

## Efficacy of Amlodipine-Noni Extract (*Morinda citrifolia L.*) Combination on Blood Pressure of Hypertension Patients

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### Abstract

The prevalence of hypertension in Indonesia continues to increase and causes high mortality due to complications. Hypertension complications can be prevented by pharmacological therapy. A preliminary study at Brati Health Center found that many hypertensive patients use noni (*Morinda citrifolia L.*) extract as an adjunction therapy to amlodipine. This study determined the efficacy of amlodipine-noni extract combination on the blood pressure of hypertensive patients. An analytic observational design with a cross sectional approach were used in this study. Non-complicated hypertensive patients at the Brati Health Center were divided into groups K1 (amlodipine with risk factors), K2 (amlodipine without risk factors), K3 (amlodipine-noni extract with risk factors), and K4 (amlodipine-noni extract without risk factors). Efficacy was measured using the average increase/decrease in blood pressure for 6 month. Result of Kruskal-Wallis test stated a significant difference in systolic blood pressure between groups ( $p < 0.001$ ), followed by Mann-Whitney test that K3 group had the lowest increase in systolic blood pressure ( $p < 0.05$ ). For the average of diastolic blood pressure, there is no significant difference between groups ( $p > 0.499$ ). The combination of amlodipine-noni extract prevented an increase of systolic blood pressure in hypertensive patients with risk factor at the Puskesmas Brati, but could not for diastolic blood pressure.

**Keywords:** Amlodipine; diastolic pressure; hypertension; *Morinda citrifolia*; systolic pressure

### INTRODUCTION

Hypertension is a disease with high morbidity, which is characterized by symptoms of an increase in systolic blood pressure  $> 140$  mmHg and/or diastolic blood pressure  $> 90$  mmHg<sup>1</sup>. According to the World Health Organization (WHO), in 2019, the number of people with hypertension in the world reached 1.28 billion people, and mainly occurred in low to medium income countries<sup>2</sup>. Meanwhile in Indonesia, the prevalence of hypertension in the population aged over 18 years has reached 34.1% in 2018. The increase in hypertension cases increases mortality due to complications such as heart disease, kidney failure, and stroke. In addition, in 2018, the cost of services for hypertension patients according Social Security Agency of Health (BPJS Kesehatan) reaching 3 trillion rupiah<sup>3</sup>.

Patients with hypertension are recommended to perform repeated blood

pressure measurements every 7-14 days for diagnosis and/or evaluation of hypertension control. Uncontrolled hypertension can cause disease complications in various organs. Many environmental, genetic, or social factors can influence the occurrence of these complications of hypertension<sup>4</sup>. Several factors can be controlled to prevent complications of hypertension, include managing salt/alcohol consumption, reducing smoking, reducing stress, and managing food consumption to prevent obesity<sup>5</sup>. Prevention and control of hypertension can also be carried out with strategies for providing pharmacological therapy to patients<sup>4</sup>.

Pharmacological therapy can be done by giving antihypertensive drugs such as diuretics, ACE (Angiotensin-Converting Enzyme) inhibitors, Angiotensin II receptor blockers (ARB),  $\beta$ -blockers, and Calcium Channel Blockers (CCB). Amlodipine is one of the drugs that

is often used in health centers<sup>6</sup>. In addition of synthetic drugs, the use of juice therapy and traditional herbal medicines is also widely practiced by the community because they are considered cheap and harmless.

An example of herbal therapy used by the community is noni extract. Noni fruit (*Morinda citrifolia* L.) is known to have antithrombotic, antioxidant, analgesic, anti-inflammatory, xanthine oxidase inhibitor, and antibacterial activity. Noni fruit also has anti-tumor and anti-cancer effects. The anti-tumor and anti-cancer effects are known from the results of research by the American Association for Cancer Research which suggests that alcoholic noni extract can increase the life span of mice with Lewis lung cancer compared to controls<sup>7</sup>.

Preliminary research that has been carried out in Brati Health Center illustrated the habit of hypertension patients to use noni extract, as adjunction therapy of drugs from the doctor. The information about efficacy of noni extract for lowering blood pressure obtained from pharmacists at the Brati Health Center. This study continued to analyze the efficacy of the amlodipine-noni extract combination as an antihypertensive treatment in Brati Health Center.

## METHOD

### Research design, population and sample

This study was used an analytical observational design with a cross sectional approach. The research has been approved by the Health Research Ethics Commission of the Faculty of Medicine, Universitas Muhammadiyah Semarang with the number of 032/EC/FK/2021. Research respondents were the entire population of non-complicated hypertension patients at the Brati Health

Center, Grobogan Regency, Central Java, Indonesia who did treatment in February 2021. The total of respondent was 85, which was divided into four groups K1 (the group of amlodipine with risk factors), K2 (amlodipine without risk factors), K3 (amlodipine-noni extract combination with risk factors), and K4 (amlodipine-noni extract combination without risk factors). The dose of amlodipine used by the patient was 5 mg once a day, while the dose of noni extract was 2 capsules (500 mg/capsule) twice a day.

### Data collection techniques

There were three variables in this study, first is the independent variable (the type of antihypertensive drug used), second is the dependent variable (blood pressure), and third is the moderator variable (risk factors that can affect blood pressure). The moderator variables studied including age, smoking activity, psychosocial or stress conditions, salt consumption, rest patterns, and alcohol consumption. Patients are then categorized based on the presence or absence of risk factors. A questionnaire used to detect the risk factors has been tested with validity and reliability on 20 respondents outside the research location with the same characteristics population.

For dependent variable, the antihypertensive efficacy in each group of respondent was measured from the average decrease or increase in blood pressure every month, within a 6 month examination period. Data collection on blood pressure was carried out using data collection techniques from patient medical records at the Brati Health Center.

### Analysis of research results

The questionnaire for respondents was tested for validity using Pearson product moment analysis, and was declared valid with an r value 0.775 to

0.902 (value > r table 0.444; N=20;  $\alpha=0.005$ ). The reliability test was carried out with Cronbach Alpha analysis, and was declared reliable with Alpha of 0.967 (value > 0.6). To assess the efficacy of the

combination of amlodipine-noni extract in lowering blood pressure the Kruskal Wallis test was used followed by the Mann-Whitney Test.

**RESULT**

*Table 1. Characteristics of hypertensive patients (respondents) at the Brati Health Center based on gender, work history, and types of risk factors*

Type of Risk Factor (RF)	Category	Frequency	Percentage (%)
Gender	Men	31	36.5
	Women	54	63.5
Profession	Housewife	22	25.9
	Farm worker	10	11.8
	Farmer	5	5.9
	Private employee	4	4.7
	Entrepreneur	22	25.9
	Bank employee	2	2.4
	Teacher	9	10.6
	Civil servant	1	1.2
	Retired	10	11.8
Age	< 55 (RF -)	56	65.9
	≥ 55 (RF +)	29	34.1
Smoking Behavior	Non-smoking (RF -)	67	78.8
	Smoking (RF +)	18	21.2
Alcohol Consumption	Not consuming (RF -)	85	100
	Consuming (RF +)	0	0
Psychosocial and Stress	Normal (RF -)	85	100
	Low stage (RF +)	0	0
	Moderate stage (RF +)	0	0
	Severe (RF +)	0	0
	Very severe (RF +)	0	0
Salt Consumption	Good consumption (RF -)	84	98.8
	Bad consumption (RF +)	1	1.2
Sleep patterns	Good (RF -)	85	100
	Bad (RF +)	0	0
Total Respondents		85	100

**Respondents characteristic**

Patients with hypertension who did treatment at the Brati Public Health Center in February 2021 have the characteristics of being dominated by the female gender (63.5%). Meanwhile, based on the characteristics of risk factors, respondents had risk factors for the elderly (34.1%), smokers (21.2%), and excessive salt consumption (1.2%) (Table 1). Respondents with at least 1 risk factor were distinguished from respondents without risk factors during the analysis of the

efficacy of the amlodipine-noni extract combination.

Based on the criteria for hypertension suffered by the respondent, 85.7% of patients at the Brati Health Center who took single drug amlodipine had hypertension grade 2. For patients taking the combination of amlodipine-noni extract, the most of patients have grade 1 hypertension (58.1%), followed by high normal grade hypertension (34.9%). Therefore, it can be concluded that the severity of hypertension at the beginning of the study was higher in the group with

amlodipine single drug users. If based on the criteria for the presence or absence of risk factors, the amlodipine-noni extract

combination with risk factor group dominates with a total of 45.9% (Table 2).

Table 2. Characteristics of hypertensive patients (respondents) at the Brati Health Center based on the category of severity of hypertension and drug user groups

Groups	Respondents Description	Normal elevated (%)	Hypertension Stage 1 (%)	Hypertension Stage 2 (%)	Total (%)
K1	Amlodipine with risk factor	2 (2.3)	3 (3.5)	13 (15.3)	18 (21.2)
K2	Amlodipine without risk factor	0 (0)	1 (1.2)	23 (27.1)	24 (28.2)
K3	Amlodipine-noni extract with risk factor	14 (16.5)	22 (25.9)	3 (3.5)	39 (45.9)
K4	Amlodipine-noni extract without risk factor.	1 (1.2)	3 (3.5)	0 (0)	4 (4.7)
		17 (20.0)	29 (34.1)	39 (45.9)	85 100%

### Results of the efficacy analysis of the amlodipine-noni extract combination

After 6 months of observing the blood pressure of hypertensive patients at the Brati Health Center, the systolic blood pressure in all group increased compared to the initial observation (month 1). Based on the results of Kruskal Wallis analysis, there is a significance difference in the mean increase in systolic blood pressure in

all groups (p-value 0.001). For diastolic blood pressure, the K4 group experienced a decrease diastolic blood pressure (Table 3), but the results of the Kruskal Wallis test showed no significance difference in all groups of respondents (p-value 0.499). From these results, it can be concluded that there is no difference in efficacy between amlodipine and amlodipine-noni extract combination drug for lowering the patient's diastolic blood pressure.

Table 3. Description of the mean ± standard deviation (SD) of changes in systolic and diastolic blood pressure of hypertensive patients at the Brati Health Center for 6 months of observation.

Groups	Respondent Description	Mean ± SD of Systolic* (mmHg)	Mean ± SD Diastolic* (mmHg)
K1	Amlodipine with risk factor	5.34 ± 6.23	0.18 ± 1.57
K2	Amlodipine without risk factor	5.54 ± 4.96	0.63 ± 0.73
K3	Amlodipine-noni extract with risk factor	2.04 ± 5.25	1.55 ± 4.55
K4	Amlodipine-noni extract without risk factor	6.95 ± 1.09	-0.10 ± 1.65

\*Value (-) is a decrease in blood pressure and the value (+) of an increase in blood pressure

Table 4. The results of the Mann-Whitney analysis of the average increase in systolic blood pressure in all groups of hypertensive patients at the Brati Health Center

	K1	K2	K3	K4
K1	-	0,533	0,019*	0,195
K2	0,533	-	0,001*	0,164
K3	0,019*	0,001*	-	0,003*
K4	0,195	0,164	0,003*	-

Note \*significance value

From the results of the table 4, there is a significant difference in the increase in systolic blood pressure between groups K1 and K3 (p-value 0.019), K2 and K3 (p-value 0.001), and K3 and K4 (p-value 0.003). Based on these results, it can be concluded that the lowest increase in systolic blood pressure occurred in the group of users of the amlodipine-noni extract combination drug with risk factors (K3).

In addition to testing the efficacy of the amlodipine-noni extract combination, this study also analyzed differences in systolic and diastolic blood pressure in patients with risk factors (age > 55 years and cigarette consumption). For the risk factors of alcohol consumption, psychosocial and stress factors, alcohol consumption, and the rest patterns were not tested in this study.

*Table 5. The results of Mann-Whitney analysis of the difference in mean systolic and diastolic blood pressure in hypertensive patients with or without risk factors at the Brati Health Center*

No	Risk Factor	Systolic Blood Pressure (p value)	Diastolic Blood Pressure (p value)
1	Age	0,048*	0,521
2	Smoking Behavior	0,125	0,788

The results of this study, only age caused a significant difference in systolic blood pressure of hypertensive patients at the Brati Health Center. Diastolic blood pressure was not affected by age and the smoking behavior (Table 5).

## DISCUSSION

Based on the characteristics of the respondents, most of the hypertensive patients at the Brati Health Center were less than 55 years old. An increase in blood pressure is usually associated with increasing age. In this study, it was found that age only affects systolic blood pressure. This study is in line with the results of other studies which state isolated hypertension or increases in blood pressure only in systolic, can occur after the age of 50 years<sup>8</sup>. In theory, increasing age will reduce the flexibility of blood vessels. In addition, aging is usually associated with

the cardiac and autonomic nervous systems<sup>9</sup>.

Of all hypertensive patients at the Brati Health Center, 63.5% are women. This study is in accordance with the results of other studies which state that hypertension patients is mostly female<sup>10</sup>. Systolic blood pressure will increase, especially in women who have experienced menopause. The average age of menopause is 40-50 years. Therefore, women with the age of less than 55 years already have a risk of increasing systolic blood pressure<sup>11</sup>. One of the causes of the increased risk of hypertension in women is an imbalance of the available estrogen and progesterone hormones. Estrogen and progesterone can protect blood vessels from oxidative reactions due to pollution, food, and so on, and prevent vessels from inflammation. The hormone estrogen also affects the balance of the renin-angiotensin system in

the kidneys, which functions to maintain stable blood pressure<sup>10</sup>.

Another risk factor studied was cigarette consumption. In this study smoking is not considered a risk factor that affecting both systolic and diastolic blood pressure of hypertensive patients at the Brati Health Center. In theory, the nicotine in cigarettes can increases blood pressure. Nicotine give a signal to the adrenal glands to release epinephrine which causes constriction of blood vessels. This situation causes the heart to work harder and eventually causes increases in blood pressure. In addition to nicotine, the carbon monoxide concentration in smokers are high, makes the heart pump faster to supply the oxygen into the organs and tissues of the body<sup>12</sup>. Although in theory cigarettes can increase blood pressure, the research data is still inconsistent. The research of Andriani *et al.* (2020) stated that there was an increased in blood pressure in smokers. The increase in blood pressure differs between women and women. In men, smoking does not increase blood pressure, while in women smoking can increase systolic blood pressure<sup>13</sup>. Meanwhile, a study in Nepal stated that there was no relationship between cigarette consumption and an increase in blood pressure<sup>14</sup>.

To determine the efficacy of the amlodipine-noni extract combination, the severity category of hypertensive patients at the Brati Health Center was evaluated. At the beginning of the study, most of the amlodipine single drug users were categorized as patients with hypertension grade 2. On the other hand, patients who used the amlodipine-noni extract combination were mostly classified patients with hypertension grade 1 and high normal grade. The respondents from Brati Health Center has known to consume

noni extract to maintain blood pressure and not complain of side effects.

From the data shown in table 3 and 4, it can be said that there is a difference in efficacy between the use of amlodipine and the combination of amlodipine-noni extract on the average systolic blood pressure of hypertensive patients at the Brati Health Center. After the Mann Whitney follow-up test, it was concluded that the K3 group (hypertensive patients with risk factors using the combination drug amlodipine-noni extract) had the lowest average increase in systolic blood pressure ( $p < 0.05$ ). This means that the combination of amlodipine-noni extract prevents an increase in systolic blood pressure when compared to the administration of amlodipine alone. In this study, blood pressure monitoring was carried out for 6 months, but most of the patients who used the combination of amlodipine-noni extract had consumed noni extract for more than 6 months. This is also the possibility that causes differences in the severity of hypertension in patients at the beginning of the study. Patients taking amlodipine alone had a worse severity of baseline hypertension stage than patients taking noni-extract combination drugs.

Amlodipine as a blood pressure-lowering drug has good effectiveness if taken in the right dose. Amlodipine can be taken as a single drug or in combination with other drugs to treat hypertension. Amlodipine belongs to the CCB group, and works as a vasodilator by inhibiting calcium ions from entering vascular and myocardial smooth muscle cells so that peripheral resistance decreases and muscles relax. The advantages of CCB are the direct effect on the atrioventricular and sinoatrial nodes, can reduce peripheral resistance without significant reduction in heart function, and also relatively safe when combined with  $\beta$ -blockers. In

addition, absorption of amlodipine occurs slowly to prevent a sudden drop in blood pressure. This drug also does not require a dose adjustment in impaired renal function<sup>15</sup>.

The results of this study are in accordance with the theoretical and research study of noni fruit which is considered by Indonesian peoples as a plant that has traditional medicinal properties for health. Research on the antihypertensive effect of Noni fruit has been reported by several researchers, including in the form of tea or juice. Both noni fruit dosage forms have been shown to reduce systolic and diastolic blood pressure of human respondents<sup>16,17</sup>. In addition to humans, the antihypertensive effect of noni fruit has also been proven in experimental animal studies. Ethanol extract of noni fruit can reduce systolic blood pressure of Wistar rats induced by epinephrine<sup>18</sup>. In addition, the ethanolic extract of noni fruit can also reduce systolic and diastolic blood pressure, and reduce arterial blood pressure in dexamethasone-induced hypertensive rats<sup>19</sup>.

Noni fruit can be used as an antihypertensive because it contains the active substances scopoletin and xeronine which can lower blood pressure. Scopoletin works by decreasing peripheral resistance. The amount of peripheral resistance is highly dependent on the contractility of vascular smooth muscle. Vascular smooth muscle contractility can be influenced by vascular endothelial function, because the endothelium is synthesized and secreted various vasoconstrictor and vasodilator substances. In addition, scopoletin also has a spasmolytic effect, and cause dilation of blood vessels or vasodilation due to smooth muscle relaxation, which resembles the way antihypertensive drugs work<sup>20</sup>. Meanwhile, xeronine is known to have a diuretic effect that is able to work synergistically to lower blood pressure<sup>21</sup>.

In addition to scopoletin and xeronine, *in silico* studies have also been carried out to determine the mechanism of action of secondary metabolites from noni extract. Several metabolites such as apigenin, yopaaoside A, peucedanocoumarin, pteryxin, soranjidiol from noni methanol extract have been shown to bind to the ACE enzyme and are equivalent to the control drug captopril<sup>22</sup>.

Based on this research, noni fruit can be further researched and developed into a traditional medicine. This fruit is known to have a bitter taste and unpleasant odor, making its use uncomfortable. This makes researchers try to make a dosage form of liposome nanoparticles to reduce the bitter taste of noni. In addition, liposomes are a good carrier to reduce toxic effects, increase the solubility and penetration of the compounds<sup>23</sup>.

## **CONCLUSION**

The combination of amlodipine-noni extract was proven to prevent an increase in systolic blood pressure in hypertensive patients with risk factors at the Brati Health Center (p value 0.001), but not for diastolic blood pressure (p value 0.499).

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