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REVIEW ON PHARMACOLOGICAL ACTIVITY OF GARLIC (ALLICIN)

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ABSTRACT

The chemical constituent present in garlic (illicit) show the various pharmacological action which is as ant carcinogenic, antiseptic, antibacterial, antifungal, antioxidant, analgesic, antihypertensive, allium sativa is reach in several sulfur containing phytoconstituent such as allin, allicin, ajoenes, vinyldithiinis, and such as quarantine, the allicin play the measure role in inhibition of fungal growth. In vivo allicin dilates the mesenteric circulation of the cat independent of prostaglandin release or beta adrenergic mechanism**.**

INTRODUCTION

Allicin, also known as allyl 2-propenethiosulfinate, diallyl thiosulfate, or S-allyl cysteine sulfoxide, is a volatile sulfur-containing substance that is present in various Allium species, including white garlic (Allium sativum L.) and other Field garlic, wild garlic (A. Ursinus L.), and elephant garlic (A. ampeloprasum L.)Alpine leek (A. victorialis L.) and garlic (A. vineale L.). It is believed to bea major bioactive organosulfur molecule produced inAllium species, which gives it its distinctively strong flavor and aroma. Allicin is really the most prevalent thiosulfinate in fresh garlic; according to Rybak, Calvey, and Harnly (2004), it typically makes up 70% (w/w) of all thiosulfinates in fresh garlic, or roughly 0.4% of its fresh mass. Regarding One fresh garlic clove contains 4-5 milligrams of allicin, and its presenceis readily identifiable.[8]

TAXONOMY OF ALLICIN

CLASSIFICATION

Kingdom	**Plantae**
Division	**Angiospermae**
Class	**Monocotyledons**
Subclass	**Liliidae**
Series	**Coronarie**
Order	**Liliacae**
Family	**Alliacae**
Genus	**Allium L..**
Species	**Sativum**

Biosynthesis of Allicin

Allicin is a thiosulfinate, and its structure was determined by Stoll and Seebeck in 1948. In nature allicin is produced after damage of the plant tissue by an enzymatic reaction. The precursor of allicin is the non-proteinogenic amino acid alliin (S-allyl-L-cysteine sulfoxide). Alliin and other S-alkyl-L-cysteine sulfoxides are hydrolysed by the enzyme alliinase, and in the case of alliin this reaction leads to production of dehydroalanine and allyl sulfenic acid. Two molecules of allyl sulfenic acid condense spontaneously to one molecule of allicin. Alliin is found in garlic (*Allium sativum*) and ramsons (*Allium ursinum*). Interestingly, onion (*Allium cepa*) does not synthesize alliin, but its isomer isoalliin(trans-(+)-S-(1-propenyl)-L-cysteine sulfoxide). The biosynthetic route to alliin is still not clear. Pioneering work by Granroth, who reported two possible biosynthetic pathways based on radioactive labeling experiments, has up to now not been bettered. His findings are shown in.

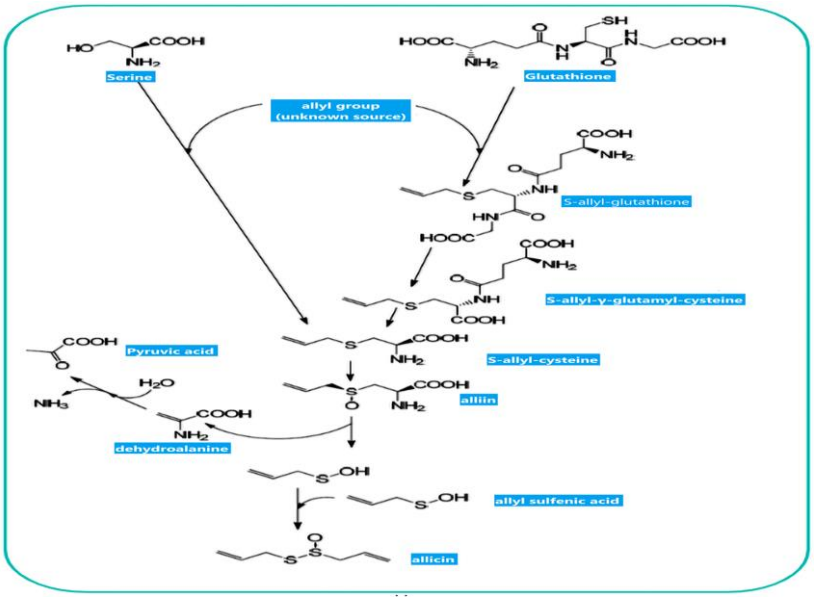

Figure No. 1: (Biosynthesis of Allicin).

Allicin biosynthesis: Two biosynthetic routes result in S-allylcysteine. The observation of 14C-labeled S-allylcysteine following feeding plants with 14C-labeled serine and applying several alkyl mercaptans led Granroth to posit that serine is one potential substrate for S-allylcysteine biosynthesis. Another pathway resulted from GSH to S-allylcysteine. The allyl-group source has yet to be determined. S-allylcysteine, after oxidization, is converted to alliin as an "inactive" precursor of allicin. Enzymatic hydrolysis of alliin produces allyl sulfenic acid, which can be condensed spontaneously to allicin. This figure adapted from Borlinghaus et al. induced cardiac oxidative damage in human cancer patients. Not least interesting to highlight is that allicin, while reactive sulfur species with oxidizing properties, is also capable to oxidize thiols in cells, such as glutathione and cysteine residues in proteins. Protein thiols oxidation can lead to protein structure changes, i.e. through disulfide bond formation. Redoxtriggered structural proteins changes can result in function loss or gain, and therefore these characteristics may explain the wide variety of biological activities attributed to this intriguing molecule. Thus, and considering the above highlighted aspects, this report aims to provide the most updated evidence on this matter, dealing a special focus on allicin impact in human health (including clinical trials), also emphasizing its pharmacokinetics and safety profiles, and even the most prominent biological effects (i.e. antimicrobial, antioxidant, anticancer, antidiabetic, immunomodulatory and cardioprotective) in an acidified paste compared to other processing garlic conditions. Allicin is an unstable compound, which is quickly decomposed to other oil- and water-soluble organosulfur compounds. In addition, allicin is also highly reactive, being even able to form covalent bonds through redox biotransformations. Electron-withdrawing effect of oxygen atom in thiosulfinates creates an electrophilic sulfur centre which readily reacts with thiol groups. Indeed, the main allicin antimicrobial effect derives from its reactivity with thiol groups of proteins, including various enzymes. Generally, disulfide bonds formation fails in cell cytosol, due to a high reducing environment, which converts S-S bonds back to cysteine -SH groups. Pharmacokinetics of garlic phytochemicals are a misunderstood area. Indeed, allicin bioavailability (bioequivalence) is a great question, since allicin formation from alliin and alliinase usually occurs after consumption, under enzyme-inhibiting gastrointestinal conditions. On the other hand, the optimum activity of the purified allinase enzyme is at pH 7.0 and 35 °C and becomes inactivated at pH values below 3.5 or with heating. Thus, in order to protect allinase enzyme, many brands of garlic supplements have adopted an enteric-coated formulation to prevent stomach disintegration. Absorption depends on many factors, such as physicochemical properties (e.g. molecular size, steric configuration, solubility,

hydrophilicity, pKa, etc.), and it can be related to the presence of food matrices and drugs in gastrointestinal absorption with liver and kidney metabolism. In case of allicin high-protein meal, it can briefly raise pH to 4.4 or higher, which can safe alliinase enzymatic activity. Allicin could be detected after 1 h exposure by diffusion through the gas phase. This aspect is of great interest for allicin application as vapor inhalation in the treatment of lung diseases, especially tuberculosis. A novel microparticul ate formulation has been developed for the pulmonary application were alliin and alliinase are separately encapsulated into microspheres consisting of lactose as a stabilizer and as an excipient, releasing their component in the presence of water. Allyl methyl sulfide, allyl methyl disulfide, diallyl sulfide, diallyl disulfide, diallyl trisulfide, dimethyl sulfide, and acetone were detected in the breath of volunteers after consumption of 38 g raw garlic. Maximum concentrations of allyl methyl disulfide, diallyl sulfide, diallyl disulfide, and diallyl trisulfide, dimethyl sulfide were reached within 2–3h. The area under the curve (AUC) of the main breath allicin metabolite (allyl methyl sulfide) was determined for 23 types of garlic products in healthy individuals (6 female and 7 male) after 32 h consumption. Allicin bioavailability or bioequivalence values ranged from 36 to 104% for enteric tablets; 80-111% for non-enteric tablets; 26-109% for garlic powder capsules; 16% for boiled; 30% for roasted; 19% for pickled and 66% for acid-minced garlic foods. S-allyl cysteine sulfoxide, as other garlic constituents, is known to undergo the first-pass effect following rapid gastrointestinal absorption with liver and kidney metabolism. The water-soluble organosulfur compound of garlic, S-allyl cysteine, is rapidly and easily absorbed in the gastrointestinal tract and mainly distributed in plasma, liver, and kidney after oral administration in rats, mice, and dogs. In overall, published data indicated that allicin, while a natural product with beneficial properties, is of great interest. A particular intention should be given to allicin pharmaceutical formulation, its delivery and compatibility with food matrices and other drugs, due to its biosynthesis, instability, reactivity and volatility characteristics.[5]

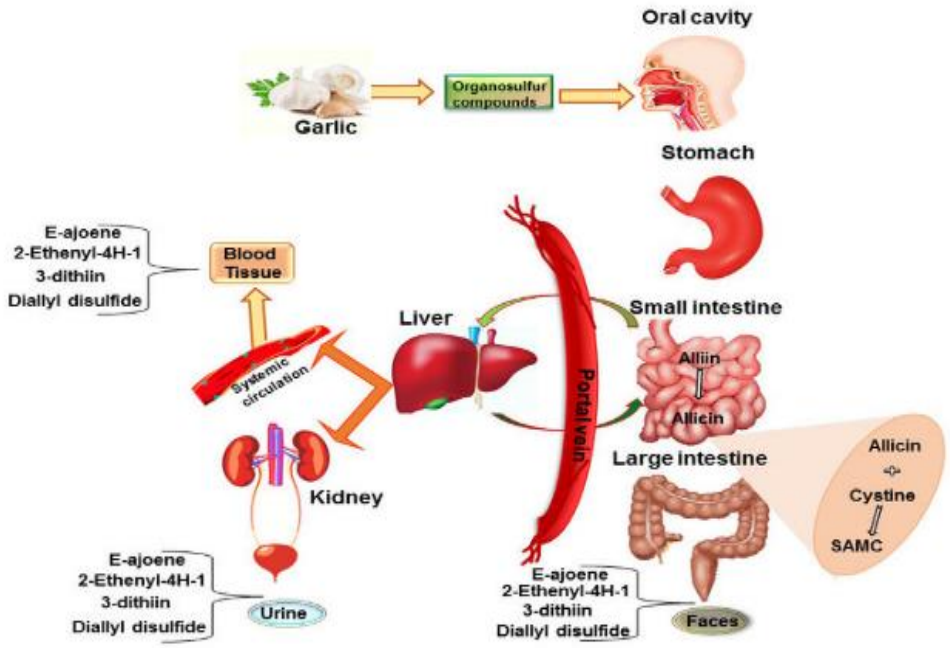

Figure No.: 2 (Different Pharmacological Activity of Allicin).

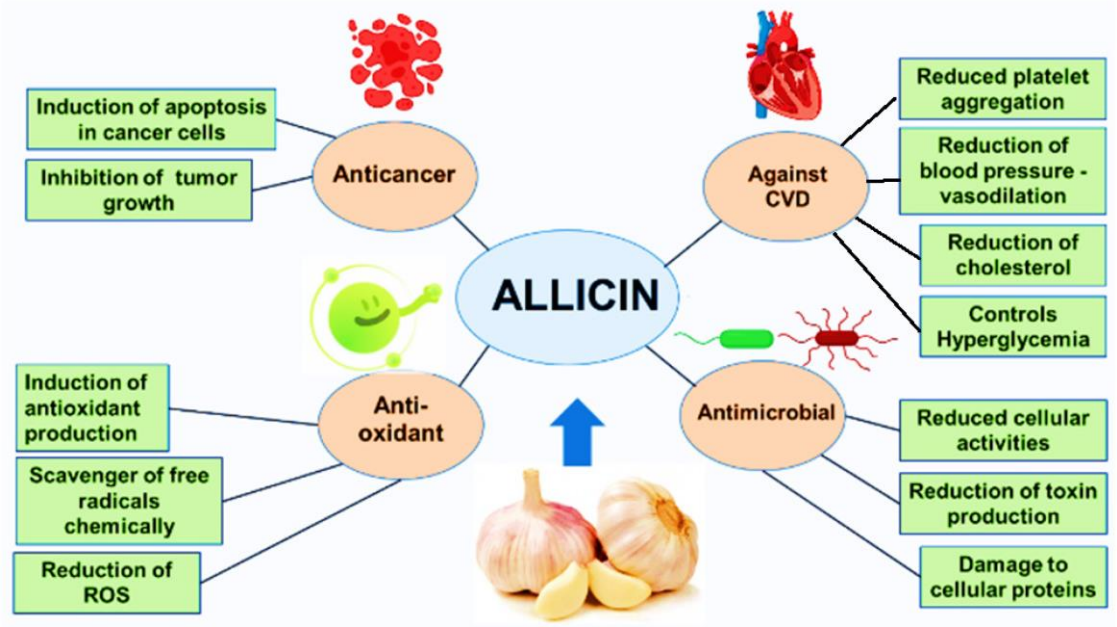

Figure No. 3: Pharmacological Activity Of Allicin.[5]

PHARMACOLOGICAL ACTIVITIES OF ALLICIN

1) Antimicrobial activity

The underlying basis of allicin's antibacterial activities, which is its molecular mechanism, has not been fully explained. Nevertheless, by the thiol-disulfide exchange that is possible in proteins as well as glutathione. The functional mode mechanism of action via which allicin displays its antibacterial advantages include numerous physiological functions, including as

lipid production and RNA synthesis manufacturing. It has been demonstrated that allicin inhibits the formation of acetyl CoA, which involves acetate kinase and Aspartate aminotransferase

Asfaq and Inamdar reported that the frequent garlic intake promotes internal antioxidant activities and reduces oxidative adverse effects either by increasing the endogenous antioxidant synthesis or reducing the production of oxidizers such as oxygen-free radical species (ORS). Gentamycin is an antibiotic that has been used to treat several types of bacterial infections and was reported to promote hepatic damage through raising aspartate transaminase and alanine aminotransferase enzymes in addition to lowering the plasma albumin level. It is demonstrated that garlic protects against gentamycin- as well as acetaminophen-induced hepatotoxicity by improving antioxidant status, and regulating oxidative stress. As ROS seems to be at the core of many ailments, it is justified to assume that the antioxidant effect of garlic might be through modulation of ROS, increasing glutathione and cellular antioxidant enzymes. Moreover, garlic extract was found to increase the activities of some antioxidant enzymes (e.g., superoxide dismutase (SOD)) and decrease glutathione peroxidase (GSH-Px) in hepatic tissues of rats. Notably, several reports indicated that AGE rich in flavonoid, phenol, and different sulfur compounds e.g., SAC shows high radical scavenging activity. Additionally, AGE acted by stimulating the expression of different antioxidant enzymes, namely glutamate-cysteine ligase modifier (GCLM) and heme oxygenase-1 (HO-1) subunit by the nuclear factor erythrobia-2 related factor 2 (Nrf2)-antioxidant response element (ARE) pathway that is responsible for human endothelial cells protection against oxidative stress. Alliin, the major compound isolated from AGE, showing wide-spectrum antioxidant activities by controlling ROS generation and preventing mitogen-activated protein kinase (MAPK). Moreover, it was reported to prevent ROS production by inhibiting NADPH oxidase 1, and thus, inhibiting the osteoclast fusion caused by receptor activator of nuclear factor-kappa B ligand. Allicin, DADS, and DATS are the main antioxidative compounds that showed an antioxidant effect in lower doses at the physiological level. Saponins extracted from garlic were reported to scavenge intracellular ROS and protect mouse-derived C2C12 myoblasts towards growth inhibition and H2O2-induced DNA damage Interestingly, Abdel-Daim et al. reported that DAS exhibited potent antioxidant and cytoprotective activities and these activities may be due to suppressing the enzymatic activity of cytochrome P450-2E1 and thereby reducing the generation of reactive

oxygen and nitrogen species or by inducing the mRNA expression of Nrf2 and heme-oxygenase 1 enzyme.

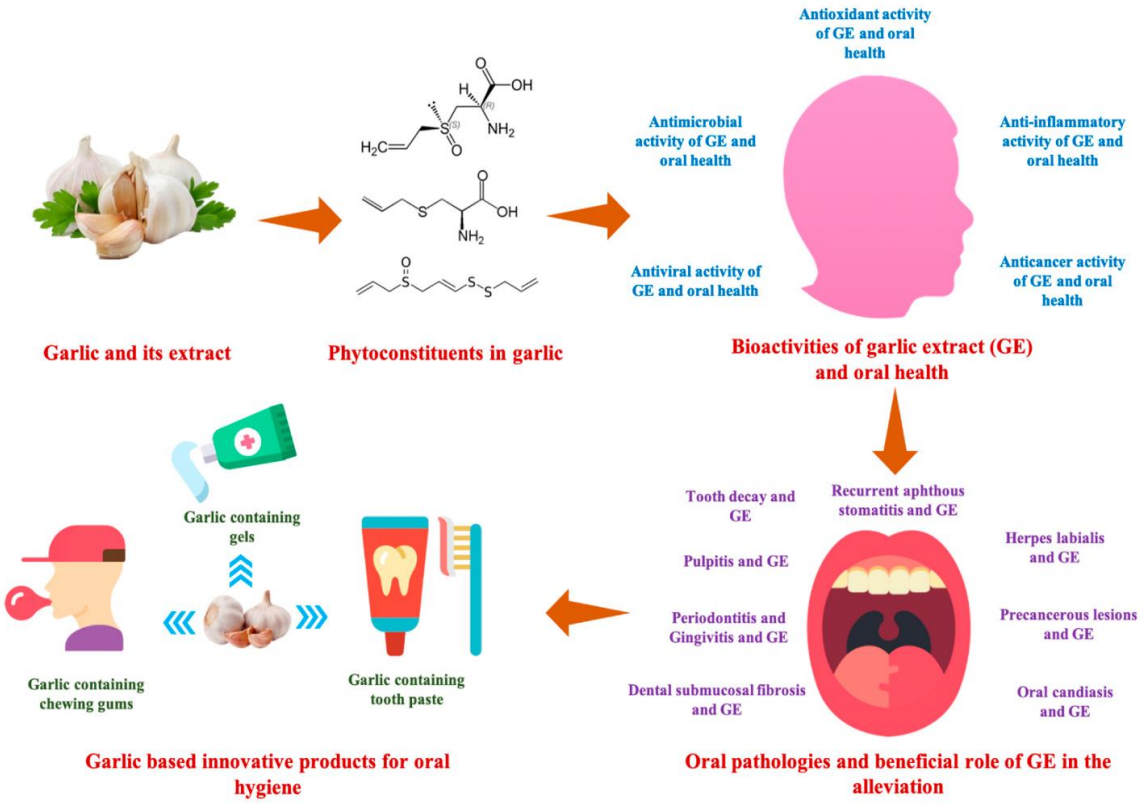

Figure No. 4: Pathologies and Pharmacological Activities of Allicin.

Allicin anticancer effects 6.1. In vitro studies nowadays, allicin anti-proliferative and pro-apoptotic effects are well-established on several cancer cell. Allicin exerts its anticancer effects by diverse mechanisms of action. For instance, allicin induces redox defenses depletion and, consequently, apoptosis is triggered. Miron et al. described the allicin effect at 5 μM on human promyelocytic leukemia-derived cells HL60, and human myelomonocytic cells U937. In both cases, allicin treatment was able to oxidize -SH functions in several biomolecules (i.e. cysteine, glutathione, proteins, and peptides), shifting intracellular redox status. The emerging glutathione depletion led to cell death, and to an overall anti-proliferative activity. Pathways involved in apoptosis that would be mediated by allicin could be both caspase-mediated or caspase-independent. For instance, Zhang et al, described cytochrome c release from mitochondria and increased caspase3, -8, and -9 activation. At the same time, apoptosis-related genes Bax and Fas upregulation occurred. In the case of caspase-independent mechanism, protein kinase A (PKA) and apoptosis-inducing factor involvement were suggested. A similar effect on the cellular redox state was also shown by

Cha et al. in U87MG human glioma cells. In this case, ERK1/2 MAP kinases. and Bcl-2/Bax mitochondrial pathway were found to be responsible for apoptosis triggering effect. Bcl-2/Bax was also involved during allicin and interleukin-24 combination treatment of human hepatocarcinoma SMMC-7721 cells. Allicin was also capable to induce apoptosis through NF-E2-related factor-2 (Nrf2), despite this is mostly described as an anti-apoptotic agent. In this study, Bat-Chen et al. investigated the in vitro anti-proliferative potential on several colon cancer cell lines, showing an increase in hypodiploid DNA content, Bcl-2/ Bax involvement and cytochrome c release to the cytosol.[1,2,3,4]

2) Antifungal Activity

Garlic extracts showed a broad spectrum fungicidal effect against a wide range of fungi including Candida, Torulopsis, Trichophyton, Cryptococcus, Aspergillus, Trichosporon, and Rhodotorula species. Recently, garlic extract was found to inhibit the Meyerozyma guilliermondii and Rhodotorula mucilaginosa germination and growth. Another study reported the antifungal activity of various A. sativum extracts namely aqueous, ethanolic, methanolic, and petroleum ether against human pathogenic fungi such are Trichophyton verrucosum, T. mentagrophytes, T. rubrum, Botrytis cinerea, Candida species, Epidermophyton floccosum, Aspergillus niger, A. flavus, Rhizopus stolonifera, Microsporum gypseum, M. audouinii, Alternaria alternate, Neofabraea alba, and Penicillium expansum. The garlic extract acted by affecting the fungal cell wall and causing irreversible ultrastructural changes in the fungal cells, which lead to loss of structural integrity and affected the germination ability. These changes in the cytoplasmic content lead to nucleus and cell organelles damage that ultimately leads to cell death. Moreover, allicin and garlic oil showed potent antifungal effects against Candida albicans, Ascosphaera apisin, and A. niger and they acted by penetrating the cellular membrane as well as organelles membranes like the mitochondria and leading to organelles destruction and cell death. DADS and DATS separated from garlic essential oil showed antifungal activity against a number of fungi. In addition to that, saponins extracted from A. sativum exhibited antifungal activity against Botrytis cinerea and Trichoderma harzianum.[9,10,11]

3) Anti-Protozoal Activity

Various studies reported the anti-protozoal activity of garlic extracts and its phytochemicals against several protozoan parasites. For instance, an in vitro study revealed that the aqueous, ethanolic, and dichloromethane A. sativum extracts exhibited anthelmintic activity against

Haemonchus contortus and the ethanolic extract was the most effective one, while aqueous garlic extract showed potent activity against Trichuris muris and Angiostrongylus cantonensis. Garlic was also examined in vivo and in vitro against Taenia taeniaeformis, Hymenolepis microstoma, H. diminuta, Echinostoma caproni, and Fasciola hepatica. Abdel-Hafeez et al. [6showed that garlic extract inhibited the growth of Blastocystis spp. in vivo and this activity attributed to that garlic extracts contains several phytochemicals e.g., thiosulfinates are one of the bioactive compounds that possess antibacterial activity that is related to thiol enzymes inhibition which presents in several microorganisms. Allicin also acts by preventing the parasite's RNA as well as DNA and protein synthesis. Moreover, allicin and DATS, phytochemicals isolated from garlic extract, showed antiparasitic activity against Entamoeba histolytica, Plasmodium falciparum, Babesia, Theleria, Trypanosoma brucei, and Giardia lamblia. Ajoene also exhibited antiparasitic activity by inhibiting the human glutathione reductase and T. cruzi trypanothione reductase. Hazaa et al. reported the activity of garlic oil toward broad-spectrum microorganisms such are Cochlospermum planchonii, Plasmodium, Giardia, Leishmania, and Trypanosoma.[12,13,14,15,16]

4) Antiviral Activity

The antiviral activity of garlic extracts has been evaluated against influenza B, human rhinovirus type 2, human cytomegalovirus (HCMV), Parainfluenza virus type 3, herpes simplex type 1 and 2, vaccinia virus, and vesicular stomatitis virus. Interestingly, in vivo experiment exhibited the antiviral activity of garlic extract and they reported that garlic showed protective activity against influenza viruses by improving the production of neutralizing antibodies when given to mice and this activity was based on the presence of several phytochemicals namely, ajoene, allicin, allyl methyl thiosulfinate, and methyl allyl thiosulfinate. Allicin acts by preventing several thiol enzymes, while ajoene's antiviral activity was due to the prevention of adhesive interaction and fusion of leukocytes.[6,7]

5) Antihypertensive Activity

Varshney and Budoff reported the essential function of garlic in the control of cardiovascular risk factors as it is known to significantly decrease systolic as well as diastolic blood pressure. Garlic formulations have been broadly used to inhibit and relieve cardiovascular disorders such as hypertension, arrhythmia, thrombosis, hyperlipidemia, and atherosclerosis. Several experimental and human studies reported the antihypertensive effect of garlic extracts and its derived bioactive molecules. For example, Sobenin et al. showed the plasma

fibrinolytic activity of garlic extracts and they found that it increased fibrinolytic activity in both healthy and acute myocardial infarction participants. Moreover, in vivo experiment exhibited the antihypertensive effect of aqueous garlic extract in '2 kidney 1-clip' model of hypertension in rat by reducing thromboxane B2 and prostaglandin E2 level and thereby reduced hypertension in tested rats. Garlic administration at a dose of 100 mg/kg for 5 days resulted in complete prevention of acute hypoxic pulmonary vasoconstriction caused by endothelin-1 in isolated rat pulmonary arteries and they found that garlic acts by reducing endothelin 1 and angiotensin II production. The mechanism of antihypertensive effect of garlic extracts is that garlic contains many active sulfur molecules that have been shown to stimulate endothelium-constricting and -relaxing factors leading to lower blood pressure. Garlic has also been shown to stimulate the production of both nitric oxide (NO) and hydrogen sulphide (H2S) that finally leads to vasodilation. Therefore, garlic is used as a medicinal plant for controlling blood pressure worldwide. Furthermore, garlic exhibited a significant role in inhibiting thrombosis as well as platelet adhesion or aggregation in humans. The AGE was reported to prevent both ADP-activated platelets binding to immobilized fibrinogen and platelet aggregation by inhibiting GPIIb/IIIa receptor and increasing cAMP. Furthermore, garlic has been reported to reduce the risk of plasma viscosity, unstable angina, and peripheral arterial occlusive disorders and increase the elasticity of the blood vessels and perfusion of capillaries. The gamma-glutamylcysteine isolated from garlic was reported to decrease the blood pressure by inhibiting the angiotensin-converting enzyme (ACE). Dubey et al. revealed that allicin shows remarkable activity in reversing systolic blood pressure caused by dexamethasone and enhances body weight and food intake in hypertension caused by dexamethasone in rats.[17,18,19,20]

CONCLUSION

The synthetic drug-based treatment now in use has a number of unfavorable side effects. A solution that is safe, efficient, and reasonably priced is required to modulate metabolic pathways and halt the progression of the disease. Because ginger and its active components suppress NF-kB, COX-2, and LOX (inflammatory mediators), they also induce apoptosis and tumor suppressor genes, which lower the risk of a number of diseases. The active components in ginger inspire optimism for new treatment approaches for a range of illnesses. Subsequent studies ought to concentrate on clinical trials to examine their efficacy and precise function in modifying metabolic pathways. This review gives researchers the essential knowledge about

the potent pharmacological qualities of ginger and its active constituents to aid in their comprehension of these compounds' mechanisms of action, which may include.

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