EFFECTIVENESS OF GIVING MORINGA LEAF EXTRACT (*MORINGA OLEIFERA*) IN REDUCING BLOOD PRESSURE: SYSTEMATIC REVIEW

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ABSTRACT

Hypertension, which is an increase in blood pressure, has a prevalence based on Riskesdas in 2018 at the age ≥18 years, which is around 34.1%. Various treatment methods have been developed because if hypertension is not treated it can cause symptoms and serious complications. Other than using chemical drugs such as beta-blockers or ACE inhibitors, people are starting to consider therapy with natural ingredients such as Moringa leaves (Moringa oleifera). It contains compounds that have an antihypertensive effect such as flavonoids and potassium. This study aims to determine the compound, effectiveness, and mechanism of Moringa leaf as an antihypertensive by using a systematic review method. This method is carried out by searching literature using certain keywords based on PRISMA-P, and then data from ten literatures is extracted to be discussed and concluded based on the objectives. The result, obtained various compounds in Moringa leaf extract have certain mechanisms in lowering blood pressure such as flavonoid compounds, such as kaempferol and quercetin, as well as other compounds such as several organic acids, potassium, and alkaloids. Moringa leaf extract also effectively lowers blood pressure in animals and humans with different doses. This study concludes that the administration of Moringa leaf extract can effectively reduce blood pressure due to the antihypertensive mechanism caused by the phytochemical content.

Keywords: Moringa leaf, *Moringa oleifera*, Blood pressure, Hypertension; Antihypertensive

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INTRODUCTION

Hypertension, which means increased blood pressure, is stated in data from the World Health Organization (WHO) in 2015, having around 1.13 billion people worldwide. 1 The prevalence of hypertension in Indonesia itself from 2013 to 2018 continues to increase. Riskesdas 2018 data states that the percentage of hypertensive patients based on measurement results in the Indonesian population aged ≥18 years is 34.1%. 2 Hypertension, which means increased blood pressure, is a condition when the pressure in the blood vessels gradually increases over a long period. Hypertension is known as a silent killer because hypertension sufferers do not initially feel the symptoms. 3 However, in severe hypertension, various symptoms can usually appear, such as headaches, aches, discomfort in the nape of the neck, a feeling of spinning or floating, increased heart rate, and other symptoms which of course can interfere with daily activities. 2 Hypertension can also be a major risk factor for various diseases such as heart disease, stroke, congestive heart failure, vision disorders and kidney disease. Pharmacological and non-pharmacological health efforts have been carried out to treat this disease. Pharmacological treatments that are often used for hypertension are angiotensin-converting enzyme Inhibitors (ACE-I), angiotensin receptor blockers, calcium antagonists, diure, tics, and beta blockers.

However, various factors, such as the strong cultural beliefs of the Indonesian people, mean that long-term use of chemical drugs is avoided because if these drugs are used for a long period, they can cause a buildup of chemicals in the body, making the patient afraid. Some people also prefer the concept of back to nature and have the idea that herbal medicines also have the same properties as chemical medicines, so they consider alternative medicines such as herbs as a treatment for hypertension.

One of the alternative medicines that has been proven to lower blood pressure comes from the plant, namely Moringa. 8 Moringa was chosen as a medicinal plant that has a high potential for use because it can grow well in tropical climates like Indonesia with fairly easy care. Research also proves that the part of the Moringa plant that has the greatest influence on reducing blood pressure is the leaves because they contain compounds such as flavonoids which have an ACE inhibitor effect and antioxidants and potassium which have a diuretic effect. The efficacy of Moringa leaves as an antihypertensive has been proven in several studies so a literature study using a systematic review method is needed to evaluate the results of various relevant studies related to the compounds, effectiveness, and mechanism of action of Moringa leaves as an alternative treatment for treating hypertension.

METHODS

This study uses a systematic review method, which is a term to refers to research methodology carried out by collecting, evaluating, and interpreting various studies with a focus on certain topics with secondary data as samples. 11 Literature collection was carried out based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) in 2020.12 The entire research was conducted from April 2021 to January 2022. The literature search was carried out in 3 publication data centers, namely PubMed, Science Direct, and Google Scholar using the keywords "Moringa oleifera" OR "Moringa Leaves" AND “Hypertension” OR “Blood Pressure”. The screening process was carried out using journal inclusion criteria, namely using Indonesian and English, published from 2016 to 2021, variables using Moringa leaf extract and hypertension, and data obtained using in vivo tests and clinical trials. Meanwhile, exclusion criteria include studies that only use in vitro research methods or are written using the review method. Next, a research feasibility test was carried out using research instruments from The Joanna Briggs Institute for tests on humans and the Systematic Review Center for Laboratory Animal Experimentation (SYRCLE) for tests on animals. The literature that has been obtained is then extracted, namely by reviewing the general and specific aspects of the research. Data synthesis is also carried out by collecting similar data from the results of various studies to be evaluated and summarized to meet objectives and draw conclusions.

RESULT

Researchers identified 487 pieces of literature after searching electronic databases. A total of 25 journals were obtained from the Pubmed database, 441 journals from the Science Direct database while the other 21 journals came from the Google Scholar database. After selection was carried out based on year of publication, 164 journals were eliminated because they were published more than 5 years ago. A total of 33 similar studies were also found in different databases so they had to be eliminated and one of them had to be used. 26 journals must be eliminated because their full data cannot be accessed, leaving a total of 264 journals that have passed the elimination process and will be screened.

After passing the screening, 148 journals had to be excluded because they used the review method, and 29 journals were also excluded because they only conducted in vitro research. Furthermore, based on matching the inclusion criteria and

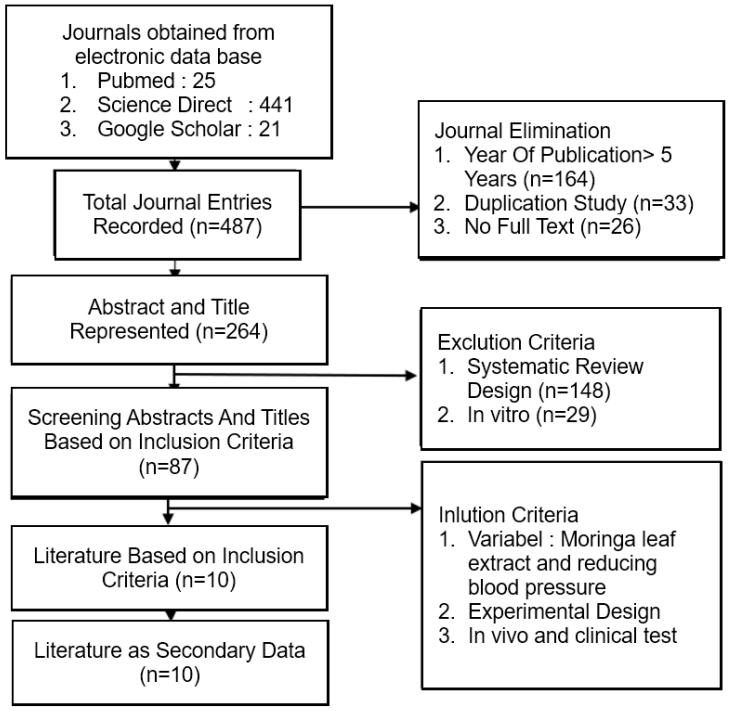

Figure 1. Stage of Literature Selection Based on PRISMA-P

research methods, the final results were obtained, namely 10 relevant studies that would be used and their feasibility tested using the review instrument. Figure 1 shows the literature search flow based on PRISMA.

Analysis of the methodological quality in each study was carried out using the critical appraisal instrument from The Joanna Briggs Institute (JBI) in the quasi-experiment category for human samples. 13 The results, with a total of 3 pieces of literature that used this instrument, fulfilled more than 70% of the JBI criteria by assessing the variables research, sample and population, intervention, research results, and statistical analysis used so that the risk of bias in determining the literature is quite low. Other instruments used for research using animal samples come from the Systematic Review Center for Laboratory Animal Experimentation (SYRCLE) with a true experiment research design. 14 There are 7 literature included in this category and an assessment of sample randomization, blinding, intervention, and follow-up was carried out. further research results and results show that all literature has a fairly low risk of bias because it successfully fulfills more than some of the SYRCLE criteria. This shows that the 10 pieces of literature are suitable for use in this research.

Data from all studies that have been tested for feasibility are then extracted and reviewed based on general information such as the author's name, year of publication, design, and research results which are then entered into the data extraction table (Table 1). Even though the research methods were different, the results were generally the same, namely that Moringa leaf extract could cause blood pressure to decrease significantly compared to the control group, both in experimental animals and in hypertensive patients. Various compounds in each study that were known to play a role in the antihypertensive mechanism were also identified. The compounds found were phenolic groups such as flavonoids and their derivatives, alkaloids, organic acids, and fatty acids.

The results of similar research are collected in a data synthesis table according to predetermined parameters. The data that has been collected will be discussed in detail and then conclusions will be drawn. The data

synthesis process in this study generally shows the results that Moringa leaf extract is effectively used as an antihypertensive both in experimental animals (Table 2) and in hypertensive patients (Table 3). This was taken based on the comparison of blood pressure reduction between treatment groups. Data regarding the extraction process and compound identification from each study as well as test data on the antihypertensive mechanism of Moringa leaves were also synthesized to determine the main route of Moringa leaf extract in lowering blood pressure

Table 1. Literature Data Extraction Results

Author	Design	Sample	Results
Attakpa et al [15], 2017	*Randomized Controlled Trial*	40 Wistar male rats	Compound: Fatty acids Moringa leaf extract reduced blood pressure significantly ($p<0.05$) depending on the dose given except in normal mice
Acuram dan Hernandez[16], 2019	*Randomized Controlled Trial*	Female mice of the ICR strain consisting of several groups with 5 mice in each group	Moringa leaf extract lowered blood pressure significantly, no significant differences were found in blood pressure between doses
Adefegha et al[10], 2019	*Randomized Controlled Trial*	66 Male albino mice consisting of 11 groups (n=6)	There was a significant decrease in BP in the Moringa leaf extract group at all doses, but the best results were shown for Moringa leaves at a dose of 2%.
Aekthammarat et al[17], 2019	*Randomized Controlled Trial*	Wistar male rats consisting of 6 treatment groups	Isoquercetin, catechins, tannins, and other phenolic compounds Giving Moringa leaf extract at TH (30 or 60 mg/kg/day) reduces TDS depending on the dose.
Gbankoto et al[18], 2019	*Randomized Controlled Trial*	Wistar strain rats consisting of 4 treatment groups	Alkaloids, tannins, flavonoids, triterpenoids, steroids, and anthocyanins. Blood pressure decreased significantly after administering Moringa leaf ethanol extract
Aekthammarat et al[19], 2020	*Randomized Controlled Trial*	Wistar strain male rats consisting of several groups (n=6)	There was a significant decrease in blood pressure shortly after being given Moringa leaf extract depending on the dose
Kumolosasi et al [20], 2021	*Randomized Controlled Trial*	A total of 65 Sprague-Dawley rats	Compound: Chlorogenic Acid Moringa leaf extract significantly affects ($p<0.05$) ertensive rats on systolic and diastolic pressure.
Yanti dan Nofia[21], 2019	*Quasi-experimental*	16 hypertensive patients	There was a significant difference in blood pressure before and after intervention with Moringa leaves
Zebua et al[8], 2021	*Pre- experiment*	25 hypertensive patients Panti Jompo Guna Budi Bakti Medan	There were significant categorical changes in hypertensive patients before and after the intervention using Moringa leaves
Riniasih dan Hapsari[22], 2021	*Quasi experiment*	60 elderly hypertensive patients	Moringa leaves have a significant effect in lowering blood pressure in hypertensive patients

The results of research using experimental animals (Table 2) overall show significant differences in blood pressure values between the negative control, intervention group, and positive control. The values obtained depend on the dose, as in research conducted by Attakpa et al15, the blood pressure values of male Wistar rats decreased after being given intervention at different doses. The difference in blood pressure was significant ($p < 0.05$) compared with the negative control at all dose levels. The reduction in blood pressure in Moringa leaf extract at a dose of 200 mg/kg also showed a significant difference compared to the reduction at a dose of 400 mg/kg. Meanwhile, a comparison between doses of 400 mg/kg and 600 mg/kg did not show a significant difference because the blood pressure reduction value after the intervention was not much different. Similar things were also found in other studies, namely a decrease in blood pressure in the intervention group after the treatment period with results that could be compared to the positive control group.

Table 2. Synthesis of Research Data with Experimental Animals

Author	Negative Control	Blood Pressure After Intervention	Positive Control
Attakpa et al [15], 2017	250 mmHg	200 mg/kg = 225 mmHg 400 mg/kg = 175 mmHg * 600 mg/kg = 175 mmHg *	-
Acuram dan Hernandez[16], 2019	108,64 mmHg	Methanol Extract 300 mg/kg/days: 90,97 mmHg * Ethyl acetate dosage 300 mg/kg/day: 87,71 mmHg *	-
Adefegha et al[10], 2019	± 230/190 mmHg	Moringa leaf 2% : ±120/80 mmHg ** Moringa leaf 4% : ±180/125 mmHg *	Lisinopril 10 mg/kg : ±125/90 mmHg**
Aekthammar at et al[17], 2019	189,9 mmHg	30 mg/kg : 177,0 ± 2,7 mmHg * 60 mg/kg : 152 ± 0,7 mmHg**	Captopril 5 mg/kg : 160,8 ± 2,6 mmHg**
Gbankoto et al[18], 2019	159,60 mmHg	500 mg/kg/days: 102,40 ± 5,07 mmHg*	Losartan 100 mg/kg/days : 88,20 ± 5,76 mmHg*
Aekthammar at et al[19], 2020	144.16 mmHg	Percentage reducing MAP 1 mg/kg i.v. : 2,31 * 3 mg/kg i.v. : 6,09 * 10 mg/kg i.v. : 8,43 ** 30 mg/kg i.v. : 8,57 **	-
Kumolosasi et al [20], 2021	±210/160 mmHg	Ethanol Extract 1 ml/100 g BW : 121,40/76,84 mmHg ± SD** Aquos Extract 1 ml/100 g BW : 133,40/98,05 mmHg ± SD**	Perindopril 9.8 mg/kg : ±120/80 mmHg** Irbesartan 98 mg : ±130/90 mmHg**

(Significance values were compared with negative control (*): <0.05, (**): <0.001)

Research with samples of hypertensive patients (Table 3), one of which was conducted by Yanti and Nofia21, showed a decrease in blood pressure values before and after intervention in the form of administering 250 ml of boiled Moringa leaf water for 7 days. Research with the same intervention by Zebua et al8 also showed results, namely a reduction in the degree of hypertension in patients after consuming Moringa leaf boiled water 6 of them managed to reach the normal blood pressure range. Other research conducted by Riniasih and Hapsari22 apart from finding that Moringa leaves had a significant effect ($p<0.05$) on reducing blood pressure, also found a significant difference in the Mann-Whitney test between treatments using Moringa leaves and plain warm water. The results of testing on hypertensive patients prove the effect of Moringa leaf extract on reducing blood pressure.

Table 3. Synthesis of Clinical Trial Data

Author	Blood Pressure Before Intervention	Negative Control	Blood Pressure After Intervention
Yanti dan Nofia, 2019	153,50/94,38 mmHg ± SD	-	129,56/86,25 mmHg ± SD**
Zebua *et al.*, 2021	1. Hypertensioni : 14 responden 2. Pra-Hypertension: 11 responden	-	1. Hypertension : 19 responded 2. TD Normal : 6 respondent**
Riniasih dan Hapsari, 2021	164/103 mmHg ± SD	164/103 mmHg ± SD	148/89 mmHg ± SD**

(Significance values were compared with blood pressure before intervention (**): <0.000)

DISCUSSION

It is believed that Moringa leaves can be used as an herbal medicine in treating hypertension because various active compounds have been proven to be found. These various compounds certainly influence antihypertensive mechanisms. Research conducted by Gbankoto et al18 identified the chemical content of secondary metabolite groups such as alkaloids, tannins, flavonoids, triterpenoids, steroids, and anthocyanins. Another test carried out by Aekthammarat et al17 specifically proved the phenol group compounds contained in Moringa leaf aqueous extract along with the levels of each compound in each gram using the High-Performance Liquid Chromatography-Diode Array Detector (HPLC-DAD) method. The components and levels of each phenolic compound that have been identified are Isoquercetin (811.37 µg/g), Catechin (767.72 µg/g), Tannic acid or tannin (632.84 µg/g), Gallic acid (212 .67 µg/g), Quercetin (204.66 µg/g), Apigenin (40.32 µg/g), and Rutin (1.06 µg/g). (17) Evaluation of fatty acid levels in Moringa leaves using techniques of gas-liquid chromatography carried out by Attakpa et al15 showed results namely saturated fatty acid levels of 49.21%, monounsaturated fatty acids at 3.55%, polyunsaturated fatty acids at 60.30%, omega-6 fatty acids 9.70%, and omega-3 fatty acids 48.57%.

The results of a review of research data prove that Moringa leaf extract has antihypertensive activity from various mechanism pathways caused by the compound content in it (Figure 2). Potassium has a function as a diuretic which increases the release of Na+ and H2O thereby reducing the volume of extracellular fluid so that blood volume decreases. 18 The diuretic effect is also caused by flavonoid compounds, especially kaempferol and quercetin which have been proven to function as ACE inhibitors in research conducted by Acuram and Hernandez16. Inhibition of the angiotensin-converting enzyme (ACE) causes a decrease in angiotensin levels which has the

effect of reducing salt and water retention so that blood volume decreases due to increased excretion of Na+ and H2O. A decrease in blood volume will result in a decrease in venous return which directly affects stroke volume so that blood pressure decreases. Another mechanism is antioxidants caused by the presence of flavonoid compounds causing an increase in the activity of glutathione, catalase enzymes, and superoxide dismutase enzymes. 10 The increase in the activity of these antioxidant components causes a decrease in the production of free radicals so that oxidative stress which results in endothelial dysfunction decreases. A decrease in endothelial dysfunction accompanied by a decrease in angiotensin II levels results in the relaxation of blood vessels which of course results in a decrease in blood pressure. The mechanism through which nitric oxide formation is seen is based on the increase in arginine due to inhibition of the arginase enzyme. Arginine increases eNOS so that activation of the eNOS-sGC pathway which converts guanosine triphosphate to guanosine monophosphate (cGMP) will stimulate relaxation of vascular muscles. antihypertensive.

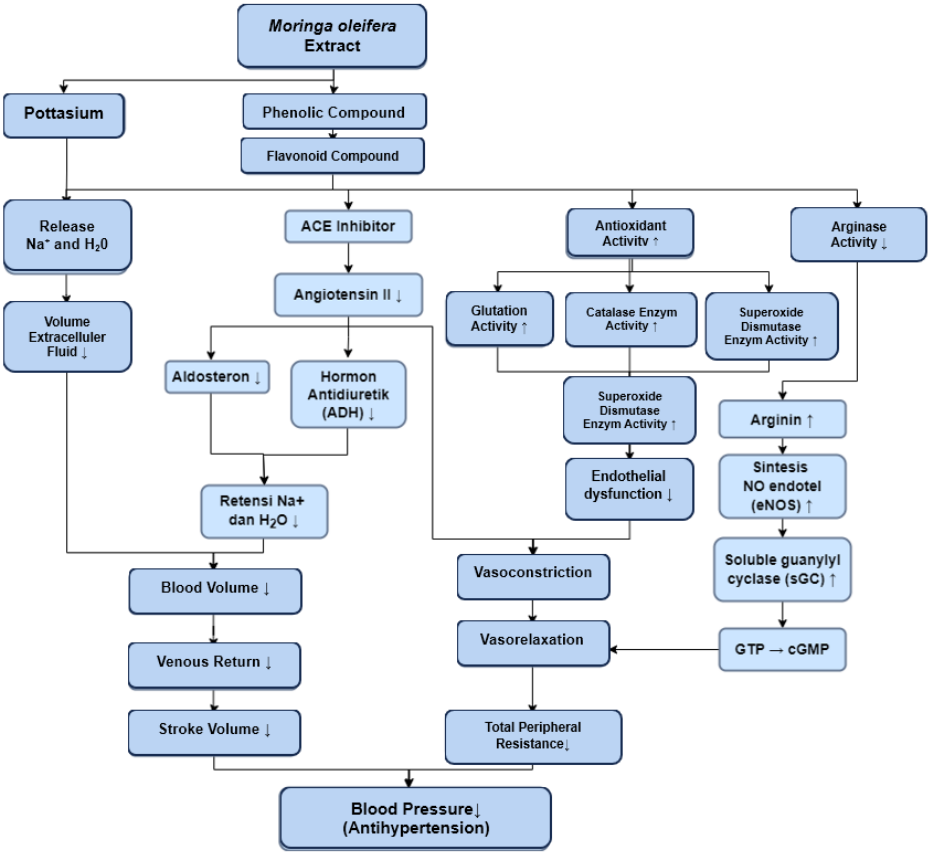

Figure 2. Antihypertensive Mechanism of Moringa Leaves

The effectiveness of administering Moringa leaves in reducing blood pressure also depends on the dose given. One example is research by Acuram and Hernandez16 which used a multilevel maceration extraction method on experimental animals of the ICR strain of mice, showing that there was a significant difference ($p < 0.05$) in the blood pressure of mice after 4 weeks at a dose of 10 mg/kg. /day or 300 mg/kg/day compared with the control group so that a minimum dose of 10 mg/kg/day can effectively reduce blood pressure. Apart from that, toxicity tests on mice showed that the methanol extract of Moringa leaves did not show toxicity up to a dose of more than 2,000 mg/kg with a lethal

dose of 50% (LD50) being in the position of 8,000 mg/kg >LD50 >5,000 mg/kg because of the test results in mice showed that doses of 5,000 and 8,000 mg/kg caused 33% and 67% mortality. 16 Research on different types of mice and doses was also carried out by Kumolosasi et al20. Determination of the effective dose in Sprague-Dawley rats using 3 different doses of Moringa leaf ethanol extract showed that there was a significant difference between BP in the group given the 500 mg/kg dose and the positive control group ($p < 0.001$). Giving a dose of 1,000 mg/kg BP values were comparable to the positive control which had a significant difference compared to the negative control group ($p < 0.001$).

The results of administering Moringa leaf extract can be compared with antihypertensive drugs. Several studies with positive controls in the form of antihypertensive drugs include the angiotensin II receptor blocker (ARB) group, such as the use of losartan in the study by Gbankoto et al16 and irbesartan in the study by Kumolosasi et al20. Another class of drugs, namely angiotensin-converting enzyme inhibitors (ACE-I) were used in research by Adefegha et al10 which used lisinopril as a positive control, and captopril which was used by Aekthammarat et al17. There was a significant difference ($p < 0.05$) in the two groups compared to the negative control group. This statement can be used as a basis that Moringa leaf extract can be used as an alternative therapy for hypertension because it has effects comparable to antihypertensive drugs at certain doses. Even so, if we look at the specific blood pressure values, the blood pressure values after administering chemical drugs are still lower than with Moringa leaf extract.

CONCLUSION

Moringa leaf extract contains various active compounds, especially from the phenolic group such as flavonoids and their derivatives, alkaloids, and potassium which have an important role in the antihypertensive mechanism of Moringa leaves. Administration of Moringa leaf extract as an antihypertensive has been proven to be effective in reducing blood pressure by providing a significant difference ($p < 0.05$) between the treatment group and the negative control group. The antihypertensive mechanism of Moringa leaf extract that has been proven is inhibition of angiotensin-converting enzyme, diuretic activity, antioxidant activity, and vasorelaxation through activation of the nitric oxide formation pathway.

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