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REVIEW

Potential of garlic (*Allium sativum*) in lowering high blood pressure: mechanisms of action and clinical relevance

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Abstract: Garlic supplements have shown promise in the treatment of uncontrolled hypertension, lowering blood pressure (BP) by about 10 mmHg systolic and 8 mmHg diastolic, similar to standard BP medication. Aged garlic extract, which contains *S*-allylcysteine as the bioactive sulfur compound, in particular is standardizable and highly tolerable, with little or no known harmful interaction when taken with other BP-reducing or blood-thinning medication. Here we describe biologically plausible mechanisms of garlic's BP-lowering effect. Garlic-derived polysulfides stimulate the production of the vascular gasotransmitter hydrogen sulfide (H_2S) and enhance the regulation of endothelial nitric oxide (NO), which induce smooth muscle cell relaxation, vasodilation, and BP reduction. Several dietary and genetic factors influence the efficiency of the H_2S and NO signaling pathways and may contribute to the development of hypertension. Sulfur deficiency might play a part in the etiology of hypertension, and could be alleviated with supplementation of organosulfur compounds derived from garlic.

Keywords: garlic, *S*-allylcysteine, hydrogen sulfide (H_2S), nitric oxide (NO), redox signaling, hypertension

Hypertension

Hypertension, or chronically elevated blood pressure (BP) (systolic/diastolic BP [SBP/DBP] ≥140/90 mmHg at the brachial artery), is a multifactorial condition implicated in the development and progression of cardiovascular disease. Hypertension is among the most important modifiable risk factors for cardiovascular disease.[1]

High BP affects nearly 1 billion people globally and about 30% of adults in Western countries.[1] An estimated 70% heart attacks, strokes, and chronic heart failure are attributed to hypertension, leading to 37% of cardiovascular deaths in Western countries and 13.5% globally.[2,3]

Epidemiological studies have indicated a continuous association between BP and cardiovascular risk, suggesting that a reduction of high systolic BP (SBP>140 mmHg) by 20 mmHg or a reduction of high diastolic BP (DBP>90 mmHg) by 10 mmHg is associated with a 50% risk reduction in developing cardiovascular disease.[4]

However, a steady increase of SBP with age is expected, whereas DBP tends to fall after middle age, with studies in elderly and middle aged populations suggesting a nonlinear J- or U-shaped relationship between BP and mortality.[5,6]

Therefore, appropriate assessment of an individual's BP status is important to guide whether antihypertension therapy is indicated or to avoid potential overtreatment. While office BP monitoring is most practical – with improved accuracy achieved after 5–10 minutes rest, repeated automated measures, ideally on

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both arms[7,8] – sustained elevated readings using a 24-hour ambulatory BP monitoring (24-h ABPM) independently predict increased cardiovascular risk of 27% for every 10 mmHg increase in 24-h ABPM SBP.[9] Elevated nighttime BP, in particular, has been associated with increased risk of cardiovascular events including stroke and myocardial infarction.[9]

Twenty percent of individuals demonstrate white-coat hypertension, defined as elevated office BP but normotensive 24-h ABPM.[10] White-coat hypertension, however, has been associated with functional and structural cardiovascular abnormalities, including reduced arterial elasticity, left ventricular diastolic dysfunction, and enlarged arteries, similar to persistent hypertension.[11] Therefore, treatment of individuals with white-coat hypertension may still be of benefit.

While management of BP in family practice has increased in the past 20 years, a large proportion (23%) remain uncontrolled with persisting SBP ≥140 mmHg or DBP ≥90 mmHg independent of the treatment.[7,12–14]

Current guidelines for treatment of hypertension recommend starting monotherapy with any of the standard BP medication classes, including angiotensin-converting enzyme inhibitors, angiotensin II-receptor blockers, calcium-channel blockers, or diuretics in patients with uncomplicated hypertension.[15,16] While guidelines are clear about when to consider treatment with BP medication, they are less clear about which BP medication class to start treatment with in patients with uncomplicated hypertension and no comorbidities; treatment is dependent on personal preference and experience of the treating doctor.

Guidelines further recommend follow-up after at least 6 weeks to check the effectiveness of treatment and potential change of BP medication regime by adding other BP medication classes, increasing dosage, or changing BP medication type, depending also on tolerability and potential side effects.[15]

Approximately 40% of hypertensive patients can achieve the target BP of <140/90 mmHg with monotherapy, independent of the type of antihypertensive medication used. About 40% require combination therapy with two agents, and 20% need to take three or more antihypertensive medications to achieve BP control.[14,17] However, adverse reactions from antihypertensive medication may occur in a significant number of patients and are more likely when multiple drugs are prescribed.[18] Adverse reactions include fatigue, dizziness, cough, headache, myalgia, angioedema, renal impairment, gastrointestinal upsets, hyperglycemia, and electrolyte disturbances.[18]

Long-term patient persistence with antihypertensive treatment is unsatisfactory,[19,20] with only 44% of patients adhering to the treatment regimen in the long term.[20,21] While physician-related barriers to effective management of uncontrolled hypertension, such as therapeutic inertia, contribute to this problem,[22,23] patient motivation and satisfaction are equally important.[24] Persistence varies with the type of medication[20,21] and is associated with the severity and frequency of adverse events,[18] as well as with the complexity of treatment.[24]

Several factors play a role in the development of hypertension, including genetic variability, lifestyle, and dietary influences. While genetic variability is estimated to contribute about 30% to individuals' BP profiles,[25,26] lifestyle and dietary choices play an important role in BP modulation and control.[13]

Research suggests a body mass index (=weight/height^2) between 18.5 kg/m^2 and 25 kg/m^2 to be the desired range for Caucasians. Reductions in SBP of 5–20 mmHg per 10 kg weight loss can be achieved in overweight hypertensives.[13] In addition, 30 minutes of regular daily moderate aerobic exercise (eg, brisk walk) can reduce SBP by 4–9 mmHg,[13] while optimizing vitamin D levels (serum >75 nmol/L) can improve SBP by 3–4 mmHg in hypertensives.[27,28]

Other lifestyle factors influencing BP include smoking, alcohol intake, and stress. Smoking cessation has been estimated to lead to a BP reduction of up to 10 mmHg in hypertensives,[29] alcohol consumption exceeding 1–2 standard drinks per day may influence BP by 2–4 mmHg,[13] and continuous stress and insufficient quality sleep may push the BP by up to 10 mmHg.[30]

Diet plays an important role in BP control, with the adoption of the dietary approaches to stop hypertension or a Mediterranean diet achieving BP reductions between 8 mmHg and 14 mmHg systolic in hypertensives.[13,31] In addition, a meta-analysis including 13 trials (n=543 hypertensives) of vitamin C intake of 500 mg daily was associated with a reduction of BP of up to 5 mmHg systolic.[32] While moderation of sodium intake has been recommended, recent research suggests a greater importance of an adequate ratio between sodium and potassium (NaCl/KCl) intakes for optimal cardiovascular health.[33,34]

Other nutritional medical approaches to hypertension management include increased consumption of lycopene, mainly from tomato and watermelon,[35] cocoa,[36] and garlic, discussed here.

Interest in complementary and nutritional medicine has been increasing, with about 50% of Australians, including those with cardiovascular conditions, regularly using complementary therapies.[37–40] As motivation to self-care may

influence patient compliance,[41] there is scope to explore the integration of effective nutritional and other complementary therapies in antihypertensive management.

Garlic and hypertension

Garlic (*Allium sativum*) has been used as a spice, food, and medicine for over 5,000 years, and is one of the earliest documented herbs utilized for the maintenance of health and treatment of disease.[42] In some of the oldest texts on medicine, eg, the Egyptian Ebers papyrus dating around 1500 BC and the sacred books of India, "the Vedas" (1200–200 BCE), garlic was recommended for many medicinal applications, including circulatory disorders.[43] In ancient Greece, garlic was used as a diuretic, as recorded by Hippocrates, the father of modern medicine.[44] In addition to its cardiovascular benefits, garlic has traditionally been used to strengthen the immune system and gastrointestinal health.[42] Today, this intriguing herb is probably the most widely researched medicinal plant.

More recently, garlic has been shown to have BP-lowering properties. A meta-analysis including 20 clinical trials suggested garlic to be superior to placebo in lowering BP in hypertensive patients on average by 8–9 mmHg in SBP and 6–7 mmHg in DBP, $P<0.0001$).[45] Trials included in the meta-analysis were considered high quality, reporting adequate allocation concealment, randomization, double blinding, and low attrition. This reduction in BP reported in the meta-analysis is comparable to the BP-lowering effects of common antihypertensive medications.[13,46] While garlic supplementation reduced BP significantly in hypertensive patients, it did not appreciably affect patients with normal BP.[45,47–49] In addition, response to and effectiveness of garlic supplementation appears to be dependent on individual genetic and dietary factors, with SBP reductions of up to 40 mmHg in responders and a proportion of 25%–33% nonresponders, independent of garlic dosage, in a 3-month trial.[50]

Types and components of garlic, tolerability, and safety

Several types of garlic preparations are available, including raw and freshly cooked garlic, garlic oil, garlic powder, and aged garlic extract. Functional sulfur-containing components described in garlic include alliin, allicin, diallyl sulfide, diallyl disulfide, diallyl trisulfide, ajoene, and *S*-allylcysteine.[51,52] Allicin, formed by enzymatic reaction from alliin, the main compound found in fresh raw garlic and garlic powder, is volatile and unstable. Allicin is destroyed by cooking, and has the potential to trigger intolerance, gastrointestinal complaints, and allergic reactions,[53–55] and raw garlic taken in high doses can reduce red blood cell count.[56] Garlic essential oil contains diallyl disulfide and diallyl trisulfide and no water-soluble allicin. Commercially available garlic oil preparations often include only a small amount of garlic essential oil in a vegetable oil base, complicating comparability and standardization of products.[53] In contrast, *S*-allylcysteine, the main active compound in aged garlic extract, is stable and standardizable, and has been found to be highly tolerable.[36,51,54,55,57,58]

The majority of clinical trials studying the effect of garlic on BP used either garlic powder or aged garlic extract.[45,48] Side effects of garlic supplements, reported by about a third of the participants in these trials, were generally mild, and included burping, flatulence, and reflux in the first few weeks of the trial.[47,50] A small number of the population (4%–6%) may experience more severe gastrointestinal disturbances with therapeutic dosages of garlic supplements.[47,50,59,60] Lower tolerance of sulfur-containing foods such as garlic, onion, and leek may be reversed by supplementation with molybdenum and/or vitamin B_{12}, often deficient in affected individuals.[61,62]

Despite the general advice, evidence is weak for garlic preparations causing harmful interactions if taken in addition to blood-thinning, blood-sugar-regulating, or anti-inflammatory medications.[56,63,64] Physicians and patients need to be mindful, however, of a potentially harmful interaction of garlic with protease inhibitors in antiretroviral therapy.[63] It is generally recommended that high doses (equivalent to >4 g of fresh garlic or 3 mg allicin) should be avoided in patients taking antithrombotic medications including warfarin, due to the antiplatelet properties of garlic.[65] However, a trial using higher concentrations of aged garlic extract (10 mL/day, containing 14.7 mg *S*-allylcysteine) for patients on warfarin therapy found no increase in the incidence of hemorrhage compared with placebo.[64]

Mechanisms for blood pressure-lowering effect of garlic

Several mechanisms of action for the BP-lowering properties of organosulfur compounds in garlic have been postulated, including mediation of intracellular nitric oxide (NO) and hydrogen sulfide (H_2S) production as well as blockage of angiotensin-II production, which in turn promotes vasodilation and thus reduces the BP.[66–71]

The strongest evidence of and insights into the mechanisms of the BP-lowering effect of garlic supplementation involve endothelium-dependent vasodilation, and thus, this review

will focus on the current knowledge of the physiological and biochemical processes within blood vessels.

Vasorelaxation

The relaxation of vascular smooth muscle cells is an element of the physiological mechanisms for lowering BP. Reduced responsiveness of blood vessels to relax from constriction following autonomic nervous, endocrine/prostanoid, or shear stress signaling is thought to be an important factor in the pathophysiology of hypertension, as indicated by experimental and clinical evidence.[72]

NO, redox signaling, and the effect of garlic on hypertension

The soluble gas NO is a well-known factor in the mechanism for acetylcholine-induced (parasympathetic) vasodilation. NO is synthesized from L-arginine by at least three isoforms of NO synthase (NOS) in the endothelium by endothelial NOS (eNOS), in nerve cells mainly by neuronal NOS, and in macrophages by inducible NOS.[73] In some tissues and organs, including the heart, both eNOS and neuronal NOS are present.

Figure 1 illustrates vascular NO signaling pathways, including the effect of NO on vasodilation, and a potential influence of garlic organosulfur compounds.

eNOS-derived NO induces relaxation of smooth muscle cells and, thus, increased dilation of all types of blood vessels, via a guanylyl cyclase-dependent mechanism.[73] Lack of NO production by eNOS is believed to be a major causal factor in the development of vascular dysfunction and hypertension.[74,75]

eNOS, a highly regulated and complex enzyme, is inactive while bound to caveolin, and can be activated through calcium-responsive binding of calmodulin via hormonal or neuronal activation or shear stress-induced phosphorylation (Figure 1). The production of NO requires L-arginine as substrate and tetrahydrobiopterin (BH_4) as a cofactor. BH_4 levels have been reported to decrease with aging and cardiovascular disease, and a lack of BH_4 results in so-called eNOS uncoupling, resulting in the generation of high levels of superoxide (O_2^-) and low levels of NO.[73]

Redox signaling involves reversible oxidation–reduction of cysteinyl residues of proteins in cell membranes or within cells in response to the redox potential of the extracellular cysteine/cystine (CyS/Cys-S-S-Cys) pool.[76] Increased plasma cystine concentration and/or oxidized plasma metabolites have been associated with increased prevalence of human pathologic conditions, including decreased flow-mediated dilation, reversible myocardial perfusion defects, and persistent atrial fibrillation.[77] Thus, dietary factors affecting extracellular thiol/disulfide redox potential in human plasma could be important in cardiovascular disease.[77]

Oxidative stress, defined as "a disturbance in the pro-oxidant/antioxidant balance in favor of the former" has been an intensively researched field of inquiry in the past few decades.[78] However, this definition has been challenged by a number of authors following recent advances in the understanding of redox signaling, and changes in the redox status of tissues have been shown to be part of cellular signal transduction.[76,79–81]

It has been postulated that hypertension, too, may be a result of a disruption in redox signaling rather than being caused by an imbalance of oxidants and antioxidants.[82–84]

It has been suggested that the redox status of the cellular milieu affects the activity of eNOS and thus modulates NO-dependent pathways in the endothelium.[85,86]

Aged garlic extract in cell culture prevented endothelial cells from "oxidative stress" by increasing cellular concentrations of thiol antioxidants, such as cysteine and glutathione (GSH) while shifting the ratio of oxidized GSH to reduced GSH (Figure 1).[87]

Moreover, aged garlic extract was shown to normalize NO output from endothelial cells by preventing the decline of BH_4 levels.[87] Relevant levels of BH_4 prevent NO uncoupling and superoxide generation, which are thought to improve endothelial dysfunction, and potentially reducing the progression to atherosclerosis.[87]

In addition, *S*-glutathionylation of eNOS at two highly conserved cysteine residues reversibly decreases NOS activity with an increase in superoxide generation, resulting in impaired endothelium-dependent vasodilation.[86] *S*-glutathionylation can be reversed, however, by thiol agents. *S*-glutathionylation of eNOS is thought to be a pivotal switch providing redox regulation of cellular signaling, endothelial function, and vascular tone.[86] Furthermore, while uncoupling of eNOS leads to potent inactivation of NO through its reaction with superoxide (O_2^-), this reaction forms the potent oxidant peroxynitrite ($ONOO^-$) (Figure 1). Peroxinitrite has long been considered to be a highly toxic metabolic by-product, damaging biomolecules including proteins, lipids, and DNA. However, there have been new insights demonstrating that $ONOO^-$ is also involved in various signaling pathways, including a mechanism of vasodilation independent of cGMP.[88]

While NO clearly is an important signaling molecule, its overproduction has been implicated in various pathologies,

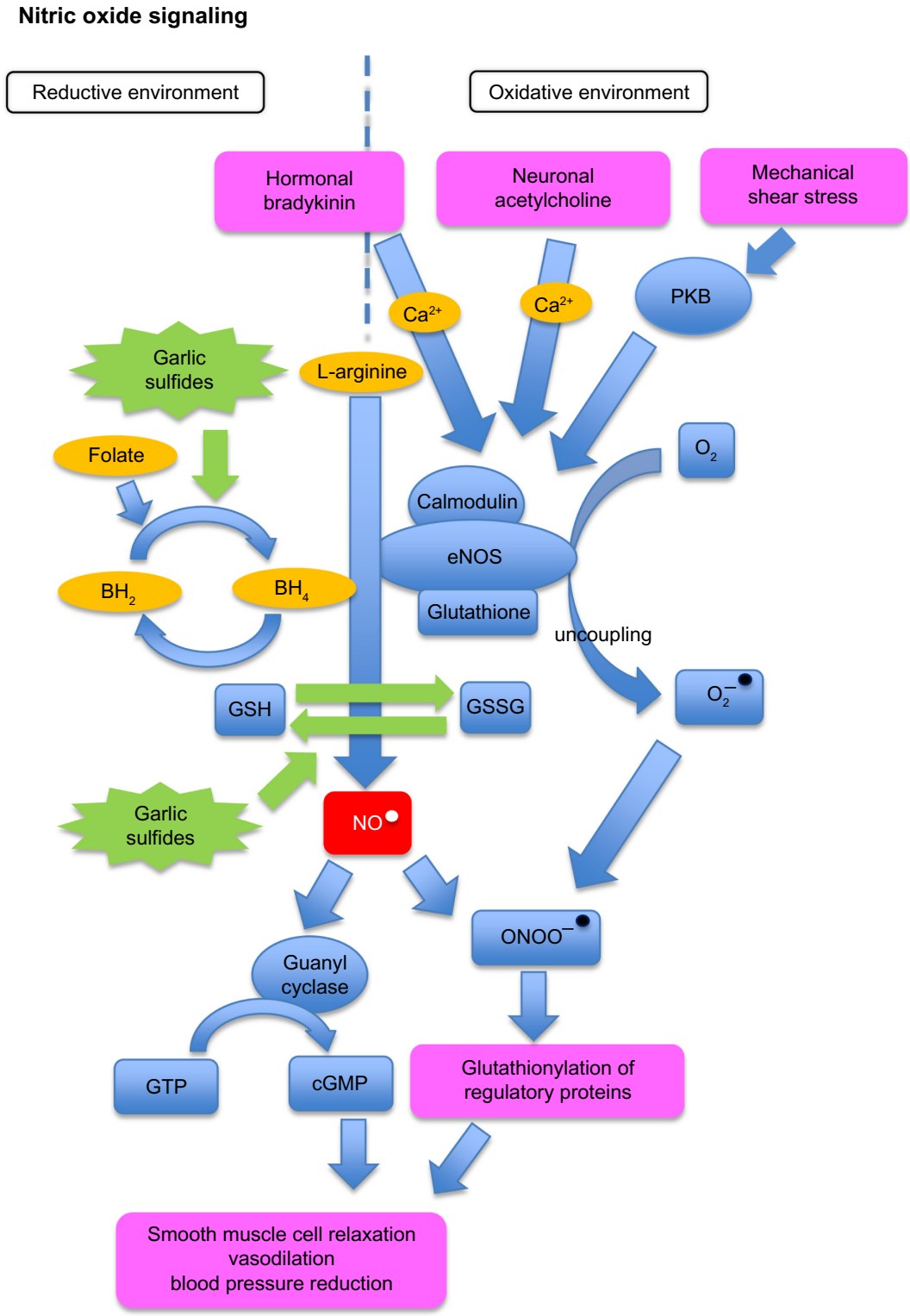

Figure 1 Effect of garlic on blood pressure via the NO pathway.

Notes: Blue rectangles illustrate metabolites, blue circles represent enzymes, orange circles are dietary cofactors, green star shapes are garlic and other organosulfur-containing nutrients, red rectangle represents NO, and purple rectangles denote direct and indirect influence of NO on vasodilation and blood pressure. NO pathway: in the presence of BH_4, eNOS produces NO, which triggers pathways leading to smooth muscle cell relaxation and vasodilation. eNOS uncoupling leads to the formation of O_2^-. NO and O_2^- combine to form $OONO^-$, which rapidly reacts with thiols and tyrosine residues of proteins, which in turn, leads to vasodilation and BP reduction independent of cGMP. Garlic and other dietary organosulfides may play a role in the regulation of the NO signaling pathway by creating a more reductive environment and therefore supporting NO production.

Abbreviations: BH_2, dihypdrobiopterin; BH_4, tetrahydrobiopterin; Ca^{2+}, calcium ion; cGMP, cyclic-guanosyl-monophosphate; GSSG, oxidized glutathione; eNOS, endothelial-nitric-oxide-synthase; GSH, reduced free glutathione; GTP, guanosyl-tri-phosphate; NO, nitric oxide (radical); ONOO, peroxynitrite; O_2, oxygen; O_2^-, superoxide anion radical; PKB, protein kinase-B.

including angiogenesis, mitochondrial dysfunction, and heart failure.[89,90] "Nitrosative stress" may cause hyper-nitrosylation of various regulatory enzymes leading to dysregulation of several cellular and physiological processes including inhibition of autophagy.[91]

Moreover, hyperproduction of NO may also lead to upregulation of mammalian target of rapamycin (mTOR), the central regulating molecule of the major signaling pathways for cell metabolism, growth, proliferation, and survival.[91] According to one theory of aging, the mTOR signaling pathway, driving developmental growth early in life, leads to age-related diseases through hyperfunction later in life.[92] In fact, there is a growing list of physiological malfunctions linked to overstimulation of this NO-dependent signaling pathway, ranging from insulin resistance to neurodegenerative diseases to cancer, and even including hypertension itself. If NO enhances rather than inhibits mTOR signaling, there is cause for concern with pharmacological interventions increasing NO bioavailability, and potentially introducing unwanted effects.

The highly regulated NO signaling pathways described earlier depend on organic thiols and other sulfur-containing molecules, and thus may be impaired in sulfur deficiency. Garlic and other alliums, such as leek and onion, with their high content of polysulfides may help in providing the nutrients needed for maintaining or restoring optimum redox balances for a number of eNOS-dependent signaling pathways important in vascular relaxation.

H_2S production and the effect of garlic on hypertension

A second vascular gaseous signal transmitter is H_2S.[93] H_2S exists in micromolar concentrations in various mammalian tissues, including the brain, nervous system, vascular smooth muscle cells, and in the heart.[93] Endogenous H_2S production is primarily the result of two enzymes: cystathionine-β-synthase (CBS) and cystathionine-γ-lyase (CSE), whereby the nonessential amino acid cysteine is metabolized by desulfuration, releasing sulfur in a reduced oxidation state and generating H_2S. In addition, 3-mercaptopyruvate sulfur-transferase and cysteine aminotransferase localized to the endothelium of the thoracic aorta have also been reported to produce H_2S from cysteine and α-ketoglutarate.[94] Experiments with CSE knock-out rodents have found reduced levels of H_2S and hypertension.[95] Also, spontaneously hypertensive rats have reduced expression of CSE in aortic tissues and lowered plasma levels of H_2S.[24,96,97]

Figure 2 illustrates the H_2S production pathway, the connection to the methylation cycle and homocysteine (HCy), the effect of H_2S on vasodilation, and influence of garlic-derived polysulfides on this pathway.

The H_2S-dependent BP-reducing effect is thought to be primarily mediated through sulfhydration of ATP-sensitive potassium (K_{ATP}) channels, which in turn leads to voltage-sensitive channel opening and relaxation of vascular smooth muscle cells.[98]

However, other potassium channels may also be affected by H_2S, and additional mechanisms have been suggested in determining the opening/closing of K^+ channels, including nitrosylation, and a possible cooperation between H_2S and NO.[98]

While the relationship between NO and H_2S in controlling vascular relaxation is still unclear (eg, both upregulation and inhibition of eNOS by H_2S have been reported),[99] there is convincing evidence that H_2S shares at least some of the vasorelaxing signaling role with NO and H_2S deficiency and therefore can contribute to vascular dysfunction including hypertension.[84,93,94,100,101]

Nonenzymatic conversion of garlic-derived organic polysulfides to H_2S

In a series of elegant experiments, Benavides et al[69] showed that garlic-derived polysulfides can produce H_2S under physiologically relevant O_2 conditions in rat aortic tissue. They provided evidence for a mechanism involving reduced thiols. While it is unknown which garlic bioactives can release H_2S nonenzymatically, it has been hypothesized that the major bioactive *S*-allylcysteine found in aged garlic extract may also act as a substrate for the enzyme CSE to produce H_2S.[102]

H_2S deficiency and supplementation

There is conflicting evidence about the potential age-related decline in vascular H_2S production, but any impairments of H_2S signaling may differ among tissues, with the liver being less susceptible to functional changes with age than less vital organs including the vasculature, which would be consistent with the triage theory of nutritional deficiencies.[103,104]

It is generally understood that most H_2S gets oxidized within mitochondria to thiosulfate and further to sulfate. Thiosulfate formed from H_2S through mitochondrial oxidation can undergo reduction and thus recycling by an enzymatic process dependent on dihydrolipoic acid (the reduced form of lipoic acid).[105] While most H_2S oxidation occurs within mitochondria, extra-mitochondrial oxidation occurs by reactive oxygen species and reactive nitrogen species.[106] Thus,

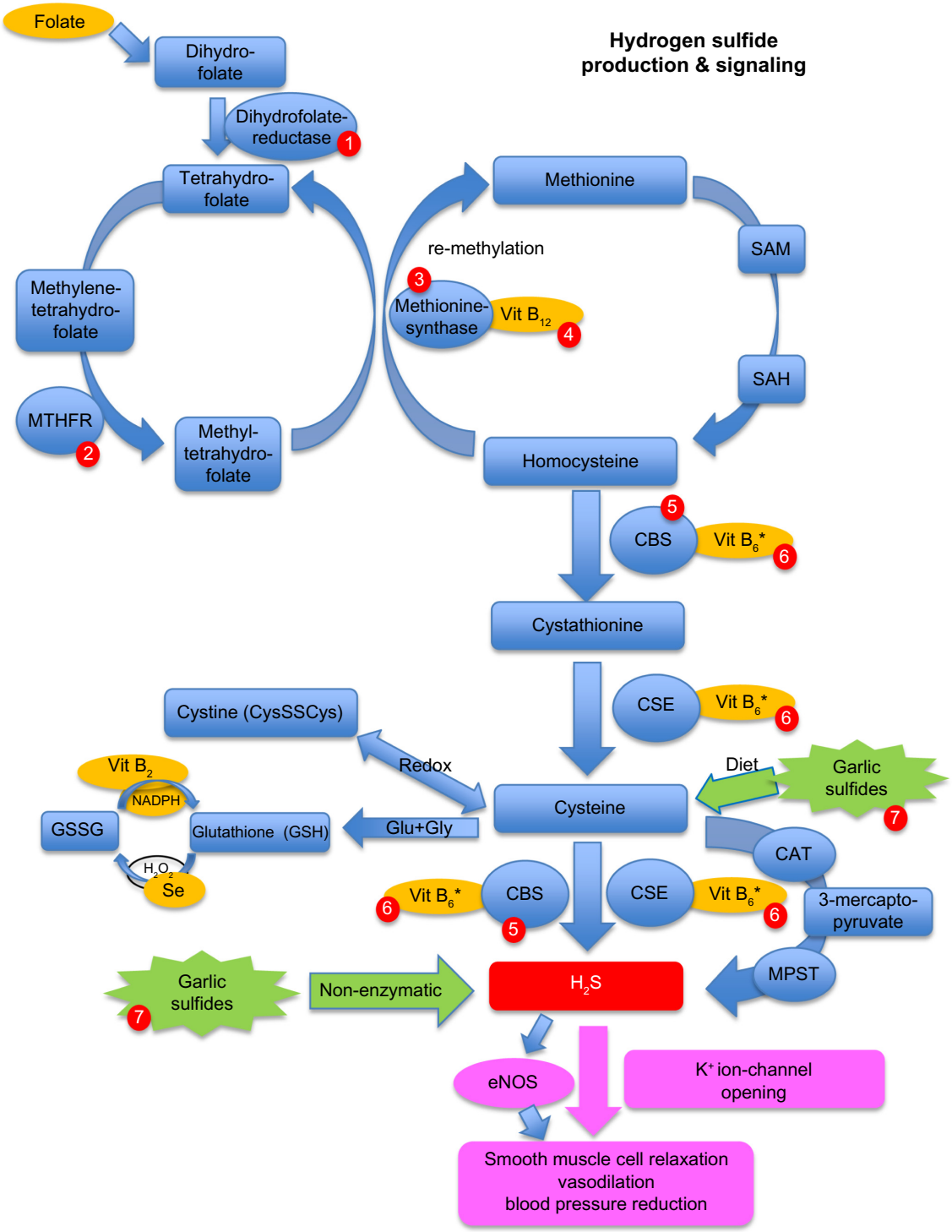

Figure 2 Effect of garlic on blood pressure via the hydrogen sulfide (H_2S) pathway, and influence of dietary and genetic factors on homocysteine levels.

Notes: Blue rectangles illustrate metabolites, blue circles represent enzymes, orange circles are dietary cofactors, green star shapes show garlic and other polysulfide-containing nutrients, red rectangle indicates H_2S, and purple rectangles represent direct and indirect influence of H_2S on vasodilation and blood pressure. Red circles 1–7: Influence of dietary and genetic factors on H_2S pathway 1= genetic polymorphism, homozygous for deleterious allele, leads to impaired folate metabolism. 2= common polymorphisms, some of which lead to increased homocysteine and decreased methylation and SAM levels; these respond well to folate supplementation. 3= genetic defects lead to increased homocysteine levels. 4= low Vit B12 levels lead to increased homocysteine levels. 5= defect in CBS enzyme leads to increased homocysteine levels and reduced H_2S production. 6= low Vit B_6* levels may increase homocysteine levels and reduce H_2S production, and may respond to Vit B_6 supplementation. 7= dietary intake of garlic polysulfides and thiosulfides can increase H_2S nonenzymatically, and may ameliorate genetic defects in the CBS enzyme, or dietary deficiencies in Vit B_6 and/or the sulfur-containing amino acids cysteine and methionine.

Abbreviations: CAT, cysteine-amino-transferase; CBS, cystathionine-β-synthase; CSE, cystathionine-γ-lyase; CysSSCys, oxidized cysteine/cystine; eNOS, endothelial nitric oxide synthase; Glu, L-glutamic acid; Gly, glycine; GSSG, oxidized glutathione; GSH, reduced glutathione; H_2O_2, hydrogen peroxide; K^+, potassium ion; MPST, mercapto pyruvate sulfur transferase; NADPH, nicotinamide adenine dinucleotide phosphate; MTHFR, methylene-tetra-hydro-folate reductase; SAH, S-adenosyl-homocysteine; SAM, S-adenosyl-methionine; Se, selenium; Vit B_6*, activated form of Vit B_6 = pyridoxal-phosphate; Vit B_2, vitamin B_2 (riboflavin); Vit B_{12}, vitamin B_{12}.

tissue concentrations of H_2S can be expected to be lower in more oxidative environments. On the other hand, high concentrations of H_2S are toxic, and there is evidence that H_2S in high concentration itself causes formation of superoxide by inhibiting mitochondrial oxidative phosphorylation. This may be a possible negative feedback mechanism for limiting excessive H_2S concentrations.[107] This suggests that the H_2S signaling pathway in vasorelaxation has a similar effect to NO signaling, without the potentially detrimental consequences of chronic overproduction of the gasotransmitter.

Approximately two cloves of garlic per meal have been estimated to release sufficient H_2S for maintaining the balanced blood vessel constriction.[93] Other dietary H_2S donors besides alliums include sulforafane from crucifers, some fermented foods including "thousand year egg," and the infamous Asian durian fruit.[108]

Garlic, hypertension, and elevated HCy

Many clinical and epidemiological studies have found a positive correlation between HCy plasma levels, endothelial dysfunction, and cardiovascular disorders.[109–111] Conditions linked to endothelial dysfunction, such as acute ischemic stroke with greater arterial stiffness and stress-induced hypertension, have been reported in hyperhomocysteinemia (HHCy).[112,113] Furthermore, serum concentrations of the sulfur-containing thiols HCy, cysteine, and GSH have shown to be independently associated with cardiovascular risk scores at the population level.[114] However, whether elevated levels of HCy are primary or secondary risk factors for cardiovascular disease is less clear.[115,116] There is a clear negative correlation between elevated HCy levels and brain and cognitive function.[117,118]

Elevated levels of HCy might be a consequence of impaired endothelial production of H_2S.[119] The transformation of HCy into cysteine is catalyzed by the enzymes CBS and CSE as part of the transsulfuration pathway (Figure 2).[94,120] CBS and CLE are also among the few enzymes in mammals with the capacity to produce H_2S. The chemical reaction facilitated by CBS is a vitamin-B_6-(pyridoxal-phosphate)-dependent condensation of either serine or cysteine and HCy.[119] CBS is the rate-limiting enzyme necessary for terminal removal of HCy. Deficiencies in CBS activity caused by genetic mutations of the *CBS* gene are the most frequent cause of familial HHCy.[121] There are at least 153 mutations known to exist in the *CBS* gene, with several significantly reducing CBS activity.[121] These genetic *CBS* deficiencies can be divided into two major allelic variance types: vitamin B_6 responsive and vitamin B_6 nonresponsive.[122,123] Individuals with some of these genetic variants are likely to have both decreased production of H_2S and elevated levels of HCy. While cases with a vitamin B_6-responsive variant can be treated with ongoing B_6 therapy, cases affected by vitamin B_6 nonresponsive variants continue to have impaired production of H_2S, but may benefit from supplementation with nutritional H_2S donors, such as garlic. Thus, consumption of garlic, which can produce H_2S nonenzymatically,[69] may benefit conditions related to impaired production of H_2S, such as hypertension, even without lowering HCy.

On the other hand, in carriers of a deficient methylene-tetra-hydro-folate-reductase (*MTHFR*) variant, elevated HCy due to impaired remethylation may cause increased levels of H_2S, which has been linked to an increase in platelet activation and may contribute to the development of recurrent arterial and venous thrombosis in these patients.[124] It is therefore possible that supplementation with H_2S-boosting nutrients, such as garlic, may be counterproductive in individuals with MTHFR deficiency.

Furthermore, both CBS enzyme deficiencies and deficiencies in sulfur-containing amino acids (especially methionine and cysteine) are known to result in low levels of GSH, which plays important roles in cellular redox status and signaling. Elevated levels of HCy and decreased levels of cysteine and GSH have been found in a population with a low dietary intake of protein and sulfur-containing amino acids, and might be regarded as biomarkers of sulfur deficiency.[125] A correlation between low red blood cell GSH and increased plasma HCy has been linked to an increased incidence of hypertension.[126] Garlic, with its high content of sulfur compounds (including *S*-allylcysteine), has the potential to alleviate sulfur deficiencies caused by low-protein diets, which may also influence BP in these individuals.

Garlic's potential effect on HCy levels has been reported in a small clinical trial of atherosclerosis patients randomized to aged garlic extract (P=0.08).[127] Additionally, in an animal model of HHCy, induced by a severely folate-depleted diet in rats, aged garlic extract decreased plasma HCy concentrations by 30%.[128] In contrast, elevated levels of HCy caused by mild folate deficiency did not change significantly by garlic supplementation.[128]

Thus, garlic may have an effect on HCy metabolism independent of the effect of B vitamins in addition to boosting H_2S production.

Renin–angiotensin–aldosterone system and the effect of garlic on hypertension

Other potential mechanisms of action for garlic's effect on hypertension have been proposed, including the potential of garlic blocking angiotensin-II production by inhibition of the angiotensin-converting-enzyme (ACE), as suggested in a number of cell culture and animal studies.[67,71,129] ACE is a component in the renin–angiotensin–aldosterone system, and inhibitors of ACE are used as standard BP-controlling pharmaceuticals. However, animal and cell culture experiments were mainly conducted with fresh garlic compounds, containing allicin (*S*-allyl-cysteine sulfoxide), which has a very low sustained bioavailability in human tissues.[55] Therefore, the antihypertensive effect of garlic via the proposed angiotensin-converting enzyme inhibitor mechanism seems less plausible than its H_2S-stimulating and NO-regulating properties.

Conclusion

Garlic, particularly in the form of the standardizable and highly tolerable aged garlic extract, has the potential to lower BP in hypertensive individuals similarly to standard BP medication, via biologically plausible mechanisms of action. Primarily, polysulfides in garlic have the potential to upregulate H_2S production via enzymatic and nonenzymatic pathways, which promote vasodilation and BP reduction.

Several dietary and genetic factors, including folate, vitamin B_6, and vitamin B_{12} deficiency, and known genetic variants of the *MTHFR* and *CBS* genes, influence the efficiency of H_2S production, and could be important contributors to hypertension in these individuals, which may also explain individual responsiveness to garlic supplementation seen in clinical trials.

Polysulfides in garlic may also influence regulation of NO redox signaling pathways, including NO-mediated vasodilation and reduction of BP. Future clinical trials could explore the potential influence of nutritional status and genetic factors on the individual's responsiveness to garlic therapy for hypertension.

Disclosure

The authors report no conflicts of interest in this work.

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