm 0.96$  mmHg vs  $9,49 \pm 1.37$  mmHg  $P > 0.05$ ). Di samping itu pemberian fitofarmaka dua belas minggu tidak mempengaruhi kadar elektrolit plasma, kadar lipid plasma maupun kadar gula darah. Selain itu tidak ditemukan efek samping yang berarti pada pemberian fitofarmaka maupun Amlodipine selama penelitian berlangsung. Pada penelitian ini dapat disimpulkan bahwa fitofarmaka dapat menurunkan tekanan darah sistolik maupun diastolik setara dengan Amlodipine serta tidak ditemukan efek samping yang berarti bagi penderita hipertensi ringan dan sedang selama waktu penelitian. (*Med J Indones* 2002; 11: 195-201)

### Abstract

In Indonesia *Apium graveolens* and *Orthosiphon stamineus* benth have been used to as traditional medicines to lower blood pressure. Since at present time is available as a combination of those phytopharmaca in the market, therefore, it is necessary to conduct a study to evaluate the effectivity and side effects of those phytopharmaca toward hypertensive subjects. A randomized double blind controlled trial was conducted at area of Monica – Jakarta in South of Jakarta from 3 July until 29 October 2001 toward mild and moderate hypertensive subjects. The first group (72 subjects) received phytopharmaca (*Tensigard*<sup>®</sup> which contains *Apium graveolens* and *Orthosiphon stamineus* benth) 3 x 250 mg, while the second group (70 subjects) had Amlodipine 1 x 5 mg. Observation were conducted for 12 weeks, and the parameter observed were systolic and diastolic blood pressure (SBP and DBP), plasma lipid, blood glucose before and after treatment, and electrolyte with two week intervals. The Results revealed that the phytopharmaca treatment for 12 weeks lowered SBP and DBP equivalent to Amlodipine (SBP  $24.72 \pm 1.63$  mmHg vs  $26.27 \pm 2.18$  mmHg;  $P > 0,05$ ; DBP  $10.00 \pm 0.96$  mmHg vs  $9.49 \pm 1.37$  mmHg;  $P > 0.05$ ). Phytopharmaca treatment for 12 weeks did not influence plasma electrolyte, as well blood glucose levels. There was not a significant side effects noted for both phytopharmaca and Amlodipine during the study period. In conclusion, the trial reveals that the phytopharmaca lowered systolic and diastolic blood pressure equivalent with Amlodipine among mild and moderate hypertensive subjects. During the study period there was not a significant side effect noted. (*Med J Indones* 2002; 11: 195-201)

**Keywords:** blood pressure, phytopharmaca, side effect, plasma electrolytes

Hypertension is an important risk factor for coronary heart disease. Several studies in Indonesia reported

that the hypertensive prevalence ranged from 17% to 22%.<sup>1</sup> Based on Joint National Committee (USA) consensus VI,<sup>2</sup> the first step of hypertension treatment is a life style changes. If the life style changes failed, pharmacological treatment is given.

A number of Indonesian people consume some traditional herbs to treat hypertension. One of the phytopharmaca for treating hypertension is Tensigard® (a product of PT Phapros, Semarang) which contains *Apium graviolens* and *Orthosiphon stamineus benth.* The previous phase one and two<sup>3,4</sup> trial proved that these phytopharmaca lowered blood pressures significantly.<sup>4</sup> These phytopharmaca contain active compounds which able to lower blood pressure, i.e. apigenin and manitol which have function as calcium antagonist and diuretics respectively.

*Orthosiphon stamineus benth* is predicted have a dominant diuretic effect to lower high pressure.<sup>6-7</sup> Therefore, this study is to prove to what extend these phytopharmaca lowering blood pressure among mild and moderate hypertensive subjects, and to investigate some related side effects.

## METHODS

This study was conducted at area Monica-Jakarta in South of Jakarta from July 3 until October 29 2001. Subjects were derived from MONICA (Monitoring of Trend in Cardiovascular Disease) Jakarta population study. The population consisted of 1800 subjects, where 400 subjects suffered from high blood pressure. There were one hundred and sixty subjects suffering from mild or moderate hypertensive who were eligible for this study based on inclusion and exclusion criteria and those who state to join the study. The inclusion criteria were subjects aged 25 - 70 years, essential hypertension, did not take anti hypertensive treatment for the last two weeks.

Hypertension was defined as follows: Diastolic blood pressure 95 - 114 mmHg, or systolic blood pressure 160 - 199 mmHg. Blood pressure was derived from average of two measurements in sitting position. While exclusion criteria were: (1) Pregnant or lactating women; (2) Women who were taking hormonal contraceptive methods; (3) Subjects suffering from angina pectoris (4) Subjects suffering from infarct, stroke, transient ischemic attack (TIA), percutaneous transluminal cardio angiography (PTCA) within the last six months; (5) Subjects who were suffering from heart failure (NIHA classes II-IV), severe arrhythmia, AV block; (6) History of secondary hypertension, such as hiperaldosteronism, Pheochromocytoma, kidney vascular stenosis, coarctation of the aorta, cushing syndrome, (7) Abnormal liver function as diagnosed by two or more laboratory liver function

tests; (8) Kidney failure; (9) Orthostatic hypotension in accordance with the other anti-hypertensive drugs; (10) Severe hypertension (blood pressure 200/115 mmHg or more); (11) Hypersensitive to Ca-channel blocker; (12) Blood donor for the last four weeks; (13) History of alcohol dependency, unstable psychology which caused could not be able to sign inform consent; and (14) Who were still joining the other drug study.

Upon signing inform consent, the would be subjects were randomized divided into two groups. After having washed out for one week, all subjects began to follow the treatment. The first group received phytopharmaca (Tensigard® a produced of PT. Phapros, Semarang) 3 x 250 mg/day, and the second group had Amlodipine 1 x 5 mg/day and 2 x 1 placebo/day in order the oral drug frequency as well the capsule size and color identical for the two groups. Each capsule of phytopharmaca contains Apii herba extract of *Orthosiphonis folium* (75:25) 99,40 %. While the placebo contains sacharose.

Amlodipine was selected for this study as the comparative drug because at present time this anti-hypertensive drug has been proved to control hypertension and calcium antagonist is widely used. If within two weeks there was no blood pressure decrease, the doses increased into 2 x 2 capsules, which contain 250 mg phytopharmaca, and for Amlodipine. 1 x 10 mg. In case by increasing these doses there was no response, the respective subject was discontinued for this study, and given taken a suitable anti-hypertensive drugs.

Subjects who fulfilled inclusion and signed inform consent went for twice blood pressure assessments taken on sitting position by five minutes intervals, body weight, body height, heart rate, laboratory tests (haemoglobin, white blood cell, total cholesterol, high density lipid (HDL), low density lipid (LDL), triglyceride, blood sugar, liver function, kidney function, electrolytes: kalium, chloride, magensium, and natrium), chest x-ray, and electrocardiography. Subjects were given phytopharmaca or Amlodipine 90 tablet or capsules, and were asked to make a revisit on the day 15. These procedures were repeated every two weeks. Subjects' evidence to take medication was seen by the rest of the drugs given.

Comprehensive laboratory tets were performed at the beginning and at the end of the study. Where as electrolites test were performed every two weeks.

Hemoglobine and white blood cells were done by taking 1 ml blood EDTA, and was measured by flow citometry using technicon (TH 3). Tests for plasma cholesterol, triglyceride, HDL-cholesterol and LDL-cholesterol were carried by taking 0.3 ml serum by photometri methods using Hitachi 917 tool. Blood sugar test was carried out by taking 0.3 ml serum and measured by photometry methods using Hitachi 917 tool. The same methods were carried for SGOT, SGPT, ureum, creatinine and uric acid. While for blood electrolyte was performed by ISE (Ion Selective Electrode) methods using AVL tool.

Numeric data were analysed by two samples t-test for normal distribution data, and Mann-Whitney test for abnormal distribution data. Categorized data were analysed using Pearson's chi-square or Fisher exact statistical tests. The similarity was considered if there is a  $P > 0.050$  based on the results of significant statistical tests. All statistical tests were based on two tail tets. All caculation were performed by using SPSS software version 10.

Ethical Committee of the National Cardiac Center Harapan Kita approved this study.

## RESULTS

At the beginning of the study eighty subjects participated in this study for each groups. During the study period there were 18 subjects discontinued the study (eight subjects from the phytopharmaca group, and 10 subjects belonged to Amlodipine group). There were several reasons for discontinuing this study, such as: (1) The subjects could not afford the side effect; (2) The subjects felts that the medicines were not suitable; (3) The subjects moved to other address and could not be followed-up; (4) Other reasons.

Table 1 shows that phytopharmaca and Amlodipine groups were similarly distributed with respect to gender, smoking habits, family history. Furthermore, more phytopharmaca group than Amlodipine group who had dislipidemia ( $P = 0.117$ ).

In addition Table 2 shows that the two groups were also similarly distributed with respect of age, blood pressure on entry, laboratory (except for LDL), and electrolytes findings. Tensgard<sup>®</sup> group had a significantly higher LDL level compared with Amlodipine group ( $P = 0.033$ ).

Table 1. Some characteristics of subjects

	Phytopharmaca (N=72)	Amlodipine (N=70)	P
<b>Gender</b>			0.922
Male	54	52	
Female	18	18	
<b>Smoking habits</b>			0.600
No	38	40	
Yes	34	30	
<b>Dislipidemia</b>			0.117
No	29	40	
Yes	43	30	
<b>Family history</b>			0.423
No	29	45	
Yes	43	18	
<b>Diabetes mellitus type II</b>			0.414
No	62	63	
Yes	10	7	

Table 2. Some characteristics of subjects

	Phytopharmaca (N=72) Mean ± SD	Amlodipine (N=70) Mean ± SD	P
<b>Age (years)</b>	59.60 ± 1.05	61.03 ± 1.26	0.378
<b>Physical performance</b>			
Body weight (kg)	61.40 ± 1.32	61.18 ± 1.47	0.913
Height (cm)	157.48 ± 0.85	158.72 ± 0.97	0.340
<b>Blood pressure on entry</b>			
Systolic (mmHg)	163.68 ± 1.64	165.76 ± 2.04	0.460
Diastolic (mmHg)	96.67 ± 0.77	96.69 ± 1.18	0.825
<b>Laboratory (mg/dl)</b>			
Total cholesterol	205.81 ± 4.66	196.06 ± 4.29	0.090
HDL	41.62 ± 1.47	42.02 ± 1.39	0.971
LDL	131.07 ± 4.35	120.08 ± 3.32	0.033
Triglyceride	164.00 ± 8.29	186.54 ± 17.3	0.270
Fasting blood sugar	101.99 ± 3.76	105.29 ± 4.83	0.455
SGOT	20.96 ± 1.00	21.77 ± 0.88	0.254
SGPT	23.25 ± 1.66	22.35 ± 2.13	0.979
<b>Electrolytes (mmol/dl)</b>			
Kalium	4.53 ± 0.08	4.53 ± 0.10	0.287
Chloride	104.59 ± 0.42	104.07 ± 0.48	0.734
Magnesium	2.13 ± 0.06	2.11 ± 0.05	0.860
Natrium	140.98 ± 0.26	140.88 ± 0.28	0.794

Table 3 and Table 4 show that diastolic and systolic blood pressure gradually decreased in both groups. Systolic and diastolic blood pressure were prominent different decreases between two groups were noted during week of 4 and 6 ( $P = 0.027$  and  $0.078$  respectively).

Table 3. Systolic blood pressure on entry and the decrease by week of treatment

Week	Phytopharmaca (N = 72)		Amlodipine (N = 70)		P
	Systolic blood pressure	Decrease from the entry measurement	Systolic blood pressure	Decrease from the entry measurement	
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
Week 0	163.68 ± 1.64	-	165.76 ± 2.04	-	-
Week 2	149.51 ± 1.90	14.17 ± 1.88	149.41 ± 2.30	16.36 ± 2.05	0.433
Week 4	149.79 ± 1.60	13.89 ± 1.86	146.02 ± 1.96	19.75 ± 1.79	0.027
Week 6	143.54 ± 1.36	20.14 ± 1.78	141.67 ± 1.61	23.83 ± 2.11	0.180
Week 8	142.78 ± 1.79	20.90 ± 2.08	141.27 ± 1.39	24.49 ± 1.97	0.220
Week 10	140.69 ± 1.14	22.99 ± 1.73	140.34 ± 1.53	25.42 ± 2.13	0.371
Week 12	139.15 ± 1.18	24.72 ± 1.63	139.49 ± 1.73	26.27 ± 2.18	0.563

Table 4. Diastolic blood pressure on entry and the decrease by week of treatment

Week	Phytopharmaca (N = 72)		Amlodipine (N = 70)		P
	Diastolic blood pressure	Decrease from the entry measurement	Diastolic blood pressure	Decrease from the entry measurement	
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
Week 0	96.67 ± 0.77	-	96.69 ± 1.18	-	-
Week 2	91.39 ± 0.86	5.28 ± 0.99	91.27 ± 1.09	5.42 ± 1.17	0.924
Week 4	91.04 ± 0.87	5.63 ± 1.09	88.05 ± 1.18	8.64 ± 1.33	0.078
Week 6	89.10 ± 0.81	7.57 ± 0.98	86.58 ± 0.88	10.17 ± 1.18	0.090
Week 8	88.26 ± 1.06	8.40 ± 1.06	86.78 ± 0.89	9.92 ± 1.39	0.381
Week 10	87.22 ± 0.62	9.44 ± 0.89	86.61 ± 0.99	10.08 ± 1.36	0.685
Week 12	86.76 ± 0.82	10.00 ± 0.96	87.20 ± 0.88	9.49 ± 1.37	0.756

Among phytopharmaca subjects, at the end of the study systolic blood pressures the average decreased was 24.72 mmHg. This is almost the same figure among Amlodipine subjects (26.27 mmHg). The same decreases were also noted for diastolic blood pressures. These means both drugs were suitable to control mild and moderate hypertension. It can be concluded that there was no difference between phytopharmaca and Amlodipine to control mild and moderate hypertension.

Table 5 indicates that there were no significant changes in term of laboratory findings on electrolytes,

plasma lipids, and fasting blood sugar between at the entry and at the end of the study on both groups.

Table 6 shows that the most frequent side effect was dizziness. For each groups revealed there were 14 (19%) subjects who experience of having dizziness. The other side effects were considered to be rare, and the was no significant difference between two groups.

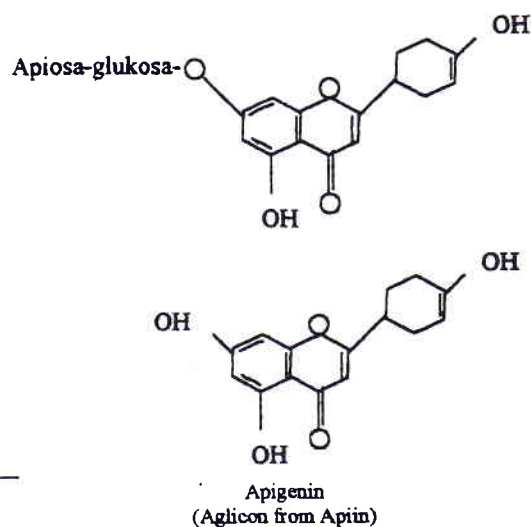
There was one subject who develops TIA (Temporary Ischemic Attack) among Tensgard® group. In addition, there was noted one subject among Amlodipine group who experience of having unstable angina. The two cases could be managed by nitrate treatments.

Table 5. Change of electrolyte, plasma lipid, and fasting blood sugar

	Phytopharmaca (N=72)		Amlodipine (N=70)		P
	On entry	The end	On entry	The end	
Kalium	4.53 ± 0.08	4.17 ± 0.06	4.35 ± 0.10	4.07 ± 0.07	0.782
Chloride	104.59 ± 0.42	103.89 ± 0.33	104.07 ± 0.48	104.06 ± 0.29	0.314
Magnesium	2.13 ± 0.06	2.14 ± 0.03	2.11 ± 0.05	2.16 ± 0.03	0.469
Natrium	140.98 ± 0.26	141.50 ± 0.25	140.88 ± 0.28	141.58 ± 0.26	0.927
Total cholesterol	205.81 ± 4.66	215.75 ± 5.54	196.06 ± 4.29	203.79 ± 4.39	0.643
HDL	41.62 ± 1.47	42.33 ± 1.22	42.02 ± 1.39	42.85 ± 1.58	0.935
LDL	131.0 ± 4.35	145.46 ± 4.98	120.08 ± 3.32	133.12 ± 3.79	0.797
Triglyceride	164.00 ± 8.29	139.64 ± 7.81	186.54 ± 17.30	152.77 ± 13.19	0.523
Fasting blood sugar	101.99 ± 3.76	106.19 ± 4.30	105.29 ± 4.83	108.46 ± 4.09	0.864

Table 6. Some side effects

	Phytopharmaca (N=72)	Amlodipine (N=70)	P
Dizziness	14	14	0.934
Faint	3	1	0.324
Libido decrease	1	1	0.984
Tibial edema	0	0	-
Flushing on face	1	0	0.322
Nausea	1	4	0.162
Frequent urinating	0	0	-
Sleepy	1	2	0.543
Tachycardia	2	2	0.977
Bradycardia	0	0	-



## DISCUSSION

Phytopharmaca is a development of traditional medicine. The basic difference between traditional medicine and phytopharmaca is the active chemical component on phytopharmaca is quantitatively known, whereas on the traditional medicine the only known is source of extract.<sup>6</sup> Furthermore, the other important things on phytopharmaca there are phase I, II, and III clinical trial evidence. On the other hand, the traditional medicine is based on empirical experiences or descendance belief.

In this study the phytopharmaca is a domestic Indonesian product by gathering traditional medicines to be a created phytopharmaca named "Tensigard®". In fact this phytopharmaca has been available in the market as a traditional medicine (*jamu*). This phytopharmaca needs a clinical trial.

Tensigard® is a phytopharmaca consisted of extract of *Apium graveolens* or in Indonesian language is called

*sēledri* for 74% and extract of *Orthosiphon stamineus* (*kumis kucing*) for 11%, and added with lactose, magnesium stearat, and texapon.

*Apium graveolens* leaf contains *atsiri* oil, protein, calcium, phosphate salt mineral, vitamin A, B and C. The stick leaf of and the seed contain apium and apigenin.<sup>8</sup>

One capsule of Tensigard® consisted of active substance of apigenin for 11.04 mg and *Orthosiphon stamineus benth* 8.4 mg.

Previous reports<sup>5,10</sup> apigenin has an effect for aorta vasorelaxation or vasodilatation among isolated rats by mechanism contraction inhibition by means of calcium released (calcium antagonist),<sup>9-10</sup> The other report<sup>6</sup> reported that apigenin has an effect to inhibit protein kinase C or has an effect protein Kinase-C inhibitor on rat aorta. This inhibition of cyclic nucleotide phospho-diesterase decreases calcium release.<sup>11</sup>

Therefore, *apigenin* has been proved to have a similar effect with Calcium channel bloker.<sup>9-11</sup> Whereas, *Orthosiphon stamineus* extract contains Methyl-ripariochromene p (MRC). The MRC has a vasodilator effect, lowering cardiac output. In addition it has a diuresis effect.<sup>12</sup> This effect is similar with beta blocker efect.<sup>12</sup> Therefore, the phytopharmaca has a similar effect with calcium channel blocker, a mild beta blocker and diuretic. These three effects are lowering blood pressure. This study reveals that systolic as well as diastolic blood pressures for both groups (phytopharmaca and Amlodipine) decreased, and there was no significant difference.

The slope of systolic and diastolic blood pressure decreased among phytopharmaca was not as sharp as the Amlodipine group. However, it reached significant results at week 12. This means that phytopharmaca is relevant to control mild and moderate hypertension.

Diuretic effect for this phytopharmaca<sup>11-13</sup> was not prominent. There was no diuretic complaint from the study subjects. In addition, there was no diuresis effect toward blood electrolyte profiles. The same results were also noted for plasma lipids<sup>14,15</sup> Effect on plasma lipids is similar with the previous report on rats.<sup>15</sup> The phytopharmaca had no significant effects on blood sugar. This means there would be nor hyperglycemia or hypoglycemia.

The phytopharmaca had no clear beta-blocker effect. This can be seen that there were only a small number of subjects who had a decreased libido, bradycardia, etc. among the two groups.

There was no tibial edema and tachycardia found. One subject was found to be TIA among Amlodipine group. Further anamnesis revealed that two years the subject suffered several times from TIA.

Whereas one subject who had unstable angina among phytopharmaca group revealed that this is the first time. The subject had several risk factors, such as a fifty year-old male, heavy smoker and had dislipidemia. It seems that unstable angina was not related to the phytopharmaca. He had a four-day hospitalization and he had heparinization and nitrate in accordance with the study protocol.

Transient ischemic attack as well as angina pectoris were found on the second and third day after discontinuation of hypertensive treatment.

Even though the phytopharmaca contains diuretics, it is not proved that hypokalemia occurred on the phytopharmaca treatment. This means that the predicted the effect of calcium antagonist was more dominant compared with diuretic effect. In addition, the plasma lipid levels as well as blood sugar level did not change significantly.

This study noted that on both groups when SBP blood reached 130-140 mmHg and DBP reached 90 – 80 mmHg, even though the treatment were continued, there was drastic blood pressure decrease or hypotension. The combination effect of calcium blocker, beta-blocker and mild diuretic for The phytopharmaca seems to be tolerated to decrease blood pressure in accordance with Amlodipine.

In conclusion, this trial revealed that the phytopharmaca, which contains *Apium graviolens* and *Orthosiphon stamineus benth*, lowered systolic and diastolic blood pressure equivalent with Amlodipine among mild and moderate hypertensive subjects.

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