I. Edible part of garlic: Garlic bulb

5.1. Chemistry Garlic bulb

The Chemistry of garlic has gone long way ever since the discovery of odor causing compounds. The presence of unusual high content of sulfur compounds in garlic compared to other food plants and the long recognized pharmacological activities of sulphur containing compounds could be a probable reason for the greater interest in exploring its chemistry (Augusti, 2006; Block, 1985; Lanzotti, 2006; Lawson, 1996).

5.1.1. Organosulfur constituents of garlic (Block, 1992)

The odor of garlic is weak when the bulb is intact, when damaged the smell grows stronger. The organosulfur constituents of the garlic is not the mirror of the intact garlic, it varies from whole to crushed garlic as well as in the garlic preparations based on the subjective treatment conditions.

5.1.1.1. Chemistry of Intact garlic:

The whole garlic is well known to be odor free until the cloves are cut or crushed indicating that allinase and the cysteine sulfoxides are stored in separate compartments. Sixteen nonprotein organosulfur compounds have been found in whole cloves. The primary sulphur containing constituents in whole garlic are S-alk(en)yl-L-cysteine sulfoxides (ACSOs) and $\gamma$-glutamyl-S- alk(en)yl cysteines. $\gamma$-glutamylcysteine is more abundant in mature bulbs than in immature young bulbs, and rapidly decreases at sprouting, which in turn is accompanied by increase in concentration of alliin, and related amino acids (methiin and isoalliin). Garlic contains three ACSOs which are capable of producing thiosulfinates viz,

$(+)$-S-allyl-L-cysteine sulfoxide (Allin)

$(+)$-S-methyl -L-cysteine sulfoxide (methiin)

$(+)$-S-trans - propenyl -L-cysteine sulfoxide (isoalliin).

Garlic also contains a cyclic cysteine sulfoxide, cycloalliin which cannot be cleaved by allinase and hence produces no thiosulfinates.
5.1.1.2. Chemistry of crushed garlic:

The crushed garlic possessed the odor of freshly cut garlic. Twenty three nonprotein organosulfur compounds have been found in crushed cloves. When garlic is crushed, the thiosulfinates originate from S-alk(en)yl-L-cysteine-S-oxide through an enzymatic reaction catalyzed by allinase giving initially sulfenic acids. These are highly reactive intermediates that immediately produce thiosulfinates by condensation reaction. The precursor compounds present in whole garlic and the constituents of crushed garlic are listed in table 5.1 and figure 5.1.

The major thiosulfinate in garlic is:

Allicin ( Allyl 2-propene thiosulfinate) - CH$_2$ = CHCH$_2$-SS (=O)-CH$_2$CH=CH$_2$) from the precursor compound with allyl residue allin (Figure 5.1).

Others thiosulfinates are:

- Allyl methyl thio sulfinate \{CH$_2$ = CHCH$_2$-SS(=O)CH$_3$\}
- Methyl allyl thio sulfinate \{CIH$_3$ -SS(=O)-CIH$_2$CH=CH$_2$ \}
- Allyl trans -1- propenyl thiosulfinate \{(E) CH$_2$ = CHCH$_2$-SS (=O)-CH=CH$_3$\}
- Trans -1- propenyl allyl thiosulfinate \{(E)CH$_3$ CH=CH-SS(=O)CH$_2$CH=CH$_2$\}

Thiosulfinates are very unstable compounds and on rearrangement leading to a wide variety of derived sulfur compounds, which take part in further transformation and give rise to biologically active sulphur compounds. Allicin is the progenitor for a number of other compounds (Freeman & Kodera, 1995). At higher temperatures (about 100$^\circ$C) poly-sulfur compounds are formed containing up to five sulfur atoms, eg: diallyltrisulfide (DATS), diallyltetrasulfide (DATTS), diallylpentasulfide and diallylhexasulfide.
**Table 5.1:** Total sulphur compounds in whole and crushed garlic cloves

<table>
<thead>
<tr>
<th>Compound</th>
<th>Whole garlic mg/g fresh weight</th>
<th>Crushed garlic mg/g fresh weight</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>S (+)-alk(en)yl-L-cysteine sulfoxides</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S-allyl cysteine sulfoxide (Allin)</td>
<td>5-14</td>
<td>nd</td>
</tr>
<tr>
<td>S-methyl cysteine sulfoxide (methiin)</td>
<td>0.5-2</td>
<td>nd</td>
</tr>
<tr>
<td>S-trans-1-propenyl cysteine sulfoxide (isoallin)</td>
<td>0.2-1.2</td>
<td>nd</td>
</tr>
<tr>
<td>S-propyl cysteine sulfoxide</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>Cycloallin</td>
<td>0.5-1.5</td>
<td>0.5-1.5</td>
</tr>
<tr>
<td><strong>γ-glutamyl-S- alk(en)yl cysteines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>γ-glutamyl - S- trans -1- propenyl cysteine</td>
<td>3-9</td>
<td>3-9</td>
</tr>
<tr>
<td>γ-glutamyl - S- cis -1- propenyl cysteine</td>
<td>0.06-0.15</td>
<td>0.06-0.15</td>
</tr>
<tr>
<td>γ-glutamyl-S- allyl cysteine</td>
<td>2-6</td>
<td>2-6</td>
</tr>
<tr>
<td>γ-glutamyl-S- methyl cysteine</td>
<td>0.1-0.4</td>
<td>0.1-0.4</td>
</tr>
<tr>
<td>γ-glutamyl-S- propyl cysteine</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td><strong>Thiosulfimates</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allyl 2-propene thiosulfinate (alllicin)</td>
<td>nd</td>
<td>2-6</td>
</tr>
<tr>
<td>Allyl methyl thiosulfinate</td>
<td>nd</td>
<td>0.3-1.5</td>
</tr>
<tr>
<td>Allyl trans-1-propenyl thiosulfinate</td>
<td>nd</td>
<td>0.05-1.0</td>
</tr>
<tr>
<td>Methyl trans-1-propenyl allyl thiosulfinate</td>
<td>nd</td>
<td>0.02-0.2</td>
</tr>
<tr>
<td>Methyl methane thiosulfinate</td>
<td>nd</td>
<td>0.05-0.1</td>
</tr>
</tbody>
</table>

nd- Not detected

Source: Lawson, 1996.
Figure 5.1: Formation of organo-sulphur compounds during metabolic pathways of whole crushed and processed garlic

5.1.1.3. Chemistry of Processed garlic: (Amagase et al., 2001; Iciek et al., 2009)

The chemical constituents in garlic preparations differ considerably from one another depending on the processing conditions. Fresh garlic is not tolerated in large amounts by many people, the reasonable amount of 3-5 g of fresh garlic and many pharmaceutical preparations of garlic are well tolerated. An appropriate extraction process can eliminate the undesirable compounds while retaining other active components which can provide maximal health benefits. The various preparations of garlic are listed below.
• **Raw garlic homogenate**

Raw garlic homogenate is the major preparation of garlic that has been subjected to intensive scientific study, because it is the regular manner of garlic consumption. Raw garlic homogenate is the same as that of an aqueous extract of garlic. Allicin is the major thiosulphinate compound found in garlic homogenate.

• **Garlic powder**

Dehydrated, pulverized garlic cloves, their composition and the allinase activity can be identical to those of fresh intact garlic. However, the dehydration temperature should not exceed 60°C above which allinase is inactivated.

• **Aged garlic extract**

Storing sliced raw garlic in 15–20% ethanol for 20 months produces aged garlic extract (AGE). During this aging process, the odorous, harsh and irritating compounds in garlic are converted naturally into stable and safe sulfur compounds. This whole process is supposed to cause a considerable loss of allicin and to increase concentration of compounds, such as S-allylcysteine (SAC), S-allylmercaptocysteine, allixin and selenium which are stable and highly bioavailable. It also contains saponins, flavonoids and small amounts of oil soluble sulphur compounds.

• **Garlic oil**

  a. **Steam-distilled garlic oil**: Medicinally used garlic oil is mostly prepared by steam distillation. Garlic oil contains diallyl, allyl methyl, dimethyl mono to hexa sulphides and vinyl-dithiins.

  b. **Oil-macerated garlic oil**: The oil macerated garlic oil is prepared by grinding garlic cloves and mixing it with vegetable oils (such as soy bean oil, wheat germ oil, peanut oil and others) before the oil soluble components are separated. It contains vinyl-dithiins, sulfides and ajoenes.

  c. **Ether extracted garlic oil**: Garlic oil from ether extracted garlic homogenate contains vinyl-dithiins, allyl sulphides and ajoenes.

Table 5.2 and figure 5.2 lists various preparations of garlic and their constituents.
Table 5.2: Garlic preparation and constituents (Verma et al., 2008)

<table>
<thead>
<tr>
<th>Garlic preparation</th>
<th>Chemical constituents</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oil macerate of garlic</strong></td>
<td>Residual amount of Allin and sulfides, 2-vinyl-4H-1,3-dithiin, 3-vinyl-4H-1,2-dithiin, ajoene (E- ajoene, Z- ajoene)</td>
</tr>
<tr>
<td><strong>Steam distilled garlic oil</strong></td>
<td><strong>Acyclic molecules</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Monosulfide:</strong> Diallyl sulfide (DAS)</td>
</tr>
<tr>
<td></td>
<td><strong>Disulfides:</strong></td>
</tr>
<tr>
<td></td>
<td>Allyl methyl disulfide (AMDS), Diallyl disulfide (DADS)</td>
</tr>
<tr>
<td></td>
<td><strong>Trisulfides:</strong></td>
</tr>
<tr>
<td></td>
<td>Allyl methyl trisulfide (AMTS), Diallyl trisulfide (DATS)</td>
</tr>
<tr>
<td></td>
<td><strong>Tetrasulfides:</strong></td>
</tr>
<tr>
<td></td>
<td>Diallyl tetrasulfide (DATTS), allyl methyl tetra sulphide, dimethyl trisulphide, penta sulphide, hexa sulphide</td>
</tr>
<tr>
<td></td>
<td><strong>Cyclic molecules</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Dithiins:</strong> 2-vinyl-[4H]-1,3-dithiin (2-VDT), 3-vinyl-[4H]-1,2-dithiin (3-VDT)</td>
</tr>
<tr>
<td><strong>Ether extracted garlic oil</strong></td>
<td>Vinyl dithiins (5.7 mg/g), Allyl sulfides (1.4 mg/g)</td>
</tr>
<tr>
<td></td>
<td>Ajoenes (0.4 mg/g)</td>
</tr>
<tr>
<td><strong>Aged garlic extract (AGE)</strong></td>
<td><strong>Water-soluble compounds</strong></td>
</tr>
<tr>
<td></td>
<td>S-allyl cysteine (SAC), S-allyl mercaptocysteine (SAMC)</td>
</tr>
<tr>
<td></td>
<td>saponins, flavonoids, N-Fructosyl arginine, selenium</td>
</tr>
<tr>
<td></td>
<td>N-Fructosyl glutamate, Allixin (phenolic compounds)</td>
</tr>
<tr>
<td></td>
<td>Small amount of <strong>oil-soluble sulfur compounds</strong> (allyl sulfides)</td>
</tr>
<tr>
<td></td>
<td>Diallyl sulfide (DAS), Diallyl disulfide (DADS)</td>
</tr>
<tr>
<td></td>
<td>Trialllyl sulfide, Diallyl polysulfides and others</td>
</tr>
<tr>
<td><strong>Garlic powder</strong></td>
<td>Similar to raw garlic allin, allinase, ( \gamma ) glutamyl-S-allyl L cysteine, scordine (thiol glycoside), small amount of oil soluble sulfur compounds</td>
</tr>
<tr>
<td></td>
<td>Others: Glutamyl peptides, steroid, triterpene saponins, spiroside, sativoside, lectins, flavonoids. Polysaccharides-frutans, adenosine, selenium</td>
</tr>
<tr>
<td><strong>Garlic protein</strong></td>
<td>Essential aminoacids</td>
</tr>
<tr>
<td></td>
<td>Rich in: cysteine, arginine, methionine</td>
</tr>
<tr>
<td></td>
<td>Low in : lysine, histidine, leucine, threonine</td>
</tr>
<tr>
<td><strong>Raw garlic homogenate</strong></td>
<td>Allin, allyl methyl thiosulphonates, 1-propenyl allyl thiosulfinate, ( \gamma ) glutamyl-S-alkyl-L-cysteine and adenosine</td>
</tr>
</tbody>
</table>
Figure 5.2: Major organo-sulphur compounds present in different garlic preparations.

5.1.2. Nonsulfur constituents of garlic:

- **Saponins:** (Lanzotti, 2006; Williamson, 2002)
  
  Furostanol saponins: Protoeruboside-B, Sativoside-B1, Proto desgalactotigenin
  
  Spirostanol saponins: Eroboside-B, Sativoside-B1
  
  Steroidal saponins: Proto isoeroboside-B, isoeroboside-B

Aglycones: β- chlorogenin, apigenin, laxogenin, gitogenin, diosgenin, sitosterol

Protoeruboside-B was the first furostanol saponin isolated from the bulbs. The spirostanol analogue, eruboside B, has been obtained by enzymatic hydrolysis of the furostanol derivative proto-eruboside B (Figure 5.3).
Figure 5.3: Saponins of garlic bulbs

• **Flavonoids and phenolics:** Quercetin, Myricetin, Apigenin, Rutin, Kaempferol, N-feruloyl tyrosine and N-feruloyl tyramine; Isoflavone: Genistein.

• **Amino acids:** Alanine, arginine, aspartic acid, asparagine, histidine, leucine, methionine, phenyl alanine, proline, serine, threonine, tryptophan and valine.

• **Monoterpenoids:** Citral, α- and β-phellandrene, geraniol and linalool.

• **Minerals:** Calcium, phosphorous, iron, iodine, cobalt, copper, sodium, potassium, selenium, germanium, tellurium and zinc.

• **Vitamins:** Biotin, Niacin, β-carotene, riboflavin, ascorbic acid, thiamin, folic acid and others.

• **Carbohydrates:** Sugars, Pectins and Fructans

• **Enzymes:** Allinase, peroxidases, myrosinase, superoxide dismutase, catalase, ATPase, polyphenol oxidase, phenyl alanine ammonia lyase, alcohol dehydrogenase, esterase and phosphoglucose isomerase.

• **Additional constituents:** Lectins (mannose binding lectins - ASA I and ASA II), prostaglandins, nucleic acid - adenosine, fatty acids, glycolipids, phospholipids, peptides, fibers, plant hormones and phytic acids.

### 5.2. Medicinal properties of garlic bulb

Garlic is an excellent natural spice and functional food with repertoire of therapeutic potential in many pathological conditions and has many supportive scientific literatures to its credit. The multi-target response of garlic has much to offer than just to impart flavor to the food stuffs. It is also known as the “Wonder Drug among all Herbs”. Modern scientific studies unearth the wonders of this ancient super food and proven as a valuable herb and universal medicine. Garlic has attracted particular attention in modern medicine because of its widespread health use around the world. In some Western countries, the sale of garlic preparations ranks with those of leading prescription drugs (Banerjee & Maulik, 2002). According to figures of spice board, India has exported 14,750 tonnes valued garlic at Rs 55.65 crore for the April-September 2010 corresponding to 4,500 tonnes during the same period in last fiscal (Business standard, 2010). Many culinary and pharmaceutical preparations of garlic are available in the commercial market today. Garlic and its preparations have been widely recognized as agents for prevention and treatment of cardiovascular and other metabolic diseases, atherosclerosis, hyperlipidemia, thrombosis, hypertension and diabetes.
5.2.1. Effects on heart and circulatory system

A. Atherosclerosis and lipid metabolism

The medicinal value of garlic is best known for its lipid lowering and antiatherogenic effects. In many studies, garlic consumption decreases significantly the content of total serum cholesterol, LDL and very low density lipoproteins (VLDL) and also increases significantly the level of high density lipoproteins (HDL). Garlic causes direct antiatherogenic (preventive) and antiatherosclerotic (causing regression) effects at the artery wall (Banerjee & Maulik, 2002; Vazquez-Prieto & Miatello, 2010).

Garlic depressed the hepatic activities of lipogenic and cholesterogenic enzymes such as malic enzyme, fatty acid synthase, glucose-6-phosphate dehydrogenase and 3 hydroxy-3-methyl-glutaryl-CoA (HMG CoA) reductase. It also exerts hypocholesterolemic effect by inhibiting hepatic cholesterol biosynthesis, enhance cholesterol turn over to bile acid, its excretion through GIT and inhibiting cholesterol absorption from intestinal lumen. It also makes the LDL cholesterol resistant to oxidation and it is a powerful mechanism accounted for the benefits of garlic in atherosclerosis (Omar & Nabi, 2010).

B. Antihypertensive effect

Increased consumption of garlic is associated with lower incidence of hypertension in population. Garlic powder preparations are considered as adjuvant in the treatment of hypertensive patients. Garlic and its constituents exhibits prostaglandin like effects (PGE2), which decreases peripheral vascular resistance. It also inhibits angiotensin converting enzyme, regulates the production and function of both endothelium derived relaxing and constricting factors, exerts direct relaxant effect on smooth muscles, indirect vasodilator effect by inducing the nitric oxide and hydrogen sulphide synthesis and increase adenosine levels by inhibiting adenosine deaminase enzyme (Agarwal, 1996; Baluchnejadmojarord et al., 2003a; Hosseini et al., 2007; Patumraj et al., 2000).

C. Effects on blood coagulation and fibrinolysis

Garlic extracts inhibit platelet aggregation induced by a number of physiologically important aggregating agents (ADP, collagen and adrenalin) by different mechanism viz, modification of platelet membranes, inhibition of calcium mobilization and inhibition of several steps of the arachidonic acid pathway in platelets. Garlic causes
non-competitive and irreversible inhibition of cyclooxygenase. It also reduces the formation of thromboxane B₂ which is a powerful platelet aggregator. Ajoene, the constituent of garlic may interact directly with the putative fibrinogen receptor (GPIIb/IIa) thereby promotes aggregation (Bordia, 1998; Rahman, 2007).

5.2.2. Antimicrobial activity

Due to the occurrence of unpleasant side effects and increasing resistance to the synthetic pharmaceuticals, there has been an increasing interest to explore natural alternatives as antimicrobial agents. In folk medicine, garlic has been used for centuries in several societies against parasitic, fungal, bacterial and viral infections. Recent chemical characterization of garlic compounds has revealed that the sulphur compounds are the main active antimicrobial agents. However, some proteins, saponins and phenolic compounds can also contribute to this activity. Due to its greater antimicrobial activity, garlic can act as a natural preservative to control the microbial growth.

A. Antibacterial activity

Garlic inhibits the growth of gram-positive, gram-negative and acid-fast bacteria, as well as inhibit toxin production. Garlic is effective against *Pseudomonas, Proteus, Escherichia coli, Staphylococcus aureus, Klebsiella, Salmonella, Micrococcus, Bacillus subtilis, Mycobacterium, enterobacteria* and *Clostridium*, some of which are resistant to penicillin, streptomycin, doxycycline and cephalixin. Garlic also exerts bactericidal effects against dental pathogens. The major active antibacterial components in vivo are the allicin-derived organo-sulphur compounds, such as DAS, DADS and ajoene, as well as other thiosulfinates isolated from oil-macerated garlic. DAS and DADS from garlic can protect against the *Helicobacter pylori* infection and, therefore, to reduce the risk of gastric neoplasia (Tripathi, 2009)

B. Antiviral activity

The antiviral activities of various commercial garlic products have been studied against herpes simplex virus Types 1 and 2, influenza A and B viruses, human cytomegalovirus, vesicular stomatitis virus, rhinovirus, human immunodeficiency virus (HIV), viral pneumonia and rotavirus. Antiviral activities of these products dependent on their preparation process and the products with the highest levels of
allicin and other thiosulfimates, mainly DADS, DATS and ajoene, have the best antiviral activities (Reuter et al., 1996).

C. Antifungal activity

Garlic and its derivatives showed great effectiveness against a broad spectrum fungi and yeasts, including Candida, Trichophyton, Torulopsis, Rhodotorula, Cryptococcus, Aspergillus and Trichosporon, as well as a synergistic activity with amphotericin B in vitro, one of the main antifungal drugs. The active compounds of garlic destroy fungal cells, decreasing the oxygen uptake, reducing cellular growth, inhibiting the synthesis of lipids, proteins and nucleic acids, changing the lipid profile of the cell membrane and inhibiting the synthesis of the fungal cell wall. The main active antifungal agents from garlic extracts are the breakdown products of allicin, including DATS, DADS, DAS and ajoene, which have a greater antifungal effect than allicin (Singh & Singh, 2008).

D. Antiparasitic activity

Garlic extracts are effective against Opalina ranarum, Opalina dimidicita, Balantidium entozoon, Entamoeba histolytica, Tripanosoma brucei, Leishmania, Leptomonas and Crithidia. Garlic is effective against Giardia lamblia and Giardia intestinalis. In China, DATS synthesized easily and is prescribed for the treatment of giardiasis and infections by E.histolytica and Trichomonas vaginalis. Allicin, ajoene and other organo-sulphur compounds from garlic are also effective antiprotozoals (Coppi et al., 2006; Ross, 2003).

5.2.3. Antioxidant activity

Among garlic-derived products, AGE is the preparation with higher antioxidant activity, even more than fresh garlic and other commercial garlic supplements. This is due to its extraction procedure, which increases stable and bioavailable of water-soluble organo-sulphur compounds content with potent antioxidant activity. Phytochemicals in aged garlic extract (AGE) may act in synergistic or additive way and exert their antioxidant action by scavenging ROS, by enhancing the cellular antioxidant enzymes superoxide dismutase, catalase and glutathione peroxidase, and by increasing glutathione in the cells which are important defence mechanism in living cells. It also decreases the risk of cardiovascular and cerebrovascular disease by inhibiting the lipid peroxidation and oxidation of LDL (Marta et al., 2007).
AGE also exerts anti-inflammatory effect by inhibiting oxidative stress-induced activation of nuclear factor kappa B (NF-xB), which is implicated in the expression of pro-inflammatory enzymes, such as inducible nitric oxide synthetase (NOS) and cyclooxygenase-II (COX-II). It exerts protection against ionizing radiation and UV light-induced damage. In addition, it protects the erythrocytes membrane against oxidative stress inhibiting the formation of abnormally dense erythrocytes, which are believed to play an important role in the clinical manifestations of sickle cell anemia and protects against cardio toxicity and liver toxicity induced by several oxidant environmental, chemical and medicinal substances (Banerjee et al, 2003; Wilson & Demmig-Adams, 2007).

Finally, AGE also has anti-aging effects, it promotes neuronal cells survival, increasing cognitive functions, memory and longevity and slowing down age-related impairment of learning behavior and memory. Due to this neurotrophic activity attributed to AGE, the garlic could be a potential natural alternative for the treatment of neurodegenerative diseases, such as alzheimer's disease or dementia (Rahman, 2003).

5.2.4. Anticancer and antimutagenic effects

Garlic and its constituents are proven for its chemopreventive or anti carcinogenic activity in particular their capacity to inhibit tumor growth and the cellular proliferation. It also possess anti mutagenic activity. The sulphur compounds of garlic, as diallyl sulfide have an effect on DNA repair mechanisms, avoiding mutations and preventing the initiation of carcinogenesis. The US National Cancer Institute concluded that garlic may be the most potent food having protection against cancer development. But the minimum intake of garlic is required to reduce cancer risk remains to be determined (Iciek et al., 2009).

It exhibits anticancer activity by alteration of carcinogen metabolism, inhibition of procarcinogens activation, inhibition of oxidative damage due to their antioxidant action, inhibition of cellular proliferation by induction of apoptosis, inhibition of cell division, prevention of chromosomal damage (anti elastogenic effect), anti inflammatory effect by inhibition of lipoxygenase and cyclooxygenase activities and by potentiation of the immune system. Selenium compounds in garlic possess chemo preventive action (Das, 2002; Herman-antosiewicz et al., 2007).
5.2.5. Immunomodulatory effect

Garlic may be a promising candidate as a biological immune response modifier, being able to maintain the homeostasis of immune function, stimulating necessary functions and suppressing unnecessary functions. Modification of immune function by garlic may contribute to the treatment and prevention of certain diseases caused by immune dysfunction and it may also be used synergistically in conjunction with other antifungal agents due to its capacity to enhance the host cellular immunity.

Garlic is found to be effective to prevent the immune suppression caused by different agents, such as chemotherapy, UV irradiation and psychological and physical stress. The maintenance of immune stimulation offers protection against cancer and impairment of immune defenses, as occurs with acquired immunodeficiency syndrome (AIDS) and improves aging-related cognitive deterioration. Garlic exerts an anti-allergic and antitumor effect through direct and/or indirect modification of immune function, stimulating the lymphocytes and antibodies proliferation and production. Several low-molecular-weight sulphur compounds extracted from garlic, such as DAS and SAC, carbohydrates in the garlic extract and protein fraction from garlic have immune-stimulating properties (Reuter et al., 1996; Marta et al., 2007; Williamson, 2002).

5.2.6. Antidiabetic activity:

According to the survey conducted by Ryan et al in 2001, Garlic is one among the commonly used alternative medication in diabetes as well as by healthy individuals (Ryan et al., 2001). In recent years, many studies on garlic focused towards its antidiabetic activity as well as in treating diabetic related complications. The traditional anecdotal reports of garlic use in diabetes have been proved in preclinical and in clinical settings as well its beneficial role in preventing or delaying diabetic complications.

5.2.6.1. Preclinical antidiabetic studies on garlic

Scientific reports on garlic preparations and constituents on glycemic control in normal animals, STZ and alloxan induced diabetic animal models, fructose and high fat diet induced insulin resistance, stress and thyroxine induced hyperglycemia mainly validates the preventive and curative potential of garlic against diabetes and its complications. Few antidiabetic studies on garlic preparations are mentioned in table
5.3 and 5.4. Many authors have correlated the blood glucose lowering effect of garlic by various possible mechanisms. Glucose lowering activity is mainly attributed to sulphur compounds of garlic. It acts as insulin secretagogue by stimulating insulin release from functional pancreatic cells, as insulin sensitizer at the target tissues and as insulin sparing agent by preventing inactivation of insulin. The hypoglycemic principles of garlic may directly stimulate of functional pancreatic beta cells to secrete insulin or its release from bound insulin (Sheela et al., 1992, Jain & Vyas, 1975). Indirectly, stimulate the pancreatic secretion of insulin by gastrointestinal hormones like pancreozymin or regulation of insulin action by an enhanced transport of blood glucose and utilization to peripheral tissues especially to skeletal muscles by enhancing glycogen synthase activity (Mathew & Augusti, 1973, Liu et al., 2005). Also, the constituent allicin from crushed garlic combines readily with compounds containing –SH groups and it spares insulin from sulphhydryl group inactivation thereby increasing its half life and it can be effectively combined with compounds like cysteine thereby enhance endogenous insulin effect to bring about reduction in blood glucose (Mathew & Augusti, 1973, Adoga & Ibrahim, 1990). Based on the recent meta analysis conducted by kook et al, the constituents of garlic showed better anti diabetic effect than the extracts (Kook et al., 2009).

The constituents in garlic and its preparations increases liver glycogen levels and normalizes enzymes of carbohydrate metabolism viz, liver hexokinase and glucose-6-phosphatase (Sheela et al., 1992, Saravanana et al., 2009b). Allin isolated from garlic ameliorated diabetic condition almost to the same extent as did glibenclamide and insulin. Allicin from garlic the effect was comparable to tolbutamide in diabetic rabbits (Augusti & Sheela, 1996, Mathew & Augusti, 1973). The antidiabetic effect of garlic could be due to the formation of a colloidal type suspension in the stomach and intestines when the mucilaginous fiber of garlic is hydrated, therefore affecting gastro-intestinal transit and slowing glucose absorption (Mostofa et al., 2007). Garlic improved insulin sensitivity on diabetic animals as assessed by insulin resistance index (Seo et al., 2009; Prieto et al., 2010). Garlic also inhibits carbohydrate digesting enzyme α-amylase there by prevents glucose absorption from GI tract (Nickavar et al., 2009).

The antidiabetic spices may be used in conjunction with existing antidiabetic drugs to have better therapeutic benefits and to minimize the dosage (Srinivasan, 2005a).
Combining of active ingredients of garlic with some synthetic drugs has some beneficial impact (Herman et al., 2005). Interestingly, metallo-alixinate complexes ie, vanadyl and zinc complexes with allixin, a unique nonsulfur phytoalexin in dry garlic shown to ameliorate diabetes and metabolic syndrome as it acts on many intracellular signaling targets (Sakurai & Adachi, 2005; Sakurai et al., 2010). Bis(allixinato)oxovanadium(IV) complex (VO(alx)₂), Zn(II)-Allixin (Zn(alx)₂) and Zn(II)-thioallixin-N-methyl (Zn(tamn)₂) was found to be more effective antidiabetic agent with insulin-mimetic activity (Adachi et al., 2006c; Adachi et al., 2006b).

5.2.6.2. Clinical antidiabetic studies on garlic

Clinical trials on garlic have been undertaken to prove the hypoglycemic effect in normal subjects and its efficacy diabetic individuals in table 5.5. Garlic is very well known for the antiatherosclerotic effect and many trials were conducted regarding the use of garlic in cardio vascular diseases but very few studies have been carried out in diabetic individuals. The studies conducted fail to show consistent results which necessitate the use of standardized garlic preparations. Garlic not only lowered the blood glucose levels and also showed substantial reduction in triglycerides, serum cholesterol and LDL cholesterol. The cardio protective HDL cholesterol levels were increased, this clearly proves that garlic is not only as glucose lowering agents but also has a role in preventing lipid abnormalities related to cardiovascular dysfunction associated with diabetes. The study carried out by Sovenin et al, the combination of garlic powder tablets with oral hypoglycemics significantly reduced blood glucose levels as it can be beneficial in preventing atherogenic effect of tolbutamide as well as dose reduction in diabetic therapy (Sovenin et al., 2008). Trials can be conducted on the use of garlic at prediabetic condition will certainly convey beneficial outcome to the society. The results from clinical studies warrant the carefully controlled study to delineate the beneficial role of garlic in diabetes and it can be very well tolerated by patients.
Table 5.3: Effect of Garlic preparations in diabetes

<table>
<thead>
<tr>
<th>Garlic preparation</th>
<th>Dose and Study duration</th>
<th>Diabetic model</th>
<th>Main results</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fresh Garlic juice</td>
<td>10 ml/kg; p.o, 30 days</td>
<td>STZ 60 mg/kg; Rats</td>
<td>↓ Glucose and improved oxidative stress.</td>
<td>Mahdi et al (2003)</td>
</tr>
<tr>
<td></td>
<td>1 ml/ 100 g; p.o, 4 weeks</td>
<td>Alloxan 120 mg/kg; Rats</td>
<td>↓ Glucose, urea, creatinine and bilirubin. ↓ AST, ALT, LDH, ALP, AcP, ↑TBARS. Amelioration of renal and hepatic damage.</td>
<td>El-Demerdash et al (2005)</td>
</tr>
<tr>
<td>Garlic oil</td>
<td>500 mg/kg; p.o, 7 weeks</td>
<td>STZ 60 mg/kg; Rats</td>
<td>Attenuates the progression of structural nephropathy</td>
<td>Al-qattan et al (2008)</td>
</tr>
<tr>
<td></td>
<td>10 mg/kg; p.o, 15 days</td>
<td>STZ 60 mg/kg; Rats</td>
<td>↓ Glucose and lipids, Protection against free radical production in diabetes.</td>
<td>Anwar et al (2003)</td>
</tr>
<tr>
<td></td>
<td>100 mg/kg; p.o, 3 weeks</td>
<td>STZ 65 mg/kg; Rats</td>
<td>↑ Insulin, ↑ glycogen, ↓ NEFA, improved insulin resistance index.</td>
<td>Liu et al (2005)</td>
</tr>
<tr>
<td></td>
<td>50 mg/kg; p.o , 28 days</td>
<td>STZ 60 mg/kg; Rats</td>
<td>↓ platelet count, ↑ WBC’s, ↓ clotting factors V, VII, VIII: C, IX and X, reversal of hypercoagulation</td>
<td>Ohaeri et al (2006)</td>
</tr>
<tr>
<td>Aqueous garlic extract</td>
<td>100 mg/kg; 8 weeks</td>
<td>STZ 60 mg/kg; Rats</td>
<td>↑↓ glucose, ↓ ACE activity</td>
<td>Hosseini et al (2007)</td>
</tr>
<tr>
<td></td>
<td>500 mg/kg; i.p, 4 to 8 weeks</td>
<td>Fructose induced insulin resistance; Rats</td>
<td>Significant effect on 8 week treatment ↓ FBS and FIRI</td>
<td>Jalal et al (2007)</td>
</tr>
<tr>
<td></td>
<td>150 mg/kg/day; p.o, 6 weeks</td>
<td>Fructose induced insulin resistance; Rats</td>
<td>↓ Glucose, HOMA-IR index, Systolic BP, ↓ aorta NAD(P)H-oxidase activity and plasma TBARS. Prevent vascular remodelling. No significant change in TG and insulin</td>
<td>Prieto et al (2010)</td>
</tr>
<tr>
<td>Treatment</td>
<td>Dose/Time</td>
<td>Effect</td>
<td>Reference</td>
<td></td>
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</tr>
<tr>
<td>Aged garlic extract</td>
<td>5 ml/kg</td>
<td>Stress induced hyperglycemia; Mice prevent stress induced risk in DM</td>
<td>Kasuga et al (1999)</td>
<td></td>
</tr>
<tr>
<td>(pretreatment)</td>
<td>10 ml/kg; p.o</td>
<td>induce hyperglycemia; Mice prevent stress induced risk in DM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aged garlic extract</td>
<td>_</td>
<td>invitro models Inhibit the formation of advanced glycation end products, potent amadorin activity</td>
<td>Ahmad et al (2007)</td>
<td></td>
</tr>
<tr>
<td>S - Allyl cysteine</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Ethanolic extract (80%)</td>
<td>0.1,0.25,0.5 g/kg; p.o., 14 days</td>
<td>STZ 70 mg/kg; Rats ↓ Glucose, ↓ TG, ↑ Insulin. ↓ TC, Urea, uric acid, creatinine, AST and ALT.</td>
<td>Eidi et al (2006)</td>
<td></td>
</tr>
<tr>
<td>Chloroform extract</td>
<td>100 mg/kg; 16 weeks</td>
<td>STZ 70 mg/kg; Rats Anti atherosclerotic effect at coronary arteries with improved cardiac function.</td>
<td>Patumraj et al (2000)</td>
<td></td>
</tr>
<tr>
<td>Garlic powder</td>
<td>0.5 and 2% in diet; 4 weeks</td>
<td>High fat diet(22%) fat)+ STZ 40 mg/kg kg; Rats No effect on FBG,HbA1c, Liver glycogen, and serum lipids (TC,TG, HDL-c, LDL-c,↑ Insulin and improved glucose tolerance</td>
<td>Islam et al (2008)</td>
<td></td>
</tr>
<tr>
<td>Methanol garlic extract</td>
<td>250 mg/kg 500 mg/kg; p.o, 30 days</td>
<td>STZ 32 mg/kg; Rats Restoration of antioxidant enzymes, normalization of polyol enzymes. 250 mg/kg was more active against oxidative insult.</td>
<td>Kanth et al (2008)</td>
<td></td>
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<tr>
<td>(chopped dried garlic)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>250 mg/kg 500 mg/kg; p.o, 8 weeks</td>
<td>STZ 34 mg/kg; Rats Scavening of H2O2, Improvement against diabetic cataract by delaying the progression of lens opacity and attenuation of glycemia induced oxidative stress in lens.</td>
<td>Raju et al (2008)</td>
<td></td>
</tr>
</tbody>
</table>
### Table 5.4: Anti diabetic studies on Garlic constituents

<table>
<thead>
<tr>
<th>Garlic preparation</th>
<th>Dose and Study duration</th>
<th>Diabetic model</th>
<th>Main results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allicin</td>
<td>0.25g/kg; p.o, 4 hrs</td>
<td>Alloxan; Rabbits</td>
<td>↓ glucose, ↑ Insulin, ↑ glycogen</td>
<td>Mathew et al (1973)</td>
</tr>
<tr>
<td>S-allyl cysteine sulfoxide</td>
<td>200 mg/kg; 1 month</td>
<td>Alloxan 180 mg/kg; Rats</td>
<td>↓ glucose, ↓ lipid, ↓ ALP, ↓ AcP, ↓ LDH &amp; glucose 6 phosphatase, ↑ Hexokinase</td>
<td>Sheela et al (1992)</td>
</tr>
<tr>
<td>Ajoene</td>
<td>0.02 or 0.05 % in diet; p.o, 8 weeks</td>
<td>Diabetic KK-A⁺; Mice</td>
<td>↓ Glucose, ↓ TG and ↓ water intake</td>
<td>Atsuhioko et al (2005)</td>
</tr>
<tr>
<td>Di allyl trisulfide</td>
<td>40 mg/kg; p.o, 3 weeks</td>
<td>STZ 65 mg/kg; Rats</td>
<td>↑ Insulin, ↑ glycogen, improved insulin resistance index.</td>
<td>Liu et al (2005)</td>
</tr>
<tr>
<td>S-allyl cysteine (SAC)</td>
<td>100 and 150 mg/kg; p.o, 45 days</td>
<td>STZ 55 mg/kg; Rats</td>
<td>↓ glucose, HbA1c, urea, uric acid, and creatinine, ↓ serum ALP, AST, ALT, ↑ serum insulin and protein, improved glucose tolerance</td>
<td>Saravanana et al (2009a)</td>
</tr>
<tr>
<td>S-allyl cysteine (SAC) - pretreatment</td>
<td>30mg/kg; i.p, 15 days</td>
<td>ICV (Intra cerebro ventricular) injection of STZ 2.57 mg/kg; Mice</td>
<td>SAC prevented cognitive and neurobehavioral impairments, protection of antioxidant defense system, protection of apoptotic parameters like DNA fragmentation, expression of Bcl2 and p53.</td>
<td>Javed et al (2011)</td>
</tr>
</tbody>
</table>
### Table 5.5: Clinical studies of garlic preparation

<table>
<thead>
<tr>
<th>Garlic preparation</th>
<th>Dose and Study duration</th>
<th>Design</th>
<th>Study sample and condition</th>
<th>Main results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garlic powder</td>
<td>Garlic powder tablets 300 mg thrice daily</td>
<td>12 weeks, randomized, double-blind study</td>
<td>42 healthy subjects</td>
<td>↓ TC &amp; LDL-c. No change in HDL-c, TG, serum glucose, BP</td>
<td>Jain et al (1993)</td>
</tr>
<tr>
<td>Ethyl acetate extract</td>
<td>daily dose of 2 x 2 capsules (each capsule containing ethyl acetate extract from 1 g peeled and crushed raw garlic)</td>
<td>3 months, randomized controlled study</td>
<td>60 subjects with CAD</td>
<td>↓ LDL-c, TG &amp; TC, ↑ HDL-c and fibrinolytic activity. No effect on fibrinogen and blood glucose</td>
<td>Bordia et al (1998)</td>
</tr>
<tr>
<td>Garlic powder tablet</td>
<td>Garlic tablet 300 mg/day (standardized to provide 1.3% alliin equivalent to 0.6% allicin)</td>
<td>12 week randomized, single-blind, placebo controlled study</td>
<td>70 T2DM Subjects associated with dyslipidemia</td>
<td>↓ TC and LDL-c. No change in TG, ↑ HDL-c</td>
<td>Ashraf et al (2005)</td>
</tr>
<tr>
<td>Garlic extract</td>
<td>300 mg garlic extract 3 times a day</td>
<td>4 weeks</td>
<td>45 T2DM subjects associated with hyperlipidemia</td>
<td>↓ TC and LDL-c. No significant change in TG, HDL-c and blood glucose</td>
<td>Afkhami-Ardekani et al (2006)</td>
</tr>
<tr>
<td>Garlic extract</td>
<td>Enteric coated garlic extract (standardized to 1.12% allicin or 5.6 mg/tablet)/ day</td>
<td>12 weeks, randomized, double-blind, placebo-controlled study</td>
<td>136 hypercholesterolemic subjects</td>
<td>No change in TC, TG, LDL-c and HDL-c, no changes in plasma glucose, liver and renal functions.</td>
<td>Satitvipawee et al (2003)</td>
</tr>
<tr>
<td>Garlic powder tablets</td>
<td>300 mg of dehydrated garlic powder/ twice a day</td>
<td>4 week, double-blinded placebo-controlled study</td>
<td>60 Subjects with T2DM</td>
<td>↓ Fasting blood glucose, serum fructosamine and TG</td>
<td>Sobenin et al (2008)</td>
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<tr>
<td>Diallyl sulphide</td>
<td>Diallyl sulphide in vitro platelet aggregation</td>
<td>18 subjects with T2DM with &gt; 2 years duration</td>
<td>Reduction in adenosine induced platelet aggregation</td>
<td></td>
<td>Kumar et al (2011)</td>
</tr>
</tbody>
</table>

† - Increase; ↓ - Decrease; ↑↓ - No change; p.o.- per oral; i.p.-intraperitoneal; AST- Aspartate amino transferase; ALT- Alanine amino transferase; LDH- Lactate dehydrogenase; ALP- Alkaline phosphatase; AcP- Acid phosphatase; TBARS- Thiobarbituric acid reactive substance; NEFA- Nonesterified fatty acid; ACE- Angiotensin converting enzyme; FBS- Fasting blood sugar; FRI- Fasting insulin resistance index; HOMA- homeostatic model assessment; DM-diabetes mellitus; TG- Triglycerides; TC- Total cholesterol; HbA1c- glycated haemoglobin; HDLc- High density lipoprotein cholesterol; LDLc- low density lipoprotein cholesterol; TAG- Triacyl glycerol; BP- blood pressure; TAOC- Total antioxidant capacity.
5.2.6.3. Use of Garlic in diabetic complications

Recently diet modulators, natural products and spice therapies have become the major approaches being proposed in the treatment of diabetes which helps not only in glycemic control but also in minimizing risk factors for diabetic complications (Chandra et al., 2007). From previous findings in context to diabetes, garlic and its various preparations act as antihyperglycemic and alleviate co-morbidities associated with diabetes. There are many interesting therapeutic benefits of garlic which could contribute effectively in chronic diabetes and also in preventing or delaying the development of complications as presented in figure 5.4. From the experimental study, the effective dosage of 25-50 g fenugreek seeds, 5-6 cloves of garlic or 50 g (1 bulb) onion and 1 g turmeric powder incorporated in the daily diet of diabetics could serve as an effective supportive therapy in the prevention and management of long term complications of diabetes (Srinivasan, 2005a).

A. Diabetic macro vascular complications

The medicinal value of garlic is best known for its lipid lowering and antiatherogenic effects and could act as an cardio protective agent. In many studies, garlic consumption decreases significantly the total cholesterol, LDL, VLDL and increases significantly the levels of high density lipoproteins. The constituents of garlic and its preparations depress hepatic activities of lipogenic and cholesterolgenic enzymes. The powerful mechanism of garlic is to make the LDL cholesterol resistant to oxidation, their by promotes strong benefit in atherosclerosis (Huang et al., 2004; Ou et al., 2003). It inhibits the differentiation of monocytes into CD36 expressing macrophages by inhibiting the activation of PPARγ pathway resulting in reduced uptake of oxidized LDL in vitro which is an important process in the development of atherosclerotic plaques (Morihara et al., 2010). Allicin decreased homocysteine levels in rats which is an important risk factor for the development and progression of atherosclerosis (Herman et al., 2005).

The advantage with *Allium* products that they do not stimulate the synthesis of a risk factor like cholesterol which is invariably not controlled by many synthetic drugs though it has better control on diabetes (Sheela et al., 1995). The sulphur compounds of *Allium* species are strong deterrents to lipid synthesis and good acceptors of hydrogen. It is known that sulfoxide aminoacids and disulfides can consume NADPH
and interact with –SH group enzymes which are necessary for cholesterol and lipid synthesis and also retard the conversion of glucose and galactose to their corresponding polyols which is the key factor of polyol pathway or increasing their excretion through gastrointestinal tract (Sheela et al., 1992; Srivastava et al., 1989). Hypolipedemic activity of garlic may be partly due to the increased activity of lipase enzyme in the liver and serum, resulting in the reduction of the levels of circulating total esterified fatty acids in the blood (Adoga & Ibrahim, 1990). The triacyl glycerol lowering effect of garlic is due to inhibition of fatty acid synthesis and lowering of cholesterol is due to inhibition enzyme hydroxyl methyl glutaryl CoA reductase which participates in cholesterol synthesis (Eidi et al., 2006).

Garlic indirectly affects atherosclerosis by reduction of hyperlipedemia, hypertension, and prevents thrombus formation (El-Demerdash et al., 2005). Garlic extract proven to reduce thickening of arterial wall, arteriolar wall and the basement membrane of capillaries in coronary vessels of diabetic rats and also improved cardiac function. Multiple components in garlic have the potential to normalize many risk factors, help to prevent or delay the endothelial cells from becoming dysfunctional and could offset the risk of cardio vascular complications (Patumraj et al., 2000).

Diabetes has been associated with reduced transketolase activity which activates all the major biochemical pathways leads to the debilitating complications. The activation of transketolase enzyme divert glycolytic metabolites away from the pathways of glucose over use and into the pentose phosphate pathway which proven to prevent development of the complications. Interestingly, garlic extract treatment in rats shown to elevate the levels of transketolase in RBC and certainly it could be an added benefit (Ali et al., 1991).

B. Diabetic micro vascular complications

The metabolic intervention through natural dietary ingredients is gaining importance in the management of cataract. Glycemic mediated oxidative damage in lens were countered by treatment with garlic. It act by various mechanisms like suppression of polyol enzymes to restore membrane integrity, restoration of electrolytes and antioxidant reserves, prevention of protein aggregation, down regulation of mRNA iNOS transcript, TBARS, carbonyl content and also improved transparency of lens, thereby delayed the progression of diabetic cataract (Raju et al., 2008). Garlic treatment inhibited the excessive accumulation of polyols and hydration of lenses,
also normalizes polyol enzymes in hepatic and intestinal tissues (Srivastava et al., 1989; Kanth et al., 2008).

Garlic treatment reversed proteinuria resulted from glomerular injury, a progressive selective marker of diabetic nephropathy and attenuates the intensity of the progression of diabetic structural nephropathy. It also improved renal function by partially ameliorating creatinine clearance, protein/creatinine ratio and blood urea nitrogen (Liu et al., 2006, Thomson et al., 2007, Al-qattan et al., 2008). The blockade of renin angiotensin system (RAS) strategy is a landmark in the management of diabetic nephropathy by slowing the progression of kidney damage (Ahmad, 2008). Garlic treatment benefit renal function in diabetes through its regulatory effect on blood pressure by decreasing serum ACE (angiotensin converting enzyme) activity which plays a major role in renin angiotensin system (Hosseini et al., 2007).

The role of garlic in diabetic neuropathy has limited animal data and area still to be explored. Treatment with ethanol extract of garlic has shown to reduce nociceptive response in various nociceptive models like tail flick, hot plate and formalin induced paw edema in diabetic condition and revealed its centrally mediated analgesic effect (Kumar & Reddy, 1999).

5.2.6.4. Add on benefits of garlic in diabetes

A. Antioxidant effects of Garlic

The antioxidant effect of garlic would have great value for overcoming oxidative load in diabetes. Several constituents in garlic and garlic preparations can scavenge free radicals, protect membranes from damage, maintains cell integrity and it has the potency to enhance the activity of the antioxidant enzymes such as superoxide dismutase, catalase and glutathione peroxidase (Chandra et al., 2007; Drobiova et al., 2009; Lee et al., 2009; Hfaiedh et al., 2010; Saravanan & Pommurugan, 2011a). S-allyl cysteine constituent of aged garlic extract has been reported to inhibit NF-κB activation in dose dependent manner and may protect against intracellular oxidative stress which is generated by following interaction between advanced glycation end products and its receptors (Ide & Lau, 2001). Garlic shown to decrease NADPH oxidase activity in rat diabetic aorta which could have possible role in mitigation of complications (Prieto et al., 2010). The protective mechanism(s) of garlic against oxidative insult may be linked to its bioactive components which perhaps chelate the
metal ions (Cu, Zn, Mn) thereby scavenge the superoxide ions and subsequently
inhibiting the oxidation of protein moieties and thus contributing to the healthy
acellular redox status (Kanth et al., 2008)

**B. Anti thrombotic, fibrinolytic anti platelet activity of Garlic**

One of the stable active constituent of garlic called ajoene exhibit antithrombotic
activity and potent as aspirin. Oral feeding of garlic extracts in diabetic animals
increased fibrinolytic activities with decrease in platelet aggregation (Patumraj et al.,
2000). Garlic has the potential to intervene in many steps in the coagulation pathway
especially garlic oil showed reversal of hypercoagulation in diabetic rats by
intervening with clotting factors, which would benefit diabetics in improving
cardiovascular health (Kiesewetter et al., 1991; Ali & Thompson, 1995; Ohaeri &
Adoga, 2006).

**C. Antihypertensive effect of Garlic**

Garlic extract strongly inhibit serum ACE (angiotensin converting enzyme) activity
which could be beneficial in protecting against cardiovascular complications in
diabetes (Hosseini et al., 2007). Garlic is suggested to lower blood pressure through
its prostaglandin like mechanism. The effect could also be due to direct relaxing effect
on vascular smooth muscle or by causing hyperpolarization by decreasing
intracellular calcium levels (Patumraj et al., 2000; Baluchnejadmojarord et al.,
2003a).

**D. Antiinflammatory effects of garlic**

In formalin induced paw edema, garlic extract decreased the thickness and weight of
paw of diabetic mice. The thiosulfimates of garlic could be responsible for its anti
inflammatory action through inhibition of inflammatory cell influx (Kumar & Reddy,
1999). *In vitro* studies proven that garlic and its constituents proven to cause down
regulation of proinflammatory genes responsible for inflammation thereby prevents or
delay chronic proinflammatory diseases like diabetes. The constituents of garlic
maintains NF-κB in its inactive state, thus preventing the synthesis of cyclooxygenase
and lipoxygenase. Thus, limiting the production prostaglandin and leukotriens which
are considered as messengers of inflammation (Wilson & Demmig-Adams, 2007).
E. Antiglycative effect of garlic

The therapeutic intervention with aged garlic extract and S-allyl cysteine inhibited the formation of glucose and methylglyoxal derived AGEs at multiple stages and showed potent amadorin activity (Ahmad & Ahmad, 2006; Ahmad et al., 2007). The sulphur constituents of garlic also exhibited antiglycative activity in plasma isolated from NIDDM patients (Huang et al., 2004; Liu et al., 2007).

F. Antimicrobial activity of garlic

Diabetic patients are at a greater risk of contracting infections and it is advantageous to use garlic, since it possesses antihyperglycemic and anti-infective activity. Few authors, reported the antimicrobial effects of garlic in diabetic mice and rats infected methicillin-resistant *Staphylococcus aureus* and *Candida albicans* respectively (Tsao et al., 2007; Bokaeian et al., 2010). Many literatures are available on the antimicrobial activity of fresh garlic, garlic preparations and constituents against range of bacteria, viruses and parasites.

Figure 5.4: A scheme of the antidiabetic effect of garlic, showing possible roles of garlic in diabetes and its complications

Source: Liu et al., 2007
G. Miscellaneous

The determination of total plasma homocysteine has become a very useful tool because moderately elevated values of circulating homocysteine constitute an important risk factor for the development and progress of occlusive vascular affections and of ischaemic heart disease in diabetic patients (Hankey & Eikelboom, 1999). Intake garlic have proven as an effective way to reduce plasma homocysteine levels (Yeh & Yeh, 2006). Garlic also proven to be beneficial in depression, Alzheimer’s diseases, nervous disorders, aging and fatigueness and are yet to be confirmed in diabetic animal models (Dhingra & Kumar, 2008). Garlic is rich in vitamins and minerals, which would provide adequate nutrition to the diabetic individual.

5.2.7. Garlic, the miraculous and magical herb

Garlic is blessed with myriad therapeutic benefits which would very well correlates with diabetes, will have effects beyond its antihyperglycemic action. Though it cannot be preferred for florid acute conditions, it can be recommended for chronic use because of its broad spectrum of therapeutic applications as anti inflammatory, anti oxidant, antiatherogenic, anti hypertensive, anti hyperlipedemic, plays major role in coagulation-fibrinolytic system as anti thrombotic and inhibit platelet aggregation, anti bacterial, antifungal, anti viral, anti parasitic, diaphoretic, expectorant, antispasmodic, anti cancer, immunomodulatory, antihepatotoxic, aphrodisiac, ageing, chemoprevention, energy booster, in detoxification. None of the available synthetic medication can hold these benefits or the drugs in pipeline for diabetes and its complications. Garlic intake could be considered as an add on therapy to existing medications in order to improve the quality of life in diabetic condition (Baluchnejadmojarord et al., 2003a).

The need of the hour is requirement of multivalent drug with mutitarget intervention addressing all the components of diabetic syndrome in order to prevent and delay the development of complications. Garlic will entirely fit into this regimen where diabetes is concerned. Many plant extracts could be combined to get in a synergistic effect, but in case of garlic it appears like different garlic preparations could be combined to achieve desired therapeutic effect, since not only the garlic preparations but its main constituents viz, allin of garlic powder (Sheela et al., 1992, Sheela et al., 1995,
Augusti et al., 1996), transient compound allicin of crushed garlic (Mathew et al., 1973), S-allyl cysteine of aged garlic extract (Ho et al., 2008), diallyl trisulfide of garlic oil (Liu et al., 2005) and ajoene of garlic oil macerate (Atsuhiko et al., 2005) itself proven to be beneficial in diabetic condition.

Undoubtedly, additive or synergistic effects between components occur and the activity cannot be reproduced by the isolation of a single active component in case of garlic. Garlic influences several key molecular targets in disease prevention (Spigelski & Jones, 2001). By considering its diverse action, Powolny and Singh termed the multitarget effects of garlic as ‘promiscuous’ and compared them with multiple pharmacological aspects of aspirin (Powolny et al., 2008) and Butt et al in their recent review termed garlic as ‘Nature’s protection against physiological threats’ (Butt et al., 2009).

**5.2.8. Adverse effects:** (Borrelli et al., 2007; Koch, 1996)

Herbal medicinal products are highly popular. Surveys show, for instance, that 9.3% of the adult population uses natural health products and 57% of users also reported taking a conventional medicine in the same period. Most users perceive that herbs are efficacious, and in some instances, more efficacious than conventional medicines. This perception may be a major contributing factor influencing the sustained and increasing popularity of herbs. Although herbs are often promoted as natural and therefore harmless, they are not free from adverse effects which necessitate the evaluation of their safety.

Garlic is one of the best-researched/best-selling herbal remedies and is also commonly used as a food and a spice. Garlic is the top-selling herbal supplement in the USA. Garlic appears to be generally safe. However, clinical trials, case reports and case series have highlighted the possibility that this herb may cause adverse effects, including herb drug interactions.

Garlic odour: garlic breath and body odour.

Allergic reactions: allergic contact dermatitis, generalized urticaria, angiedema, pemphigus and anaphylaxis.

Occupational allergy: contact dermatitis, respiratory adverse events (asthma, dyspnoea, cough, rhinitis, rhino conjunctivitis).
Photo allergy: photo allergic contact dermatitis.

Cutaneous manifestations: garlic burns.

Coagulation alterations: Spinal epidural hematoma, increased clotting time, postoperative bleeding, retrobulbar hemorrhage.

Gastrointestinal adverse effects: Nausea, bloating, flatulence severe: small intestinal obstruction, epigastric and esophageal pain, hematemesis, hematochezia.

Others: Hypotensive effects, myocardial infarction, Meniere's disease.

5.2.9. Drug Interactions: (Jani & Mehta, 2007; Pittler & Ernst, 2007)

The widespread use of herbal drugs alarmed its possible interaction with the conventional drugs. This is especially important with respect to drugs with narrow therapeutic indexes. Herbal medicines follow modern pharmacological principles. Hence, herb drug interactions are based on the same mechanisms as drug-drug interactions. Herb-drug interactions can thus have both a pharmacokinetic (changes to plasma drug concentration) and pharmacodynamic (drugs interact at receptors on target organs) basis. Patients who self-medicate with herbs for preventive and therapeutic purposes may assume that these products are safe because they are 'natural,' but some products cause adverse effects or have the potential to interact with prescription medications. Clinical evidence suggests that taking garlic can result in pharmacokinetic or pharmacodynamic interactions that might represent a potential risk to patients taking conventional medicines, particularly in subjects under anticoagulant or antiretroviral therapy.

Garlic has complex cardiovascular effects including antiplatelet activity and hence could theoretically interact with anticoagulant/antiplatelet drugs. Garlic may interfere with blood clotting. Therefore, individuals who have hemophilia or other bleeding disorders should avoid eating or using large amounts of garlic. High doses of supplemental garlic should be stopped about two weeks before scheduled surgery.

Anti coagulants (Warfarin and fluindione): hemorrhagic risk

Antiplatelet drugs include clopidogrel and Ticlid

Protease inhibitors (Saquinavir): Reduce its plasma concentration
Protease inhibitors (Ritonavir): Inhibit the metabolism of garlic constituents and potentiate the toxicity of garlic on the gastrointestinal tract.

Anti diabetic agent (Chlorpropamide): Hypoglycemia

Garlic is broken down by certain enzymes in the liver, excessively large amounts of it possibly may interfere with the use of prescription drugs that are processed by the same enzymes. Some of these drugs are:

- Allergy drugs such as fexofenadine.
- Antifungal drugs such as itraconazole and ketoconazole.
- Cancer drugs such as etoposide, paclitaxel, vinblastine, or vincristine.
- Drugs for high cholesterol such as lovastatin, pravastatin, and simvastatin.
- Oral contraceptives.

5.2.10. Dosage of garlic bulb:

Garlic is the cheapest way to prevent many disease conditions and liberal consumption of garlic is safe and offer many benefits. Definitely, garlic is the one among the spice which adds years to life and life to years. Average daily consumption of fresh garlic has been reported to be 20 g (about 4-5 cloves) and 10 g fresh garlic per day represents a safe level when eaten with meal (Koch, 1996). According to Williamson, Fresh garlic: 2-5 g; Dried powder: 0.4-1.2 g; Oil: 2-5 mg and Solid extract: 300-1000mg (Williamson, 2002). Green lasuna: Four palas of lasuna is small, six palas is medium and eight or ten palas is the best one (Tiwari, 2002).

II. Non edible parts of Garlic

The garlic bulbs are known for its benefits since ages, even other parts of garlic plants such as peel (skin or husk), root and leaf are not explored scientifically for its therapeutic value.

5.3. Garlic peel

The papery, protective layers of "skin" over garlic are generally discarded in culinary practice. In Korea, immature whole heads are used in culinary purpose with the intact tender skins. Garlic skins or peels are an industrial waste of agro-food industry. They have not been studied for their health benefits because they are not an edible part of garlic. There are only few reports on the chemical composition and pharmacological
activity of garlic skins. Some dietary supplements made of onion skins have been sold in the functional food and nutraceutical market in Japan, but there are no supplements available based on garlic skins (Ichikawa et al., 2003). Garlic bulbs yield approximately 760 g of cloves and 240 g of outer and inner husks per kilogram.

5.3.1. Chemical constituents

On enzymatic hydrolysis of garlic skin contains p-coumaric acid, ferulic acid, and sinapic acid. Six phenyl propanoids have been identified viz, N-trans-Coumaroyloctopamine, N-trans-feruloyloctopamine, guaiacylglycerol-β-ferulic acid ether, guaiacylglycerol-β-caffeic acid ether, trans-coumaric acid and trans-ferulic acid (Figure 5.5). Flavonols such as quercetin, myricetin and kaempferol were also present in garlic peel (Nacem et al., 2009).

![Chemical structures](image)

*Figure 5.5: Phenyl propanoids identified from garlic peel*

Garlic husk reported to have 7 times greater total polyphenols than garlic bulb, and the nonedible garlic husk had 1.5 times greater radical scavenging activity than the edible part. Polyphenol compounds found in garlic husk could be an antioxidant source (Kim et al., 2009). The dry scales of garlic contain large amount of
carbohydrates called pectin. Pectins absorb large amount of water and are used commercially in Egypt to make jellies, cosmetics, and pharmaceuticals. The yield of pectin from garlic scales is 27%, but it is only 0.3% from the cloves. The reddish purple colour of inner garlic scales has shown to contain three anthocyanins, cyanidin-3-glucoside, which is the main one, and two other cyanidin-3-glucoside which are acylated at the glucose (Lawson, 1996).

5.3.2. Medicinal uses:

Garlic peel extract exhibited good DPPH radical scavenging activity and the effect was attributed to phenyl propanoid compounds (Ichikawa et al., 2003). Methanol extract also exhibited anti-inflammatory, analgesic activity and anticonvulsant activity in preclinical studies (Sivakumar & Venkataraman, 2010). Garlic peel, an inexpensive and easily available material, was found to very effective to remove methylene blue from aqueous solutions of industrial waste (Hameed & Ahmad, 2009). ‘Tira-capeta’ cigarette has been used as a brain tonic for the years by Brazilians. It is a combination of nine plants and one among them is peel of single bulb garlic. The extract of this cigarette exhibited CNS activity where it stimulates the glutaminergic and cholinergic systems and blocks the dopaminergic system and causes stimulant and depressant effect (Rodrigues et al., 2008).

Dietary supplementation with garlic bulb and garlic husk resulted in significantly greater protein content, increased unsaturated fatty acids, decreased saturated fatty acids and lower fat content in broiler chicken thigh muscle. It also decreased total cholesterol and LDL-cholesterol levels in the blood and also improved the meat quality of broiler chicken fed with garlic bulb and husk supplementation. Garlic husk was a better antioxidant resource for broiler diets than garlic bulb (Kim et al., 2009).

5.4. Garlic leaves

Garlic leaves are a popular vegetable in many parts of Asia. The leaves are cut, cleaned, and then stir-fried with eggs, meat or vegetables. Allicin, the primary active constituent of garlic bulb, appears in lower amounts in the leaves. It offers a similar profile of benefits and risks in comparison to garlic bulb. A novel amino caid glycoside, (X)-N-(1-deoxy-1-D-fructopyranosyl)-S-allyl-L-cysteine sulfoxide was isolated from a hydrophilic extract of the leaves but not found in the cloves. It inhibited the in vitro platelet aggregation induced by adenosine diphosphate or
epinephrine (Lawson, 1996). Allin obtained from leaves by controlled condition in situ had shown higher therapeutic potency in alloxan antidiabetic model using rats (Nasim et al., 2011).

5.5. Garlic Roots

In traditional medicine, Garlic roots are used as infusion for eliminating worms. The root contains two steroidal glycosides, sativoside R1 & sativoside R2 and two phenolics namely N-feruloyltyrosine & N-feruloyltyramine (Figure 5.6). The phenolics of garlic root exhibited antifungal activity against *Fusarium culmorum* (Lanzotti, 2006).

**Steroidal Glycoside:**

![Steroidal Glycoside Diagram]

**Phenolics:**

![Phenolics Diagram]


**Figure 5.6:** Phytoconstituents of garlic root
III. List of Patents on Garlic

5.6. United States patents on garlic

5.6.1. Garlic for various therapeutic indications

Therapeutic uses of garlic for sickle cell disease (US Patent 6254871)

Garlic in treating hypertension and dyslipidemia (US Patent 20070160695)

Ajoene, as alcohol dehydrogenase inhibitor (US Patent 20080102142)

Use of garlic extract as both preventive and therapeutic agents for human prostate and bladder cancers (US Patent 6465020)

Garlic in treatment for tinnitus and psoriasis (US Patent 20030232098; 5165932)

Use of garlic as antithrombogenic and antibiotic (US Patent 4917921)

Garlic in treating herpes simplex virus and human papillomavirus (US Patent 4795636; 20080213410)

Site-specific in situ generation of allicin using a targeted alliinase delivery system for the treatment of cancers, tumors, infectious diseases and other allicin-sensitive diseases (US Patent 7445802)

Garlic as immune potentiative and infection protective agent (US Patent 5741494)

Garlic as antifungal and anti-inflammatory (US Patent 20080249186; 20080206370; 20100098676)

Garlic as mosquito, insect and pesticidal repellent (US Patent 5733552; 20080206272; 20080255237)

Dental and oral preparations from garlic oil for removing tobacco tars in teeth and oral mucosal tissue of smokers (US Patent 5514366)

5.6.2. Garlic in combination for various therapeutic indications

Pharmaceutical composition comprising metadoxine and garlic oil for preventing and treating alcohol-induced fatty liver and steatohepatitis (US Patent 20100062090)

Synergistic mixtures of garlic and lycopene for preventing LDL oxidation (US Patent 6555134)

Shark liver oil and garlic oil topical analgesic (US Patent 5032400)

Garlic in polyherbal formulation for blood sugar regulation (US Patent 6787163)
Method of decreasing cholesterol and triglycerides levels with a composition containing fish oil, garlic, rutin and capsaicin (US Patent 6326031)

Nutritive composition for cardiovascular health containing fish oil, garlic, rutin, capsaicin, selenium, vitamins and juice concentrates (US Patent 6440464)

Garlic enriched with organic selenium compounds for nutritional supplementation (US Patent 7014874)

Use of garlic in prevention and treatment of obesity in polyherbal formulation (US Patent 7135199; 7192613)

Garlic powder in herbal solution used for hair growth and hair loss (US Patent 5674510)

Herbal tonic containing garlic to improve respiration, aids in the elimination of toxins and improves overall vitality (US Patent 6582702)

Dietary food supplement containing garlic for to lower blood pressure and to sustain blood glucose levels (US Patent 7348033)

Garlic in reducing serum homocysteine concentration (US Patent 6129918)

Garlic in herbal composition for treatment and maintenance of hormone dependent conditions, osteoporosis, circulatory conditions, and for use as an immunostimulant (US Patent 20070122497)

Onion & garlic biohydrolysates, their use as natural flavorings (US Patent 6759068)

Jelly health foods containing odorless garlic (US Patent 5401526)

Anti adipose topical treatment composition based on garlic bulbs extracts, and cosmetic and therapeutic uses (US Patent 6852343)

Preparation of cholesterol lowering composition of garlic (US Patent 20040067267)

Prevention and treatment of garlic in herbal formulation for vascular-related disorders such as vascular re-occlusion or restenosis and diseases associated with pathological angiogenesis such as cancer, ocular or inflammatory diseases (US Patent 6866864)

Combination of natural products are used in many indications, garlic is one among them. Many patents are available for the use of garlic in various indications viz, fatigue, wound healing, antimicrobial, mycoplasma associated disease, preventing urinary tract infections, decreasing beta amyloid protein, atherosclerosis (US Patent 7932288; 20090068167; 5705152; 7335638, 20060263455; 6080778; 7732410)
5.6.3 Garlic preparations

Fermented garlic composition (US Patent 6146638)
Method for making improved garlic product (US Patent 6197354)
Method of manufacturing a lemon-basil garlic marinade (US Patent 6171639)
Controlled-release garlic formulations (US Patent 6270803)
Process for deodorizing garlic (US Patent 5260090)
Garlic alliinase covalently bound to carrier for continuous production of allicin (US Patent 6689588)
Method for manufacturing health food, utilizing garlic (US Patent 5523086)
Method of processing garlic and preparing ajoene-containing edible oil products (US Patent 5612077)
Method and product for eliminating undesirable side effects of eating vegetables such as onion or garlic (US Patent 6007809)
Method for producing tablet comprising natural allicin (US Patent 20110212082)
Antiviral agents containing a fermentation product of garlic by lactic acid bacteria (US Patent 20100143514)
Method of preparation of aged garlic extract, fermented garlic, edible garlic oil containing ajoene and deodorized garlic extract were patented (US Patent 20070031574; 6146638; 5612077; 4377600)
Garlic processor and Garlic peeler (US Patent 6752340; 6968778)

5.7. Indian patents on Garlic

Improvements relating to the manufacture of garlic powder (Indian Patent 65138; 134964)
Process of producing stable garlic preparation (Indian Patent 40890)
A garlic skin peeling machine (Indian Patent 240633)
A process for the preparation of a flavor enriched garlic powder (Indian Patent 190148)
Garlic pod extractor (Indian Patent 164514)
Process for the preparation of insecticidal principles of garlic (Indian Patent 144278)