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# A Review of the Therapeutic Effects of Garlic in Lowering Blood Pressure: A Comprehensive Analysis of Recent Mechanisms and Existing Clinical Data

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**ABSTRACT**

Hypertension is a medical condition characterized by an elevation in systolic blood pressure equal to or greater than 140 mmHg and/or diastolic blood pressure equal to or greater than 90 mmHg. Hypertension elevates the likelihood of developing cerebrovascular disease and mortality. The administration of conventional antihypertensive drugs frequently leads to the occurrence of adverse effects. Moreover, a significant proportion of the population in developing nations, approximately 70%, currently favors the utilization of herbal remedies as opposed to conventional pharmaceuticals. Garlic is a herbal plant known for its antihypertensive properties. This review specifically examines the current mechanisms by which garlic acts as an antihypertensive and presents the clinical evidence available to date regarding garlic's effectiveness in lowering blood pressure. The present mechanism by which garlic acts as an antihypertensive agent involves its anti-inflammatory, vasorelaxant, antioxidant, anti-apoptotic effects, enhancement of microbiota activities, and improvement of heart function. The antihypertensive effect of garlic is derived from its organosulfur content. Based on multiple clinical trials, the majority of studies have found that administering interventions in the form of capsules containing garlic or aged black garlic extract leads to a decrease in blood pressure. Garlic has anti-hypertensive effects, especially in the form of aged black garlic extract.

## 1. Introduction

Hypertension remains a significant worldwide health issue, primarily due to the escalating incidence, frequent occurrence of complications, and suboptimal rates of control. It is projected that over 1.2 billion individuals worldwide will suffer from hypertension in 2019.[1] The incidence of hypertension in Indonesia has decreased from 8.4% in 2018 (based on physician diagnosis) to 8.0% in 2023.[2] Hypertension is a highly influential risk factor for nearly all cerebrovascular diseases.[3] In addition, hypertension elevates the likelihood of mortality from diverse ailments. Based on data from the United States National Health Interview Survey (NHIS) on 213,798 participants, hypertension significantly increased mortality risk in 17 to 67 reported causes of death.[4]

Hypertension is characterized by an elevation in systolic blood pressure equal to or greater than 140 mmHg and/or diastolic blood pressure equal to or greater than 90 mmHg. In Indonesia, the management of hypertension involves both pharmacological and non-pharmacological interventions. The commonly prescribed antihypertensive medications include angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), thiazides, calcium channel blockers (CCB), and diuretics. The administration of these medications frequently results in side effects such as coughing, headaches, edema, increased frequency of urination, constipation, and hyperkalemia.[5] Approximately 70% of the populace in developing nations opt for herbal products over conventional medications as their primary means of maintaining health, including disease prevention and treatment.[6]

Garlic (*Allium sativum*) has traditionally been used in Indonesia as a natural medicine to lower blood pressure and cholesterol, and relieve heart diseases.[7]

Garlic is recognized for its presence of diverse bioactive compounds that possess the ability to reduce blood pressure.[8] Multiple studies, including preclinical[9–11] and clinical trials[12–15], have demonstrated the efficacy of garlic as an antihypertensive agent.

Currently, the exact mechanism of garlic's antihypertensive action has not been clearly defined. In this review, we describe and summarize recent literature on the antihypertensive effects of garlic. We also analyzed differences between clinical studies on garlic as an antihypertensive agent, as well as future suggestions to fill in the existing knowledge gaps.

## 2. Methods

Literature search was carried out with the PubMed search engine by using the keywords "garlic" AND ("hypertension" OR "blood pressure"). Clinical trial articles published in English between 2010 and 2023 which included blood pressure data before and after garlic supplementation were included in this review. Article types, year of publication, and language were screened using PubMed's filters. Clinical trials involving pregnant women, children, and patients with hypertensive urgency or emergency were excluded. Initial search retrieved 20 articles, of which 8 articles were included in this review.

Literature search on garlic's antihypertensive mechanism of action was also carried out with the PubMed search engine with the same set of keywords. Articles on preclinical studies using animal models published in English between 2019 and 2023 were included in this study. Filters were used to screen for articles' year of publication and language. Out of 105 articles retrieved in the initial search, 4 articles were included in this review.

## 3. Garlic's Nutrient Content and Bioactive Compounds

As a popular spice and health supplement, garlic is an easy-to-grow vegetable. Garlic contains more than 200 chemical constituents, including minerals, vitamins, carbohydrates, volatile oils, amino acids, and enzymes. The levels of these nutritional and bioactive substances may vary depending on the processing method used.[16]

The bioactive constituents found in garlic consist of organosulfur compounds, including diallyl thiosulfonate (allicin), S-allyl-cysteine (SAC), S-allyl-cysteine sulfoxide (alliin), E-ajoene, Z-ajoene, diallyl sulfide, diallyl disulfide, and diallyl trisulfide. Approximately 82% of the sulfur content in garlic is composed of the mentioned sulfur components. Raw garlic contains organosulfur compounds that exhibit greater digestibility compared to cooked garlic. Garlic possesses over 20 phenolic compounds, surpassing the majority of vegetables in quantity.[18,19] The total flavonoid content in fresh garlic is 36.1 mg/kg, while the polyphenolic compounds range from 12.64 to 22.66 mg/g. Additionally, the antioxidant activity of fresh garlic ranges from 9.92 to 40.41 mol Trolox/g.[20] The bioactive contents of garlic are presented in Figure 1.

The levels of bioactive substance components in garlic are influenced by the cooking process. As an illustration, the concentration of allicin is significantly higher in raw garlic compared to simmered garlic (6771.03 ± 93.9 vs 274.30 ± 5.9 μg/g).[21] Raw garlic contains high concentrations of γ-glutamyl-cysteine. Alliin is naturally synthesized from these constituents when garlic is stored at low temperatures. The cell membranes of garlic can be damaged by processes such as cutting, heating, or chewing. This damage triggers the release of the enzyme alliinase, which breaks down alliin into thiosulfinates. Allicin and other thiosulfinates undergo simultaneous decomposition into diallyl sulfide, diallyl disulfide, diallyl trisulfide, dithiins, and ajoene. Thiosulfinates, particularly alliin, serve as the primary precursors responsible for imparting the characteristic aroma to garlic. Additionally, this organosulfur compound plays a vital role in the therapeutic advantages.[20]

**Table 1. Nutritional contents of garlic**[17]

| Nutritional Composition/100g food | Fresh Garlic |
|---|---|
| Water (g) | 71 |
| Energy (cal) | 112 |
| Protein (g) | 4.5 |
| Carbohydrate (g) | 23.1 |
| Fat (g) | 0.2 |
| Fiber (g) | 0.6 |
| Ash (g) | 1.8 |
| Calcium (mg) | 42 |
| Iron (mg) | 1.0 |
| Sodium (mg) | 46 |
| Potassium (mg) | 665.7 |
| Thiamine (mg) | 0.22 |
| Riboflavin (mg) | 0.07 |
| Niacin (mg) | 0.3 |
| Vitamin C (mg) | 15 |

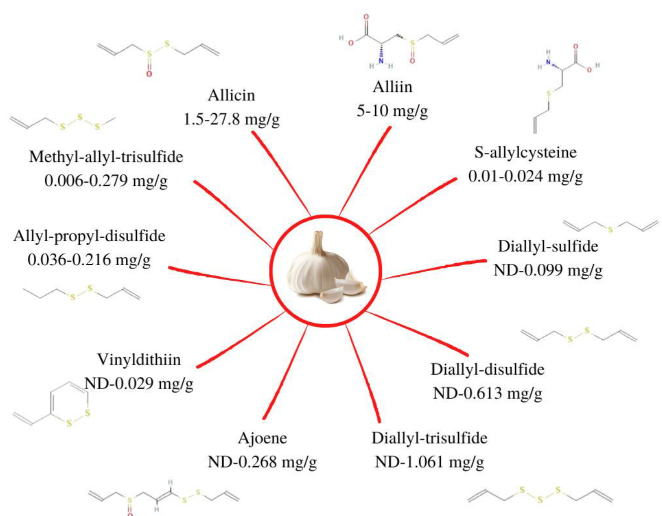


**Figure 1. Compositions of organosulfur in fresh garlic (data obtained from references[21],[22]); ND: Not detectable**

## 4. Antihypertensive Mechanism of Garlic

Garlic exerts its antihypertensive effects possibly by multiple mechanisms of action, such as anti-inflammatory, antioxidant, anti-apoptotic, vasorelaxant, cardiovascular enhancement, and by altering microbial populations (Figure 2). These mechanisms had been exhibited in various preclinical trials. The summary of this preclinical trial study can be seen in Table 2.

### 4.1. Preclinical studies

Liu et al. (2022)[9] demonstrated the advantageous effects of allicin in spontaneously hypertensive rats (SHR), a mouse model of hypertension. The study involved three groups of mice: SHR, SHR + allicin (14 mg/kgBW, 1x/day for four weeks), and the Wistar-Kyoto (WK) group of mice. The SHR mice group receiving allicin exhibited significantly reduced systolic blood pressure (SBP) and diastolic blood pressure (DBP) compared to the group of SHR mice that did not receive allicin (141.03 ± 10.32 vs. 208.37 ± 13.0 mmHg; 97.03 ± 9.47 vs. 160.10 ± 14.76 mmHg; $p < 0.01$). The study revealed that the group of mice treated with allicin exhibited a reduced left ventricular wall thickness compared to the group of SHR mice ($p < 0.05$). However, there were no notable variations in terms of ejection fraction, fractional shortening, and cardiac output among the three groups. The allicin group exhibited a reduction in the percentage area of cardiac fibrocollagen compared to the SHR group. In addition, the group of mice treated with allicin exhibited a notable decrease in the levels of proliferating cell nuclear antigen (PCNA), IL-6, TNF-α, IL-1β, and reduced expression of the CaMK II and NF-κB genes. Furthermore, allicin administration increased smooth muscle 22α (SM22α) protein expression, while also reducing the levels of p65, NF-κB p50, and NLRP3. Allicin was also shown to enhance calcium homeostasis.[9]

In a study conducted by Cui et al. (2020)[10], ten groups of SHR mice were used, which included control group, the allicin 7 mg/kg group, the allicin 14 mg/kg group, the allicin 14 mg/kg + propargylglycine (PAG) 32 mg/kg (an inhibitor of H2S synthase), and the captopril group 50 mg/kg. The intervention lasted for four weeks. Both groups of mice receiving allicin at doses of 7 mg/kg (SBP: 168.22 ± 2.63 mmHg, DBP: 121.19 ± 7.04 mmHg) and 14 mg/kg (SBP: 141.01 ± 2.47 mmHg, DBP: 87.0 ± 3.16 mmHg) exhibited significantly reduced blood pressure. The experimental group exhibited a decrease in blood pressure compared to the control group (SBP: 194.20 ± 8.62 mmHg, DBP: 155.23 ± 5.63 mmHg) after four weeks ($p < 0.01$). The group receiving 14 mg/kg of allicin exhibited a notably lower blood pressure compared to the group administered with a dosage of 7 mg/kg of allicin and the group administered with a dosage of 14 mg/kg of allicin in combination with a dosage of 32 mg/kg of PAG. The in vitro rat mesenteric arterial rings (RMAR) test in this study utilized Sprague Dawley mice. The vasorelaxation induced by allicin is attributed to its interaction with the endothelium. The absence of endothelium in RMAR results in a diminished vasorelaxation response to allicin. The administration of allicin resulted in a significant increase in both cGMP and cAMP levels when compared to the control group.[10]

**Table 2. Several preclinical studies regarding the effects of garlic as an anti-hypertensive**

| No. | Model Subject | Exposure | Results | Ref. |
|---|---|---|---|---|
| 1. | 20 male SHRs and 10 male WKYs rats aged 12 weeks | Subjects were divided into three groups, namely the WKY group (n=10), the SHRs group (n=10), and the Allicin group (SHRs treated with Allicin, n=10) | • Significantly decreased SBP and DBP in Allicin group vs SHRs group<br>• Significantly decreased percentage of fibro collagen area in Allicin group vs SHRs group<br>• Decreased levels of PCNA, IL-6, TNF-α, IL-1β, p65, NLRP3, CaMK II and NF-κB gene expression (Allicin group)<br>• Increased expression of SM22α protein and improved calcium homeostasis (Allicin group). | 9 |
| 2. | Male Sprague-Dawley rats for in-vitro rat mesenteric arterial rings testing<br>50 SHRs male rats for blood pressure testing | Subjects were divided into five groups, namely control group (n=10), allicin dose 7mg/kg group (n=10), allicin 14 mg/kg group (n=10), allicin 14 mg/kg + PAG 32 mg/ kg (H2S inhibitor) (n=10), and captopril 50 mg/kg group (n=10) | • There was a significant decrease in SBP and DBP and the blood pressure lowering effect was even stronger at a dose of 14 mg/kg vs 7 mg/kg<br>• Allicin interacts with the endothelium and induces vasorelaxation via rat mesenteric arterial rings test<br>• Allicin significantly increased cGMP and cAMP levels compared to the control group | 10 |
| 3. | 50 male SHRs mice (10 weeks old) | Subjects were divided into five groups, namely positive control group, blank, hydrolysate garlic protein (GPH), GPH-P (pepsin), and GPH-T (trypsin). | • GPH-P and GPH-T groups had a faster decrease in SBP and DBP than captopril after 4 hours of drug administration<br>• Protein in garlic suppresses lipid peroxidation, and prevents cell damage due to the effects of $H_2O_2$<br>• Inhibits ACE production at certain concentrations | 11 |
| 4. | Albino Wistar rats consisted of 12 who were healthy and 24 who had metabolic syndrome (MS). | Subjects were divided into three groups, namely the healthy group, the untreated MS group, and the MS-DT group (dose 40 mg/kg) | • There was a significant decrease in DBP in the MS-DT group vs MS and control groups<br>• DT improves cardiac performance by increasing ejection fraction and fractional shortening<br>• Increases nitrite ($NO_2^-$) levels and reduces superoxide radical ($O_2^-$) levels.<br>• There is upregulation in the expression of genes such as endothelial nitric oxide synthase (eNOS), superoxide dismutase (SOD)-1, SOD-2, and Bcl-2.<br>• There was a significant downregulation in the expression of genes Bax, caspase-3, caspase-9, NF-κB, and TNF-α | 23 |

DBP: Diastolic Blood Pressure; DT: Diallyl-trisulfide; PAG: Propargylglycine; SBP: Systolic Blood Pressure; SHR: Spontaneous Hypertensive Rats; WKYs: Wistar Kyoto

In another study conducted by Gao et al. (2020)[11], five groups of SHR mice were utilized to assess variations in blood pressure. These groups included a positive control group (received captopril at a dosage of 5 mg/kg), a blank group (received normal saline), a GP group (received garlic protein at a dosage of 50 mg/kg), a GPH-P group (received GP-hydrolysate with pepsin at a dosage of 50 mg/kg), and a GPH-T group (received GP-hydrolysate with trypsin at a dosage of 50 mg/kg). The intervention was followed by blood pressure measurements at 0, 2, 4, 6, 8, 12, and 24-hour intervals. Following a four-hour intervention, the GPH-P and GPH-T groups exhibited a more rapid decline in SBP and DBP compared to the captopril group. The antihypertensive effect of GPH-P and GPH-T is only sustained for 10-12 hours. Additionally, this study revealed that the protein present in garlic possesses antioxidant properties, suppresses lipid peroxidation, and offers a safeguarding effect against $H_2O_2$-induced damage. In addition, garlic protein possesses the capacity to hinder angiotensin-converting enzyme (ACE) at specific concentrations. The half inhibition concentration ($IC_{50}$) for GP, GPH-P, and GPH-T is 3.61, 0.99, and 0.87 mg/mL, respectively.[11]

Jeremic et al. (2020)[23] conducted a study on Wistar albino mice. The mice were divided into three groups: a control group consisting of healthy mice, a group with metabolic syndrome (MS), and a group with MS treated with diallyl trisulfide (DT) at a dosage of 40 mg/kg every other day for four weeks. The findings demonstrated that the administration of DT resulted in a significant decrease in DBP when compared to both the MS and control groups ($p < 0.05$). In addition, administering DT enhances cardiac performance, specifically by increasing ejection fraction and fractional shortening. Additionally, this study revealed that DT had a substantial impact on elevating nitrite ($NO_2^-$) concentrations and diminishing superoxide radical ($O_2^-$) levels. Following DT administration, there was a notable upregulation in the expression of genes such as endothelial nitric oxide synthase (eNOS), superoxide dismutase (SOD)-1, SOD-2, and Bcl-2. Conversely, there was a significant downregulation in the expression of genes *Bax*, caspase-3, caspase-9, NF-κB, and TNF- α.[23]

The presence of microbes is also believed to have a role in the development of hypertension. Multiple microbial species possess the capacity to synthesize short-chain fatty acids (SCFAs) such as butyrate, propionate, and succinate. The synthesis of SCFAs exerts a safeguarding impact on the cardiovascular system owing to the anti-inflammatory capacity of SCFAs. Additionally, a decrease in the number of Lactobacillus species capable of producing peptides that possess ACE inhibitory properties is associated with hypertension.[24] The study conducted by Reid et al. (2018) on hypertensive patients employed intervention in two distinct groups. During a 12-week duration, group 1 was administered Kyolic aged garlic extract capsules, which contained 1.2 g of powdered garlic extract and 1.2 mg of S-allyl-cysteine, twice daily. In contrast, group 2 received cellulose placebo capsules. Administration of garlic capsules promoted the proliferation of *Lactobacillus* and *Clostridia* populations. There was a strong positive correlation (r = 0.561, $p$ = 0.01) between the growth of bacterial population and blood pressure.[25]

### 4.2. Garlic as an anti-inflammatory

Garlic exerts its anti-inflammatory effect by decreasing the levels of IL-6, TNF-α, and IL-1β, as well as the expression of the CaMK II, and NF-κB genes p65, NF-κB p50, and NLRP3. Low-grade chronic inflammation may excessively activate the immune response. This will in turn cause endothelial dysfunction, which leads to hypertension. Several pro-inflammatory cytokines, including IL-1β, IL-6, IL-17, TNF-α, and IFN-γ, are implicated in the development of hypertension. These pro-inflammatory cytokines induce hypertension by increasing oxidative stress, initiating microvascular remodeling and sodium retention, diminishing NO production, initiating renal fibrosis, and reducing glomerular filtration rate.[26]

An inflammasome is a protein complex located in the cytoplasm that is involved in the cellular stress response, and the recognition of patterns associated with pathogens and cellular damage. NLRP3 is a prominent component of the extensively researched inflammasome and plays a crucial role in the activation of caspase 1, which in turn stimulates the production of IL-1β and IL-18, thereby initiating the inflammatory response.[27] Preclinical trials showed that inhibiting NLRP3 resulted in a decrease in blood pressure.[28] NF-κB contributes to the development of hypertension by promoting the production of NLRP3. NF-κB is a transcription factor that can bind to different genes involved in controlling the expression of pro-IL-1β and NLRP3.[29] Long-term suppression of NF-κB in the hypothalamic paraventricular nucleus can delay the progression of hypertension by augmenting the production of anti-inflammatory cytokines and reducing the levels of NLRP3 and IL-1β.[30] Activation of CAMK II in vascular smooth muscle cells and cardiomyocytes can ultimately lead to the expression of pro-inflammatory genes through the involvement of NF-κB. Additionally, it can activate the inflammasome using a Toll-like receptor (TLR-4).[9] The SHR animal test revealed a correlation between a reduction in CAMK II protein expression and a decrease in blood pressure in the experimental animals.[31] Garlic shows great potential as a treatment for hypertension due to its ability to decrease or prevent the activation of inflammatory factors.

### 4.3. Garlic as a vasorelaxant

Garlic exerts a vasorelaxant effect by suppressing the production of ACE. ACE catalyzes the hydrolysis of Angiotensin I, converting it into Angiotensin II, which is a potent vasoconstrictor. Angiotensin II induces

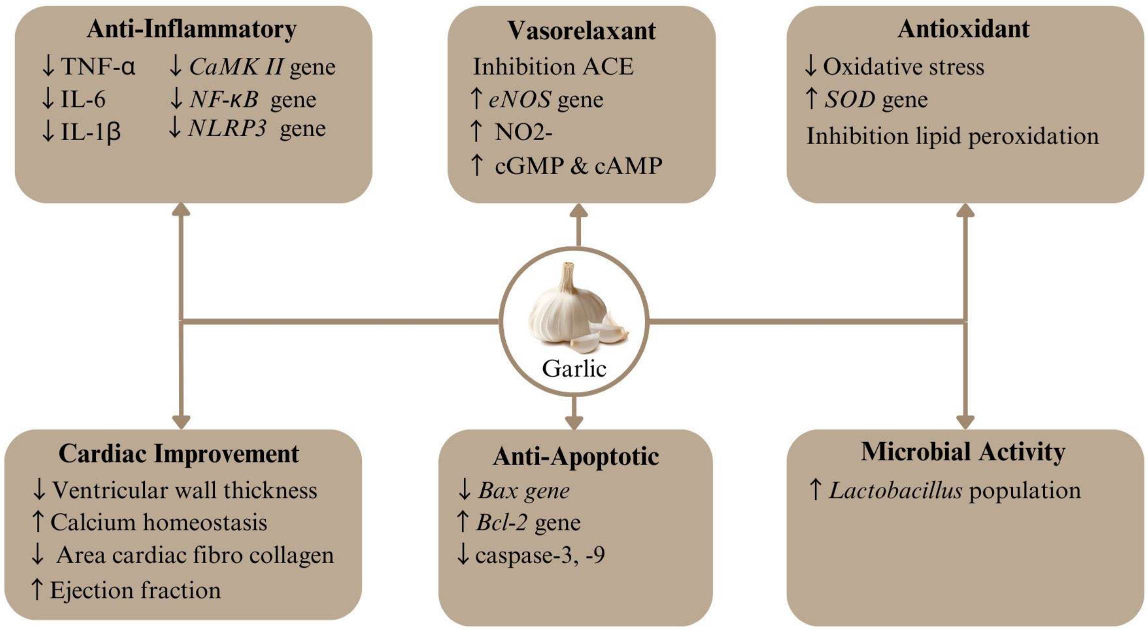


**Figure 2. Potential mechanisms of garlic as an antihypertensive. The mechanism of garlic extracts and the active substances in it has anti-inflammatory properties[9], vasorelaxant[10,11,23], antioxidant[11,18,19], improves cardiac function[9,23], anti-apoptosis[23], and influences microbiota activity[25]. ACE: Angiotensin-converting enzyme; CAMK II: Calcium/calmodulin-dependent kinase II; cAMP; cyclin adenosine monophosphate; cGMP; cyclin guanosine monophosphate; eNOS: NO synthase; IL: Interleukin; NF-κB: Nuclear factor-kappa B; NLRP3: NOD-like receptor pyrin domain-containing protein 3; SOD: Superoxide dismutase; TNF: Tumor necrosis factor**

vasoconstriction in vascular smooth muscle and promotes the retention of water and sodium, resulting in an elevation of blood volume and subsequent rise in blood pressure.[32]

Garlic can enhance the expression of the eNOS gene. eNOS is an enzyme involved in the synthesis of nitric oxide (NO). Nitric oxide (NO) serves as a signaling molecule and plays a crucial role in various physiological processes such as angiogenesis, immune response, neural communication, regulation of vascular tone, and platelet aggregation.[33] Reduced eNOS expression is linked to increased vulnerability to hypertension, migraine, retinopathy, preeclampsia, diabetic nephropathy, and erectile dysfunction.[34]

Garlic additionally increases the levels of $NO_2$, which possesses vasodilatory properties. $NO_2^-$ acts as a vasodilator through two mechanisms: Nitric oxide (NO) is generated under hypoxic conditions with the assistance of nitrite reductase. In normoxic environments, sulfur compounds are produced by the degradation of oxidants, such as hydrogen peroxide ($H_2O_2$). During the hypoxic pathway, the soluble guanylyl cyclase (sGC) enzyme becomes active, resulting in the synthesis of cGMP. Afterward, the activation of cGMP-binding kinase protein kinase G1α (PKG1α) occurs, which then triggers vasodilation. PKG1α can be synthesized under normal oxygen conditions by converting $H_2O_2$ into thiol and forming disulfide oxidation. This process results in the production of a smooth muscle relaxant.[35] Hughan et al. (2020) conducted a study where hypertensive patients with metabolic syndrome were given 40 mg nitrite therapy three times a day for 12 weeks. The results showed a notable decrease in both SBP and DBP.[36]

### 4.4. Garlic as an antioxidant

Hypertension is influenced by oxidative stress conditions. Elevated concentrations of reactive oxygen species (ROS) can lead to a decline in cellular activity and tissue deterioration. Vasoconstrictor agents include reactive oxygen species such as hydrogen peroxide ($H_2O_2$) and oxygen ($O_2$). Both $O_2$- and $H_2O_2$ can hinder the ATPase transport of $Ca^{2+}$ to the sarcoendoplasmic reticulum, leading to a decrease in $Ca^{2+}$ transport within the reticular system and resulting in an accumulation of $Ca^{2+}$ in the cytoplasm. This mechanism can induce the contraction of vascular smooth muscle.[11] Garlic has an antioxidant effect because it includes flavonoids, phenols, and other organosulfur compounds, including SAC, which has a potent radical scavenging function. Garlic can also increase the production of several antioxidant enzymes that shield endothelial cells from oxidative stress, including glutamate-cysteine ligase modifier (GCLM) and heme oxygenase-1 (HO-1) components.[18,19] Garlic's saponin content can also eliminate intracellular ROS and shield DNA in C2C12 myoblast mice from damage induced by $H_2O_2$. Saponin content in garlic can also provide DNA protection from damage caused by H2O2 in C2C12 myoblast mice and destroy intracellular ROS.[37]

### 4.5. Garlic may improve gut microbial populations

The role of gut microbiota in reducing blood pressure may involve multiple pathways. *Lactobacillus* bacteria can modulate the renin-angiotensin system through the synthesis of peptides that function as ACE inhibitors, namely Val-Pro-Pro and Ile-Pro-Pro. Additionally, *Lactobacillus* may also enhance lipid levels in the blood profile and contribute in decreasing body weight. Furthermore, *Lactobacillus* may enhance the body's assimilation of minerals and phytoestrogens, which possess the ability to dilate blood vessels.[38,39] The presence of bacteria in the intestinal tract of experimental animals had been shown to influence the regulation of their blood pressure.[40,41]

### 4.6. Garlic as an anti-apoptotic

In addition to the inflammatory process, apoptosis also plays a role in vascular remodeling in hypertension. A study using SHR mice as experimental subjects found that at three and five weeks, the expression of the Bax protein in the SHR group was markedly higher compared to the expression of the Bcl-2 protein in the control group (WK mice).[42] Liu et al. (2019) conducted a study involving 60 patients with congestive heart failure (CHF) and 30 healthy individuals as controls. The study revealed a noteworthy elevation in Bax protein expression and a notable reduction in Bcl-2 protein levels among CHF patients when compared to the control group. In addition, there was a direct correlation between the expression of Bax and the severity of CHF, while there was an inverse correlation between the expression of Bcl-2 and the severity of CHF.[43]

Bax is pro-apoptotic, while the Bcl-2 protein is anti-apoptotic. The Bcl-2 protein is located mainly in the mitochondrial membrane, nuclear membrane, and smooth endoplasmic reticulum. The Bax protein is primarily found in the cytoplasm and migrates to the mitochondrial membrane in response to an apoptotic signal that initiates apoptosis and damage to the mitochondrial membrane. The process of apoptosis will decrease myocardial cells, decreasing cardiac contractility and raising the severity of heart disease.[43] The ability of garlic to reduce the expression of the *Bax* gene and increase the expression of the *Bcl-2* gene means that garlic has a protective effect on the heart from the dangers of ischemic injury.

Apart from that, garlic also reduces the expression of the caspase-3 and caspase-9 genes. Since it is involved in deciding cell death, caspase-3 has been the most studied of these caspases. Under physiological conditions, caspase-3 is inactive. A rise in blood pressure causes stress on the endoplasmic reticulum, which activates caspase-3 in the endoplasmic reticulum. Nuclear proteins, skeletal proteins, and DNA repair enzymes are all harmed by this damage. This process will cause apoptosis in cells such as myocardial cells.[44]

### 4.7. Garlic as cardioprotector

It is believed that the actions of garlic as a cardioprotectant come from its ability to lower blood pressure and lipid levels in the blood, boost antioxidant activity, and inhibit platelet aggregation.[45] Garlic, especially SAC, increases NO levels by stimulating eNOS. Improvement of cardiac function is associated with decreased vascular resistance. Thus, garlic can enhance blood flow to the heart muscle and regulate the function of the left ventricle. In addition, garlic is recognized for its ability to impede the progression of coronary artery calcification.[46]

## 5. Clinical Trials of Garlic Against Hypertension

Multiple clinical trials have been conducted to establish garlic as an effective therapy for hypertension.[15,50,51] Table 3 presents a concise overview of the clinical investigations on garlic's impact on hypertension.

**Table 2. Clinical studies of garlic on blood pressure**

| Country | Sample size | Exposure | Results | Ref |
|---|---|---|---|---|
| Spain | 77 patients with grade I hypertension | In the initial two weeks, all of the patients received placebo therapy. Then, the patients were divided into two groups, namely group L received aged black garlic extract (250 mg, containing 0.25 mg SAC), and Group A received a placebo (maltodextrin, 250 mg). Duration of intervention: 12 weeks | Administration of garlic extract significantly reduced systolic and diastolic blood pressure (after 12 weeks of intervention) by 1.8 and 1.5 mmHg, respectively. Apart from that, giving aged black garlic can also increase nitric oxide levels and reduce ACE activity. | 15 |
| Spain | 67 patients with moderate hypercholesterolemia | Two groups of patients were created: group 1 received one tablet per day of aged black garlic extract (1.25 mg SAC), | Following a six-week intervention, there was a notable disparity in the decrease of blood pressure (Δ reduction in BP) between group 1 and group 2 (-1.85 mmHg vs 1.77 | 47 |

| Country | Sample size | Exposure | Results | Ref |
|---|---|---|---|---|
| | | while group 2 received placebo tablets (250 mg maltodextrin). Duration of intervention: 6 weeks | mmHg, p = 0.007). No statistically significant difference was observed in SBP (p = 0.694). | |
| Iran | 80 patients with PCOS | Patients were divided into two groups, namely group 1 received garlic supplements 800 mg/day and group 2 placebo (contains starch). Duration of intervention: 8 weeks | There were no significant differences in SBP ($p = 0.071$) and DBP ($p = 0.464$) in group 1 compared to group 2. | 48 |
| Sweden | 93 patients with a Framingham risk score ≥ 10 | There were two groups: group 1 received 600 mg of aged black garlic capsules, which they took two of twice a day for a total of four capsules per day, and group 2 received two starch capsules, which they took twice a day. Duration of intervention: 12 months | There was a noticeable decrease in systolic blood pressure (SBP) after taking garlic supplements, with a reduction from 148 to 140 mmHg (p = 0.027). Nevertheless, there was a negligible alteration in SBP in the placebo group. Group 1 did not exhibit any noticeable decrease in DBP. | 49 |
| India | 40 patients newly diagnosed with metabolic syndrome | All patients received crushed raw garlic supplementation of 100 mg/kg 2x/day. Duration of intervention: 4 weeks | There was a significant decrease in SBP after garlic supplementation compared to before supplementation (140.22 ± 5.39 vs 150.25 ± 14.65 mmHg, $p < 0.0001$). The same phenomenon was observed in DBP, which dropped following garlic treatment (84.10 ± 3.65 vs 96.40 ± 9.21 mmHg, p < 0.0001). | 50 |
| Pakistan | 210 patients with grade 1 hypertension | There were seven subject groupings formed, numbered A through G. Group A received garlic extract tablets of 300 mg, group B 600 mg, group C 900 mg, group D 1200 mg, group E 1500 mg, group F received atenolol 100 mg/day, and Group G received placebo. The duration of the intervention is 24 weeks. | Group E experienced a substantial ($p < 0.005$) decrease in SBP of 5.23% as opposed to group G (0.15%). Group D had the most DBP reduction, at 6.74%, compared to 1.10% ($p < 0.005$) for the placebo. | 51 |
| Australia | 79 patients with uncontrolled hypertension | Four groups were involved in the intervention: group 1 was the control group (placebo), group 2 consumed one 240 mg capsule of Kyolic aged garlic extract, group 3 consumed two 480 mg capsules, and group 4 consumed four 960 mg capsules daily. Duration of intervention: 12 weeks. | The largest significant reduction in SBP was found in group 3, amounting to 9.7 ± 4.8 mmHg compared to group 1 ($p = 0.03$). However, in DBP there was no significant difference between the group that received garlic extract and placebo. | 52 |
| Australia | 50 patients with uncontrolled hypertension | Two groups of patients were created: group 1 received four capsules containing 960 mg of Kyolic aged garlic extract, whereas group 2 received a placebo. Duration of intervention: 12 weeks | A significant reduction was seen in SBP in group 1 compared to controls at week 12 (15.2 vs 7.4 mmHg, $p = 0.036$). However, based on DBP, there was no significant difference between group 1 and group 2 ($p = 0.242$). | 53 |

## 6. Garlic's Nutrient Content and Bioactive Compounds

There are multiple techniques for preparing garlic, such as consuming it in its raw or cooked form, producing garlic powder, boiling garlic, and creating aged garlic extract. In Indonesia, the traditional method for utilizing garlic as an antihypertensive is by consuming boiled garlic water.[12–14] Aside from by boiling, garlic can also be consumed as an herbal remedy by ingesting four cloves daily.[54] Preclinical research has demonstrated the potential of garlic to reduce blood pressure,[9,10,11,23] but its effectiveness in clinical trials remains uncertain due to various factors.

Diverse studies have produced disparate findings. For example, a study[15,50,51] observed a notable reduction in SBP and DBP. Another trial[48] did not show any noticeable decrease in SBP or DBP. Some studies[47,49,52,53] reported a significant decrease in either SBP or DBP, but not both. Several factors may contribute to variations in the results of clinical trial studies, such as:

a. Differences in the demographic characteristics of the sample. Individuals diagnosed with polycystic ovary syndrome (PCOS) face a heightened risk of developing hypertension as a result of an overabundance of androgen hormones.[55] The precise mechanism by which garlic combats PCOS remains unknown thus far. Moreover, the inclusion of individuals with an average age of 60 years or older in most studies can have an impact on the efficacy of drugs within the body. The physiological processes of drug absorption, distribution, metabolism, and elimination experience a decline in old age. Interference with these four processes can lead to reduced drug availability, alterations in drug concentration in the bloodstream, heightened drug toxicity, and buildup of drugs in the bloodstream.[56]
b. How garlic supplementation was administered. Variations in garlic types naturally result in differences in their composition. Fresh garlic exhibits a greater concentration of allicin compared to black garlic, with levels of 11.28 ± 0.22 g/kg and 2.31 ± 0.07 g/kg, respectively. The allicin compound is primarily responsible for its antihypertensive effect.[57] In addition, existing literature have not looked into the potential effects of garlic when consumed traditionally.
c. The treatment duration between studies varied. Wang et al. (2015) conducted a meta-analysis study that found that taking garlic supplements at a dosage of 480 mg would result in the most significant reduction in high blood pressure after a 12-week treatment period. The hypotensive effect becomes more pronounced with higher dosage and longer treatment duration.[58]

Based on existing literature and accounting for these differences, future clinical studies should be performed on 18 to 60-year-old patients with essential hypertension without comorbidities for at least 12 weeks. Extracts from fresh garlic with a dose threshold of at least 1200 mg/day shows potential for future studies and developments.[51]

Multiple ongoing clinical trials and pre-clinical investigations have shown the potential of garlic as an antihypertensive drug. Although garlic is a promising medication, using it as an antihypertensive agent comes with several challenges. These include determining the optimal therapeutic dose to lower blood pressure, controlling side effects (such as gastrointestinal effects and taste and smell of the drug), and incurring manufacturing costs.

## 7. Conclusion

This review examined the potential of garlic as an antihypertensive agent by exploring its anti-inflammatory, antioxidant, anti-apoptotic, and vasorelaxant properties. These effects have the potential to enhance microbiota activity and improve heart function. Multiple clinical trials have consistently demonstrated that garlic can reduce blood pressure levels. The majority of the international studies employed capsules containing either garlic extract or aged black garlic extract. Future studies should consider including patients with essential hypertension from appropriate age groups, taking into account the route of administration, dose and treatment duration to reach optimal antihypertensive effects of garlic.

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## 9. References

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