Advantages of Garlic in Treating Hypertension: A Review Article

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ABSTRACT

Supplements with garlic have shown promise for the control of uncontrolled hypertension by lowering systolic blood pressure (BP) by about (10) mmHg as well as (8) mmHg diastolic, comparable to typical BP medication. Here, we outline scientifically tenable explanations for garlic's ability to reduce blood pressure. Garlic-derived polysulfides increase direct modulation of endothelial nitric-oxide (NO) as well as the vascular gasotransmitter sulfides (H2S), which results in smooth muscle cell relaxation; vasodilation; and a decrease in blood pressure. The effectiveness of a H2S and no signaling pathways is influenced by a few dietary and genetic factors, and this may help to cause hypertension. Organosulfur compounds made from garlic may help treat sulfur deficiency, which may contribute to the etiology of hypertension.

Keywords: Hypertension, Garlic, blood pressure, polysulfides, nitric oxide, hydrogen sulfide

Introduction

The greatest cause of illness and mortality worldwide is cardiovascular disease (CVD). are at high risk due to hypertension. About one in three persons have high blood pressure worldwide, also referred to as hypertension. It frequently has no symptoms but greatly increases a person's risk of acquiring stroke or cardiovascular disease. [1]. For both the avoidance of cardiovascular disease and its linked illnesses, the management of hypertension is crucial [2]. Anti-Acetylcholinesterase Inhibitors, angiotensin-II receptors blocker; Thiazide diuretics and calcium channel blockers with dihydropyridine are typically prescribed as first-line anti-hypertensive medications[3].As first-line anti-hypertensive drugs, doctors frequently give Thiazide diuretics, dihydropyridine calcium channel blockers, angiotensin II receptor blockers (ARBs), angiotensin-converting enzyme inhibitors (ACEIs),[4].Despite the existence of those proven anti-hypertensive drugs with high blood pressure and uncontrolled hypertension still affects many people globally. Many previous studies from different countries have shown More than fifty percent of those surveyed were uninformed that they had hypertension, and only 32.5% of patients had their blood pressure under control with medication. It is obvious that uncontrolled hypertension needs to be managed differently if further morbidity and mortality are to be avoided [5].

The hypertension

SBP/DBP stands for systolic/diastolic blood pressure. 140/90 mmHg just at brachial artery, often known as hypertension, is really a multifactorial condition that has been linked to the start and development of cardiovascular disease. One of the most point higher

cardiovascular disease risk factors is hypertension [1]. Over 1 billion individuals worldwide and around 35% of adults suffer with hypertensive. Hypertension is thought being the primary cause of 75% of strokes, heart attacks, and prolonged heart failure, which accounts for 36 percent of cardiovascular mortality from Western nations and 13% worldwide [6]. a diminution in higher systolic blood pressure (sbp ≥140 / mmHg) with a decrease or 20 mmHg in higher diastolic blood pressure (dbp ≥ 90 / mmHg) ten mmHg is related on the 50percent on average reducing risk in developing cardiovascular disease, according to epidemiological research [7]. However, research in old and populations in their Middle Ages reveal J/ nonlinear and U/ shaped association blood pressure and mortality, with SBP increasing steadily with age and DBP declining beyond middle age [8]. Although there has been an increase in BP management in family practice over the last twenty years, a significant portion (23%) still has uncontrolled hypertensive with sustained SBP >140 mmHg or >90 mmHg DBP regardless of treatment [9]. Current recommendations recommend starting monotherapy with any of the popular BP medication groups, including such angiotensin II-receptor blockers; angiotensin-converting enzyme inhibitors; in patients with uncomplicated hypertension. blocker; calcium-channel blockers; or diuretics [10]. Unaffected by the kind of antihypertensive drug taken, 45% hypertension people can attain 140/90 mmHg is the desired blood pressure. using one therapy. 20% people must require 3 or more antihypertensive medications, and about 40% need combination therapy with two drugs to get their blood pressure under control. Antihypertensive medication side effects, however, may occur in a large proportion of patients and are more common when numerous medications are administered. Fatigue; wooziness; coughing; headaches; myal gia, angioedema, renal dysfunction, and digestive problems; along with electrolyte abnormalities and hyperglycemia are examples of adverse effects [11]. Antihypertensive patient perseverance throughout the long run is not satisfactory, approximately 44% of patients consistently follow their treatment plan throughout time [12]. The emergence of hypertension is influenced by a few variables, including dietary, lifestyle, and genetic influences. While it is believed that roughly 30% determines a person's BP profile determined by hereditary variability, way of life, and diet decisions which crucial in hypertensive regulation [13]. The optimum range of body mass indices for Caucasians, according to research, is around 18 to 25 kg per m2. Overweighted hypertensives can reduce SBP by 5 to 20 /mmHg for every ten kg lost. Stress, alcohol consumption, and smoking are additional lifestyle choices that affect blood pressure. If you consume more than two standard drinks each day, you could affect blood pressure from 2 to 4 /mmHg, smoking cessation may lower blood pressure by as much as ten mmHg in hypertensives, and ongoing stress and inadequate sleep may raise blood pressure by up to 10 mmHg [14]. A Mediterranean diet or even the dietary strategies to stop hypertension can lower blood pressure in hypertensives by 8 to 14 mmHg systolic. Food plays a significant effect in blood pressure control. Also, a meta-analysis of 13 trials (N = 544 hypertensives) found that 500 mg of vitamin C daily was linked to a drop in blood pressure of up to 5 mmHg systolic. While it has been suggested to limit salt intake, recent research points to the greater significance of maintaining a suitable ratio of sodium to potassium “NaCl:KCl” intake to the best cardiovascular fitness [15].

Garlic

Since ancient times, people have utilized garlic (Allium sativum) for a variety of purposes. It is especially valued for its cardioprotective qualities, which include the ability to reduce blood pressure. the outcomes of numerous meta-analyses of medical studies on the antihypertensive garlic properties were ambiguous [16]. Yet, the most recent research showed that individuals who have hypertension and slightly raised cholesterol levels can benefit from taking garlic supplements. More than ten trials using pure garlic powder have revealed that taking a

supplement containing garlic at levels of 600 to 900 mg per day has significant benefits in blood pressure for people with hypertension but not in people with normotension [17]. Like this, within the medical investigation by researchers, 12 weeks of therapy using a supplementary meal of garlic homogenate led to a substantial decrease for SBP and DBP both only in hypertensive individuals. Research using age garlic extract, a different garlic preparation made by naturally aging for more than 10 months, showed the most consistent results [18]. Given that it has been AGE demonstrated dramatically lower in blood pressure people with uncontrolled high blood pressure, it is possible this treatment could employ the powerful adjunct treatment of excessive hypertension. previous research intriguingly showed that age reduced arterial rigidity, reduced inflammatory, so as enhanced stomach flora in a way that was advantageous to cardiovascular health [19]. Moreover, AGE has been demonstrated to raise NO levels in mouse plasma, enhance peripheral circulation of hypertensive rats, and cause vasorelaxation depending on the endothelium at separated rings of aorta in rats [20].

As the herb allicin has shown to have angiotensin II-inhibiting as well as vasodilating actions, it has been regarded as a primary active component in garlic supplements. The amino acid glutamyl-S-allylcysteine (GSAC), in addition to allicin, also have an impact by blocking ACE and promoting relaxation that is both endothelium-dependent and independent [18]. In AGE, the aging process results in the chemical conversion of allicin and GSAC for more sulfur compounds like SAC and S1PC. SAC's ability to prevent renal damage as well as hypertensive of 5/6 nephrectomized rats has been linked to its antioxidant capabilities. S1PC has been demonstrated to drastically reduce blood pressure in both single and repeated administrations in rats with hypertension by altering several regulatory substances, including Tryptophan, lyso-phosphatidylcholine, and histidine. Due to its multiple active components, AGE's anti-hypertensive mechanisms seem to operate in different ways [21]. Most of the research have shown that supplements containing garlic are highly safe. Several studies have examined the potential side effects of garlic usage, including bad body odor, breath, also moderate gastrointestinal issues. Those negative consequences are clearly seen in research utilizing fresh garlic; however, they reduced by AGE treatments [22].

Hypertension and garlic

One of the first herbs to be used to maintain health or treat sickness is allium sativum (garlic), that's served like a spice; foods; and medical usage since over 5,000 years. Garlic was advised for numerous medical purposes, including circulatory diseases, in some of the earliest literature on medicine, including the Egyptian plants from circa more than1400/ BC as well an ancient book about India, "the Vedas" 1200 to 200 bce,[23]. Garlics employed as a diuretic in ancient Greece, according to Hippocrates, the founder of modern medicine. Garlics were long utilized for support the immune system, as well as the digestion in contrast to its cardiovascular effects [24].

Most subsequently, garlics were found to have blood pressure lowering effects. Garlic is more effective than a placebo in lowering bp in hypertensive people by an average of 8 to 10/ mmHg of in accordance with a macro of 20 studies, SBP is 6-7 mmHg and DBP is 6-7 mmHg randomized trial. The metaphysical - included analysis trial were deemed to be of good caliber since they provided acceptable attrition, allocation concealment, randomization, and double blinding rates. Drops of blood pressure that was noted with in meta-analysis is analogous to how commonly prescribed antihypertensive drugs lower BP stands for blood pressure. Garlic supplementation has a significant impact. lowered hypertensive patients' blood pressure but had little effect on normal blood pressure patients. Considering SBP reduction ranging around 40/ mmHg among responder as well as a nonresponder proportion of 25% to 33%, independence on dosage for garlic, for three months experiment, it also indicates that response to it and effectiveness for garlic

supplements are based on individual genetic or dietary characteristics [25].

Garlic varieties, ingredients, tolerance, and safety

Garlic formulas are available in an array of flavors and textures, which include aged garlic extract; Garlic, both raw and cooked; garlic powder and garlic oil. Dialyl sulfide, diallyl disulfide, diallyl trisulfide, ajoene, and S-allylcysteine are examples of functional sulfur-containing substances found in garlic. The primary ingredient for fresh garlic or alliin, garlic powder, undergoes an enzymatic reaction to produce the volatile and unstable allicin. Cooking destroys allicin, which can cause intolerance, gastrointestinal problems, and allergic reactions. additionally, consuming a lot of raw garlic will lower your red blood cell count [26]. Diallyl disulfide as well as diallyl trisulfide are present in garlic essential oil, but there is no allicin that is water soluble. Garlic essential oil is frequently present in small quantities in available commercially garlic oil preparations, making it difficult to compare and standardize goods. The primary active ingredient of extract of aged garlic, S-allylcysteine, is dependable; standardizable; as well as shown very acceptable [27].

Many of the research investigations examining the impact of garlic on blood pressure employed either aged garlic extract or garlic powder. Almost a third of those taking garlic supplements complained of mild side effects, such as burping, gas, and reflux within the initial few weeks of the experiment. At therapeutic quantities of garlic supplements, a small proportion of the population “4% to 6%” can develop more severity gastroenteritis symptoms [28]. Vitamins B12 and/or molybdenum, supplements, which are frequently inadequate in affected people, can improve a person's ability to tolerate foods that contain sulfur, such as garlic, onions, and leeks [29].

Despite the widespread recommendation, there is little proof that taking garlic preparations along with blood thinners, blood sugar stabilizers, or anti-inflammatory drugs will cause negative interactions. However, there is a potential negative interaction between garlic and protease inhibitors within antiretroviral therapy that doctors and patients should be aware of. Due to the antiplatelet characteristics of garlic, it is typically advised that excessive doses (equal of >4 g garlic, fresh / 3 mg allicin) should be avoided with people using antithrombotics medicines, as well as warfarin [30]. Risky on bleeding did not rise in a trial utilizing greater doses with (10 mL) aged garlic extract per 24hr, comprising S-allylcysteine 14.7 mg) of people receiving warfarin therapy in comparison to placebo, though [31].

Mechanisms of Garlic's Blood Pressure-Reducing Effect

Organosulfur compounds in garlic are thought to lower blood pressure through several mechanisms, including the compromise of nitric oxide intracellular (NO) as well as production of hydrogen sulfide (H2S) and the interruption of the production of angiotensin II, and as a result encourages vasodilating lowers blood pressure. This examination will concentrate in present understanding on such biochemically and physiologically reactions occurring within blood vessels because it contains the most compelling evidence for and understanding of the mechanisms underlying endothelium-dependent vasodilation that is thought to lower blood pressure when garlic supplementation is taken [32].

The association between NO; redox signaling; garlic with hypertension.

One well-known component of the acetylcholine-induced (parasympathetic) vasodilation process is the soluble gas NO. With in endothelium as NOS in endothelial cells (eNOS), among nerves cell primarily NOS neuronal, even macrophage through NOS inducible, which produced from l-Arginine for at three isoforms from the non-synthases (NOS). Both neuronal, eNOS are found on several organs and tissues, including the heart. Using a guanylyl cyclase-dependent process, eNOS-derived NO causes smooth muscle cells to relax, increasing the dilation among all types of blood arteries.[33] Vascular insufficiency and hypertension are thought to emerge as a result of eNOS's inability to produce NO. When eNOS is coupled to caveolin, a highly controlled

and complicated enzyme, it is dormant. Nevertheless, shear stress-induced phosphorylation and calcium-responsive coupling of calmodulin can both activate eNOS [34]. L-arginine serves as the substrate as well as tetra-hydrobiopterin 'BH4' serves like the contributor to the NO synthesis. Ageing and cardiovascular disease have been linked to lower BH4 levels, and a lack of BH4 causes what is known as eNOS uncoupling, which produces high superoxide (O2) levels and low NO levels [33]. Redoxs signal is the process by which proteins with cysteinyl residues in cell membranes or inside of cells undergo reversible oxidation-reduction as a result of extracellular cysteine/cystine redox potential Pool of CyS/Cys-S-S-Cys. Higher incidence of human pathologic diseases, such as reduced reversible flow-mediated dilation cardiac abnormalities, as well as persistent atrial fibrillations have been linked to elevated cysteine levels in plasma content as well as oxidized plasma metabolite [35]. Throughout recent times, a substantial amount of research has been conducted on the phenomenon for oxidative stress, which was described as "a disturbance within pro-oxidant/antioxidant ratio in favor of the former." After recent developments in the study in redox signaling, a number of scientists have disputed this notion, and it has been demonstrated that changes mostly in redox status in tissues are a component of biological signal transduction [36]. After recent developments in the understanding on redox signaling, a number of scientists have disputed this notion, and it has been demonstrated that changes there in redox status of tissue are a component of biological signal transduction [36]. According to certain theories, hypertension may also be brought on by a malfunction in redox signaling instead of an unbalanced production of antioxidants and oxidants. According to certain theories, the cellular environment's redox status influences eNOS activity, which in turn modifies the endothelium's NO-dependent pathways [37,38]. Moreover, eNOS is reversibly reduced in NOS activity by S-glutathionylation at two highly conserved cysteine sites, which raises superoxide production and impairs endothelium-dependent vasodilation. Thiol agents can, however, undo the effects of S-glutathionylation. It is believed that eNOS's S-glutathionylation is an important switch that controls redox for cellular communication, endothelial function, as well as vascular tone. Moreover, whereas eNos decoupling results in a powerful inactivation of the no through the creation of the powerful oxidant peroxynitrite (ONOO), this process also produces superoxide (O2). The highly hazardous metabolic byproduct peroxinitrite had also long been thought to harm macromolecules like proteins; lipids; and DNA. However, recent discoveries show ONOO is also engaged of several signal pathway, such as vasodilation mechanisms unrelated to cGMP [39].

Although NO is undoubtedly a crucial signaling molecule, excessive amounts of it have been linked to several diseases, such as heart failure, angiogenesis, and mitochondrial dysfunction. Condition known as "nitrosative stress" can result in the hypernitrosylation of multiple enzymes that regulate other enzymes, which can lead on the dysregulations of a few physiological and cellular processes the suppression of autophagy [40]. whereas excessive NO, generation might boost the activity of mTOR, the key regulator a principal signal pathway of cell metabolism; cell growth; cell proliferation; and survival. In fact, a long variety of physiological disorders, including hypertension itself, insulin resistance, neurodegenerative disorders, and cancer, are being linked on overstimulation of such a NO-dependent signaling pathway. There's still cause for worry because pharmaceutical therapies could increase NO bioavailability and perhaps introduce undesired consequences if NO increases rather than suppresses mTOR signaling [41].

Production of H2S and how garlic affects hypertensive.

H2S is a second vasculature gaseous signaling transmitter. H2S can be found in mammalian tissues at micromolar concentrations, along with the brain, central nervous, smooth muscle cells in the vascular system, and the heart. 2 different enzyme,

cystathionine-synthase (CBS) but also cystathionine-lyase (CSL), are involved (CSE), are principally responsible for the synthesis of endogenous H2S [42]. These enzymes catalyze the desulfuration of the non-essential amino acid cysteine, which releases sulfide in such a decreased oxidation state and produces H2s. Also, it has been shown that 3-mercaptopyruvate sulfur-transferase is found inside the endothelial of the thoracic aorta. or the enzyme cysteine aminotransferase create H2S from cysteine and -ketoglutarate [43]. Decreased levels of H2S as well as hypertension have been seen in experiments using CSE knock-out rats. Moreover, spontaneously hypertensive rats exhibited lower plasma levels of H2S and lower expression of CSE into aortic tissues [44].

According to current theories, the H2S-dependent BP-lowering impact is predominantly mediated by the sulfhydration on Potassium-sensitive ATP (KATP)channel, that turns causes opening of a voltage-sensitive channel as well as relaxing of smooth muscle cells in the arteries. However, alternative processes, such as nitrosylation and a potential collaboration between H2S and NO, have been proposed in influencing to opening/closing of K+ channels. Other potassium channels might be impacted by H2S. There is strong evidence that H2S needs to share at least a partial role of vasorelaxing signaling with the H2S deficiency and can as a result, make a contribution to vascular dysfunction, including hypertension. This is true even though the relationship among both H2S and NO throughout regulating vascular relaxation remains uncleared (e.g., both upregulated as well as inhibition of eNOS through H2S have been reported).[45].

Garlic, high blood pressure, and increased HCy

Several clinical and epidemiological research have discovered a connection between elevated levels of HCy in the blood, endothelial dysfunction, and cardiovascular issues. Hyperhomocysteinemia has been associated with conditions like ischemic stroke, acute and increased stiffness of the arteries with hypertension caused by stress (HHCy). Also, it has been demonstrated that the population-level serum levels of sulfur-containing thiols HCy, cysteine, and GSH are independently correlated with cardiovascular risk scores [46]. It is less apparent, nevertheless, whether high concentrations of HCy constitute both primary and secondary risk elements of coronary artery disease. Elevated HCy levels have a definite unfavorable association with cognitive and brain function.[47].

Elevated HCy levels have a definite unfavorable association with cognitive and brain function. The trans-sulfuration pathway's enzymes CBS and CSE catalyze the conversion of HCy into cysteine. Among the few mammalian enzymes capable of producing H2S are CBS and CLE. Serine or cysteine condensation with HCy is the chemical reaction that CBS promotes, and this condensation is dependent on vitamin B6 (pyridoxal phosphate) [48]. The rate-limiting enzyme, CBS, is required for the final elimination of HCy. Familial HHCy is most frequently caused by deficiencies of CBS activity brought on by hereditary abnormalities of the CBS gene. The rate-limiting enzyme, CBS, is required for the final elimination of HCy. Familial HHCy is most frequently caused by deficiencies of CBS activity brought on by hereditary CBS gene mutations [49]. At least 153 known mutations as in CBS gene, some of which sharply lower CBS activity. The two main allelic variation kinds of these hereditary CBS deficits are vitamin B6 responsive as well as vitamin B6 nonresponsive. Those who have a few of these genetic variations are probably going to produce less H2S and have higher amounts of HCy. Patients affected with vitamin B6 ineffective variations continuous to poor H2S generation, otherwise it may profit form augmentation with dietary garlic, for example, is an H2S donor. Examples of such a vitamin B6 receptor variation could managed the continuing B6 medication. Consuming garlic, which can create H2S nonenzymatically, may therefore be beneficial for illnesses like hypertension that are linked to poor H2S generation, even if it does not lower HCy [50].

Additionally, low levels of GSH, which are crucial for cellular redox state and signaling,

are known to be caused by both impairments in CBS enzymes and shortages in amino acids containing sulfur, particularly cysteine and methionine. Population of low dietary intake consumption the proteins or amino acids containing sulfur has been discovered to have elevated levels for HCy as well as decreased levels to cysteine and GSH, which may be considered indicators of sulfur insufficiency. There is a connection between elevated plasma HCy and decreased red blood cell (GSH) or an uptick in the prevalence of hypertension. Garlic can treat sulfur deficits brought around diets low in protein, and it affects the pressure in those who consume it. Garlic contains a large amount of sulfur compounds, particularly S-allylcysteine[51].An atherosclerosis patient randomized with aged garlic extract in a modest clinical trial has revealed that garlic may have an impact on HCy levels (P=0.08). Moreover, garlic extract that has been aged reduced HCy concentrations in plasma about 30 percent on a rat model for HHCy produced from a diet that was substantially deficient in folate [52]. Incontrast, supplementing with garlic had little effect on the high levels of HCy brought on by a modest folate deficit. Hence, in addition to increasing the generation of H2S, garlics also impact on metabolism of HCy that is separate from such of vitamin B effect [53].

Garlic's ability to lower blood pressure and the renin-angiotensin-aldosterone system.

Several cell culture or animal studies have identified other possible action mechanisms for garlic's ability to reduce blood pressure, such as the possibility that it prevents by preventing the growth of angiotensin-II. ACE stands for angiotensin-converting enzyme (ACE). It is a part of Renin-angiotensin-aldosterone (RAA) system, ACE inhibitor is common medications usage to lower blood pressure. However, fresh garlic constituents including allicin “S-allyl-cysteine sulfoxide”, which is relatively poor long-term bioavailability into tissues of human, were mostly used in animal and cell culture investigations [54]. Hence, compared to its H2S-stimulating and NO-regulating capabilities, garlic's antihypertensive action on suggested inhibitor of angiotensin-converting enzyme route appears to be less likely.

Conclusion

Garlic can lower blood pressure in hypertensive persons similarly to conventional blood pressure medications, through biologically plausible action mechanisms, particularly using such standardizable and highly tolerated aged garlic extract. Specifically, garlic polysulfides may increase H2S generation through enzymatic and nonenzymatic routes, which supports vasodilation and lowers blood pressure. Numerous dietary or genetic factors, such as a lack of folate; vitamin B6; and vitamin B12, as well as recognized MTHFR genetic variants but also gene of CBS, impact an effectiveness of production of H2S and the major causes of people hypertensive. This is also clarifying why different people respond differently to the supplementation with garlic that has been demonstrated to lower blood pressure on clinical trials. Garlic polysulfides may also affect how pathway of NO redox signaling are regulated, including vasodilation mediated by NO with reduced BP. Clinical trials in the future might examine how a person's dietary status and genetic makeup may affect how well they respond to garlic treatment for hypertension.

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