

## ARTICLE REVIEW: EFFECTIVENESS OF COMBINATION OF PLANT EXTRACTS AS ALTERNATIVE HYPERTENSION THERAPY

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Submitted: January 24, 2025    Revised: April 10, 2025    Accepted: April 13, 2025

### ABSTRACT

Hypertension is a global health problem requiring effective and safe management. Conventional therapies often face challenges, such as drug resistance, side effects, and patient non-compliance, increasing the need for alternative therapies. This article aims to review the effectiveness of plant extract combinations as antihypertensive therapies. This study used a literature review approach to studies published in the last 10 years, focusing on the mechanism of action, effectiveness, and synergistic potential of plant combinations. The results showed that combinations such as *Anredera cordifolia* (ten.) v. *Steenis* and *Sonchus arvensis* L. provided a decrease in systolic blood pressure (SBP) by 27.95 mmHg and diastolic blood pressure (DBP) by 33.89 mmHg, approaching the effectiveness of standard drugs such as valsartan. The main mechanisms include the inhibition of angiotensin-converting enzyme (ACE), vasodilation through the release of nitric oxide (NO), and diuretic effects. The combination of plant extracts shows potential as a safe and effective alternative; however, further clinical trials are needed to strengthen these findings.

**Keywords:** Combination of Plant Extracts, Antihypertensive, Alternative Therapy.

### INTRODUCTION

Hypertension is one of the most pressing global health problems, with a significant prevalence and impact. Data from the Global Burden of Disease show that hypertension had the highest age-standardized mortality rate among metabolic diseases in 2019, reaching 133.88 per 100,000 population (Gyamfi et al., 2023). In Indonesia, the prevalence of hypertension is exacerbated by low awareness of treatment, with 87.1% of hypertensive individuals being unaware of their condition (Khoiry et al., 2022). Additionally, lifestyle changes, including consumption of low-nutrient and energy-dense foods through online food delivery services, increase the risk of hypertension (Mahmudiono et al., 2022). This condition demands new strategies to improve the management and control of hypertension, especially in low- and middle-income countries.

Conventional therapies face significant challenges, such as drug resistance affecting 9-18% of patients and side effects such as dizziness and fatigue (Chhabra et al., 2023). Nonadherence to treatment, which ranges from 27% to 40% globally, is also a major barrier to hypertension control (Guimarães et al., 2022). The complexity of treatment regimens and limited access to health services exacerbate the situation, especially in low- and middle-income countries (Gyamfi et al., 2023).

Plant extracts are increasingly being sought as alternative antihypertensive therapies. For example, the avocado leaf extract (*Persea americana* Mill.) has been shown to be effective in inhibiting the ACE enzyme and improving endothelial function (Sutiningsih et al., 2023). Plants, such as *Carissa edulis* Vahl and standard tea, have also been shown to reduce blood pressure through synergistic mechanisms involving vasodilation and reduced oxidative stress (Houngue et al., 2022; Muñoz et al., 2022). Advantages of these therapies include fewer side effects and diverse mechanisms of action, making them promising candidates.

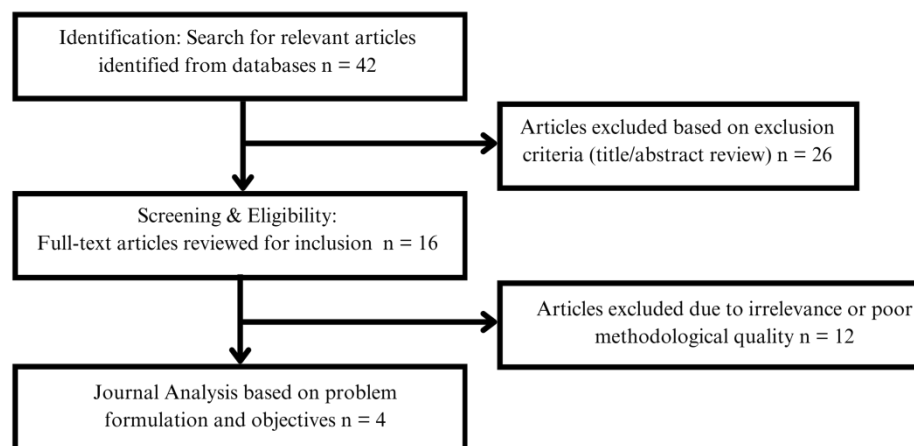
Recent studies indicate that combinations of plant extracts can provide more effective antihypertensive effects through synergy of action mechanisms (Hounguè et al., 2022; Sutiningsih et al., 2023). This combination provides increased benefits compared with single therapy, including the potential to improve inflammation and vascular function (Muñoz et al., 2022). This article aimed to review the current literature on the effectiveness of combinations of antihypertensive plant extracts as safe and effective alternatives for the management of hypertension.

Given the high public health burden of hypertension and the limitations of conventional therapies, further exploration of alternative plant-based therapies is required (Chenghua et al., 2023). Integration of these therapies with modern approaches may offer more personalized and holistic solutions, reducing hypertension-related complications and improving patients' quality of life (Cazarim et al., 2023).

## RESEARCH METHOD

**Methods:** This study used a literature review approach to evaluate the potential of plant extract combinations as alternative antihypertensive therapies. Relevant literature was identified through a search of scientific databases such as PubMed, Scopus, Web of Science, Google Scholar, and ScienceDirect using a combination of keywords such as antihypertensive plant extracts, herbal medicine, and combination therapy. The search included articles published in the last 10 years (2014–2024) that focused on studies discussing plant extract combinations and antihypertensive mechanisms. The inclusion criteria were studies discussing the mechanisms of action of plant extracts, synergistic effects, and the impact of combinations on antihypertensive parameters. Articles that did not meet the criteria, such as those only discussing the use of a single plant or those not relevant to the topic of combinations, were review articles.

From the initial search results, 42 articles were obtained. After screening the titles and abstracts, 26 articles were excluded because they were not relevant. A total of 16 articles were read in full, and 12 were eliminated because they did not meet the inclusion criteria, such as focusing on a single plant or not presenting blood pressure data. Four articles that met the final criteria were further analyzed because they discussed a combination of plant extracts with a clear mechanism of action and their effects on systolic and diastolic blood pressure.



**Figure 1. Flow of Article Search**

## RESULTS AND DISCUSSION

This study reviewed five combinations of plant extracts that are used as alternative therapies for hypertension. Each combination was evaluated based on the reduction in blood pressure. Systolic (SBP) and diastolic (DBP) blood pressures were compared to standard antihypertensive drugs, if available.

**Table I. Journal Review Results**

Plants Used	Compound Active	Mechanism Work	Effectiveness	Type Study	Reference
<i>Allium sativum</i> and <i>Punica granatum</i>	S-allyl-cysteine and gamma-glutamylcysteine .	Vasodilation via NO and hydrogen sulfide (H <sub>2</sub> S), ACE inhibition.	SBP decreases as much as 4.2 mmHg. DBP decreases as much as 4.5 mmHg. For 4 weeks.	Clinical trials (human) hypertension stage I)	(Fogacci et al., 2022)
<i>Apium graveolens</i> L., <i>Orthosiphon stamineus</i> Benth. and <i>Morinda citrifolia</i> L.	Apigenin, Sinensetin , Scopoletin	Calcium channel blocker, diuretic, as ACE inhibitors	SBP decreases as much as 16.10 mmHg. DBP decreases as much as 19.48 mmHg. The decrease significant achieved throughout test group in 30 minutes. Combination This own effectiveness comparable with captopril (2.25 mg/kg BW).	Preclinical (mice)	(Rumiyati et al., 2016)
<i>Hibiscus sabdariffa</i> and <i>Lippia citriodora</i>	Polyphenols, Catechins and Epicatechins	Improvement eNOS, ACE inhibition, NO release	SBP decreases as much as 3.76 mmHg on the 56th day after intake extract combination. DBP does not show change significant	Clinical trials (human) pre-hypertension and hypertension type 1)	(Marhuenda et al., 2021)
<i>Anredera cordifolia</i> and <i>Sonchus arvensis</i> .	Apigenin, Apigetrin , and Flavonoids (kaempferol, luteolin-7-O-glucoside, apigenin-7-O-glucoside, vitexin, luteolin)	inhibition, diuresis, vasodilation via NO	SBP decreases as much as 27.09 mmHg. DBP decreased as much as 16.09 mmHg. Combination This show results best compared to other groups for 60 minutes. With drug the comparator used was Atenolol (4.5 mg/kg BW)	Preclinical (mice)	(Suliska et al., 2021)
<i>Anredera cordifolia</i> (ten.) v. <i>Steenis</i> and <i>Sonchus arvensis</i> L.	Apigenin, Apigetrin , and Flavonoids (kaempferol, luteolin-7-O-glucoside, apigenin-7-O-glucoside, vitexin, luteolin)	ACE inhibition, diuretic activity, and vasodilation through track oxide nitrate (NO)	SBP decreases as much as 27.95 mmHg. DBP decreased as much as 33.89 mmHg. Combination own effectiveness tall for 60 minutes. With drug the comparator used with drug The comparator used was Atenolol (4.5 mg/kg BW)	Preclinical (mice)	(Sukandar et al., 2019)

*Allium sativum* and *Punica granatum*: This combination showed a reduction in SBP 4.2 mmHg and DBP of 4.5 mmHg after 4 weeks. These results are clinically significant for individuals with early stage hypertension, primarily because of the mechanism of action involving vasodilation via the release of nitric oxide (NO) and hydrogen sulfide (H<sub>2</sub>S) and inhibition of ACE. However, this study did not use a comparator drug; therefore, its effectiveness relative to standard therapies could not be evaluated (Fogacci et al., 2022).

The renin-angiotensin-aldosterone system (RAAS) is a key component in the pathophysiology of hypertension because it plays a role in regulating blood pressure and body fluid balance. This process begins with the release of renin by the kidneys, which initiates the conversion of angiotensinogen to angiotensin I. Angiotensin I is catalyzed by angiotensin-converting enzyme (ACE) to angiotensin II, a potent vasoconstrictor that increases peripheral resistance and, consequently, blood pressure (Dewi et al., 2020; Gangga et al., 2022). In addition, angiotensin II stimulates the release of aldosterone from the adrenal cortex, which triggers sodium and water reabsorption by the kidneys, increasing the circulating volume and exacerbating high blood pressure (Wanta et al., 2024).

Under hypertensive conditions, excessive RAAS activity causes endothelial dysfunction and increased sympathetic tone, two factors that pathologically amplify the hypertensive effect (Rahayuningsih et al., 2016). Therefore, conventional antihypertensive therapies, such as ACE inhibitors and angiotensin receptor blockers (ARBs), are designed to block the RAAS pathway as the main strategy for lowering blood pressure (Ayuningtiyas & Sari, 2021). Interestingly, a number of studies have shown that bioactive compounds from medicinal plants have the potential to naturally modulate RAAS.

Compared with pharmacological therapy, herbal interventions are often safer with minimal side effects, making them potentially attractive alternatives, especially for patients with a low tolerance to synthetic drugs (Sinaga et al., 2022). In addition, non-pharmacological approaches such as lifestyle modification, low-salt and high-potassium diets, and increased consumption of green leafy plants also contribute to the suppression of RAAS activity and reduction of the risk of hypertension (Yusetyani et al., 2022). The combination of herbal therapy, conventional medicine, and healthy behavioral changes creates a more effective holistic approach for long-term hypertension management.

*Apium graveolens*, *Orthosiphon stamineus*, and *Morinda citrifolia* : This combination showed a decrease in SBP of 16.10 mmHg and DBP of 19.48 mmHg within 30 minutes. This decrease was significant in all test groups and was equivalent to the effectiveness of captopril (2.25 mg/kg BW), making it a potential alternative for the management of hypertension (Rumiyati et al., 2016).

*Hibiscus sabdariffa* and *Lippia citriodora* : This combination resulted in a decrease in SBP of 3.76 mmHg after 56 days. However, DBP did not show any significant changes. The main mechanism of action involves increasing eNOS, NO release, and ACE inhibition. This study did not use a comparator drug because it focused on the effect of placebo versus the polyphenolic combination (Marhuenda et al., 2021).

Oxidative stress is one of the main pathogenic factors in the development of hypertension and is characterized by the excessive accumulation of reactive oxygen species (ROS) in the vascular system. ROS can damage endothelial cells, reduce the bioavailability of nitric oxide (NO), and trigger inflammatory processes that cause vasoconstriction and increased blood pressure (Saputri et al., 2023). Endothelial dysfunction owing to oxidative stress contributes to decreased blood vessel elasticity and increased peripheral resistance. Studies have shown that increased levels of oxidative stress biomarkers such as malondialdehyde (MDA) are closely related to the severity of hypertension and strengthen the link between oxidative stress and hemodynamic disorders (Lestari et al., 2023).

*Anredera cordifolia* and *Sonchus arvensis* (50-50 mg/kg BW): This combination showed a decrease in SBP by 27.09 mmHg and DBP by 16.09 mmHg in 60 minutes, a result that was much more significant than the control group. This combination was compared with atenolol (4.5 mg/kg BW), which showed close effectiveness (Suliska et al., 2021).

*Anredera cordifolia* (ten.) v. Steenis and *Sonchus arvensis* L (25-25 mg/kg BW): This combination recorded a decrease in SBP by 27.95 mmHg and DBP by 33.89 mmHg. These results indicate the potential of the combination as an adjuvant therapy for hypertension compared with valsartan (7.2 mg/kg BW) (Sukandar et al., 2019).

Research results show that the combination plant extract has significant effectiveness in lowering blood pressure, both in preclinical research and in clinical settings. Combination *Anredera cordifolia* (ten.) v. Steenis and *Sonchus arvensis* L. with a dose of 25-25 mg/kg BW produces the highest reduction in SBP and DBP, respectively 27.95 mmHg and 33.89 mmHg (Sukandar et al., 2019). This indicates that compounds, such as flavonoids (vitexin and luteolin), play an important role in increasing vasodilation through NO release.

Endothelial dysfunction is a pathological condition in which the endothelial lining of blood vessels loses its ability to regulate vascular tone, control coagulation, and maintain a balance between vasoconstriction and vasodilation. One of the main mechanisms that is disrupted is the production of nitric oxide (NO), which is normally produced by the enzyme endothelial nitric oxide synthase (eNOS) and functions as a powerful vasodilator. Decreased NO production causes increased peripheral vascular resistance and elevated blood pressure. In addition, low NO levels are associated with increased inflammation, excessive vascular reactivity, and cardiometabolic risks such as dyslipidemia and hyperuricemia (Cahyawati, 2022; Wantania & Lefrandt, 2016).

#### **Mechanism Supportive Work Effectiveness**

Inhibition: Combinations such as *Apium graveolens*, *Orthosiphon stamineus*, and *Morinda citrifolia* significantly hinder ACE activity, which plays a role in reducing peripheral vascular resistance (Rumiyati et al., 2016).

Vasodilation via NO: Combination such as *Allium sativum* and *Punica granatum* uses the release of NO and H<sub>2</sub>S to increase blood flow and reduce blood pressure (Fogacci et al., 2022).

Effect Diuretics: The combination of *Apium graveolens* and *Orthosiphon stamineus* shows diuretic activity that contributes to the reduction of blood pressure and plasma volume (Rumiyati et al., 2016).

#### **Effectiveness Compared to Drug Standard**

Studies have shown that several combinations have comparable effectiveness to the drug standard. The combination *Apium graveolens*, *Orthosiphon stamineus*, and *Morinda citrifolia* has similar effects as captopril (Rumiyati et al., 2016), whereas *Anredera cordifolia* and *Sonchus arvensis* approach the effectiveness of atenolol (Suliska et al., 2021).

#### **Limitations Study**

This study has a number of limitations. The duration of preclinical research on some big studies is classified as short, so that the results obtained possibly do not reflect the long-term effect of the combination extract plant on blood pressure. In addition, clinical relevance from results research on mice cannot yet be fully applied to humans without validation through clinical trials. Limitations This highlight importance study advanced for strengthen existing findings.

#### **CONCLUSION**

Based on the research results, the combination of plant extracts has significant effectiveness in lowering blood pressure, both systolic (SBP) and diastolic (DBP), through various mechanisms, such as inhibition of angiotensin-converting enzyme (ACE), vasodilation through the release of nitric oxide (NO) and hydrogen sulfide (H<sub>2</sub>S), and diuretic effects. Combination with *Anredera cordifolia* (ten.) v. Steenis and *Sonchus arvensis* L at a dose of 25-25 mg/kg BW recorded the highest reduction in SBP and DBP, respectively by 27.95 mmHg and 33.89 mmHg, approaching the effectiveness of valsartan. In addition, the combination of *Apium graveolens*, *Orthosiphon stamineus*, and *Morinda citrifolia* showed results equivalent to those of captopril, indicating their potential as an alternative therapy for hypertension. However, this study has some limitations, including the relatively short duration of the study and the limited relevance of preclinical results in humans. Therefore, large-scale clinical trials with longer durations are needed



to confirm the effectiveness and explore the potential of other combinations to improve the efficacy and minimize side effects.

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