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# POTENTIAL ANTI HYPERTENSION EFFECT *of Imperata cylindrica* : SYSTEMATIC LITERATURE REVIEW

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## ABSTRACT

*Imperata cylindrica (cogon grass)* contains flavonoids, triterpenoids, and lignans which are efficacious for diabetes, infectious diseases and hypertension. The high content of active compounds in *Imperata cylindrica* have the potential agents to lower blood pressure. This review article aimed to describe the potential roles of *Imperata cylindrica* as an antihypertensive. By using the electronic databases found in Pubmed and Google Scholar. After screening the journal articles from 2011-2021, there were seven full text articles that we discussed in this review. Through the in vivo animal and human subject studies, it was shown that the active compounds of *Imperata cylindrica* as an antihypertension. From the studies, methanol extract of *Imperata cylindrica* leaves can lower blood pressure through vasodilation mechanism and decreases smooth muscle contraction. In addition, *Imperata cylindrica* has a role in lowering blood pressure through diuretic effect by in vivo study. The flavonoids (quercetine, kaempferol and astragalin), triterpenoids (asiaticoside), and lignans (graminone B) have the effect in reducing oxidative stress, thus it inhibits vasoconstriction of blood vessels. *Imperata cylidrica* has proven potential as an antihypertensive. However, further research is needed for the use of *Imperata cyindrica* as a therapy.

Keyword: *Imperata cylindrica*, hypertension, flavonoid

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## INTRODUCTION

Hypertension is the number one cause of death in the world every year[1]. Hypertension is a non-communicable disease characterized by an increase in blood pressure in sufferers but often does not cause symptoms or is known as the silent killer[2]. According to the American Heart Association (AHA), Americans aged over 20 years suffering from hypertension have reached 74, 5 million people[3]. According to the World Health Organization (WHO) in 2011, as many as one billion people in the world suffer from hypertension. The prevalence of hypertension is predicted to increase by 2025, which is about 29% of adults in the world will suffer from hypertension[4]. The results of Riskesdas 2018 show the prevalence rate of hypertension in the population over 18 years based on national measurements of 34.11%[4].

Hypertension treatment is usually aimed at preventing morbidity and mortality due to hypertension[5]. Currently, the treatment of hypertension uses angiotensin receptor blockers, calcium channel blockers and, thiazide-type diuretics. Hypertension is a chronic disease so use of hypertension drugs in the long term can cause various side effects, because it has side effects, other alternative treatments are needed, namely using herbal plants.

One of the herbs that have efficacy against hypertension is *Imperata cylindrica*[6]. The methanol extract of *Imperata cylindrica* root has the potential to reduce hypertension because it contains phenolic compounds. Phenolic compounds are considered to be the main active substances in Imperata cylindrica[7]. Phenoxide ions contained in phenolic compounds are useful as antioxidants by donating one electron to free radicals. Oxidative stress is the key to hypertension. Endothelial cells play a major role in arterial relaxation. Nitric oxide is released by the endothelium and causes relaxation of blood vessels. Nitric oxide is rapidly degraded by the oxygen-derived free radical superoxide anion[8].

A number of studies on the activity of *Imperata cylindrica* and its active components as antihypertensives have been carried out previously. The research carried out has a different explanation so it is necessary to review which part of *Imperata cylindrica* has an antihypertensive effect. This systematic literature review is expected to provide an overview of the activity of *Imperata cylindrica* as an antihypertensive.

## METHODS

### *Sample of Research*

All excluded literature should be given reasons for exclusion according to the inclusion and exclusion criteria. The inclusion criteria in this review are in vivo research and clinical trials evaluating the antihypertensive potential of *Imperata cylidrica*, international journals using the UN language, national journals in English or Indonesian, journals published in 2011-2021, and original articles. While the exclusion criteria are secondary articles or journals, for example, review articles or reviews, journals cannot be accessed full text, journals published under 2010, in vivo articles with Cochrane scale stating not good or clinical trial articles with 2 out of 3 scales stating not good provided that the Jadad score is less than 3, the NOS scale is less than 7, and Cochrane by looking at the conditions for high risk of bias (X) less than 2, and unclear (?) 4 After obtaining the journal according to the inclusion-exclusion criteria, then a bias assessment was carried out using the Cochrane scale which saw the provisions of low risk of bias (✓) ≥3, high risk of bias (X) ≤2, and unclear (?) ≤4. The search result article data was then extracted including the author's name, year of publication of the journal, type of research, sample used, trigger of hypertension, *I. cylindrica* derivative product used, dose of use, parameters measured and the outcome obtained. After that, conclusions were drawn accordingly. with the results from the journal that has been obtained.

Jadad score and NOS- Newcastle-Ottawa for clinical trial and based on SYRCLE's risk of bias tool for animal studies Cochrane can use for animal studies. Jadad quality assessment scale for rating Randomized Controlled Trials. The higher the score, the higher the quality, this pemits an author to rank the studies in a revie. The scale was introduced in the journal article jadad. NOS – Newcastle-Ottawa quality assessment scale for case control studies in the Newcastle-Ottawa Scale (NOS) the reviewe assigns a star rating case-control studies in three areas: selection, comparability, and exposure[9].

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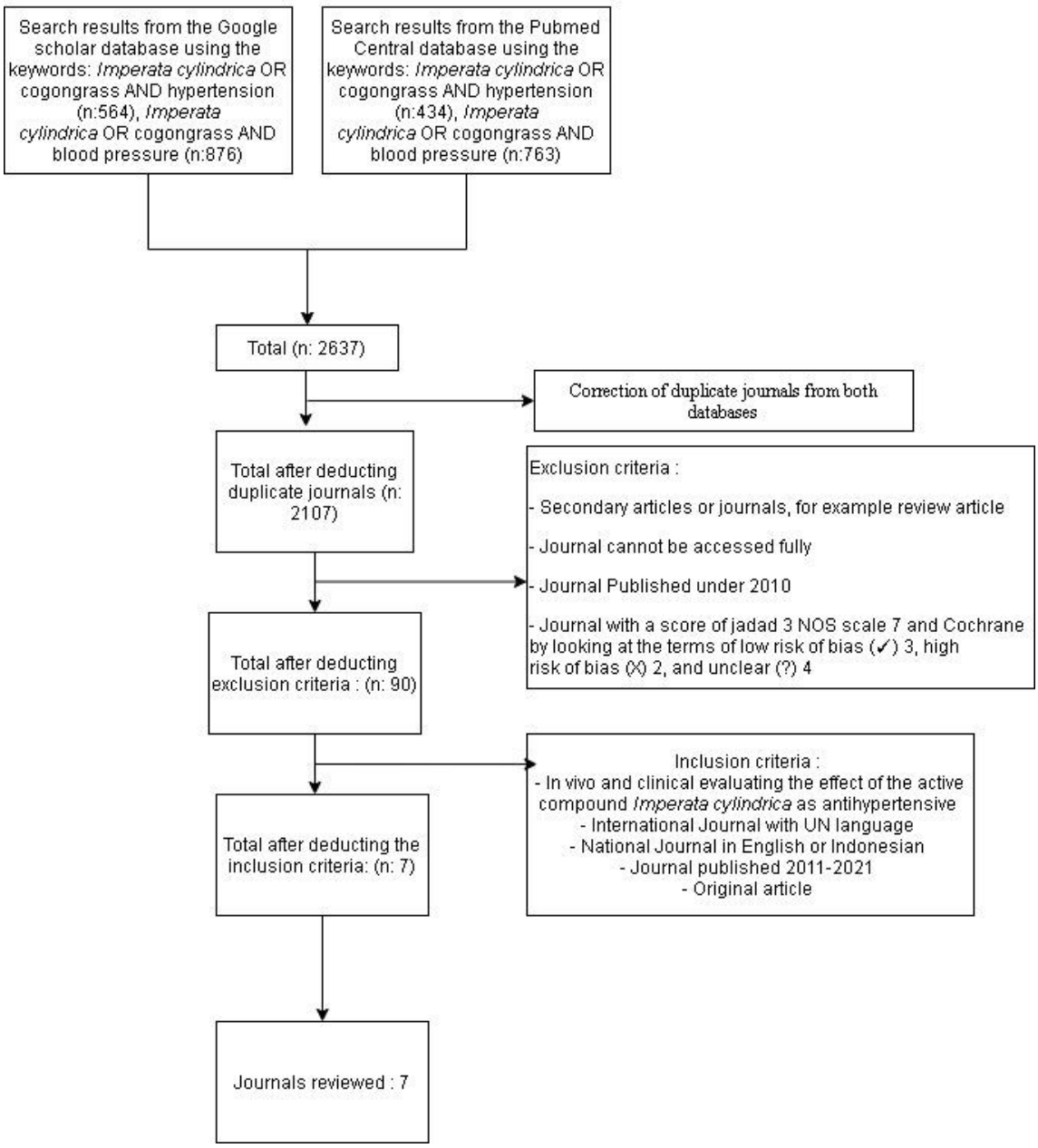


### *Instrument and Procedures*

Search data using databases, namely PubMed Central and Google Scholar. The keywords used were as follows: The database used to search the data, namely PubMed Central and google scholar, the researchers used the following keywords: *Imperata cylindrica* OR *I. cylindrica* OR cogon grass OR Alang-Alang) AND (Hypertension OR hypertension OR blood pressure. Data. which has been obtained from a keyword search and then imported to a library and then exported to Mendeley. In this step, duplication will be manually removed whenever the reviewer finds it. All excluded literature must be given a reason for exclusion according to the inclusion and exclusion criteria previously described.

### *Data Analysis*

After obtaining the journal according to the inclusion-exclusion criteria, then a bias assessment was carried out. In clinical trial articles, biased assessment uses three rating scales: the Jadad, the Newcast Ottawa Scale (NOS), and the Cochrane Risk of Bias Tool (9–11). Determination of the validity of the journal is seen through the Jadad score parameter 3, NOS scale 7, and Cochrane by looking at the terms of low risk of bias (✓) 3, high risk of bias (X) 2, and unclear (?) 4. If two of the three scales are good then the journal is valid. While in the article in vivo bias assessment uses Cochrane Risk of Bias Tool.

Once a valid journal is retrieved, the extracted research article data includes the author's name, journal publish year, type of research, samples used, the originator of hyperglicemia, the derivative product *I. cylindrica* used, the dosage of use, measured parameters and the outcome obtained. The author also extracts the parameters to assess biases Jadad scale, Newcast Ottawa Scale (NOS), and Cochrane Risk of Bias Tool. After that, the conclusion is made following the results of the journal that has been obtained.

## RESULTS AND DISCUSSION

An article search using the Pubmed Central and Google Scholar databases found 2,637 articles. We found 1440 articles on Google Scholar and 1196 on Pubmed central. Then, after eliminating duplicate articles from both databases, there were 530 articles, leaving 2,107 articles. Furthermore, 2,107 articles will be filtered using exclusion criteria. 390 journals were eliminated because they were not original articles of which some were books and review articles. The next 1612 articles were eliminated for reasons of inappropriate titles and abstracts, and 15 journal articles were eliminated even though the titles and abstracts met the criteria but could not be accessed in full text. Then the remaining 90 journals were filtered using the inclusion review criteria. At this stage, 82 articles were eliminated because some of them discussed the effect of *Imperata cylindrica* on other diseases. Then 1 journal was also eliminated because it did not use the UN language but Korean. Finally, 7 articles were obtained which were then validated. Of these 7 articles, there are 6 animal research articles, and 1 article is a clinical trial in humans. Then do the test validation obtain all valid journals so that they can be reviewed.

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## Article Bias Analysis

In this parameter, the analysis bias in *in vivo* and *in vitro* test using Cochrane Risk of Bias Tool, while in clinical trials using Cochrane Risk of Bias Tool, Jadad scale, and Newcastle-Ottawa Scale (NOS) which is then summarized in Table 1 and Figure 1 below

**Table 1. Bias analysis Cochrane risk of bias tools.**

| No | Author | Year | Cochrane | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | ***Random sequence generation*** | ***Allocation concealment*** | ***Blinding of the participant and personal*** | ***Blinding of outcome assessment*** | ***Incomplete outcome data*** | ***Selective reporting*** | ***Other bias*** | **Conclusion** |
| 1. | Erna Sulistyowati., et al | 2017 | √ | √ | ? | √ | √ | √ | √ | Good |
| 2. | E. E. Mak-Mensah.,et al | 2010 | √ | √ | ? | ? | √ | ? | √ | Good |
| 3. | Erna Sulistyowati., et al | 2020 | √ | √ | ? | √ | √ | √ | √ | Good |
| 4. | Nisa et al | 2017 | √ | √ | X | √ | X | √ | √ | Good |
| 5. | Ruslin | 2013 | √ | √ | ? | √ | √ | √ | X | Good |
| 6. | Adyaksa | 2015 | √ | √ | √ | ? | X | √ | √ | Good |
| 7. | Delima | 2014 | ? | √ | X | √ | √ | √ | √ | Good |

**Description**: √: *Low-Risk Bias* x: *High-Risk Bias* ?: *Unclear*

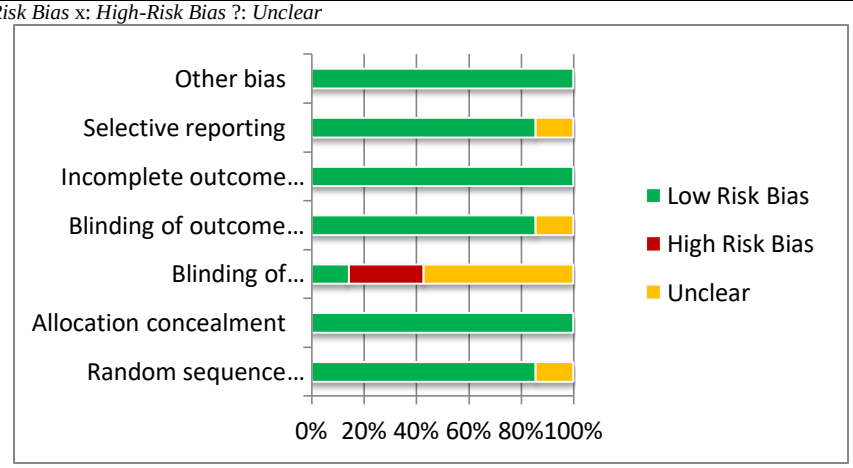


**Figure 1: Research results Graph of Bias Analysis Assessment Results with Cochrane . Parameters**

The scale above uses the Cochrane Risk of Bias Tool, this scale assesses seven aspects of the comparison which include Random Sequencing Creation, Allocation Hiding, Participant Personnel Blinding, Result

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Blinding Assessment, Incomplete Result Data, Selective Reporting, Other Bias. Cochrane is used only for human research, but based on the article I found, it was stated that in animal studies you can use Cochrane. Each assessment parameter has its own task, starting from assessing sample grouping, bias that can occur in participants or experimental animals, submission of data, and several other aspects.

**Table 2. The Validity Results of the Clinical Trial**

| No | Author | Year | NOS Scale | Jadad scale | Cochrane | Kesimpulan |
|---|---|---|---|---|---|---|
| 1. | Cho., et al | 2017 | 7 (good) | 4 (good) | Low risk | Valid |

**Conclusion: The results of the validity of the article using three scales**

**Tabel 3. Valid journal extraction results**

| No | Author | | Type of research | Sample of | Trigger of Hypertension | Derivative product *Imperata cylindrica* | Dosage of administration | Parameters measured | Outcome | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | RV | DR | RO | BP |
| 1 | Erna Sulistyowati.,et al | 2017 | *In vivo* | Male rat weight 180-200g weight 8 weeks | Oxidative stress, Induction of left ventricular hypertrophy. | Leaf powder | 5 gr 5gr 3 gr | Thickening of blood vessels | ↓ | ND | ND | ND |
| 2 | E. E. Mak-Mensah .,et al | 2013 | *In vitro* *In vivo* | Female rabbit and cat | Ringer-locke's solution of composition (mM): NaCl, 155.0; KCl, 5.7; NaHCO3, 6.0; CaCl2, 1.0 and glucose, 5.5 | Leaf | 0.024 and 0.136 mg/ml. | Blood pressure | ND | ND | ↓ | ↓ |
| 3 | Erna Sulistyowati.,et al | 2020 | *In vivo* | Wistar male rate 8 week : 180-200 mg | Menginduksi (ROS) | Leaf | 5 gr 5 gr 3 gr | Thickening of blood vessels | ↓ | ND | ND | ND |
| 4 | Nisa Ulfatun .,et al | 2017 | *in vivo* | Sprague Dawley male rat (SD) white: weight 150-250 gr : 2-3 month | prednisone as much as 1,5 mg/kg in 2.5% NaCl every day for 21 days | Root | 0,08 g; 0,16 g; and 0,32 g | Blood pressure | ND | ↓ | ND | ↓ |
| 5 | Ruslin., | 2013 | *In vivo* | Rat | Induction NaCl | Root | 60 mg 90 mg 115 mg | Blood pressure | ND | ND | ↓ | ↓ |
| 6 | Adyaksa | 2015 | *In vivo* | Ikan Zebra *(Danio rerio)* | Embryos viewing blood pressure in the night zebra | Root | 217 µg/ml (safe use) 591 µg/ml (high dose) | Blood pressure | ND | ND | ND | ↓ |

**Description**: ↓: Signifikan Decrease RV: *Remodelling vascular, DR: Diuretic, RO: Smooth muscle relaxations, BP: Blood Pressure*

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*Imperata cylindrica* has antihypertensive potential which can be seen through the outcomes of Table 3 and Table 4. A summary of imperata cylindrica as an antihypertensive in vivo study article has been described in Table 3. While Table 4 shows the results of a systematic literature review on study articles clinical. This review uses 7 journals, to be studied, of which 4 journals are international journals; (Mak-mesah & komlaga, 2013); (Sulistyowati et al., 2017); (Sulistyowati et., al 2020) (Ruslin et al., 2013) and three other journals are national journals (Nisa et al., 2017); (Pomegranate & Sari, 2014); (adyaksa et al., 2015). (Nisa et al., 2017) (Delima & Sari., 2014), (Adyaksa et al., 2015). There is 1 clinical trial journal which is a national journal (Delima & Sari, 2014. The research years used vary but we use journals in 2010-2021. Of the 7 journals there is 1 journal in 2010 (Mak-Mensah & Komalag., 2010), 1 journal published in 2013 (Ruslin et al., 2013), 1 journal published in 2014 (Pomegranate & Sari (Ruslin et al., 2013), 1 journal published in 2014 (Pomegranate & sari., 2014), 1 journal published in 2015 (Adyaksa et al. al., 2015), 2 journals published in 2017 (Nisa et., al 2017), (Sulistyowati et al., 2017) and 1 journal published in 2020 (Sulistyowati et al., 2020). The derivative product used is the root part. , (Ruslin et al., 2013, (Delima & Sari, 2014); (Adyaksa et al., 2015) (Nisa et al., 2017). Other studies using leaves (Mak-mesah & komlaga, 2010), ( Sulistyowati et al., 2017), (Sulistyowati et al., 2020)

**Tabel 4 Valid clinical trial journal extraction results**

| No | Author | Year of research | Type research | Design | Sample | Derivative product *I. cylindrical* | Dosage | Length | Research | | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | Group control | Group treatment group | BP |
| 1 | Delima | 2014 | Clinical trial | Case control | 15 partisipan | Root | 100 gram dalam 600 ml air | TD | *TD* | Meminum larutan *Imperata cylindrica* | ↓ |

**Description**: ↓: Menurun signifikan BP*: Blood pressure*

There are 4 (four) outcomes that are measured regarding the effect of *Imperata cylindrica* on hypertension. There were 7 (seven) articles reviewed, research conducted by Mak Mensah and Ruslin evaluated smooth muscle relaxation and blood pressure. Research conducted by Sulistyowati evaluated vascular remodeling in mice, which was carried out in 2017[10] and 2020[11]. Another study evaluated the decrease in diuretics, this is in the study (Nisa et al., 2017)[10]. Research conducted by Adyaksa evaluated blood pressure in zebrafish[11]. Clinical research was conducted by Delima in 2014 where this study evaluated human blood pressure given *Imperata cylindrica* solution[12]. Research conducted using various subjects. Research in 2017 used male rats weighing: 180-200g weight 8 weeks. Meanwhile, in 2020 using Wistar male rats aged 8 weeks weighing 180-200 mg. The Mak-Mensah study used rabbits and cats with Ringer-Locke's solution of composition (mM): NaCl, 155.0; KCl, 5.7; NaHCO3, 6.0; CaCl2, 1.0 and glucose, 5.5 as a trigger for hypertension. Nisa et al's 2017 study used white Sprague-Dawley (SD) male rats, weighing 150-250 g, aged 2-3 months and given prednisone as much as 1.5 mg/kg in 2.5% NaCl every day for 21 days. Ruslin egt all[15]., 2014 using rats with NaCl for the induction of hypertension and Adyaksa using zebrafish. The research is carried out using different objects and different treatments. Research by Delima et al 2014 used humans treated with Imperata cylindrica water and then their blood pressure was measured.

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**Effect of *Imperata cylindrica* as an antihypertensive through the mechanism of inhibition of ROS formation.**

Hypertension is caused by many factors, one of which is caused by Reactive Oxygen Species (ROS) which is a very reactive oxidant. Increased ROS has a negative impact, cell integrity can be damaged due to excessive ROS. Endothelium is affected by ROS where these compounds can inactivate Nitrix Oxide or degrade NO. Decreased NO formation results in smooth muscle proliferation, vasomotor dysfunction, induces apoptosis, activates endothelial expression of adhesion molecules, migrates and reorganizes cellular matrix that can interfere with vasorelaxation. This is a mechanism that initiates hypertension. Hypertension is closely related to nitric oxide, if there is a decrease in NO then there is a vasodilation disorder, a decrease in NO occurs due to the presence of superoxide levels. The vascular endothelium is associated with the presence of NO which interacts with the presence of ROS, especially superoxide[11]

The endothelium is affected by ROS where these compounds can inactivate Nitrix Oxide or degrade NO. Decreased NO formation results in smooth muscle proliferation, vasomotor dysfunction, and induces apoptosis. Research conducted by Erna Sulistyowati showed that the main active compounds in *Imperata cylindrica* include triterpenoids (asiaticoside, Asiatic acid, madecassic acid , and lupeol), flavonoids (quercetin, kaempferol, and astragalin), lignans (Graminone B) which function as antihypertensives through an anti-remodeling mechanism.Vascular Its content inhibits the occurrence of endothelial damage to blood vessels by picking up ROS that is formed so that there is no endothel damage.

**Effect of *Imperata cylindrica* as antihypertensive through smooth muscle vasorelaxation mechanism**

*Imperata cylindrica* can function as an antihypertensive through the mechanism of relaxation and dilation of the smooth muscle of blood vessels (in vivo) and digestive tract (in vitro). The content of graminone B in *imperata* has a function as an antihypertensive, with an inhibitory mechanism on the rabbit aorta. The mechanism of action of *imperata cylindrica* is the same as the administration of anti-beta blocker drugs which inactivate adenylate cyclase that produces cAMP from ATP. Decreased cAMP levels inactivate cAMP-dependent protein kinases which in turn phosphorylate L-type calcium channels. As a result, the entry of calcium into the sarcoplasm is restricted reducing contractility. Graminon B contained in *imperata cylindrica* functions as a vasodilator. Flavonoids and quercetin have the effect of decreasing heart rate, through the mechanism of sympathetic nerve activity. This mechanism is through the opening of the K+ channel, resulting in the activation of G protein, this inhibits adenyl cyclase so that ATP cannot be converted into CAMP which results in the closure of Ca2+ and Na+ channels. As a result, there is a decrease in the levels of Ca2+ and Na+ ions in the heart cells which results in the repolarization process[16].

**Effect of Imperata cylindrica as an antihypertensive through a mechanism of decreasing heart rate (ACE inhibitor).**

Angiotensin-Converting Enzyme Inhibitor (ACEi) is a compound that helps control blood pressure and the risk of heart failure, especially in improving the function and anatomy of arteries, improving endothelial function, regressing the tunica media, regressing and stabilizing atherosclerotic plaques. ACEi prevents the enzyme from producing angiotensin II which can cause blood vessel constriction thereby increasing blood pressure and helping to relax blood vessels. Drugs that are included in the ACE inhibitors work by blocking the effect of angiotensin II which acts as a vasoconstrictor. Flavonoids function as ACE inhibitors by inhibiting the conversion of angiotensin I to angiotensin II. The mechanism of ACE inhibitors is to cause vasodilation and a decrease in aldosterone secretion ACEi can also help relax blood vessels.

Aldosterone will affect the kidneys to retain sodium and water, if the release of aldosterone is inhibited, more water is removed from the body and blood pressure will drop[14]. Systolic blood pressure can be decreased by very significant difference ($p<0.01$), as indicated by the results of research the mean systolic blood pressure after drinking reed root infusion is of (95.33 ± 5.381) mmHg, more than lower than average blood pressure systolic pressure before drinking the weed root infusion was (107.07 ± 5,800) mmHg. Diastolic blood pressure can also drop with a very significant difference ($p<0.01$) by drinking root infusion reeds that are shown with results research, namely the average blood pressure diastolic after drinking alangalang root infusion was equal to (64.27 ± 3,693) mmHg, lower than average diastolic blood pressure before drinking Imperata root infusion of (70.00 ± 3,854) mmHg

**The effect of Imperata cylindrica as an antihypertensive through the mechanism of preventing left ventricular hypertrophy by reducing oxidative stress that depends on NADPH oxidase**.

*Imperata cylindrica* contains phenol which functions as an inhibitor of damage from blood vessels by improving endothelial function in blood vessels and increasing the amount of NO which functions as a blood vessel relaxation agent. (endothelial Nitric Oxide Synthase) and increase the production of NO (Nitric Oxide). In a state of oxidative stress, the amount of O2 - in the blood will increase. O2 - is a strong vasoconstrictor that can constrict blood vessels and cause an increase in blood pressure. NO will rapidly interact with O2 - to neutralize and reduce the amount of O2 - so that the bioavailability of NO in the blood will decrease. Phenol will increase NO bioavailability by activating the eNOS (endothelial Nitric Oxide Synthase) mechanism. Regulation of eNOS will produce NO which acts as a powerful vasodilator that relaxes blood vessels and lowers blood pressure.

**The effect of *Imperata cylindrica* as an antihypertensive through a mechanism of decreasing heart rate (diuretic).**

Mechanism of *Imperata cylindrica* Flavonoid content has a role as a diuretic. Through the diuretic mechanism, it causes a lot of urine output, this is usually given to patients with hypertension, diabetes insipidus. In addition, the content of saponins, flavonoids ,and alkaloids also plays a role in reducing blood pressure through vasodilation of blood vessels. Diuretics work to increase the excretion of sodium, water, and chloride, thereby reducing blood volume and extracellular fluid. As a result, there is a decrease in cardiac output and blood pressure. In addition, the content of saponins, flavonoids and alkaloids also plays a role in reducing blood pressure through vasodilation of blood vessels.

## CONCLUSION

The seven studies of *Imperata cylindrica* we included in this paper all reported beneficial effects on antihypertension. However research on *imperata cylindrica* is still very limited and few. *Imperata cylindrica* is able to have an effect on hypertension through the inhibitory effect of ROS, smooth muscle vasorelaxation mechanism, Ace inhibitors, reducing oxidative stress on NADPH oxide and lowering blood pressure through diuretics. This requires further research and further clinical trials.

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