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**RESEARCH ARTICLE**

## **The effect of Antihypertensive Herb formula of Indonesian traditional medicines against serum uric acid levels in mild Hypertensive patients**

**Ulfatun Nisa<sup>1</sup>, Peristiwa R Widhi Astana<sup>1</sup>, Hadi Kuncoro<sup>2</sup>**

<sup>1</sup>Traditional Plant and Traditional Medicine Research and Development, National Institute Health Research and Development, Ministry of Health Republic of Indonesia.

<sup>2</sup>Faculty of Pharmacy, University of Mulawarman, Samarinda, Indonesia.

\*Corresponding Author E-mail: [redfa01@gmail.com](mailto:redfa01@gmail.com)

### **ABSTRACT:**

The objective of the study was to determine the effect of herb formula consisting of *Syzygium polianthum* leaves, *Centella asiatica* leaves, *Imperata cylindrica* roots, *Myristica fragrans* seeds, *Curcuma xanthorrhiza* rhizomes, *Curcuma longa* rhizomes and *Phyllanthus niruri* herbson serum uric acid levels of patients with mild hypertension. This research method was a quasi-experimental study with pre-post control design, noncomparative, conducted at clinical of saintification of jamu Hortus Medicus over 8 weeks. As much as 60 volunteers-fulfilling the inclusion and exclusion criteria were recruited as subjects. Serum uric acid level, renal and liver function were calculated at baseline, middle and end of study (at the end 8 weeks). There was a statistically significant difference between mean serum uric acid level at baseline and the end of treatment on mild hypertensive patients with hyperuricemic, which had a p-value < 0.05 (p = 0.023 (CI 95% 0.15-1.64)). Nevertheless. the number of subjects with hyperuricemia increased from 21.6% to 23.3%. at day 56. This study concludes that the antihypertensive formula is more favorable in lowering serum uric acid levels in mild hypertensive patients which had hyperuricemia.

**KEYWORDS:** Indonesian traditional medicines, herb formula, mild hypertension, uric acid.

### **INTRODUCTION:**

Hypertension is a major health problem in developing countries, because of its high prevalence and a leading cause of the global burden of funding which a consequence of cardiovascular and renal disease<sup>1,2</sup>. Recent clinical studies have identified the positive correlation between cardiovascular disease and serum uric acid levels. It showed that hyperuricemia was significantly associated with aorta size ascending which is one of the predictors of incident congestive heart failure<sup>3,4</sup>. The relationship between hypertension and hyperuricemia is undebate. Several clinical studies revealed the role of hyperuricemia as an independent risk factor for hypertension<sup>4,5</sup>. Increasing incident hypertension as well as increasing serum uric

acid level<sup>6</sup>. Furthermore, serum uric acid level had a correlation with the anthropometric parameters for obesity, triglyceride and cholesterol level<sup>7</sup>. More than 70% of patients with hyperuricemia are obese, more than 50% with hypertension and 10-25% died from kidney disease<sup>8</sup>.

In recent years researchers have paid attention to the relationship between hypertension and hyperuricemia<sup>6</sup>. Hyperuricemia is a condition where the uric acid level exceeds the normal level (above 7mg/dl)<sup>9</sup>. Hyperuricemia as a cause or actual effect is still unclear<sup>10</sup>. Hyperuricemia increases the risk of hypertension, 13% with every 3.5mg/dl of elevated serum uric acid level<sup>11</sup>. Carotid-femoral pulse wave velocity in hypertension and hyperuricemia patients was higher than hypertension patients with serum normal level uric acid<sup>12</sup>. Even asymptomatic hyperuricemia may also influence cardiometabolic development in Japanese individuals without comorbidity<sup>13</sup>.

Since the causal link between hyperuricemia and hypertension, an antihypertensive drug might have uric acid-lowering properties to be an effective alternative therapy<sup>14</sup>. Recently, many researchers interested in the traditional system of medicine<sup>15</sup>. Mainly in several developing countries, herbal medicine plays an important role in health care services<sup>16</sup>. Indonesian traditional herbal medicine known as jamu is used to treat disease by most of the Indonesian people especially in rural areas. *Jamu* comes from Javanese tribal language which is the traditional medicine from plants<sup>17</sup>. Previous research has explained that *Syzygium polyanthum* leaves, *Centella asiatica* leaves, *Imperata cylindrica* root, and nutmeg can reduce blood pressure in white rats induced by prednisone<sup>18</sup>. Another study stated that salam leaves extract (*Syzygium polianthum*) has been shown to reduce blood uric acid levels, based on the results of pre-clinical trials in mice that work by inhibiting hypoxanthine to xanthine<sup>9</sup>. The flavonoids of salam leaves can reduce uric acid levels in white mice<sup>19</sup>. Ethanol extract of *Centella asiatica* enrichment of ingredients can reduce uric acid levels in the blood of hyperuricemic mice induced by caffeine<sup>20</sup>. Since two ingredients which as antihypertension and antihyperuricemia that can be expected that this formula can also affect serum uric acid levels in hypertensive patients.

This study aims to determine the effect of antihypertension Indonesian traditional medicine formula against serum uric acid levels of patients with mild hypertension.

**METHOD:**

The study was conducted in 2016 at Hortus Medicus jamu research house Tawangmangu belongs to the Medicinal Plants and Traditional Medicine Research and Development Center, Ministry of Health of the Republic of Indonesia. This study included 60 volunteers who met the inclusion criteria: newly diagnosed mild hypertensive patients (TDS <140 - 159mmHg, or TDD <90 - 99 mmHg), ages 18-60 years, the patient's condition was stable as evidenced by clinical and laboratory examinations and agreed to follow research by signing informed consent. Subjects were excluded if they had a history of hypersensitivity to herbs obtained through history taking and at the time of examination; comorbid conditions such as kidney, liver, heart disease, and pregnancy based on anamnesis.

The antihypertensive herb formula consists of 2 gram *Syzygium polyanthum* leaves, 3gram *Centella asiatica* herb, 3gram *Imperata cylindrica* roots, 1gram nutmeg, 5 gram *Curcuma xanthorrhiza rhizome*, 4 gram *Curcuma longa rhizome*, and 3gram *Phyllanthus niruri* herbs of doses per day. The quality control of simplicia had been tested about the microbiological examination, and Fungi

totals numbers and total plate numbers at the laboratory of the Center for Research and Development of Medicinal Plants and Traditional Medicine. Herb formula was given to patients with information about how to use it. Subjects were requested to boil 1 day pack of herb formula with 4 cups of boiled water for about 15 minutes. When there were about 2 cups of water left, turned off the heat, collected then cooled, filtered. The filtered water should be administered two times a day in the morning and evening 1 cup each. Herb formula was given for 56 days. Examination of uric acid levels on day 0, day 28 and day 56 (H-0) before drinking herbal medicine day 28 and day 56. Liver and renal function was carried out in baseline, middle and end of treatment. The patient's blood was taken threecc in the cubiti vein and then put into the vacuum tube. The blood was centrifuged, and the taken serum was inserted into the URIT® brand chemical analyzer. The normal level of uric acid as a reference in this study for women is 2.6-6.0mg/dl and for men 3.5-7.2mg/dl. The obtained data will be analyzed using the Saphiro-Wilk normality test because of the small amount of data (<50).

**RESULT:**

A total of 60 subjects attended the study to completion. The research subjects came to the research doctor once a week to be physically examined and given herb formula to be consumed every day. The baseline characteristics of the study population are shown in Table 1. Based on table 1, most of the patients didn't have a family history of hypertension and their body mass index within normal value.

**Table 1. Baseline characteristics of study participants**

| Characteristics                   | %    |
|-----------------------------------|------|
| 1. Age                            |      |
| - 20- 29 yr                       | 1,7  |
| - 30- 39 yr                       | 8,3  |
| - 40- 49 yr                       | 20,0 |
| - 50- 56 yr                       | 70,0 |
| 2. Sex                            |      |
| - Men                             | 26,7 |
| - Women                           | 73,3 |
| 3. Family history of hypertension |      |
| - Positive                        | 46,7 |
| - Negative                        | 53,3 |
| 4. Body Mass Index                |      |
| - Underweight                     | 3,3  |
| - Normoweight                     | 75,0 |
| - Overweight                      | 21,7 |
| - Obes I                          | 0    |
| - Obes II                         | 0    |

**Table 2. Distribution of serum uric acid levels**

| No | Day 0 Examination               |                        | Day 56 Examination              |                        |
|----|---------------------------------|------------------------|---------------------------------|------------------------|
|    | Normal uric acid level<br>N (%) | Hyperuricemia<br>N (%) | Normal uric acid level<br>N (%) | Hyperuricemia<br>N (%) |
| 1  | 47 (78.4%)                      | 13 (21.6%)             | 46 (76,7%)                      | 14 (23,3%)             |

Table 2 showed subjects who had higher serum uric acid levels in baseline and the end of treatment was 21.6% and 23.3%, respectively.

Information: H0 Check: Day 0  
H56 Check: Day 56 Check

**Table3. Mean uric acid level**

| Category              | Day 0       | Day 56      | p (Day 0 and day 56)          |
|-----------------------|-------------|-------------|-------------------------------|
| Serum Uric Acid level | 7.27 ± 0.66 | 6.37 ± 1.48 | 0.020.023* (CI 95% 0.15-1.64) |

t-test paired at the level of confidence 95%, \* p<0.05

Table 3 showed serum uric acid level on day 0 and the end of treatment had statistically different (p < 0.023 (CI 95% 0.15-1.64). The normal level of uric acid by the standard of the reagents used in clinical laboratories Hortus Medicus in men <7.2 and women <6.0. A decrease in serum uric acid level on mild hypertensive patients for one month was 0.9 mg/dl.

Table 4 showed serum creatinine levels at Days 0, 28 and 56 are still within normal. On the 28th and 56th day, the mean serum creatinine level was lower than Day 0. These results although did not show a statistical difference, but the creatinine decline showed improvement in kidney function. According to table 5, serum SGOT and SGPT levels were still normal at the middle and the end of treatment though there was increased serum SGOT significantly on day 56.

**Table 4. The difference in Mean of Uream and Creatinine Levels**

| Variable   | Day 0        | Day 28       | p (day 0 and day 28) | Day 56       | p (day 0 and day 56) |
|------------|--------------|--------------|----------------------|--------------|----------------------|
| Uream      | 27,55 ± 7,56 | 27,78 ± 8,09 | 0,812                | 26,58 ± 6,48 | 0,336                |
| Creatinine | 0,98 ± 0,34  | 0,90 ± 0,28  | 0,086                | 0,96 ± 0,27  | 0,074                |

\* t-test paired at the level of confidence 95%

**Table 5. The difference in Mean of SGOT and SGPT**

| Variable | Day 0        | Day 28       | p (day 0 and day 28) | Day 56      | p (day 0 and day 56) |
|----------|--------------|--------------|----------------------|-------------|----------------------|
| SGOT     | 20,01± 6,17  | 19,53 ± 5,89 | 0,549                | 23,83± 7,77 | 0,002*               |
| SGPT     | 23,86± 11,77 | 21,93± 6,68  | 0,212                | 21,48± 8,44 | 0,080                |

\* t-test paired at the level of confidence 95%

**DISCUSSION:**

In this study, there were six men had greater serum uric acid levels at baseline and nine women had hyperuricemia. Hence, women who had hypertension and hyperuricemia were more than men. It is contrasted with other studies, men were more prevalence than women. Because of the function of uric acid transporter is inhibited by estrogen and progesteron<sup>5</sup>. As much as

21,6% essential hypertensive patients were diagnosed with hyperuricemia. A similar insignificantly previous study that hyperuricemia is diagnosed in 25%-40% of the untreated patients with essential hypertension<sup>5,11</sup>. On the other hand, Helmina reported that 26 non-hypertensive samples were found in 2 samples with hyperuricemia (7.7%) and 24 samples with normal uric acid results (92.3%) while 26 samples with hypertension had elevated serum uric acid levels (100%) at Sukoharjo. The strong relationship between the increase in uric acid levels and the incidence of hypertension was indicated by the results of the Lambda correlation which were significant (p <0.05) with a strong correlation (r = 0.923) with a positive direction<sup>21</sup>. The positive correlation between hypertension and hyperuricemia has been reported in many clinical studies<sup>22</sup>. An observational study showed that hyperuricemia was correlated with the risk of increasing blood pressure with odds ratios of 2.152 and 2.133 between men and females, respectively<sup>12</sup>.

Abnormality of serum uric acid levels in hypertensive patients is a consequence of hyperinsulinemia. The excretion of uric acid is influenced by insulin. Elevation of insulin level causes a decrease in excretion of uric acid<sup>5</sup>. On the other hand, patients with essential hypertension are associated with insulin resistance which will cause an increase in uric acid levels because insulin reduces the excretion of uric acid and sodium. Hypertension causes microvascular disease which then occurs ischemic tissue so that the synthesis of uric acid increases through the degradation of ATP to adenine and xanthine. Based on previous studies of hyperuricemia in patients with hypertension can be used as an indicator of insulin resistance which is directly related to cardiovascular improvement<sup>23</sup>. Faccini reports that the release of uric acid from the kidney is inversely proportional to insulin resistance<sup>24</sup>.

The ability of uric acid elicits cardiovascular and kidney diseases through impairing endothelial integrity. Experimental studies revealed an organic anion transport system influenced uric acid to penetrate vascular smooth muscle fibers which are followed by activation of multiple signal transduction pathways, lead to elevation expression of inflammatory mediators<sup>25</sup>. In addition, uric acid is reactive oxygen species production and then promoter arterial wall destruction<sup>3</sup>. Endothelial dysfunction may contribute to several consequences leading to cardiovascular disease<sup>26</sup>. Besides activation of the Renin-Angiotensin system, decreasing renal perfusion and tubular secretion of uric acid was correlated with increasing of serum uric acid level<sup>5</sup>. In this study, the levels of urea and creatinine in the blood are still normal values, so there is no disruption in uric acid excretion. Besides renal function, liver function

play a role important in hyperuricemia because of the correlation between liver disease and high serum uric acid level<sup>22,27</sup>. Eventhough serum SGOT had increased significantly but still conclude in the range of normal value. Furthermore, SGPT is a better indicator of hepatocellular destruction by toxins<sup>28</sup> and elevation of this enzyme is unusual in non-hepatic diseases<sup>29</sup>. The biochemical characteristics of the subject in the current study showed a safety issue to renal and liver function.

While the study by Feig, Soletski, and Johnson showed an increase in uric acid levels (mean 6.5mg/dL) and plasma renin activity against a group of adolescent hypertension, and after removal of allopurinol there was a decrease in blood pressure and plasma renin activity<sup>23</sup>. Allopurinol may be utilized as a complement in hypertension therapy<sup>30</sup>, hence antihypertension traditional Indonesian medicine which containing antihyperuricemia agents have some beneficial effect to preventing cardiovascular complication. Similar to another study, antihypertension combination therapy is more beneficial than monotherapy<sup>31</sup>. In this study, a combination of traditional Indonesian medicines which is consist of *Syzygium polyanthum*, *Imperata cylindrica*, *Centella asiatica*, nutmeg, *Curcuma xanthorrhiza*, *Curcuma longa*, and *Phyllanthus urinaria*, have an activity to decrease significantly serum uric acid levels. That capability may be limited to the antihypertensive patient with hyperuricemia while it will be increase on the patient with normal serum uric acid levels. The mechanism of action lowering serum uric acid levels from inhabitation of xanthin oxidase activity which is contributing in the catabolism hypoxanthine to xanthine and xanthin to uric acid<sup>32</sup>. Clinical study showed that the mechanism of *Syzygium polyanthumas xanthin oxidase inhibitor* which inhibited conversion of hypoxanthin to xanthin and xanthin to uric acid<sup>9,26</sup>. Antihypertension formula enriched *xanthine oxidase inhibitor* can reduce blood pressure and may help in the treatment of hyperuricemic<sup>33</sup>. Since there are lowering of uric serum acid level significantly after consuming this formula, so this study showed that mild hypertensive patient which is had hyperuricemia can be treated with this formula. *Syzygium polyantum* also contains eugenol and citral as diuretics and analgetics<sup>34</sup>. *Imperata cylindrica* and *centella asiatica* can also have functioned as diuretics. A diuretic is well known can help the excretion of uric acid in urine. *Centella asiatica* had antihyperuricemia activities equivalent to allupurinol<sup>20,35</sup>. Oxidative stress hasa correlation with non-communicable diseases such as hyperuricemia and hypertension. Several of complication hypertension pathologies are associated with oxidative stress that influence of vascular functional change and remodeling<sup>36</sup>. Hence herb medicine enriches of antioxidants will be important for essential hypertension<sup>36,37</sup>.

Based on these results, it was suspected that salam leaves (*Syzygium polyanthum*) and pegagan herb (*Centella asiatica*) in a combination of antihypertension Indonesia traditional medicines may have the capability in lowering uric acid levels significantly in patients with mild hypertension. But, this study still further research to evidence antihypertensive herb formula of Indonesian traditional medicines with a large scale trial.

## CONCLUSION:

Giving a combination of antihypertension Indonesian traditional medicine formulation is more favorable in lowering serum uric acid levels in mild hypertensive patients which had hyperuricemia.

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