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Research Article

**THERAPEUTIC EFFECT OF DIETARY NITRATE AND
ALLICIN IN MODULATING HYPERTENSION**Momina Shahid¹, Shahnai Basharat¹, Syed Aamir Gilani¹, Breera Shahid², Muhammad Mustafa Qamar³¹University Institute of Diet & Nutritional Sciences, The University of Lahore, Pakistan²University of education, Lahore, Pakistan³Department of Allied Health Sciences, Sargodha Medical College, University of Sargodha, Pakistan**Abstract:**

There are many causes and factors that lead to hypertension, including a high intake of sodium and alcohol, low consumption of fruits and vegetables, deficiency of some water-soluble vitamins such as B9, B2, and fat-soluble vitamins such as C and D and a sedentary lifestyle. In recent years, therapeutic effect of dietary nitrate and allicin emerged as an essential component for normal physiological as well as pathological functioning to treat hypertension. NO₃⁻ being a potent dilator, administrates systemic blood pressure and subsequently delays atherogenesis. Various cardiovascular diseases are associated with its bioactivity including pre-hypertension, hypertension, atherosclerosis, and stroke. Allicin has antibacterial, anti-carcinogenic and antioxidant effect and acts against many microorganisms. It also has angiotensin II-inhibiting and vasodilating effects. Garlic involves two nitric oxide, and hydrogen sulfide signaling pathways that lower BP. It has the ability to enhance arterial inflammation, stiffness, and other cardiovascular indicators. Both components are considered as highly acceptable with the great safety profile as an antihypertensive treatment. Therefore, this article aimed to highlight the important role of nitrate and allicin in modulating hypertension.

Keywords: Dietary Nitrate, Allicin, Hypertension, Diastolic Blood Pressure, Systolic Blood Pressure, Cardiovascular Diseases

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INTRODUCTION:

World Health Organization defines hypertension in terms of systolic blood pressure more than 140mmHg and diastolic blood pressure more than 90mmHg. Pre-hypertension has been defined as SBP \leq 120 and DBP \geq 80 in the individuals without hypertension.¹ Hypertension is an important risk causing factor for many cardiovascular pathologies which includes atherosclerosis, ischemic heart disease, myocardial infections and stroke.²

Cardiovascular disease (CVD) is increasing speedily in the developing world and is supposed much likely to overcome infectious disease in different regions to become the top cause of death in the coming decade.³ In 2005, an approach to hypertension in urban population underdiagnose and undertreat hypertension especially in elders. They concluded to revise teaching core curriculum in teaching institutes with concern to the risks, awareness, and administration of high blood pressure.⁴

Some factors could increase the prevalence, such as high intake of sodium, high alcohol consumption, low intake of fruits and vegetables, deficiency of some water-soluble vitamins, like B9, B2, and fat-soluble vitamins C and D and a sedentary lifestyle. American Heart Association (AHA) and current diet guidelines have recommended the effective dietary strategies to cope hypertension.⁵ Cardiovascular diseases (CVD) are the most important roots of mortality and morbidity.⁶ A follow-up of 2 years was completed in three cities of South Asia, prevalence of hypertension found 30.1% in men and 26.8% in women at baseline.⁸

Dietary Nitrate:

In a recent year, therapeutic effect of dietary nitrate emerged as an important component to treat hypertension. It is an estimate that about 80% of dietary nitrates are obtained from vegetable sources.

The sources of nitrites include vegetables, fruit, and processed meats, beetroot, radish, and rocket. Beetroot is a rich source of inorganic nitrate.⁹ Green leafy vegetables give an adequate amount of nitrate extraction from the soil which is essential for growth.¹⁰

Alliin Sativum

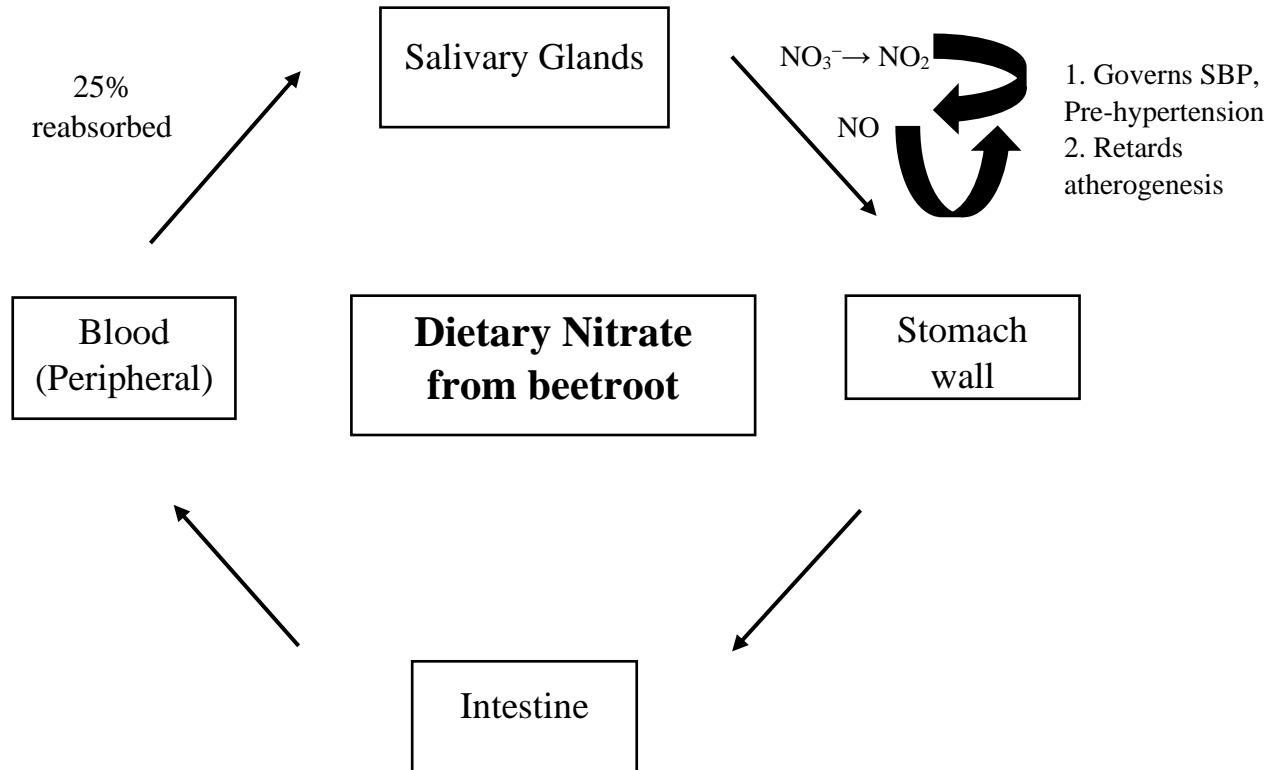
Allium sativum L is the scientific name of garlic, a bulbous herb. It can be used as a food item, spice and medicine in all regions of the world. It has the property to enhance flavor for greater palatability, and helps in lowering salt intake. Different researchers are working to discover effects of garlic on human status.¹¹ It is consumed as a medicinal supplement, with its antibacterial, anti-carcinogenic and antioxidant effect against different microorganisms. Alliin also has angiotensin II-inhibiting and vasodilating effect.¹²

Extraction of Alliin from garlic: Preparation

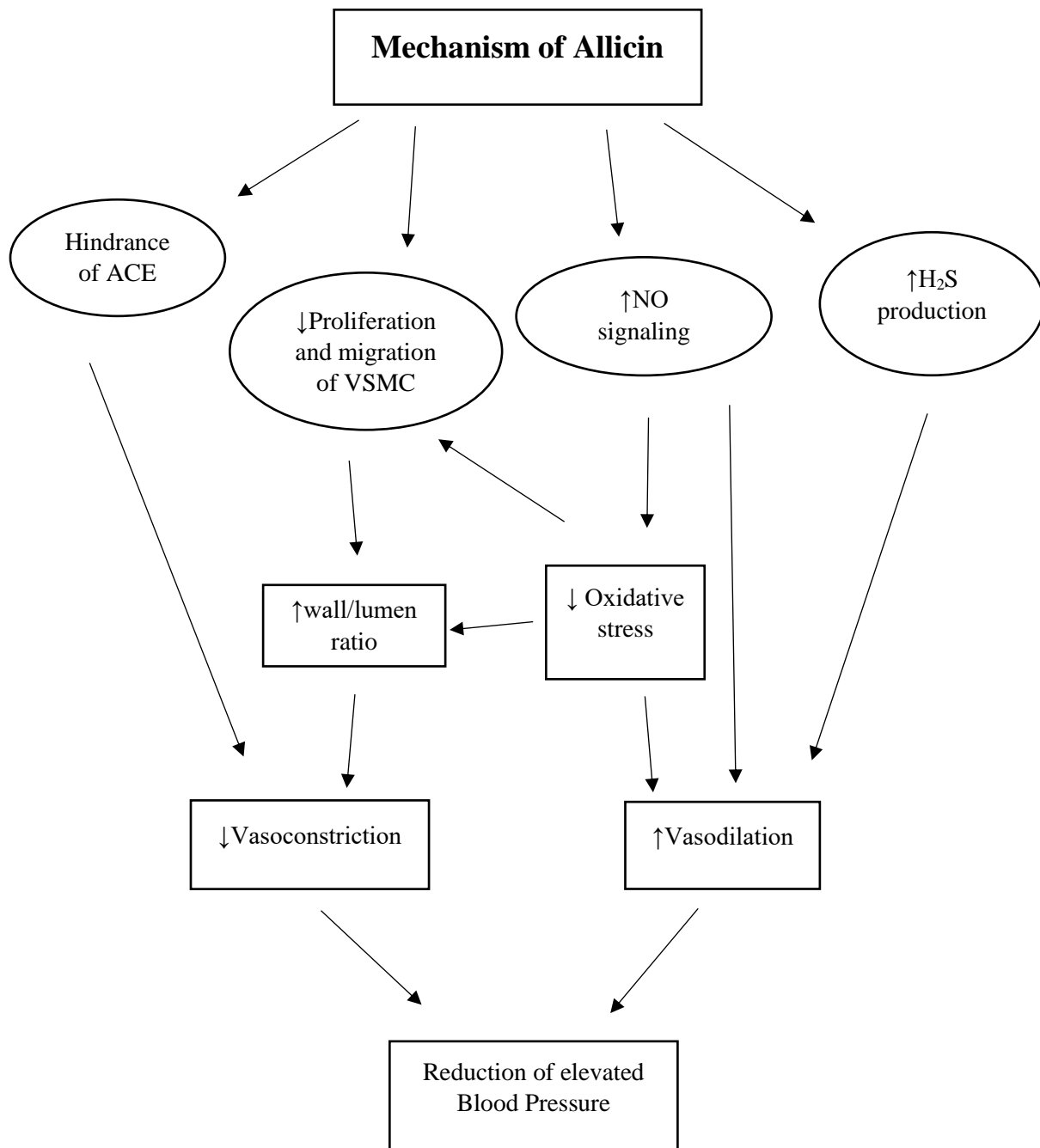
Different preparatory treatments of garlic are used to treat hypertension. Pressurized liquid extraction, ultrasound-assisted extraction techniques have high proficiency on the extraction of Alliin.¹³ It is not a stable compound, degrading within a few minutes of being produced, at high temperatures and in the presence of ethanol. It is very reactive and slightly soluble in water.¹⁴

Prevalence of Hypertension

Hypertension affects 1.13 billion people worldwide. Worldwide prevalence of hypertension is 40.8% and the control rate is 32.3%. 35.1% prevalence was observed in rural central Punjab, Pakistan.¹⁵ The rate of awareness in Australia is 62%, 72% in America which is quite highlighting, the control rates are very disappointing, 24% and 35% respectively. In the South Asian region, 8% control rate was observed in China and India with 6% in administration of hypertension. In 2025 its prevalence is expected to increase to 1.56 billion.¹⁶

Literature Review:**Mechanism of Dietary Nitrate in Hypertension:**

In the stomach wall dietary nitrate is absorbed. This dietary nitrate is reduced into nitrite (NO_2^-) and enter the entero-salivary circulation. (NO_2^-) is reduced to nitric oxide (NO) and again re-pass in the circulation to reach the acidic setting of the stomach. Various cardiovascular diseases are connected with NO bioactivity.¹⁷ Aortic blood pressure well forecast presence of cardiovascular pathologies than brachial BP and expected to damage cardiac organs. NO is expected to reduce aortic BP more than brachial BP. Ambulatory BP measurement over 24 h gives more accurate results of CVD risk and total death or mortality than clinical management of BP.¹⁸

Mechanism of Allicin in Hypertension:

Allicin or diallyl thiosulphuric acid is an active inhibitory principle of garlic, enzymatically released when the garlic bulbs are crushed.¹⁹ The mechanism of allicin is highly acceptable, and involves two pathways including the hydrogen sulfide and NO signaling pathways. Aged garlic extract has the potential to improve arterial stiffness, inflammation, and other CVD indicators. It is considered as highly acceptable with a top safety outline as an antihypertensive treatment.²⁰

Garlic have antihypertensive characteristics that are linked to stimulate intracellular NO and H₂S production, and obstruction of angiotensin II production, which results in vasodilation and thereby lowers blood pressure.²¹

Experimental Studies

In a randomized crossover study a comparison of raw and cooked beet juice (RBJ) and (CB) on Blood Pressure was made to analyze its effect of hypertensive subject. It includes twenty-four hypertensive patients from age of 25 to 68 years. Both groups consumed RBJ an CB respectively for 2 weeks. Both groups alternate treatment after 2 weeks. Each participant received RBJ (250 ml/day) and CB (250g/day).

In 2015, a study was conducted to assess the high dietary nitrate intake by consuming beetroot juice for 1 week to decrease blood pressure in hypertensive patients. 27 hypertensive patients were included in the study. Consumption of beetroot juice rich in nitrate was being compared with beetroot juice nitrate-depleted (placebo) for 1 week. Blood pressure (BP) was measured during the period of action and 24-h ambulatory blood pressure on the last day of intervention. Other results comprised were measurement of nitrate and nitrite in plasma, saliva, and urine. Researchers concluded that high intake of dietary nitrate might not be an effective way to decrease blood pressure in treated hypertensive patients. No changes were being noted with 1 week intake of nitrate-rich beetroot juice compared with the nitrate-depleted beetroot juice.²⁴

A study was conducted that analyzed the impact of inorganic nitrate and beetroot supplementation on blood pressure from 2 hours to 15 days. It involves the publications of 2006-2012. It involves 254 subjects including 7 to 30/study. Both systolic and diastolic blood pressure were measured. 16 trials were able to meet the criteria required for review. Changes in systolic than diastolic BP were being observed. These trials exposed relation between daily dose of inorganic nitrate and changes in systolic BP. Results showed that both helps in lowering systolic BP. Long-term trials are required for having better results.²⁵

Beetroot is a rich source of inorganic nitrate. It was a double-blind crossover study conducted to access the effects of sodium nitrate on Blood Pressure in 17 healthy individuals for 10 days and described a significant decrease in diastolic BP. Volunteers received either nitrate or placebo. Treatments prepared in water and could not be differentiated by sensory evaluation. During the both periods, the volunteers were forbidden to avoid all foods rich in nitrate load. No changes were observed in systolic blood pressure. The mean arterial pressure

decreased. Plasma nitrate levels were noted increased after nitrate consumption than after placebo ingestion, as were plasma nitrite levels.²⁶

In 6-week study, rat model of chronic Kidney Disease (CKD) was used to analyze the impact of allicin on hypertensive rats. On weekly basis blood Pressure was checked. It includes control groups including, CKD, and allicin treated CKD (CKDA). Different biomarkers and parameters were measured. The CKD group depicts high blood pressure and proteinuria. Treatment of allicin decreased hypertension and it also reduced the vascular reactivity to angiotensin II. Allicin also controls the antioxidant enzymes and reduce oxidative stress. Results analyzed that allicin exposed an anti-hypertensive, nephron-protective, cardio-protective, and antioxidant effects.²⁷

In order to study the effect of blood pressure with garlic in hypertensive patients a meta-analysis was conducted 1946 to 2013. It was a randomized controlled study which includes 17 different trials. Results concluded after comparing with control group that systolic blood pressure was reduced. Results of subgroups revealed that systolic BP reduced in hypertensive but not normotensive respondents. No changes were observed in diastolic BP. Meta-analysis recommends that garlic is effective in lowering blood pressure, especially in patients of hypertension.²⁸

In a meta-analysis, researches included published in 1955 and 2007 to examine the impact of garlic preparations on BP. Out of 25 studies 11 studies were suitable for meta-analysis. It was a randomized controlled trial including placebo groups, using only garlic preparations, and measured mean and standard deviations of systolic and diastolic blood pressure. Subgroup meta-analysis was also conducted by baseline BP for the 1st time. In order to analyze the link between blood pressure values and period of treatment, quantity, and BP at the initial stage of action, a meta-regression was conducted.²⁹

A study in 2006 was conducted to analyze the consequence between aged garlic extract (AGE) and raw garlic powder (RG) that which gives better results in hypertensive rats. Male rats were fed on AGE or RG powder for 10 weeks. after 4 weeks both lowered the rise of SBP as compared to the control group after starting the experimental diets. AGE affects pulse pressure (PP), recommending a progress of the pliability of the artery, on the other hand RG did not affect PP. Injurious results were noted in the RG

group which showed a decreased RBCS, improved reticulocytes.³⁰

In a study Lichtwer garlic powder was used in rats fed with 2% added diet containing cholesterol to analyze its effect on cholesterol, protein, glucose, triglyceride, and systolic blood pressure. It was a 6week trial. For the control group, normal diet was used. On the daily

basis rats were given the aqueous garlic powder to eat. Significant raise in the concentration of serum cholesterol was noticed in cholesterol fed rats vs the control group. However, a remarkable decrement in the concentration of serum cholesterol levels was observed compared to the participants who were on a diet of high cholesterol without garlic powder

Original Studies regarding dietary Nitrate and Allicin therapeutic effects in modulating hypertension

Sr.no	Study Subjects	Dietary Intervention	Duration of the Treatment	Treatment Effect	References
1.	15 healthy men and women	6.5–7.3 mmol Beetroot juice containing nitrate. <0.06 mmol beetroot juice depleted in nitrate	7 days	↓ aortic systolic BP	32
2.	15 Men 15 Women	500g Beetroot Juice. 500g Apple Juice. 500g Placebo Juice.	14 days	↓ aortic systolic BP	33
3.	68 hypertensive patients	250- ml nitrate rich, beetroot juice 250 mL nitrate-depleted beetroot juice.	4-Weeks	↓in clinic BP ↓24-hour ambulatory BP. ↓Home Blood Pressure.	34
4.	20 hypertensive patients	12.9 mmol nitrate con. beetroot juice	2-Weeks	↑ serum nitrate/nitrite. ↓ night time diastolic BP. ↓arterial stiffness.	35
5.	88 Hypertensive patients	Aged-garlic extract 1.2 g containing 1.2 mg S-allylcysteine	12-weeks	↓Mean BP. ↓ systolic BP. ↓ diastolic BP.	36
6.	79 patients	240mg, 480mg, 960mg capsules of aged garlic extract containing 0.6, 1.2, 2.4 mg of S-allylcysteine respectively.	12-weeks	↓ Blood pressure ↑Tolerability ↑Acceptability	37
7.	34 pre-hypertensive 47 mild hypertensive	300 mg dried garlic homogenate or placebo	12 weeks	↓Systolic BP in GH diet. ↓diastolic BP. ↑tolerability, anti-hypertensive effect in adults with mild hypertension. No effect was noted in pre-hypertension.	38
8.	24 hypertensive wistar rats	Nicorandil 6 mg/kg/day. Allicin 8 mg/kg/day.	8 weeks	allicin partially reverse dexamethasone induced hypertension. ↓ Anorexia. ↓ body weight.	39

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