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GARLIC (*ALLIUM SATIVUM*): PHARMACEUTICAL USES FOR HUMAN HEALTH

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ABSTRACT: The medicinal properties of Garlic are well known for a long time. Garlic is recommended as a nutritive element in the treatment of various health problems and the prolongation of human life. The present review article on garlic is to explore ancient phytomedicinal uses with modern scientific knowledge. Garlic cloves contain a colorless, odorless, soluble compound called alliin, water, and vascular enzyme alliinase. As soon as garlic clove is cut, alliin is converted to allicin by the action of enzyme alliinase. Pungent garlic smell is due to allicin. Modern scientific studies have revealed the beneficial effects of garlic on the cardiovascular system, Alzheimer's disease, diabetes, wound healing, neuro/ nephroprotection, osteoporosis, stress, aging, and anti-fungal/bacterial/viral/ Protozoans. Though, it is commonly used in food items, yet it is also recommended as pesticide/insecticide/molluscicide. The present review deals with the diversified beneficial activity of the garlic in the welfare of human beings. Although recent researches on its medicinal properties had explored its therapeutic value in the treatment of various ailments, yet a lot of studies are still required to establish garlic as a safe phytomedicine.

INTRODUCTION: There are over three hundred stains of garlic (*Allium sativum*) grown all over the world¹ and is one of the earliest known examples of the plants used in the treatment of different human health problems. Garlic is cultivated throughout the world; it appears to have originated in central Asia and then spread all over the world². The active component of the garlic is allicin³. In ancient times garlic is quoted in the treatment of rheumatism, dermatitis, abdominal pain, cough, loss of appetite, curing tumors, rabies and snake bite, fever, asthma, epilepsy, and vermifuge⁴⁻¹⁰.

Allicin (allyl 2-propenethiosulfinate or diallyl thiosulfinate) is the principal bio-activate compound present in the aqueous extract of garlic or raw garlic homogenates. When garlic is chopped or crushed, vascular enzyme alliinase is released, which act on alliin to produce allicine¹¹. Other important compounds present in Garlic homogenate are: i) propenyl allyl Thiosulphonate, allyl methyl thioslfonate, (E, Z) -4, 5, 9-trithiadodeca-1, 6, 11-triene 9-oxide (ajoene), and γ -L-glutamyl-S-alkyl-L-cysteine.

The adenosine concentration increases several-fold as the homogenate is incubated at room temperature for several hours¹². Allicin gives garlic its pungent flavor along with ample of health benefits. Garlic is rich in potassium, calcium, magnesium, iron, protein, arginine, zinc, saponins, polyphenols, and selenium¹³.

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Moreover, it is a good source of certain vitamins like Vitamin A, Vitamin B₆, and B₁ and Vitamin C¹⁴. Garlic contains at least 100 sulfur-containing compounds basic to medicinal uses¹⁵. The efficacy of garlic content chiefly depends on the mode of its preparation. Crushing, chewing or cutting of garlic clove release the vascular enzyme alliinase that rapidly lyses the cytosolic cysteine sulfoxide^{16, 17} to form sulfenic acid (R-SOH)¹⁸, which immediately condenses to form allicin compound. The compound produces the odor of garlic. Allicin decomposes readily to allyl sulfenic acid (2-propenethial), which enters into a cascade of reactions producing alkyl disulfides, including diallyl disulfide and various polysulfanes, vinyl dithiols and ajoene¹⁹.

The present review is an effort to make a correlation between the chemistry of garlic cloves with their pharmacological/ therapeutic uses in ancient as well as in modern times to cure different diseases. Recent researches of Pérez-Torres *et al.*,²⁰ Block *et al.*,²¹ Siyo *et al.*,²² Ryu and King²³, Farrag *et al.*,²⁴ Tsukioka *et al.*,²⁵ Kodera *et al.*,²⁶ González-Marales²⁷, Albrecht *et al.*,²⁸ have extensively studied the chemistry of garlic and their effect on various health problems.

2. Therapeutic Uses: Garlic has been employed in the treatment of blood pressure²⁹, atherosclerosis, high cholesterol, heart attack and coronary heart disease³⁰ anti-aging and anti-hyperlipidemic^{30, 31} in treatment of lung, prostate, breast, stomach and colorectal cancer³². Aged garlic has pronounced immunomodulatory effects than raw garlic. Garlic is an effective therapeutic agent to check the recurrence of aphthous ulcer, and gout³³, rheumatoid arthritis³⁴, osteoarthritis, diabetes, allergic rhinitis, traveler's diarrhea, pre-eclampsia, bacterial, fungal infections and cold flue⁸. Use of garlic includes treatment of fever, whooping cough, headache, stomach ache, sinus congestion, hair loss, and hemorrhoids¹⁴. Syrup of garlic is a very precious medication for asthma and chronic bronchitis. Moreover, it is also used for fighting stress and fatigue and is found to be effective in preventing beriberi and scurvy¹⁴. The juice of garlic is used as a vermifuge. The physician recommended the inhalation of garlic oil in the ailments such as pulmonary tuberculosis, sterility, and impotency, red eyes^{8, 14, 35-39}.

2.1. Effect of Garlic on Cardiovascular Disease:

The wealth of scientific literature supports that garlic consumption has significant effects on lowering blood pressure, prevention of atherosclerosis, reduction of serum cholesterol and triglyceride, inhibition of platelet, aggregation and increasing fibrinolytic activity^{12, 40}. Both experimental and clinical studies on different garlic preparations demonstrate these favorable cardiovascular effects⁴¹.

2.2. Anti-hypertensive:

Asdaq and Inamdar proposed that concomitant use of fresh garlic homogenate (FGH) or its bioactive constituents, SACS, with captopril is very effective in controlling the high blood pressure⁴². The combined therapy of fresh garlic homogenate (FGH) 250 mg/kg with captopril (CAP) caused an effective reduction of systolic blood pressure (SBP), cholesterol, triglycerides, and glucose level. Super Oxide dismutase (SOD), the catalase activities in heart tissue were significantly elevated in rats treated with FGH^{35, 42}, SACS (S-allyl cysteine sulphoxide), CAP, FGH+CAP and SACS +CAP. Combined therapy of FGH 250 mg/Kg with CAP caused significant fall in LDH and Creatine Kinase Myocardial Band (CK-MB) activities in serum and elevation in heart tissue homogenate. Moreover, the combination of SACS with CAP exerted super-additive (synergistic) interaction with respect to fall in blood pressure and angiotensin-converting enzyme (ACE) inhibition.

In 2007, Davids W. Kraus of the University of Alabama, Benavides, *et al.*, reported that Sulfide-containing compounds found in garlic cloves are converted into H₂S gas by molecules that occupy the membranes of the RBC⁴³. Further, in 2009 Zhu of Fudan University in Shanghai, Wang *et al.*, and his colleagues observed that garlic contains a compound called S-allyl-L-cysteine that boosts the production and circulation of H₂S in the body⁴⁴. Hydrogen sulfide is involved in regulating blood pressure. It has been an established fact that nitric oxide relaxes blood vessels by activating an enzyme called guanylyl cyclase in the vessel's smooth muscle cells. H₂S has the same dilating effect on the vessels, but it acts in a different way. H₂S gas is generated by the smooth muscle cells and endothelial cells that make up blood vessels. H₂S gas activates K_{ATP} channel proteins in muscle

cell membrane, prompting potassium ions to exit the cell. Electric current created by the flow of potassium ions out of the cell limits, prevents the flow of calcium ions into cell. This change relaxes the cell and dilates the blood vessel. Dilation of vessel lower blood pressure and increases blood flows.

Several clinical studies showed that garlic reduced blood pressure in more than 80% of patients suffering from high blood pressure⁴⁵⁻⁴⁶. It has been suggested that aged garlic extract was superior to placebo in lowering systolic blood pressure in patients suffering from uncontrolled hypertension. A dosage of 240-960 mg of aged garlic extract containing 0.6-2.4 of S-allylcysteine significantly lowered blood pressure by about mm Hg over 12 weeks⁴⁷. Brankovic *et al.*, reported that intravenous administration of garlic extract produced dose-dependent, reversible hypotensive, and bradycardic effects in anesthetized normotensive rats⁴⁸. Asdaq and Inamdar,⁴⁹ investigated the protective effects of combined therapy of garlic homogenate with hydrochlorothiazide (HCTZ) in animals with hypertension and myocardial damage.

The result showed that garlic combined with HLTX increases the lactate dehydrogenase, creatinine phosphokinase, and superoxide dismutase and catalase activities in heart homogenate when used concurrently or separately. There was the restoration of normal values in body weight, systolic blood pressure, cholesterol, triglycerides, glucose, and histopathological scores in all treated groups. Furthermore, histological disturbances and hypertension were significantly ameliorated in treated animals. Moreover, a moderate dose of garlic was more effective than the low dose, while a high dose of garlic was least effective in correcting electrocardiographic changes. Thus, garlic in a moderate dose with added HCTZ has synergistic cardioprotective and antihypertensive properties against fructose and isoproterenol-induced toxicities⁴⁹.

2.3. Anti-atherosclerotic: Atherosclerotic cardiovascular disease (ASCVD) is one of the most widely recognized risk factors. Although garlic has been used conventionally in treating ASCVD, no studies on its ability to inhibit the atherosclerotic process have been reported from a pilot study of

patients with coronary artery calcification, who were concurrently administered garlic and statins⁵⁰.

Hypercholesterolaemia is a major risk factor for atherosclerosis³⁴. Reduction of cholesterol can significantly decrease the risk of cardiovascular disease. Hypercholesterolemia in rats induced by high cholesterol diet was significantly reduced serum cholesterol, triglyceride, and LDL, but no effects on serum HDL, when garlic was administered in these rats⁴¹. In *in-vitro* experiments, garlic administration suppressed LDL oxidation and increased HDL, which may be one of the protective mechanisms of the beneficial effects of garlic in cardiovascular health⁵¹. Long term application of garlic and its preparation on experimental atherosclerosis induced by a high cholesterol diet showed a 50% reduction in atheromatous lesions, particularly in the aorta⁴¹. Most of the human studies on lipid-lowering effects of garlic and garlic preparation described a significant decrease in serum cholesterol and triglyceride^{53, 54}. A meta-analysis including 39 primary trials of the effects 2 months administration of garlic preparation on total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides was performed by Ried *et al.*⁵⁴

The preventive effect of garlic on atherosclerosis has been attributed to its capacity to reduce lipid content in the arterial membrane. Allicin, S-allyl cysteine, presented in aged garlic extract and diallyl disulfide, presented in garlic oil are the active compounds responsible for anti-atherosclerotic effect^{55, 56}. The plasma fibrinolytic activity in animals (which was decreased on cholesterol feeding) was considerably increased when this diet was supplemented with garlic⁵⁷. CD 36 scavenger receptors expression on macrophages is indication of OxLDL uptake and foam cell formation during atherosclerotic lesion development.

Both *in-vitro* and *in-vivo* studies have demonstrated that the atherosclerotic risk factor homo cysteine (Hcy) induces macrophage CD36 expression as well as OxLDL uptake. However, Morihara *et al.*, noted that aged garlic extract (AGE) inhibit CD36 expression and OxLDL uptake in human macrophages by modulating the PPAR γ pathway

⁵⁸. Thus, the study suggests that the garlic extract could be useful for the prevention of atherosclerotic lesions ⁵⁸. Moreover, Lei *et al.*, suggested that diallyl disulfide (DADS) and diallyl trisulfide (DATS) protect endothelial nitric oxide synthetase (eNOS) activity against OxLDL insult, this protection can be attributed partly to their mediation of phosphatidylinositol 3-Kinase/protein Kinase B signaling and prevention of eNOS degradation ⁵⁹.

Garlic along with its water-soluble allyl sulfur-containing compound, S-Allyl-L-cysteine sulfoxide (ACSO) has shown antioxidant and anti-inflammatory activities, inhibiting the development of atherosclerosis. Apparently, ACSO inhibited pro-inflammatory cytokine-induced adhesion of monocytes to endothelial cells by inhibiting the nitrogen-activated protein kinase signaling and related intercellular cell adhesion molecule-1-expression. It also maintains mitochondrial membrane potential and suppresses the overproduction of superoxide anion in endothelial cells. Hence, these findings may provide new insights into ACSO on controlling TNF-alpha-mediated inflammation and vascular disease ⁶⁰.

2.4. Anti-thrombotic: Sumiyoshi and Wargovich reported that garlic decreases the risk of peripheral arterial occlusive diseases, plasma viscosity, and unstable angina and increases elastic property of blood vessels and capillary perfusion ⁶¹. Daily consumption of clove of fresh garlic bulb for 6 months caused in an 80% decrease of serum thromboxane B₂ in middle-aged men ⁶². *In-situ* study in a rat model, it has noted that an overall antithrombotic effect of garlic is due to modulation of fibrinolytic activity through increased plasminogen activation and thrombin inhibition ⁶³. Garlic increased the fibrinolytic activity in healthy human as well as in acute myocardial infarction patients ⁶⁴. Pre-treatment with garlic significantly inhibited intracellular Ca⁺⁺ mobilization, Thromboxane - A₂ (A potent platelet aggregator) synthesis and protected against thrombocytopenia induced by collagen or arachidonate application in rabbits. These observations indicate that garlic may be beneficial in the prevention of thrombosis. Garlic has shown to inhibit platelet adhesion or aggregation in human investigations. It has been shown that the aged garlic extract inhibited the

binding of ADP-activated platelets to immobilized fibrinogen ⁶⁵. This suggested that aged garlic extract inhibits platelet aggression *via* inhibition of the GPIIb/IIIa receptors and an increase in cAMP.

2.5. Alzheimer's Disease Protective Activity: Garlic is known for its *in-vitro* neuroprotective abilities ⁶⁶. Aged garlic has been noted to for multiple benefits, which contributes to the classic Alzheimer beta-amyloid plaque. Garlic is expected to produce cumulative benefits, and exhibits enhanced neuroprotection by virtue of being "natural statin", "natural NSAID"(a non-steroidal anti-inflammatory drug), "natural anti-oxidant", "natural anti-apoptotic agent" and "memory enhancer", a combination of many single-ingredient synthetic pharmaceutical drugs currently used for Alzheimer's therapy ⁶⁷. Unfortunately, there is a dearth of clinical studies showing of aged garlic extract in relation to Alzheimer's pathology, except for reports showing improved behaviors in senescence-accelerated mice after garlic treatment ⁶⁸. Given the multiple-mechanistic possibilities and minimal risk associated with its use, garlic seems a prudent recommendation for prevention and treatment. Since aged garlic is best studied in relation to Alzheimer's, it may be the best form to be used in the treatment of Alzheimer's disease ⁶⁹.

2.6. Anti-diabetic: Diabetes mellitus is one of the common endocrine disorder lead to hyperglycemia causing various disorders in the eyes, nerves, blood vessels, skin, and kidneys. Increased glycation of proteins and the accumulation of advanced glycation end-product (AGEPs) have been used in monitoring the pathogenesis of diabetic complications. Glycation, together with AGEP formation, is also accompanied by the formation of free radicals *via* acetoxidation of glucose and glycated proteins ³⁵. Compounds with combined antiglycation and antioxidant properties may offer therapeutic potential. Recent studies suggested that AGE suppresses the production of AGEPs *in-vitro*, and formation of glycation derived free radicals ³⁴.

S-allylcysteine, a key component of aged garlic, is a potent antioxidant and can inhibit AGEP formation. Aged garlic extract and S-allylcysteine observed more attention, is reduced in *in-vivo* AGEPs ⁷⁰. Although, experimental studies demonstrated a clear hypoglycemic effect of garlic,

the effect of garlic on human blood glucose is still not clear.

Many studies showed that garlic could reduce blood glucose levels in diabetic animals. Garlic was effective in the reduction of blood glucose in streptozotocin-as well as alloxan-induced diabetes mellitus in rats and mice^{71,72}. Short term benefits of garlic on dyslipidemia in diabetic patients were shown. Garlic significantly reduced total serum cholesterol and LDL cholesterol and moderately raised HDL cholesterol as compared with placebo in diabetic patients⁷³. S-allylcysteine, a bioactive component derived from garlic, restored erectile function in diabetic rats by preventing reactive oxygen species (ROS) formation through modulation of NADPH oxidase subunit expression⁷⁴.

Metformin and garlic treatment in diabetic patients for 12 weeks reduced fasting blood glucose (FBG), but the percentage of change in FBG was more substantial with metformin supplemented with garlic than with metformin alone⁷⁵. Chronic feeding of garlic extracts showed a significant decrease in blood glucose levels. However, some other studies showed no change in blood glucose levels in humans. Therefore, the role of garlic in diabetic patients needs to be further investigated¹². The beneficial effect of garlic on diabetes mellitus is mainly attributed to the presence of volatile sulfur compounds, such as allicin, diallyl disulfide, diallyl trisulfide, diallyl sulfide, S-allyl cysteine, ajoene, and allyl mercaptan. Garlic extracts have been reported to be effective in reducing insulin resistance⁷⁶.

2.7. Neuroprotective: High cholesterol, High Hcy (homocysteine), Hypertension and Inflammation, all risk factors for cardiovascular diseases, also involved in the risk of dementia, including its most common form Alzheimer's disease (AD). High cholesterol is also associated with the elevated beta-amyloid (A-beta), the hallmark of AD. Aging with associated oxidative damage is a major factor in both cardiovascular disease and dementia. The antioxidant property of AGE scavenges oxidants increase superoxide dismutase, catalase, glutathione peroxidase, glutathione levels, besides suppressing lipid peroxidation and inflammatory prostaglandins. Inhibition of 3-hydroxy-3-

Methylglutaryl-CoA reductase by AGE reduces cholesterol synthesis. These effects retard arterial plaque formation.

AGE decreases Hcy, lowers blood pressure, and increases microcirculation, which is important not only in diabetes management but also reduces dementia risks. AGE may also help prevent cognitive decline by protecting neurons from Abeta neurotoxicity and apoptosis. This prevents ischemia or reperfusion related neuronal death, thus improves learning and memory retention. Evidence supports the beneficial health effects attributed to AGE in helping prevent cardiovascular, cerebrovascular disease, lowering the risk of dementia, and AD⁷⁷.

2.8. Wound Healing Activity: Angiogenesis is a prime concern in successful wound healing. Impaired angiogenesis is a hallmark of the chronic wounds encountered with diabetes and venous or arterial insufficiency. Jalali *et al.*,⁷⁸ investigated the insufficiencies of different concentrations of aged garlic solution (AGS) on wound healing, gross histopathology, with the help of scanning electron microscopy (SEM) and computer-based three dimensional (3D) image-probing techniques to determine the effects of AGS on wound closure, re-epithelialization, dermal matrix regeneration and angiogenesis in rabbit⁷⁸. They noted that alcoholic extract of garlic could be considered as an available and inexpensive topical agent for accelerating and enhancement burn wound healing.

Sulfur is very important for the formation of collagen and is a major component in the synthesis of cartilage and connective tissues. It is an essential part of keratin, which is necessary for the maintenance of a healthy situation of the skin, hair, and nails. MSM can also decrease scar tissue by changing the cross-linking process in collagen to allow tissue repair and healing to take place⁷⁹. Sulfur is an important nutrient and is essential for the maintenance of connective tissues, joint function proper enzyme activity, and hormone balance⁸⁰.

2.9. Nephroprotective: Progressive renal damage, along with hypertension, is associated with oxidative and nitrosative stress. Cruz *et al.*, suggested that garlic products may be used to

ameliorate hypertension and delay the progression of renal damage. S-allyl cysteine (SAC) in AGE, has antioxidant properties⁸¹. The effects of SAC and AGE on blood pressure, renal damage, oxidative and nitrosative stress were studied in nephrectomized rats treated with SAC (200 mg/kg ip) and AGE (102 ml/kg ip) every other day for 30 days. SAC and AGE reduced hypertension, renal damage, the abundance of inducible NOS (nitric oxide synthase), besides increasing SOD activity. The antihypertensive, as well as the renoprotective effects of SAC and AGE, are associated with their antioxidant properties.

2.10. Osteoporosis: Garlic may also confer phytoestrogen effects to counter bone loss. One fascinating animal study examined the effects of garlic extracts on the intestinal movement of calcium in rats as well as to study garlic's possible role in maintaining the bone mineral content and bone tensile strength in an ovariectomized rat model of osteoporosis. The results suggest that, in this experimental model, the oil extract of garlic promotes intestinal transference of calcium by modulating the activities of both intestinal alkaline phosphatase and Ca^{+2} activated ATPase. Also, the observed low bone mineral content and low bone tensile strength in these rats were significantly restored by garlic oil supplementation. Garlic oil supplementation was able to revive the bilateral ovariectomy-induced decrease in the serum estrogen titer partially. Interestingly, the serum parathyroid hormone level, was found unaltered in these rats. The garlic oil supplements caused partial recovery in serum estrogen titer in bilaterally ovariectomized rat and also persistently associated with enhanced calcium transference and better preservation of bone mineral content⁸². Use of garlic as a treatment strategy in post-menopausal women with an osteoporotic tendency or for premature menopausal women is suggested to check osteoporosis.

2.11. Stress: Garlic appears to have the capacity for protection against the ravages of stress, which ultimately affects the autonomic nervous and neuroendocrine system. Aged garlic extract is also effective in preventing adrenal hypertrophy, hyperglycemic and elevation of corticosterone in hyperglycemic mice induced by immobilization stress⁸³. Given the extreme chronic stress during

daily life, garlic may prove useful to counter the negative impact of this stress on human physiology. Rats exposed to psychologically stressful situations aged garlic extracts significantly prevented the decrease in spleen weight, reduction of hemolytic plaque-forming-cells in spleen cells, and anti-SRBC antibody titer in serum. Moreover, a reduction in NK (Natural Killer) activities were observed in the psychological stress-exposed mice as compared with normal mice (non-stress)⁸⁴. Garlic was able to block the lipopolysaccharide-induced immune cytokine and plasma corticosterone and late choline changes following cold water immersion stress⁸⁵.

2.12. Aging: The life expectancy of a human being is remarkably increased within 5 to 6 decades: this has simultaneously increased aged related problems of the cardiovascular, brain, and immune system. These oxidative reactive agents in the body are now known to be associated with aging and age-related diseases in humans. Now the researches all over the world are concerned to arrest the aging and rejuvenate the human body. Garlic is used throughout the history of civilization to treat a wide variety of ailments, including aging. In the last 2 decades of studies, it has the anti-aging activity of garlic is extensively studied. Strong antioxidant properties of garlic can prevent cardiovascular disease, inhibit platelet aggregation, thrombus formation, prevent cancer, diseases associated with cerebral aging, arthritis, cataract formation, rejuvenate the skin, improved blood circulation and energy levels. Thus, the evidence of garlic's antioxidant properties may either prevent or delay chronic diseases associated with aging⁸⁶. In the old Indian book "Lahusun Badsha" (Garlic King) written by Swami Satya Devji Parivarjak published by Nagriprachari Sabha Varanasi, it has been mentioned that the whole human body can be rejuvenated with the help of raw garlic, honey, butter, raisins and gooseberry within 91 days. This process is given in full detail by Swami Purna Nand, who is the known scholar of the Ayurvedic system of medicine.

2.13. Antibacterial Properties: Garlic is a broad-spectrum antibiotic, killing a wide variety of bacteria. Historically, garlic has been used worldwide to fight the bacterial infection. Louis Pasteur described the antibacterial property of

garlic in 1858 for the first time⁸⁷. Garlic has been shown to be effective against a group of gram-positive, gram-negative, and acid-fast bacterial⁸⁸. These include *Salmonella*, *Escherichia coli*.³⁰ *Pseudomonas*, *Proteus*, *Staphylococcus aureus*⁸⁹, *Klebsella*⁹⁰, *Micrococcus*, *Bacillus subtilis*⁹¹, *Clostridium*⁹², *Mycobacterium*⁹³, and *Helicobacter*⁹⁴. It has been documented that garlic exerts a differential inhibition between beneficial intestinal microflora and potential harmful enterobacteria^{88,95}.

The antibacterial activity of garlic is widely attributed to allicin. It is known that allicin has sulfhydryl modifying activity⁹⁶, and is capable of inhibiting sulfhydryl enzyme. Cysteine and glutathione counteract the thiolation activity of allicin. Garlic extract and allicin have been shown to exert bacteriostatic effects on some vancomycin-resistance *enterococci*. An inhibitory synergism was noted, when used in combination with vancomycin⁹⁷. It is suggested that allicin modifies the sulfhydryl group on the enzymes of the TN1546 transposon, which encodes vancomycin resistance, enhancing susceptibility to vancomycin.

The antibacterial effect of different concentrations of garlic extract against human dental plaque microbiota has been shown in *in-vitro* study⁹⁸. The synergism between ciprofloxacin with garlic extract has been shown, but not between ampicillin and the garlic extract⁹⁹. The cloves of garlic and rhizomes of ginger, extracted with 95% ethanol, suggested to have anti-bacterial activity against multidrug clinical pathogens and can be used for prevention of drug resistant microbial disease. *Pseudomonas aeruginosa* was the most sensitive germ to the mixture¹⁰⁰. Garlic is also suggested against multidrug-resistant tuberculosis¹⁰¹.

2.14. Antiviral Properties: Garlic and its sulfur constituents verified antiviral activity against coxsackie virus species, herpes simplex virus type Ist and IInd, influenza B, Para-influenza virus type 2, Vaccinia virus, Vesicular stomatitis virus, human immunodeficiency virus type I and human rhinovirus type II. The order of compounds found in garlic for virucidal activity was ajoene > allicin > allyl > Methyl thiosulfinate > Methyl allyl thiosulfinate; no activity was found for the polar fractions, alliin, deoxyalliin diallyl disulfide or

diallyl trisulfide³⁹. Several laboratory tests have shown that garlic is an effectual treatment for both the influenza B virus and herpes simplex virus. Two independent researchers in Japan and Romania have found that garlic is able to protect living organisms from influenza virus¹⁰². A double-blind placebo-controlled study has shown significant protection from the common cold virus.

As conducted by the Garlic Center, published in *Advances in Therapy*. This is the first serious work to show prevention, treatment, and reduction of re-infection benefits from taking Allimax Powder capsules once daily¹⁰³. The investigation revealed 24 occurrences of the common cold in the garlic group compared with 65 in the placebo group, resulting in fewer days of illness in the garlic group compared with the placebo group. However, claims of effectiveness of garlic on common cold appear to rely largely on poor-quality evidence¹⁰⁴.

In case of HIV, it is thought that ajoene acts by inhibiting the integrin dependent processes¹⁰⁵. Allyl alcohol and diallyl disulfides have also proven effective against HIV-infected cells¹⁰⁶. No activity has been observed with allicin or S-allyl cysteine. It appears that only allicin and allicin-derived substances are active. Taken together, the beneficial effects of garlic extract make it useful in medicine.

2.15. Antifungal Activity: Antifungal activity was first established in 1936 by Schmidt and Marquardt whilst working with epidermophyte cultures¹⁰⁷. Ajoene is an active compound in garlic that may also play a role as a topical fungal agent¹⁰⁸. Garlic has shown to inhibit the growth of fungal elements equally along with the drug Ketoconazole, when tested on the fungi *Malessezia furfur*, *Candida*, species, as well as 35 strains of various dermatophyte species¹⁰⁹. A report from a Chinese medical journal delineates the use of intravenous garlic to treat a potentially fatal and rare fungal infection of the brain called *Cryptococcus meningitis*. In the report, the Chinese compared the effectiveness of garlic with standard medical treatment, which involved a very toxic antibiotic called Amphotericin-B. The study revealed that intravenous garlic was more effective than the drug and was not toxic regardless of its dosage¹¹⁰.

A study found that *Candida* colonies were substantially reduced in mice that had been treated using liquid garlic extract. The study also revealed that garlic stimulated phagocytic activity. This implies that infections such as *Candida* may be controlled because garlic stimulates the body's own defenses. Garlic oil can be used to treat ringworm, skin parasites and warts if it is applied externally. Lesions that were caused by skin fungi in rabbits and guinea pigs were treated with external applications of garlic extract and began to heal after seven days¹¹¹. It has been reported that garlic exhibited an antifungal effect on two species, the air-borne pathogen *Botrytis cinerea* and *Trichoderma herzianum*¹¹². Greater satisfaction with the use of garlic rather than nystatin was reported by the proteins with denture stomatitis¹¹³.

2.16. Anti Protozoal Properties: Several studies have shown that the garlic extract was effective against a host of Protozoa, including *Candida albicans*¹⁰⁷, *Scedosporium prolificans*¹¹⁴, *Tinea pedis*¹¹⁵, *Opalina ranarum*, *Balantidium entozoon*, *Entamoeba histolytica*, *Trypanosomes*, *Leishmania*, *Leptomonas*⁸⁸. Due to the occurrence of unpleasant side effects, an increasing resistance to the synthetic pharmaceuticals garlic was recommended for the treatment of giardiasis. Inhibitory activity of garlic on *Giardia* was noted with crude extract at 25 pg/ml, and the lethal dosage was established as approximately 50 pg/mL. A clinical trial done by Soffer and Mokhtar demonstrated that garlic has as an anti-giardial activity, removing all the symptoms patients within 74 h and completely removing any indication of giardiasis from the stool with 72 h at a dosage of 1 mg/ml twice daily aqueous extract or 0.6 mg/ml commercially prepared garlic capsule. It was suggested that allicin, ajoene, and organo-sulfides from garlic are effective antiprotozoal compounds¹¹⁶.

Many herbalists worldwide recommend garlic as a treatment for intestinal parasites. In some cultures, children infested with helminths are treated with enemas containing crushed garlic. Allicin exhibits anti-parasitic activity against major human intestinal parasites such as *Entamoeba histolytica*, *Ascaris lumbricoides*, and *Giardia Lamblia*¹¹⁷. *Entamoeba histolytica*, the human intestinal protozoan parasite, is very sensitive to allicin, as only 30µg/ml of allicin totally inhibits the growth

of *Amoeba* cultures¹¹⁸. Moreover, researchers have found that at lower concentrations (5µg/ml), allicin inhibited 90% of the virulence of trophozoites of *E. histolytica* as determined by their inability to destroy mono-layers of tissue-cultured mammalian cells *in-vitro*¹¹⁹.

2.17. Garlic as Pesticide/Insecticide /Molluscicide:

A garlic derived polysulfide is approved for use as a nematicide and insecticide¹⁴. It protected the plant against various infections and used as a natural pesticide. Garlic has been established as a natural pesticide¹²⁰, which can effectively control pests, makes an excellent economic, non-toxic biological pesticide in agricultural use¹²¹. Its strong aroma can mask normal host-finding or feeding cues in insects and provides an olfactory camouflage¹²², against the insect-like aphids, ants, termites, whiteflies, beetles, borers, caterpillars, slugs and armyworms¹²³. Magwenya et al., noted that garlic extracts used as biopesticides are efficient in suppressing aphid infestation on cotton. They reported that 85g chopped garlic/9 liter water could control the aphids without a compromise in cotton growth development and the corresponding yield¹²⁴.

Garlic oil is very effective on several species of mosquitoes. Crude an ethanolic extracts and garlic oil was toxic against 3rd stage of larvae of *Culex pens*, *C. tarsalis*, *Aedes aegypti*, *A. trisomiatius*, and *A. migromaculis*¹²⁵. Amonkar and Banerji also reported that diallyl disulfide and diallyl trisulfide are potent larvicide against mosquito larvae. Gareth et al., noted that garlic juice is toxic against two dipterian pests *Delia radicum* (LC₅₀-0.04%) and *Musca domestica* (LC₅₀-2.2%)¹²⁷. Garlic is often grown among flowers or root vegetables as a companion plant to protect other plants from being attacked by pests. Garlic has antimicrobial property at temperatures as high as 120 °C. Therefore, it is used as a preservative in deep-fried foods and meat. Fish are attracted towards scent of the garlic therefore it is also used for catching fish¹⁴.

Plata-Rueda et al., noted that insecticidal activity of the essential garlic oil and its compounds against the mealworm beetle, *Tenebrio molitor* in the laboratory conditions¹²⁸. Garlic essential oil caused substantial mortality and repellency in the larva, pupa, and adult stages. The best results were

obtained with concentrations of 16 and 32% in *T. molitor* as reported for other stored grain pests¹²⁸. Different concentrations of the garlic essential oil showed toxic effects on larva, pupa, and adult of *T. molitor* 48 h after topical application. The dose-response bioassay confirmed toxicity against *T. molitor*, reaching a 90% mortality rate.

Increasing concentrations of garlic essential oil in this insect have shown immediate toxic responses within 12 h of application¹²⁹⁻¹³². Comparing the contact toxicity of garlic essential oil on developmental stages of *T. molitor*, the larva was significantly more susceptible, followed by pupa and adult. The LC₅₀ and LC₉₀ of larva (0.77-1.36%), pupa (2.37-4.01%), and adult (2.03-4.73%) indicate that small quantities of the garlic essential oil are toxic in this insect, being more tolerant with age. The susceptibility of stored pest products such as *S. oryzae*, *S. zeamais*, *Sitotroga cerealella* (Lepidoptera: Gelechiidae), and *T. castaneum* may vary with the exposure at garlic essential oil applied to the body of these insects or by fumigation^{130, 132-133}.

Diallyl sulfide and diallyl disulfide demonstrated toxic activity on different developmental stages of *T. molitor*. Diallyl disulfide have stronger contact toxicity in larvae (LC₅₀= 57.68 mg ml⁻¹), pupae (LC₅₀ = 55.13 mg ml⁻¹), and adult (LC₅₀ = 81.52 mg ml⁻¹), than diallyl sulfide in larvae (LC₅₀ = 117.1 mg ml⁻¹), pupae (LC₅₀ = 48.86 mg ml⁻¹), and adult (LC₅₀ = 85.97 mg ml⁻¹). Garlic essential oil and its constituents, diallyl sulfide and diallyl disulfide, have been highly toxic to *S. zeamais* and *T. castaneum*¹²⁹⁻¹³⁰ at different developmental stages as well as other insects¹³¹. Plata-Rueda et al., noted that *T. molitor* was more susceptible to the pupal stage, followed by larvae and adults exposed to diallyl sulfide and diallyl disulfide¹²⁸. One possible explanation for the developmental stages difference is that efficacy may be affected by the penetration of the garlic compounds into the body and the ability of the insect to metabolize these compounds.

The insects exposed to the garlic essential oil and toxic compounds displayed altered locomotion activity, and muscle contractions that were observed in detailed descriptions at high concentrations. In some individuals, the paralysis was constant, with

concentrations near the LC₅₀ without recovery signs. Paralysis and muscle contractions in individuals of *T. molitor* at LC₅₀ can be explained by the toxic effect in the nervous system of the same. The rapid toxicity of essential oils and their constituents in insects indicates neurotoxic action as reported to *Delia radicum*, *Musca domestica* (Diptera: Muscidae), *Cacopsylla chinensis* (Yang et Li), and *Diaphorina citri* Kuwayama (Hemiptera: Psyllidae) with hyperactivity, hyperextension of the legs and abdomen and rapid knock-down effect or immobilization¹³⁴. Acetylcholinesterase is an enzyme that has been shown to be inhibited by garlic compounds and can act only or in synergism as diallyl disulfide, diallyl trisulfide, and allicin¹³⁵. The presence of the diallyl sulfide in garlic compounds may be responsible for the toxic effect in *T. molitor* and may cause inhibition by cross-linking with essential thiol compounds in enzyme structures, altering the functional shape of the protein and denaturalization¹²⁸.

Monosulfides, disulfides, and trisulfide breakdown products of the thiosulfates are volatile compounds and toxic to insect herbivores¹³³⁻¹³⁴. These compounds are garlic majority compounds and toxic to pests of stored products such as *S. zeamais* and *T. castaneum*¹²⁹. Garlic essential oil has a high percentage of diallyl disulfide as the main volatile compound and repellent properties to *S. zeamais* and *T. castaneum*¹³⁰. Plata-Rueda et al., reported that garlic essential oil, diallyl disulfide, and diallyl sulfide have high activities of behavioral deterrence against *T. molitor*, as evaluated by the behavioral responses of larvae and adults to different odor sources and the number of insects repelled, indicating their potential to the pest control in stored products¹²⁸.

Picardal et al., noted that the efficacy of *Allium sativum* as a potent plant molluscicide, which control the most invasive rice snail *Pomecea canaliculata*¹³⁶. Extract of garlic bulb (100%) had shown a comparable effect to those of the positive control (i.e., proven synthetic molluscicide, Niclosamide), which brought complete mortality to the snails after 24 h. Picardal et al. reported that upon the application of the AGE treatments, several behavioral changes were observed in the snail *Pomecea canaliculata*, such as hyperactivity, twisting motion, and the release of white sticky

saliva-like substances¹³⁶. Picardal *et al.*, noted that these white sticky substances were probably triggered upon the reaction of the snails mucous membrane towards the polar compounds (*e.g.*, eugenol, esters, saponins, *etc.*) of *Allium sativum*¹³⁶. Allicin is the major component of *A. Sativum*, is a phytochemical, which is highly irritant in nature and may have induced the reaction of snail's mucosal membrane. Malacology research laboratory, department of Zoology, DDU, Gorakhpur University, Gorakhpur UP, India, is working on fasciolosis control in Eastern Uttar Pradesh for the last 4 decades. They have studied the use of garlic formulations to control the fasciolosis. Extracts of garlic is used as molluscicide and cercaricide. This group of scientists has worked different aspects of garlic as molluscicide/cercaricide singly as well as with cow urines and other formulation for effective control of fasciolosis.^{38, 137-144} Water extract of garlic bulb is a potent molluscicide¹³⁷, it can kill snail *Lymnaea acuminata* and *Indoplanorbis exustus*.

Further, in 1995 Singh and Singh identified that allicin is main molluscicidal component of garlic, which is more toxic than synthetic molluscicide¹⁴⁵, Stored garlic bulb (11 month old) is more toxic to *L. acuminata* and *I. exustus* than fresh garlic bulb¹³⁹. Singh and Singh also observed that toxicity of garlic bulb extract against vector snail *L. acuminata* increases in pre- as well as post-harvest period¹³⁹.

Further, Singh and Singh have demonstrated that the toxic effect of allicin due to the inhibition of enzymes *viz.* lactic dehydrogenase, acetylcholinesterase, and alkaline phosphatase in the nervous tissue of the snail *Lymnaea acuminata*¹⁴⁰. Singh and Singh later established that allicin caused uncompetitive inhibition of acetylcholinesterase in the nervous tissue of snails exposed to garlic extracts¹⁴⁰.

Tripathi *et al.*, while studying the molluscicidal effect of cow urine, reported that a binary combination of cow urine + garlic bulb powder is very effective in killing the vector snail *Lymnaea acuminata*¹⁴¹. Rao and Singh noted that binary combination of *Allium sativum* with *Azadirachta indica*, *Cedrus deodara* oil, and *Nerium indicum* bark powder is very effective against the giant African snail, *Achatina fulika*¹⁴⁶.

Kumari and singh, for the first time, reported that larva of *Fasciola* could be killed within the body of vector snail by phytotherapy of infected snails at sublethal concentration of allicin¹⁴⁷. She noted that allicin is highly toxic against redia and cercaria larva¹³⁶. Further, she has established that allicin inhibits the acetylcholinesterase and cytochrome oxidase in cercaria larva^{38, 144}.

3. Dosage: A commercial garlic product should provide a daily dose equal to at least 4000 mg (one to two cloves) of fresh garlic. The cloves may be diced and mixed with wildflower honey for palatability. This dosage translates to at least 10 mg allicin or a total allicin potential of 4000 µg¹⁴⁸. In the dried form, this would be 300 mg of garlic powder tablet (Standardized to 1.3% allicin or 0.6% allicin yield). Two to three times per day or 7.2 g of aged garlic extract per day¹⁴⁹. In tincture form fresh bulb as a 1:2 in 95% alcohol, the dosage can be 40 drops up to six times per day.

3.1. Mode of Action: Several modes of action have been proposed. These include:

- a. Effect on drug-metabolizing enzymes. That is the induction of phase II detoxification enzyme including glutathione transferase, quinine reductase, epoxide hydrolase, and glucouronosyl transferase that inactivate toxic substances and facilitate their excretion.
- b. Antioxidant activity (garlic preparation exhibit radical scavenging activity and decreases lipid peroxidation, which is relevant in the light of the observation that tumor promotion may be involved with oxygen radicals.
- c. Tumor growth inhibition that has been documented in several carcinomas cell lines, including prostate carcinoma cells.
- d. Induction of apoptosis, which coincides with an increase in the percentage of cells, blocked in the G2/M phase of the cell cycle (Possibly through a depression in PP³⁴cdc2 kinase).
- e. Effective stimulation of the immune response (Organosulfur compounds stimulate proliferation of Lymphocytes and macrophage phagocytosis, induce the infiltration of macrophage and lymphocytes in transplanted tumors; induce splenic

hypertrophy, stimulate the release of interleukin-2 (IL-2), tumor necrosis factor- α (TNF- α) and interferon λ , enhance natural killer cell, killer cell, and lymphokine-activated killer cell activity)¹⁵⁰.

4. Side Effect or Adverse Effect of Garlic: The main side effect commonly associated with garlic intake is breath odor, especially when raw forms of herb are used.

When garlic is taken before meals, the odor is decreased⁶⁹. Nausea and Vomiting are other major adverse effects, and care should be taken in consuming high quantities. Although an entire garlic bulb produces little juice, it is potent and can act as strong emetic. Although garlic usually poses little in terms of a safety issue, there are isolated cases of topical garlic burns¹⁵¹ and anaphylaxis¹⁵². Rare garlic allergy has been attributed to the protein allinase, which allinase, which has induced immunoglobulin E (IgE) mediated hypersensitivity responses from skin prick testing¹⁵³.

As a result, the literature has generally cautioned against using garlic while using anticoagulant therapy. There is a reported case of spontaneous spinal or epidural hematoma in an 87 years old man, with associated platelet dysfunction to excessive garlic ingestion¹⁵⁴. The consumption of excessive amounts of raw garlic, especially on an empty stomach, can cause gastrointestinal upset, flatulence, and changes in the intestinal flora. There have been reports of allergic dermatitis, burns, and blisters from the topical application of raw garlic.

Garlic appears to have no effect on drug metabolism, although recent studies in healthy volunteers show conflicting results related to the effects of garlic on protease inhibitors pharmacokinetics. It has been suggested that patients taking anticoagulants use caution when taking garlic because of its antithrombotic properties. It is seen prudent to stop taking a high dosage of garlic 7-10 days before surgery because garlic prolongs bleeding time and has been associated (in one case report) with spontaneous spinal epidural hematoma.

CONCLUSION: Pharmacological studies of garlic clearly demonstrated that garlic is the superstar of health. Garlic is recommended in the diet, considered to be compulsory to stain good health.

Garlic, from crushed to the capsule, is consumed throughout the world. Garlic is used to treat cardiovascular diseases, including atherosclerosis, stroke, hypertension, thrombosis, serum cholesterols, LDL, HDL, triglyceride, and hyper-lipidemia, as well as used in Alzheimer's, diabetes, stress, neuro-protective, osteoporosis, aging and antimicrobial/antiprotozoal. Fresh powdered garlic is popular for food seasoning and should be used nowadays, with the ever-growing resistance organism garlic taken alone or with other herbal antibiotics such as grape seed extract or ginger, remains a powerful antimicrobial agent. Clearly, more studies are needed to refine the use and improve the efficiency of this important medicinal plant.

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