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REVIEW ARTICLE

Potential of *Allium sativum* in blood pressure control involves signaling pathways: A narrative review

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Abstract

The use of food products and functional foods to manage and treat several health conditions is expanding globally. Garlic (*Allium sativum*) consumption is commonly used for its potential therapeutic functions in numerous cardiometabolic disorders, including hypertension. The proposed blood pressure–reducing effects of garlic after its consumption influence several metabolic pathways, resulting in potentially beneficial health outcomes. The first postulated mechanism is nitric oxide (NO) activation, leading to vasodilation. Furthermore, garlic consumption was also shown to promote vasodilation by suppressing the renin–angiotensin–aldosterone system (RAAS) and the formation of prostaglandins, suppressing angiotensin-converting enzyme activity. The mechanism of garlic-related vasodilation is related to its high sulfur-containing content associated with forming hydrogen sulfides (H_2S). The H_2S binds to and activates vascular ATP-sensitive potassium channels (kATP), leading to hyperpolarization, which induces vasodilation. This review summarizes garlic's features and the mechanical paths that could contribute to blood pressure control.

KEYWORDS
Allium sativum, blood pressure, diuretics, functional food, hypertension

1 | INTRODUCTION

Cardiometabolic disorders (CMDs) constitute the leading cause of death (Amin, Radwan, et al., 2020). They consist of cardiovascular disease (CVD) (Yang et al., 2020), type II diabetes mellitus (Horton & Barrett, 2021), and chronic renal failure (Zheng et al., 2021). The main risk factors for CMDs are an unhealthy lifestyle (Jardim et al., 2019), which includes smoking (Ali et al., 2018), a sedentary lifestyle (Miranda et al., 2020), and poor dietary habits (Jardim et al., 2019). According to the World Health Organization (WHO), CVD accounts for 31% of all fatalities globally (Arena & Lavie, 2021). An estimated 17.9 million people died from CVD in 2019, representing 32% of all global deaths (Al-Gahtani et al., 2022). Obesity and hypertension (HTN) are two conventional CVD risk factors (Ma et al., 2020), one of the leading causes of mortality (Dwivedi et al., 2020). Following several global guidelines, HTN is diagnosed when a person's systolic blood pressure (SBP) is ≥140 mmHg and/or diastolic blood pressure (DBP) is ≥90 mmHg. Furthermore, HTN can be categorized as primary (essential) with no specific medical causes (90%–95%); or secondary, which is caused by another medical condition (5%–10%) affecting kidneys, arteries, and endocrine system (Katz & Rotstein, 2021). Up to 95% of all diagnosed HTN cases can be categorized as primary HTN (Jordan et al., 2018), whereas up to 10% can be ascribed to secondary HTN (Carey et al., 2018).

Some of the modifiable risk factors associated with the development of HTN include stress (Hackett & Steptoe, 2017), visceral adiposity (Han et al., 2021), diet (Krist et al., 2020), alcohol intake, and sedentary lifestyle (Chung et al., 2020). An increased risk of developing HTN and CVD alike is associated with adhering to high consumption of ultra-processed foods (UPFs) that are commonly rich in salt, fat, and refined carbohydrates and limited in fresh fruits and vegetables (Jones et al., 2018). Adhering to several dietary patterns has been shown to have preventive effects on the prevalence and incidence of HTN in epidemiological studies (Ali, Manzoor, et al., 2022; Zampelas & Magriplis, 2020). Based primarily on findings from prospective studies and a small number of carefully designed, randomly controlled trials with end points of the disease, plant-based dietary patterns such as the Dietary Approaches to Stop HTN diet (Akhlaghi, 2020), the Mediterranean diet (van den Brink et al., 2019), and the Nordic diet (Kurtkulagi et al., 2020), have protective effects on the onset and development of CMDs.

2 | ULTRA-PROCESSED FOOD (UPF)

The consumption of UPF is identified as one of the leading causes of HTN (Barbosa et al., 2022). Research involving over 6000 individuals aged 45 and older reported that Black Americans who eat the most UPF were 55% more likely to have high blood pressure than White adults who consumed the same amount (Newsroom, 2021). A cross-sectional study including 13,608 adults from the 2015 Canadian Community Health Survey—Nutrition found that adults in Canada who consume more UPF had a greater prevalence of HTN (Nardocci et al., 2021). In a meta-analysis of 9 studies totaling 111,594 individuals, it has been concluded that in the majority of HTN in the general population, UPF may have negative impacts (Marino et al., 2022). A Brazilian longitudinal study conducted by civil servants at a 4-year follow-up concluded that the higher consumption of UPF is related to an increased level of HTN (da Silva Scaranni et al., 2021).

According to the research, UPFs are connected to bad dietary nutrient profiles and several noncommunicable chronic diseases (Micek et al., 2021). UPFs dramatically raise the risk of cardiovascular conditions, all-cause mortality, overweight and obesity, malignancies, and depression (Chen et al., 2020). However, eating some naturally occurring or minimally processed meals, like whole grains, fruits, and vegetables, hurts weight gain (Astrup & Monteiro, 2022). Possible links between UPFs and HTN have recently gained attention. There has been research on the relationship between UPF intake and HTN; however, the results are conflicting (Ribeiro et al., 2023). Therefore, it is crucial to comprehend how the use of UPFs affects HTN entirely. Although two recent systematic reviews examined the relationship between UPF consumption and HTN, it should not be disregarded significant limitations (Barbosa et al., 2022; Pagliai et al., 2021). In contrast, some earlier research findings revealed that there was either no statistically significant association between UPF intake and HTN or that there was simply a qualitative review of the studies on this topic (Ivancovsky-Wajcman et al., 2021; Rezende-Alves et al., 2021). Consequently, it is still uncertain if consuming UPFs causes HTN. We sought to evaluate the association between adult HTN and UPF intake by a thorough meta-analysis and systematic review of observational data.

3 | ACTIVITY LEVEL

For the primary prevention and treatment of HTN, exercise is a crucial element of lifestyle therapy (Barone Gibbs et al., 2021). Numerous studies have repeatedly shown that exercise positively benefits HTN, lowering systolic and DBP by 5–7 mmHg in people with the condition (Alpsoy, 2020). Exercise has been immediately linked to sharp drops in SBP (Parsons et al., 2021). Postexercise hypotension is the instant drop in blood pressure that occurs after exercise and lasts approximately 24 h (Parsons et al., 2021). The exercise training response is known to lower blood pressure more consistently with more frequent or continuous activity (Nystoriak & Bhatnagar, 2018). The blood pressure response to exercise does not appear to be affected by age, sex, or ethnicity. However, it should be emphasized that most research has been constrained by focusing exclusively on populations of middle-aged males of European origin (Hegde & Solomon, 2015).

4 | GARLIC (*ALLIUM SATIVUM*)

Garlic is a bulbous plant (Figure 1); it grows up to 1.2 m toward the pinnacle, and its root bulb is utilized as a part of pharmaceuticals. It is

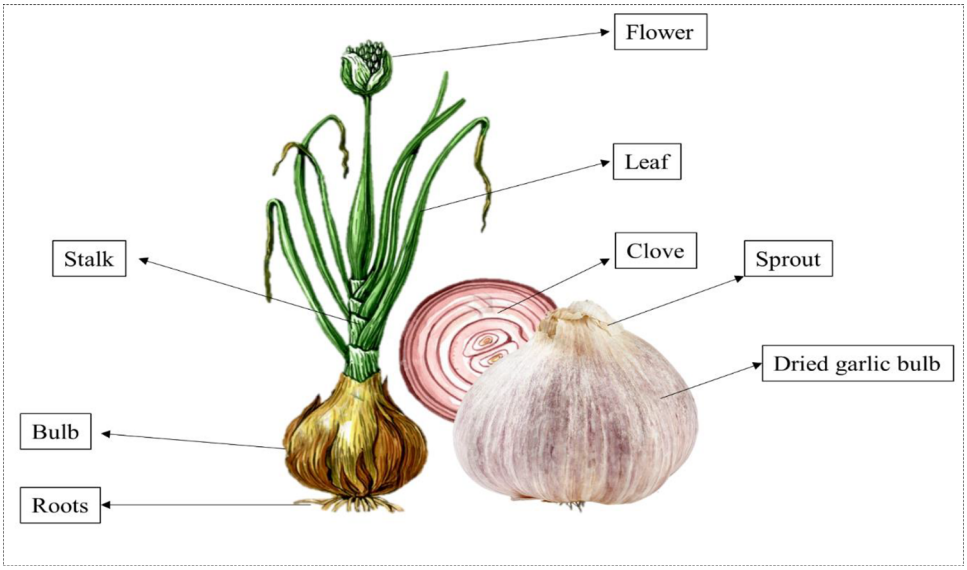

FIGURE 1 Morphology of garlic plant.

TABLE 1 Classification of hard-neck and soft-neck garlic.

Variety	Subtypes	Characteristics	Examples	References
Hard-neck	Asiatic	It contains 8–12 big cloves per bulb	Pyong Vang, Asian Tempest, Sonoran, Korean Red, Russian Red, and Asian Rose	Volk et al. (2004)
	Turban	It resembles Asiatic but with fewer cloves, usually 5–8 per bulb	Red Janice, China Dawn, Shandong, and Tzan	Tyagi et al. (2013)
	Creole	It is the prettiest garlic with striking colors and contains 8–12 cloves per bulb	Creole Red, Ajo Rojo, Burgundy, Pescadero Red, and Rose de Lautrec	Ellis et al. (2006)
	Porcelain	This type of garlic consists of four thick and smooth cloves covered with a white papery sheath	Majestic, Music, Georgian Crystal, and Romanian Red	Volk et al. (2004)
	Rocambole	It contains thinner bulb wrappers with purple striping	Amish, German Giant, German Red, Spanish Roja, and Ukraine Red	Rahman et al. (2012)
	Purple Stripe	Its wrapper is white with purple vertical stripes	Chesnok Red, Persian Star, and Belarus	Kamenetsky (2007)
Soft-neck	Artichoke	They have many cloves with more inner cloves and some purple spot	Italian Late, Kettle River Giant, Inchelium Red, Red Toch, Polish White, and Thermadrone	Nelson (2019)
	Silver skin	They have soft skin that is suited to cool climates	Baja Morado, Nootka Rose, Rose du Var, and Mount St. Helens	Walters (2008)

commonly used in several cuisines around the world as raw, processed, desiccated, or distilled steam (Shang et al., 2019). Several distinctive varieties of garlic (Table 1) and their beneficial health effects are reported in "Avesta," an accumulation of Zoroastrian scriptures that likely was gathered in the sixth century BC. Garlic was also proposed to be vital in managing several CMDs, including HTN (Ried, 2020). Various garlic products, including raw and natural garlic, oil, powder, and aged garlic extract (AGE), are available.

4.1 | Aged garlic extract (AGE)

Ethanolic extracts (15%–20%) of fresh garlic aged over a prolonged period (1.5 years) are used to produce AGE. During the developing procedure, impurities removed from garlic products are generally changed to steady and safe sulfur components. Furthermore, different toxicological examinations have affirmed the safety of AG (Kanezawa et al., 1984; Lira et al., 2020). In nuclear factor erythroid-2 related

factor 2 (Nrf2)-antioxidant response element (ARE) pathway, the AGE increased the expression of several antioxidant enzymes, including heme oxygenase-1 (HO-1) and the glutamate–cysteine ligase modifier subunit, which protected human endothelial cells from oxidative stress (El-Saber Batiha et al., 2020). Garlic saponins have been shown to scavenge intracellular reactive oxygen species (ROS) and protect mouse-derived C2C12 myoblasts from H_2O_2-induced growth inhibition and DNA damage (Kang et al., 2016). Furthermore, it was also shown that AG had more functional and medicinal activities than fresh garlic (Jang et al., 2018).

The bioactive components of garlic, such as phenols and saponins, are well established to have some positive effects in vitro and animal models (Banerjee et al., 2003; Martins et al., 2016). Different processing techniques are also shown to impact the outcome of garlic (Ali, Riaz, et al., 2022; Feng et al., 2020). Typically, fermented garlic, such as black garlic (BG), has a higher antioxidant activity than raw garlic, which has a higher antioxidant activity than crude garlic (Tahir et al., 2022). Additionally, in vitro, studies have reported that the Nrf2-ARE pathway's regulation and the augmentation of antioxidant enzyme activities might be connected to garlic's antioxidative function (Kim et al., 2017).

4.2 | Garlic oil

The benefits of garlic oil are linked to changes in the gut microbiota composition, higher NO bioavailability, increased short plasma-chain fatty acid levels, and enhanced renal mRNA expression and activity of H_2S-generating enzymes (Hsu et al., 2021). Garlic oil is produced after the steam distillation of crude garlic. The oil substance of garlic is 0.2%–0.5% and consists of a variation of sulfides such as diallyl disulfide (DADS) and diallyl trisulfide (DATS) (An et al., 2022). Garlic is thought to be a potent inhibitor of platelet aggregation (González-Ramírez et al., 2022). Lowering blood pressure induces the relaxation of smooth muscles and vasodilation by increasing the formation of the relaxing factor produced by endothelium (EDRF) (Giles et al., 2012). Garlic oil was also proposed to interfere with *Candida albicans'* typical metabolism, which is linked to the activation of essential genes involved in oxidative phosphorylation, the cell cycle, and protein synthesis in the endoplasmic reticulum (Li et al., 2016). Additionally, over 3-day treatment course, raw garlic supplementation (06 g/day) prevented *Helicobacter pylori* growth in the stomach of 15 *H. pylori*–infected patients (Zardast et al., 2016).

4.3 | Powdered garlic

Powdered garlic is used as a seasoning agent for processed sauces and supplements. Garlic is cut, dried (using several techniques), and then ground in powder. The composition of garlic powder is the same as raw garlic; however, the extents and amounts of different constituents vary; for example, the average alliin amount in garlic powder is 0.8%, but raw garlic contains around 3.7 mg/g (about 0.037%) of alliin (Lawson & Hunsaker, 2018), which could be due to the lower moisture content of the garlic powder. Garlic consumption was associated with several beneficial health outcomes such as lowering the CVD risk regulation of HTN, lowering of circulating total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C), improving blood circulation, increasing platelet-inhibited aggregation, and decreasing plasma viscosity (Aloufi et al., 2022).

4.4 | Black garlic

BG is the product of fermentation in a temperature-controlled environment after exposure for around a month. The resulting black color and sweetness, similar to fruit and odor, were reported not to be irritating compared to the unfermented garlic (Figure 2). In particular, BG has antioxidant activity mainly due to its higher levels of bioactive compounds, such as ajoene, *S*-allyl-L-cysteine (SAC), and several polyphenols, such as *p*-coumaric acid, *o*-coumaric acid, *m*-coumaric acid, diallyl sulfide (DAS), DADS, and DATS (Ahmed & Wang, 2021). In vivo, studies have shown that BG has a higher ability to increase antioxidant activity and decrease the content of malondialdehyde (MDA) in blood and liver tissue than fresh garlic (Cui et al., 2020). BG was also proposed to exhibit an antihypertensive effect by eliminating ROS in spontaneously hypertensive rats' plasma and paraventricular nuclei (Zhu et al., 2014).

4.5 | Side effects of overconsumption of garlic

Prolonged use of garlic is effective (Amin, Kassab, et al., 2020). Although garlic is used as a culinary plant in flavoring (Tesfaye, 2021) and as an addition of prominent taste (Afzaal et al., 2021), it is also customarily utilized for therapeutic purposes. Some adverse effects associated with the overconsumption of garlic include stomach discomfort and diarrhea (Timba et al., 2019), reduction in serum protein and Ca^{2+} (Imaizumi et al., 2022), anemia (Singh & Singh, 2019), bronchial asthma, contact dermatitis (Hitl et al., 2021), and inhibition of spermatogenesis in rat studies (Musavi et al., 2018). Because garlic has been an essential component of our diet for generations, it is widely believed that it is safe in various amounts (Bastaki et al., 2021). However, a few rare instances highlight a few of garlic's harmful consequences (Hitl et al., 2021).

It has been demonstrated that garlic extract at higher doses is clastogenic in mice (Lin et al., 2022). Garlic toxicity in the liver can result from overconsumption (Ozma et al., 2022). Garlic can reduce blood pressure, so it should be consumed cautiously if you take blood pressure medication (Bahha et al., 2022). Garlic can irritate the skin and prolong prolonged contact, resulting in rashes and an eczema-like condition (Mohammed & Qoronfleh, 2020). An excessive amount of garlic ingestion might result in hyphemia and internal eye bleeding that can permanently impair eyesight (Mohammed & Qoronfleh, 2020) and also cause migraines. Rats fed high doses of raw garlic

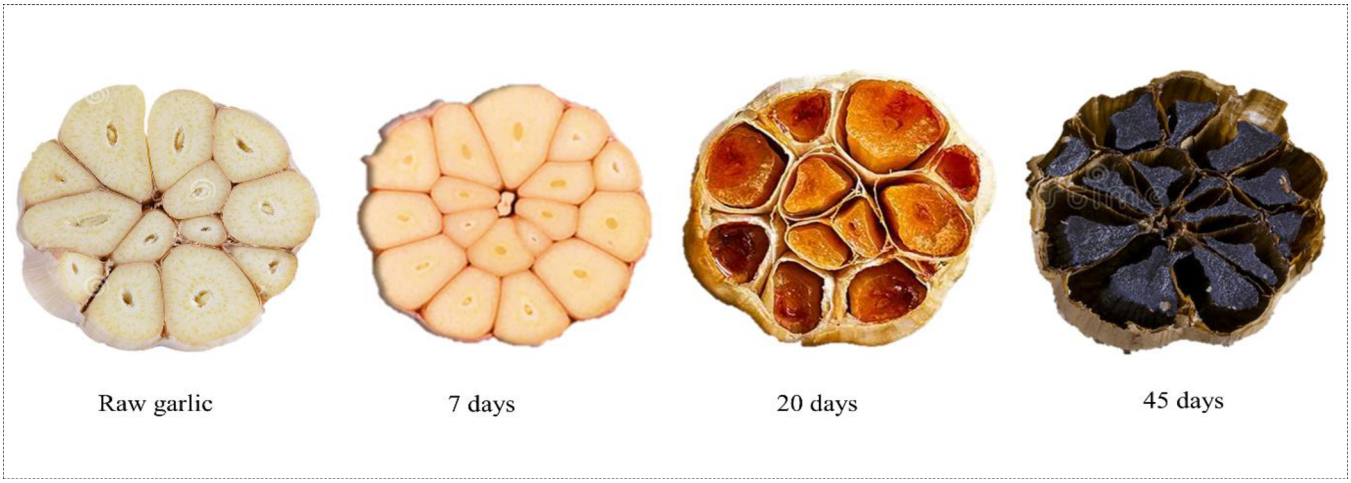

FIGURE 2 Black garlic fermentation.

for an extended period developed anemia, lost weight, and failed to grow due to red blood cell lysis (Zugaro et al., 2023). Occasionally, garlic powder poisoning has been reported (Singh et al., 2015). In rats, chronic administration of 50 mg/day of garlic powder suppressed spermatogenesis (El-Saber Batiha et al., 2020). The anti-androgenic properties of garlic are reflected by a decreased sialic acid content and decreased Leydig cell function in the testes, epididymis, and seminal vesicle. In the porta hepatis zone of an isolated perfused rat liver, higher garlic powder (200 mg/mL) or allicin from garlic led to significant cell damage that was not seen at lower concentrations (Al-Qahtani et al., 2020). The natural chemical ajoene, which is generated from garlic and found in different varieties of garlic oil, is both an inhibitor and a substrate of human glutathione reductase and is predicted to raise the oxidative stress of the corresponding cell (Bhadra, 2020). Through the promotion of peroxide generation and activation of nuclear factor kappa B, ajoene causes apoptosis in human leukemic cells (Cho et al., 2019). This is a novel feature of the garlic compound's biological profile and a crucial step in understanding the underlying molecular mechanisms of its antitumor activity (Wani et al., 2022).

The sulfoxide in garlic extract can spontaneously undertake exchange interactions with the titrable SH-groups of enzymes and proteins in the body at physiological pH and temperature, thereby reducing their activity and contributing to the toxicity as mentioned above. Papain, alcohol dehydrogenase, and alkaline phosphatase have all been shown to be inhibited by garlic (Motlagh & Pourmozaffar, 2021). The toxicity of garlic may be caused by these interactions between enzymes and their constituent parts (Zheng et al., 2021).

5 | MEDICINAL EFFECTS OF GARLIC

Due to numerous organosulfur compounds, garlic has traditionally been used as medicine for various functional purposes (antibacterial, anti-diabetic, antioxidant, and anti-inflammatory) (Alam et al., 2022). The procedure used to create aged BG (ABG) and fermented garlic from fresh garlic induces changes in biological functions. It is believed that the entire bulb of garlic, along with its oil and a few significant natural chemicals (rutin, epigallocatechin 3-gallate, gallic acid, and *o*-coumaric acid), are handy for the treatment of obesity (EL-Anany et al., 2020). According to the research done by Seo et al. (2009), adding BG to the diet in amounts of 0.2%, 0.6%, or 1.2% is very helpful in reducing weight, peritoneal fat, and epididymis fat (Afzaal et al., 2021). Contrary to popular belief, ABG has an anti-inflammatory effect that is inversely correlated with its antioxidant activity. Garlic oil helps lower inflammatory reactions. BG has good chemopreventive properties in vitro and in vivo (del Río-Celestino & Font, 2020). BG dosage reduced cell growth and caused apoptosis in the human gastric cancer cells used in the study (Farhat et al., 2021). In another experiment, murine fore-gastric cancer cell lines were injected into Kunming mice. According to the findings, BG prevented the injected tumors from growing (Wang et al., 2012). Compared to a placebo, garlic in diabetic patients unexpectedly decreased LDL cholesterol and total blood cholesterol while uniformly raising high-density lipoprotein (HDL) cholesterol (Guyton et al., 1974). A study discovered that bioactive components (*S*-allyl cysteine), imitative from garlic, directly impacted the restoration of erectile function in diabetic rats in a study published by Yang et al. (2013). By manipulating nicotinamide adenine dinucleotide phosphate hydrogen (NADPH), the process is carried out by inhibiting the generation of ROS (Yang et al., 2013). The use of garlic in the treatment of lead, mercury, cadmium, and arsenic poisoning has been demonstrated (Mehrandish et al., 2019). Some sulfur compounds can bind external poisons like food additives and heavy metals (Ebrahimi et al., 2023).

5.1 | Garlic as antioxidant agent

SAC, AG's most abundant organosulfur compound, exhibits antioxidant properties in vivo and in vitro (Vuković et al., 2023). It has been demonstrated that SAC attenuates oxidative stress in male Wistar rats' malignancies with intense renal damage (Chien et al., 2021). This

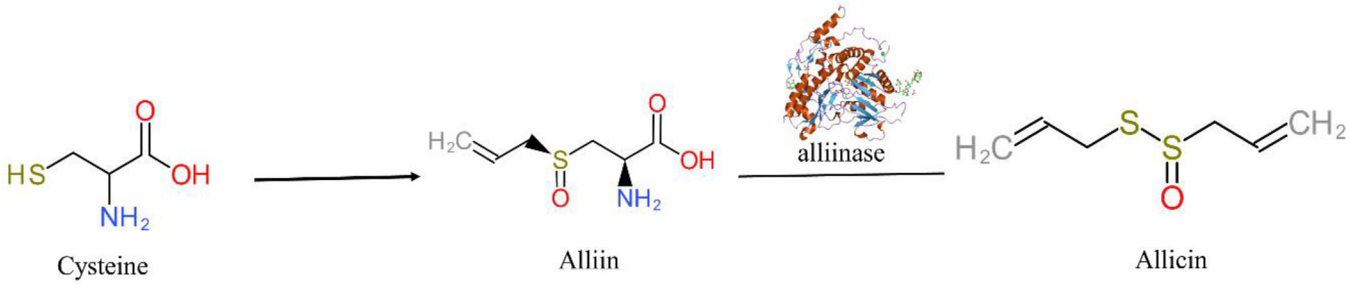

FIGURE 3 Formation of allicin by the action of the enzyme alliinase on the precursor alliin.

impact was described as SAC's capacity to trap ROS such as O^{2-} and H_2O (Maldonado et al., 2003).

Various studies indicate allicin has antioxidant properties (Farhat et al., 2021; Ma et al., 2018). Using spectroscopy, studies have shown that allicin has antioxidant properties and is very effective in eliminating free radicals (Chan et al., 2013). Oxidative stress is reduced by allicin in cardiac hypertrophy (Shi et al., 2018). Heart myocardiums were treated with angiotensin II (Ang II) to enhance ROS and prompt cardiovascular hypertrophy (Xu et al., 2019). Pre-treatment with allicin lessened ROS Ang II development activated both in vitro and in vivo (Salehi et al., 2019). This impact was accomplished by allicin because of its capacity to hinder the NADPH oxidase action in rats with induced aortic hyperplasia (Cruz et al., 2007). According to a study by Rotariu et al. (2022), allicin inhibits oxidative stress and metabolic degradation to improve HTN. It is proposed that allicin lowers blood pressure and exhibits unique vasorelaxant effects acting to prevent pulmonary HTN (Piragine et al., 2022). The formation of allicin is exhibited in Figure 3.

5.2 | Lipid-lowering effects of garlic

HTN is one of the main comorbidities linked to dyslipidemia (Otsuka et al., 2016). A study on the Japanese population showed that an elevated serum level of TC–LDL-C and non-HDL cholesterol (non-HDL-C) is associated with an increased risk of HTN (Otsuka et al., 2016). Based on several studies and literature reviews, the increased CVD burden is related to the prevalence of coexisting HTN and dyslipidemia, which ranges from 15% to 31% (Ama Moor et al., 2017; Hurtubise et al., 2016). The effects of garlic have been studied on levels of lipids in many randomized control trials (Jung et al., 2014; Sachan et al., 2021). Some meta-analyses concluded that garlic helps lower overall cholesterol levels, yet the effect size was moderate (Sachan et al., 2021; Sun et al., 2018).

5.3 | Blood pressure–lowering effects of garlic

Garlic and its products have been used as a part of traditional medicine due to its potential to prevent the onset and development of CVD (Ashfaq et al., 2021). Some of the garlic-derived bioactive compounds are summarized in Table 2. In one clinical trial, participants with uncontrolled HTN (≥140 mmHg) SBP was on average (10.2 ± 4.3 mmHg [$p = .006$]) lower in the garlic group when compared to the control after 12 weeks of the treatment (Ried et al., 2010). Interestingly, findings of meta-analyses demonstrated that AGE delivers a critical reduction in overall BP compared with different types of garlic (Ried, 2020; Wang et al., 2015). Anti-antihypertensive and other cardioprotective effects are formulated by homogenized garlic or SAC's bioactive component (Asdaq et al., 2021). It has been reported that antihypertensive bioactive garlic properties are similar to standard hypertensive medication, making garlic and its products one of the most studied medicinal plants (Emamat et al., 2020).

Mainly due to the anti-thrombotic characteristics of garlic, patients that are prescribed antiplatelet medication (warfarin) are also advised to refrain from the consumption of garlic (0.4 g of pure garlic or 3 mg of allicin) (Braun & Cohen, 2015). A trial utilizing higher amounts of AGE (10 mL/day) is relatively safe and poses no severe hemorrhagic risk for closely monitored patients on warfarin oral anticoagulation therapy (Macan et al., 2006). Although the risk–benefit ratio of AGE use needs to be considered carefully when warfarin therapy is necessary, its positive effects may benefit people with a high-risk background or who are taking cardiovascular medications (Macan et al., 2006). Garlic in moderate dosages (250 mg/kg) with added hydrochlorothiazide (HCTZ) was shown to exhibit cardioprotective and coordinated antihypertensive characteristics against the induced toxicity of fructose-isoproterenol (Asdaq et al., 2021). In a pilot study, hypertensive subjects who had taken a dosage of 2.5 g/day garlic for 10 days significantly lowered ($p < .05$) mean SBP, yet the DBP stayed unaltered (Mousa & Mousa, 2007).

5.4 | Garlic supplements

A recent clinical trial has demonstrated that garlic supplements have promising outcomes in treating uncontrolled HTN by reducing SBP (mean difference in SBP ± standard error = −5.0 ± 2.1 mmHg, $p = .016$) (Ried et al., 2016). Several constituents in garlic, such as the most abundant sulfur-containing SAC in AG (Subramanian et al., 2020), exhibit in vivo and in vitro antioxidant properties (Maldonado et al., 2003). In a dose–response trial, patients with uncontrolled HTN consumed garlic capsules (240/480/960 mg containing 0.6/1.2/2.4 mg of SAC) for 12 weeks. The study's findings indicated a significant reduction in SBP

TABLE 2 Garlic-derived bioactive compounds associated with the management of hypertension.

Compounds	Bioactivity	Reference
S-Allyl cysteine	Trap ROS such as $\cdot O_2^-$ and H_2O	Maldonado et al. (2003) and Shouk et al. (2014)
Allicin	Scavenge free radicals and inhibition of NADPH oxidase. It also shows antibiotic activity	Shouk et al. (2014)
Saponins	Increase cell viability, decrease lactate dehydrogenase leakage, and induce endogenous antioxidant activity	Kaplan (2010)
Ajoene	Hydroxyl radical scavenging activity, the inhibitory effect of NO formation	Kaplan (2010)
Phenolics	Directly quenching ROS or inducing endogenous defense	Chen et al. (2013)

Abbreviations: NADPH, nicotinamide adenine dinucleotide phosphate hydrogen; ROS, reactive oxygen species.

only by -11.8 ± 5.4 mmHg ($p = .006$). The findings of this study propose that AGE can be considered a potential remedy for uncontrolled HTN. Furthermore, AGE consumption may be considered a safe adjunct to standard antihypertensive medication (Ried et al., 2013).

Allicin (allyl-2-propenethiosulphinate) is the main organosulfur compound found in raw garlic extract. Several in vitro studies indicated that allicin has antioxidant effects (Salehi et al., 2019). In hypertensive rats with two kidneys and a clip (2K-1C), the impact of garlic and allicin on angiotensin-converting enzyme (ACE) action and blood pressure was examined. A decrease of 123 ± 4 mmHg after 4 weeks of treatment with garlic was observed in SBP in rats, which was significantly reduced by $p < .01$ compared to the control group (Hsu et al., 2021).

6 | GARLIC ENHANCES HYDROGEN SULPHIDE PRODUCTION

Hydrogen sulfide (H_2S) is present at small levels in various organs, such as the heart and smooth muscle tissues (Mishra & Kass, 2021). The H_2S is a signal gas molecule and a vasodilator identified as one of the markers associated with preventing the development and onset of CVD (Ghantous et al., 2020). The formation of H_2S derived from cysteine substrate is catalyzed by cystathionine *c*-lyase, a dependent pyridoxal-5-phosphate enzyme (Kimura, 2015). The deficiency of H_2S contributes to the changes occurring due to HTN, as demonstrated in several animal models (Meng et al., 2015). In addition, in the Wistar Kyoto rats HTN-induced NG-nitro-L-arginine methyl ester (L-NAME), the exogenous administration of NaHS (56 μmol/kg) resulted in a decreased circulation level of H_2S, which prevented the development of HTN (Saif et al., 2021; Yan et al., 2004). Studies demonstrated that garlic's vasodilatory activity was due to converting organic H_2S to polysulfide garlic for human erythrocytes (Seki & Hosono, 2015). In rats with myocardial infarction, H_2S is the SAC cardioprotective mediator. It is based on the observation that treated rats showed more excellent *S*-allyl-L-cysteine cystathionine c-lyase activity in the left ventricles and higher levels of H_2S in plasma-controlling treated animals (Seki & Hosono, 2015). Studies have also suggested that garlic and SAC showed cardioprotective effects and vasodilators affecting CSE activity and H_2S production (Adeoye et al., 2022; Citi et al., 2021). It is proposed that reducing the dependent H_2S blood pressure is mainly mediated through the potassium-sensitive sulfhydration channel (kATP) that promotes the relaxation of the sensitive channel of vascular smooth muscle cells. Therefore, the H_2S can influence another K^+ channel, and additional mechanisms have been recommended to determine the opening/closing of K^+ channels, including nitrosylation and possible cooperation between H_2S and NO (Ibraheem & Saeed, 2023). Although the relationship between NO and H_2S in managing vascular relaxation is yet not apparent (Piragine et al., 2022), it is proposed that H_2S shares at least part of the role of signaling vasorelaxant NO deficiency and H_2S and, consequently, may lead to vascular dysfunction, including HTN (Majzunova et al., 2013). It is recognized that much of the H_2S is oxidized into mitochondria to thiosulfate and sulfate. Thiosulfate synthesized by H_2S through mitochondrial oxidation can be reduced and recycled by an enzymatic dihydrolipoic acidic process (reduced form of lipoic acid) (Kashfi & Olson, 2013).

Although there are beneficial health effects associated with H_2S when levels exceed 500–1000 ppm, it can become instantly lethal (Guidotti, 2015), and there is evidence that high concentrations of H_2S cause superoxide formation to inhibit oxidative mitochondrial phosphorylation. It may be a possible negative feedback mechanism to limit the unnecessary concentration of H_2S (Horsman et al., 2019). Furthermore, this suggests that the signaling pathway in H_2S vasodilation has a similar NO signaling effect without the damaging effects of chronic gasotransmitter overload (Pieretti et al., 2020). It has been estimated that about two cloves of garlic release enough H_2S to maintain constrained blood vessel balance (Hughes, 2021). The effects of garlic on blood pressure via the H_2S pathway are exhibited in Figure 4.

7 | GARLIC AND NO PRODUCTION

The impact of garlic on the generation of NO in the vascular system can be ascribed to the activity of SAC. It was reported that SAC might improve NO production and mediates the antihypertensive effect of garlic (Ahmad et al., 2019). Enhanced NO production, the precursor of NO L-NAME, expectedly decreased plasma NO levels (Liu et al., 2019). NO production induced by AGE state inverted NOS inhibitor diphenyleneiodonium chloride indicates AGE's role in NOS activation (Förstermann & Sessa, 2012).

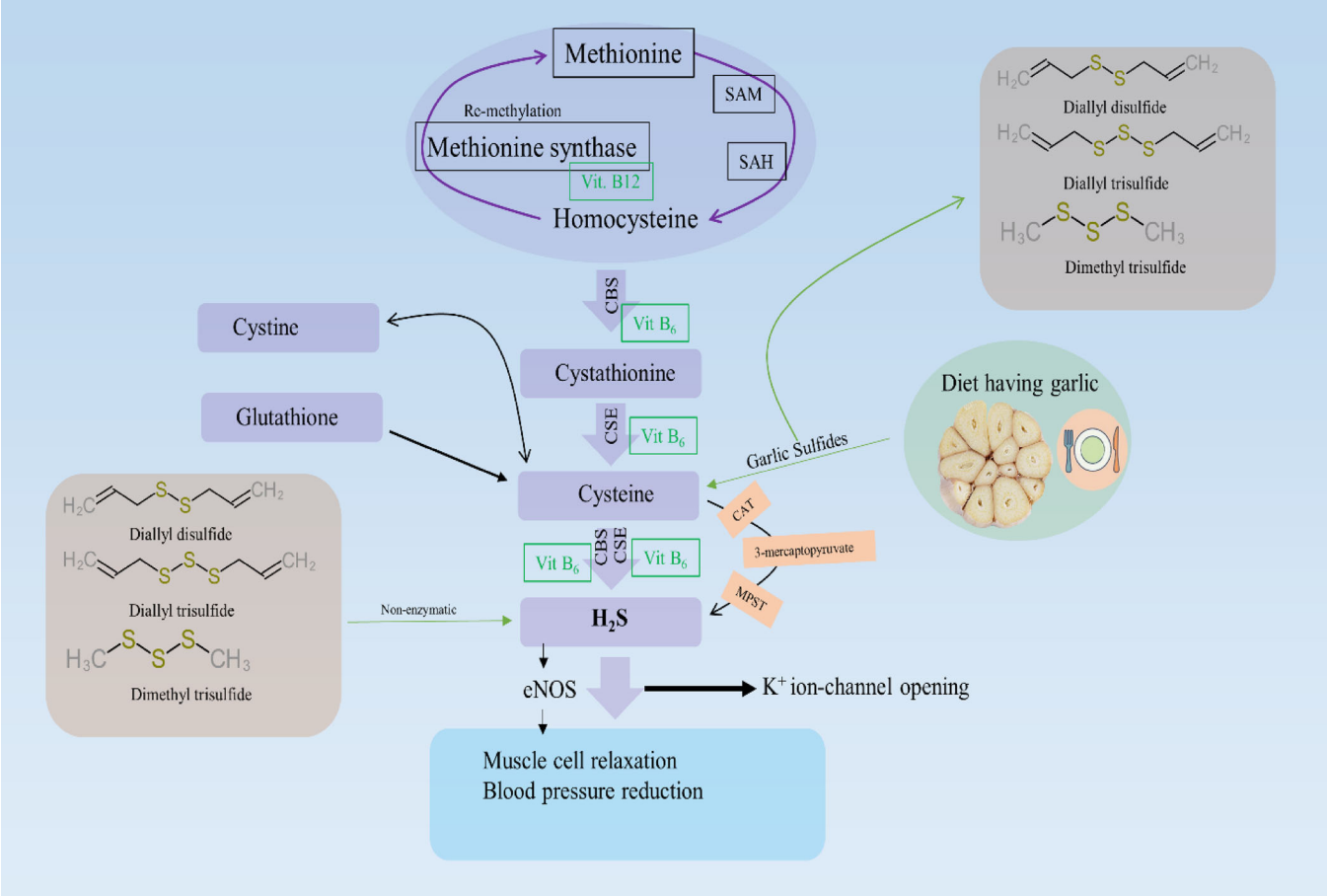

FIGURE 4 Effect of garlic on blood pressure via the hydrogen sulfide (H_2S) pathway.

Interestingly, an increase in NO production by SAC has been reported in mice examining the impact of AGE on NO production. It was found that AGE increases NO production by activating cNOS (Hou et al., 2023). Because NO is associated with inducing vasodilation and lowering blood pressure, it can be proposed that increased production is not a mechanism by which SAC and receiving its antihypertensive effects. Indeed, it is currently reported that SAC may also enhance cGMP levels associated with vasodilatation (Yu et al., 2012). In addition to AGE and SAC, fresh garlic and allicin are also reported to cause NO-dependent vasodilatation (Shouk et al., 2014). In rat mesenteric arterial rings, it has been observed that allicin (2.50–15.77 mM) causes concentration-dependent vasorelaxation that is inhibited by preincubation with the CSE inhibitor L-propargylglycine (Piragine et al., 2022).

The eNOS-derived NO induces the relaxation of smooth muscle cells and increases the blood vessels' expansion through a dependent mechanism of guanylyl cyclase (Hildebrand et al., 2022; Olson, 2012). It is proposed that the lack of NO production from eNOS is an essential factor in the expansion of vascular dysfunction and HTN (Gallo et al., 2022; Yu et al., 2012). The NO production also requires L-arginine as substrate and tetrahydrobiopterin (BH_4). The lack of BH_4 causes decoupling of the eNOS, resulting in elevated superoxide and lower levels of NO (Łuczak et al., 2020; Yu et al., 2012). The effect of garlic on blood pressure via the NO pathway is supplemented in Figure 5.

8 | GARLIC RELATED TO THE RENIN–ANGIOTENSIN–ALDOSTERONE SYSTEM (RAAS) ON HTN

Possible mechanisms of action have been proposed for garlic's effect on HTN, including blocking angiotensin II production by inhibiting ACEs (Adeoye et al., 2022). The ACE is an element of the renin–angiotensin–aldosterone system (RAAS), and ACE inhibitors are used as a medication for blood pressure control (South et al., 2020). Therefore, the antihypertensive effect of garlic via the ACE inhibitor seems less effective than H_2S and NO regulation pathways (Parim et al., 2019). Combining renin–angiotensin through two effective substances, aldosterone and angiotensin II, controls potassium balance, water and salt balance, and arterial blood pressure (Figure 6). Over the last several years, the RAAS has been critical to humans' electrolyte homeostasis and blood pressure (Holappa et al., 2020; Yamazaki et al., 2019). Identifying renal–adrenal hormone interplay was observed in studies

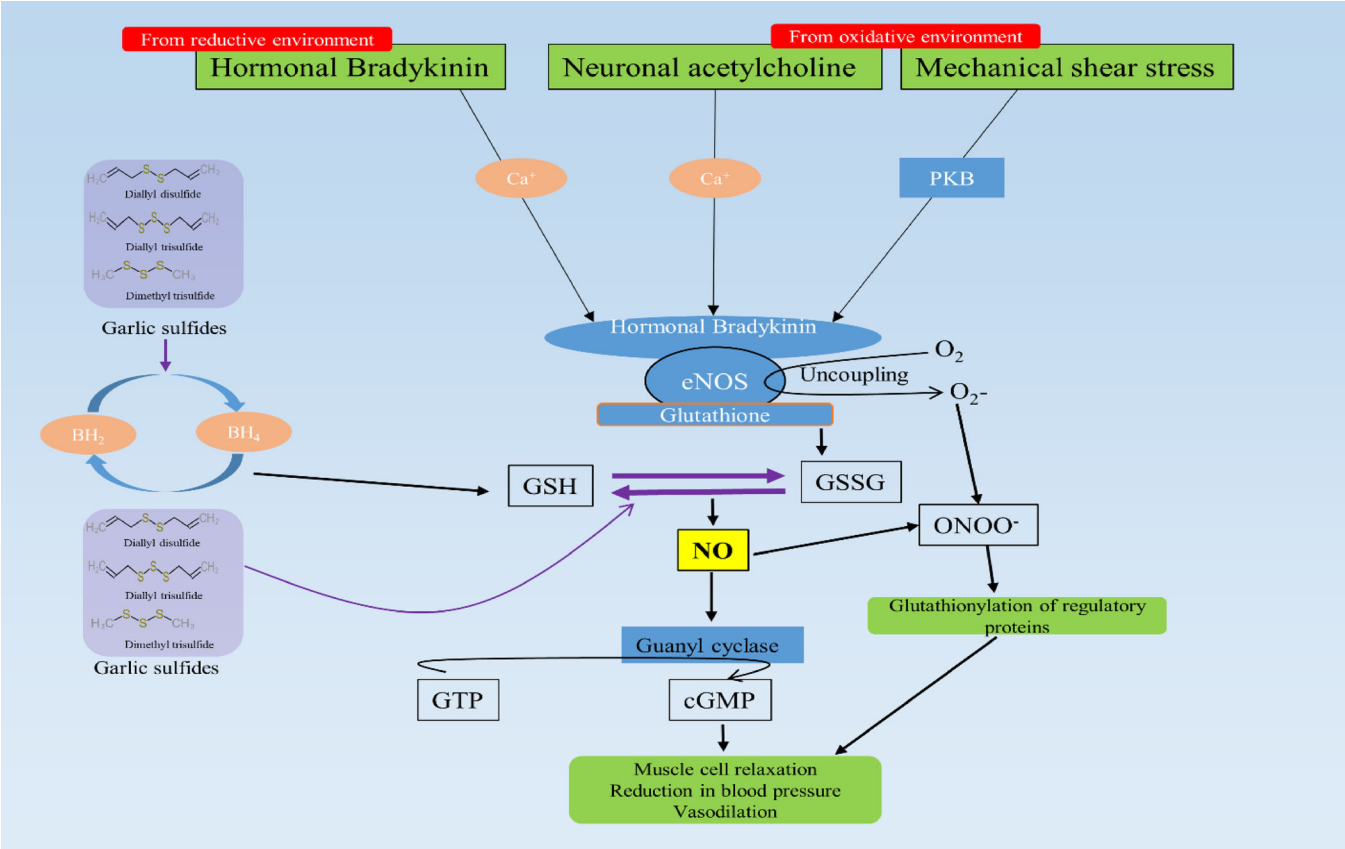

FIGURE 5 Effect of garlic on blood pressure via the NO pathway. eNOS creates NO in the presence of BH4, which activates pathways that cause smooth muscle cell relaxation and vasodilation. The production of O^{2-} is caused by the uncoupling of eNOS. NO and O^{2-} combine to create OONO−, which interacts quickly with thiols and tyrosine residues in proteins, causing vasodilation and lowering blood pressure without cGMP. Garlic and other dietary organosulfides may aid in the control of the NO signaling pathway by promoting NO synthesis by producing a more reductive environment.

of patients with malignant HTN (Raina et al., 2020). Although the role of RAAS in modulating aldosterone levels remains largely unknown, garlic and its bioactive allicin appear to adjust sodium levels via several different mechanisms, including the action of epithelial sodium channels. Na^+, the most abundant cation in extracellular fluid, is a critical factor in plasma osmosis and the volume of water (Thowsen et al., 2022). The kidney is most important in regulating sodium organ homeostasis (Su et al., 2019).

Furthermore, it was reported that garlic significantly decreased serum urea levels, which resulted in a significant increase in urine potassium ($p = .03$) compared to reperfusion, and fractional excretion of sodium and creatinine clearance were also improved, resulting in significantly prevented renal reperfusion–induced functional and histological injuries (Bagheri et al., 2011). In addition, in the 2K-1C animal model, garlic suppresses the increased expression of NHE1, an important sodium retention component, and the volume of water (Lee & Griendling, 2008; Wegmann & Nüsing, 2003).

9 | CONCLUSION

Despite biotechnological advancements, CVD remains a global challenge. Modern medication and functional foods can potentially assist with managing and reducing morbidity and mortality due to CVD in several populations. The present review provides the most recent information on the benefits of utilizing garlic and its extracts to control blood pressure. Garlic includes several vital chemicals, including SAC, saponins, flavonoids, ajoene, and certain phenolic compounds, which may benefit CMDs. Hitherto literature implies the effectiveness of garlic and its extracts or byproducts in decreasing blood pressure in hypertensive people.

Nevertheless, future research should be orientated toward investigating the effects of long-term garlic supplementation with known quantities of major bioactive compounds. Furthermore, the studies should explore the complex pathways associated with garlic's potential hypotensive and bioactive properties. These studies will provide a

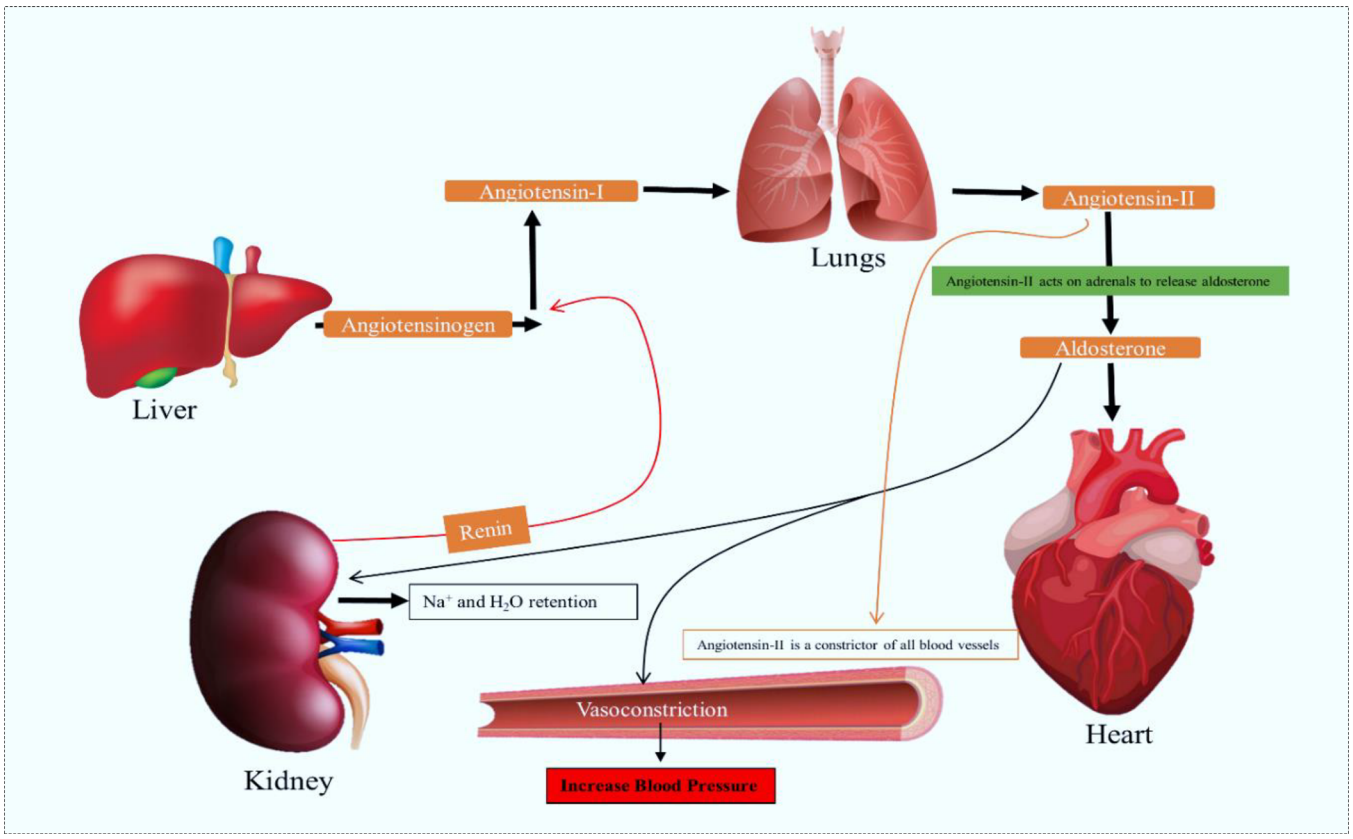

FIGURE 6 Renin–angiotensin–aldosterone system involving multiple organs associated with blood pressure. When renin is released into the bloodstream, it interacts with angiotensinogen, a circulating substrate that is proteolytically cleaved to generate the decapeptide angiotensin I. Although many other tissues in the body (heart, brain, and vascular) may also make angiotensin II (AII), vascular endothelium, notably in the lungs, possesses an enzyme called angiotensin-converting enzyme (ACE) that cleaves off two amino acids to create the octapeptide AII. Aldosterone is produced by the adrenal glands, which causes vasoconstriction in the arterioles and, as a result, a rise in blood pressure.

platform for developing adequate nutraceutical approaches using garlic, which is relatively cheap and readily available as a backbone for managing HTN.

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CONFLICT OF INTEREST STATEMENT

The authors confirm that they have no conflicts of interest to declare for this publication.

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