Pleiotropic Garlic (Allium Sativum) in the Treatment of Diabetes Mellitus and its Complications

Patial T. R1*, Patil S2, Patil A3, Patil ST4

1Department of Pharmacology Bharati Medical College and Hospital Sangli, Maharashtra, India.  
2Department of Public Health Dentistry School of Dental Sciences Karad, Maharashtra, India.

ABSTRACT
Diabetes mellitus is growing at alarmingly high rate globally. Currently available antidiabetic drugs mainly target the control of hyperglycemia. They rarely contribute significantly to correction or prevention of complications of diabetes probably except metformin, and glitazones which partially are cardioprotective. Garlic has pleiotropic effects like correction of hyperglycemia, hyperlipidemia, hypertension. It has vasculoprotective, antiatherosclerotic and cardioprotective benefits. Its antiplatelet, fibrinolytic, antioxidant, NO and H2S generating properties contribute to various beneficial actions. Garlic has anti-inflammatory properties and it has been proved to be antifungal, antibacterial, antiprotozoal and antiviral. By improving vascular health, hyperlipidemia, hyperglycemia it has been proved to be neuroprotective and nephroprotective. Its favourable action on lipogenesis, glucose metabolism and anti-inflammatory property prevents diabetic non alcoholic, fatty liver disease. Abundance of experimental data should be utilized to conduct various clinical trials on efficacy of garlic as it forms promising therapeutic tool to treat diabetes related conditions.

Keywords: Garlic, Diabetes mellitus, Diabetic complications.

INTRODUCTION
The incidence of diabetes mellitus (DM) and cardiovascular diseases are increasing at an alarming rate. By year 2025, 300 million or more of world population is likely to become diabetic. Diseases like diabetes mellitus, hypertension and obesity demand polypharmacy to fulfill the therapeutic goals. Increased intake of various types and numbers of medications makes the patient skeptical about their safety and also raise concern about the recurring cost of therapy. Hence many patients try the complementary and alternative medicines (CAM) which are easily available without the any prescription. CAM is defined as a group of diverse medical and health systems, practices and products. These are not generally considered as part of conventional medicines. Among the CAM, plant based products or foods are more recognized and accepted, garlic being one of them. The beneficial effect of garlic in many human diseases is known since centuries. Egyptian codex Ebers which is a 3500 years old document mentions the use of garlic for treatment of conditions like heart disease, tumors, bites, worms and other illness. Similar findings have been reported in the ancient Vedas and Hippocrates documents. Garlic belongs to botanical species allium and is recognized as allium sativum. It contains organosulphur compounds with activity against ailments like diabetes mellitus, cancer and cardiac disease. Garlic is known to possess several therapeutic benefits which are mainly due to its constituents S-allylcysteine sulphoxide[SACS] and S-allyl cysteine[SAC]. Garlic exhibits antithrombotic, hypolipidemic, antioxidant, antimicrobial, hypotensive and hypoglycemic properties. About 65% of weight of garlic is made up of water. The dry weight is composed of carbohydrates, sulphur compounds, proteins, fibres, free amino acids, saponins, phosphorus, potassium, sodium, zinc, sulphur and selenium. It also contains calcium, magnesium, iron, manganese, and vitamins A, C, B complex. It also has high phenolic contents. The common preparations of garlic which are investigated for therapeutic purposes are raw garlic, garlic powder, tablets, oil of oil distilled garlic, ether extracted oil of garlic and aged garlic extracts (AGE). Diabetes mellitus is a metabolic syndrome of hyperglycemia and its consequences due to relative or absolute deficiency of insulin or insulin resistance. It is often associated with hyperlipidemia, hypertension, microvascular and macrovascular disease of cardiovascular, renal or nervous system. Hyperglycemia induced excessive oxidative stress, generation of reactive oxygen species[ROS] and advanced glycation end products comprise the initiating mechanisms for complications in diabetes mellitus. Recent evidence points towards diabetes being an inflammatory disorder. Increased platelet aggregation and enhanced thrombosis along with endothelial dysfunction forms the basis for vascular complications. Pethora of allopathic drugs like sulphonylureas, biguanides, meglitinides, glitazones, alpha glucosidase inhibitors and many others are available to treat DM. But no single drug addresses all possible underlying pathologies of DM. Diabetes being a chronic disorder is often associated with hypertension and obesity.

*Author for Correspondence: drpatiltr@gmail.com
which requires polypharmacy, hence patients often opt for CAM without being aware of their actual therapeutic aspects and their adverse effects. It’s easy availability tempts them to procure and use CAM therapy. Garlic is also categorized under herbal medicines as a part of CAM which has been tried since many centuries for various ailments. Garlic has also been tried in the treatment of DM. Here is a review of various actions of garlic related to diabetes, and its complications; arising out of hyperglycemia, hyperlipidemia, hypertension, myocardial ischemia, endothelial dysfunction, oxidative stress, platelet aggregation, thrombogenesis, proteinuria, renal and hepatic dysfunctions and Alzheimers disease.

**Diabetes mellitus, platelet dysfunction and role of garlic**

In DM there is an enhanced incidence of thrombosis arising out of excessive platelet activation. The relation between DM induced hyperglycemia and platelet activation is substantially proved by various studies. In DM platelet activation and subsequent aggregation occurs due to,

- High glucose related oxidative stress and subsequent scavenging of NO.
- Hyperglycemia induced increased concentration of asymmetric dimethyl arginine (ADMA), a NO synthesis inhibitor.
- Induction of non enzymatic glycation of proteins on the platelet surface decreasing its membrane fluidity.
- Hyperglycemia induced osmotic effect and activation of protein kinase C.
- Overexpression of surface glycoproteins Ib, IIb/ IIIa and increased circulating levels of von Willebrand factor (vWF).
- Relative or absolute deficiency of insulin resulting into lack of its antagonistic effect on platelet agonists such as collagen, epinephrine, ADP and platelet activating factor (PAF).
- Hyperglycemia induced shear stress resulting into platelet activation.
- DM related enhanced systemic inflammation, oxidative stress, excessive superoxide generation and ROS resulting into increased intraplatelet calcium.
- Inhibition of NO by superoxides and impairment of endothelial function.
- Promotion of collagen induced platelet activation by reactive oxygen species.
- Hyperglycemia related reduced production of prostacyclin, a known platelet anti-aggregator.
- Inflammation induced increased expression of Fcy receptor type IIa (FcγIIa) resulting into increased platelet activation in response to collagen.
- DM related Hypercholesterolemia increasing cholesterol/phospholipid ratio in platelets, thromboxane A2 synthesis, platelet alpha adrenergic receptor density and cytosolic Ca ++ accumulation in platelets.
- High LDL or oxidized LDL on their own or by platelet aggregation agonists.
- High lipid content increasing expression of fibrinogen binding sites on platelets and secretion of dense granules.
- Decreased plasma HDL leading to diminished NO production and enhancing the incorporation of arachidonic acid in platelet membranes of coronary artery disease (CAD) patients even in the absence of LDL hypercholesterolemia.

**Antiplatelet actions of garlic**

Hyperglycemia induced platelet activation in type 2 diabetes is resistant to aspirin. Hence antiplatelet action of garlic needs to be highlighted. In a study done by Shrivastava KC et al, aqueous extract of garlic inhibited platelet aggregation induced by ADP, collagen, Arachidonate (AA), epinephrine and calcium inophore A23187 in dose dependent manner. It also reduced the formation of thromboxane from exogenous AA, inhibited phospholipase activity and lipoxygenase production in platelets. Incorporation of AA in platelet phospholipids was also suppressed. Garlic may reduce uptake and mobilization of calcium causing decreased intracytosolic calcium and reduced platelet activity. In vitro studies, as reported by Rahman K, garlic reduced cyclo-oxidase activity with subsequent reduction of thromboxane A2. Decreased mobilization of intra platelet calcium and increased intraplatelet cAMP and cGMP by garlic helps in activation of nitric oxide synthase (NOS) and rise in intraplatelet NO, which is a known platelet anti-aggregator. It also interacts with glycoprotein IIb and IIIa receptors and reduces the ability of platelets to bind to fibrinogen. Garlic also inhibited ADP and PAF along with suppression of calcium mobilization and inhibition of cyclo-oxidase activity.

Garlic enhances fibrinolytic activity along with inhibition of platelet aggregation. In human studies Bordia et al consistently showed fibrinolytic activity of garlic in healthy persons and in patients of acute myocardial infarction. In a study by Steiner M (2001), AGE in a dose of 7.2 gms/day was found to have reduced platelet aggregation and adhesion to collagen and vWF. Reduced adhesion to collagen was observed by both, high dose of 7.2 gms/ day and low dose of 2.4 gms/ day. AGE inhibited activation and aggregation of human platelets via inhibition of GP IIb/ IIIa receptor and their interaction with fibrinogen and increase in intracellular cAMP levels. Organosulfides like diallylsulfide (DADS) and diallyltrisulfides (DATS) from garlic, scavenge reactive oxygen species like superoxide radicals, hydrogen peroxide and other oxidases along with peroxinitrite (ONOO -), which are responsible for platelet aggregation, thus preventing their action. Allicin is also a good scavenger against O2-, OH and ONOO-. Fresh garlic homogenates, garlic oil, DADS, DATS, SAC, SACS and allican generate NO by activation of P13K/ PKB pathway via eNOS activation. Through generation of hydrogen sulfide (H2S) and NO in endothelial cells, garlic prevents platelet aggregation.

**Diabetes, cardiovascular health and garlic**

Cardiovascular disease in DM has multiple contributing factors like hyperlipidemia, increased platelet activation, increased plasma fibrinogen and coagulation factors along with altered glucose metabolism which needs to be
addressed adequately. LDL oxidation and oxidative stress form the important mechanisms for development of atherosclerosis and endothelial dysfunction. Garlic constituents inhibit human squalene monoxygenase and 3-hydroxy-3-methyl glutaryl coenzyme A[HMG CoA] reductase enzymes responsible for cholesterol synthesis. Garlic acts as an antiplatelet agent by various mechanisms. In hypertensive patients garlic reduced blood pressure and also reduced vascular tone. Dietary organosulfur compounds like garlic are precursors of hydrogen sulfide. After nitric oxide[NO] and carbon monoxide [CO] H2S is the newest gasotransmitter and gaseous signal molecule for various physiological and pathological conditions. H2S induces vascular smooth muscle relaxation and vasodilatation as result of kATP activation. By reducing oxidative stress, preserving mitochondrial function and by enhancing myocardial vascular density it prevents heart failure. H2S also protects against myocardial ischemia reperfusion injury. It inhibits adhesion molecule expression and smooth muscle proliferation and prevents atherosclerosis. Sulfur atoms in dietary organosulfides like garlic are good oxidant scavengers. AGE and garlic oil contain high amount of organosulfides and prevent oxidative damage. Several in vitro studies have confirmed the cardioprotective effects of garlic which are attributed to the decreased production and blocking of ROS dependent extracellular signal regulated kinase[ERK]1/2, AKT, NF-kB and SMADs signalling. L-arginine is a substrate for NO production and tetrahydrobiopterin (BH4) acts as a cofactor. BH4 levels were found lowered with ageing and cardiovascular disease. Lack of BH4 causes eNOS uncoupling resulting into generation of excess of superoxide (O2•-) and low levels of NO. AGE is known to prevent the fall in BH4 levels and normalizes NO output from endothelial cells. This prevents NO uncoupling and superoxide generation and improves endothelial function. Thus garlic provides cardioprotection.

Garlic and hypertension

Hypertension is a modifiable risk factor for cardiovascular disease. Studies done by various researchers have shown the reduction in blood pressure with garlic only in hypertensives and not in normotensives. Garlic contains functional sulphur containing bioactive compounds like Alliin, Allicin, DADS, DATS, ajoene and SAC. Alliin is volatile, unstable and destroyed by cooking. DADS and DATS are the contents of garlic’s essential oil. SAC is the stable main active component of aged garlic extract. The antihypertensive effect of garlic is due to bioactive compounds like allicin and SAC by modulating oxidative stress, increasing bioavailability of NO and gasotransmitter H2S production. This effect is also mediated through inhibition of angiotensin converting enzyme, expression of nuclear factor kappa β and proliferation of vascular smooth muscles. eNOS derived NO induces relaxation of vascular smooth muscle cells leading to vasodilatation via guanylyl cyclase dependent mechanism. BP reduction through H2S is thought to be mediated through sulphydration of ATP sensitive potassium (kATP) channels which opens the voltage sensitive channel and relaxes vascular smooth muscle cells. Garlic has potential to reduce the production of angiotensin II by inhibiting ACE which was suggested by using fresh garlic compounds containing allicin in animal models. Allicin has low sustained bioavailability in human tissues. Hence generation of NO and H2S by garlic predominates the mechanism of lowering the BP.

Antidiabetic effect of garlic

The beneficial effects of garlic in diabetes mellitus is mainly attributed to the presence of sulphur compounds like alliin, allicin, diallyl sulfide, DADS, DATS, SAC and ajone. Kumar et al treated the patients of diabetes mellitus with garlic along with metformin and found the fall in blood sugar was more in garlic group as compared to only metformin group. A study done by Thomson M et al on effect of garlic in streptozotocin induced diabetic rats showed its hypoglycemic and significant urinary protein lowering effect. They suggested that garlic may be useful in prevention of development of atherosclerosis and diabetic nephropathy. They conducted on diabetic patients with raw garlic (3.6 grams for 30 days on fasting) resulted into significant decrease in fasting hyperglycemia and lipid levels. Hypoglycemia induced by garlic may be due to increase in insulin release from pancreatic beta cells, enhanced insulin sensitivity and release of bound insulin. Allicin in garlic can combine with cysteine and spare insulin from SH group reaction and prevent insulin inactivation. Antioxidant effect of SACS may contribute to beneficial effect in diabetes.

Hypolipidemic effect of garlic

Administration of ethyllic extract of garlic or fresh garlic was found to reduce serum cholesterol. Cholesterol lowering effect of garlic was also confirmed by using primary hepatocyte cultures where garlic reduced hepatic synthesis of cholesterol and triglycerides. Triacylglycerol lowering effect of garlic appears to be due to inhibition of fatty acid synthesis. In high fat fed rats, plasma triglycerides was reduced by garlic. In animal studies garlic depressed hepatic activity of cholesterogenic and lipogenic enzymes like HMG CoA reductase, glucose 6 phosphate dehydrogenase and malic enzyme. Garlic was also found to enhance hepatic degradation of cholesterol to bile acids. Various clinical trials conducted on hyperlipidemic patients for a duration ranging from 4weeks to 11 months showed decrease in total cholesterol level. Meta-analysis conducted by zeng et al in 2012 and Ried et al in 2013 concluded that garlic was effective in lowering the cholesterol and can prove to be a safer alternative to conventional cholesterol lowering drugs.

Garlic inhibits oxidative stress

The most important ROS in cardiovascular disorders are superoxide anion radical [O2•] and hydrogen peroxide[H2O2]. Peroxynitrite [ONOO−] is generated by reaction between superoxide and NO. Consumption of NO by this reaction affects endothelial function and CVS health. ONOO− mediates lipid peroxidation of LDL resulting into proatherogenic oxidized LDL. ROS is also responsible for platelet aggregation, monocyte adhesion, vascular smooth muscle

IJPPR, Volume 8, Issue 7: July 2016
apoptosis, inflammatory gene expression, proliferation and migration of adhesion cells and for defective endothelial function and vasorelaxation. Sulfur atoms in dietary organosulfides like AGE and garlic oil are good ROS scavengers and prevent ROS induced damage SAC is the major watersoluble organosulfide compound in AGE and scavenges peroxinitrite. Allicin, DADS, and DATS are good scavengers of O$_2$, H$_2$O$_2$, and ONOO$^-$. Likewise DADS and DATS are reported to reduce cellular peroxide levels in oxLDL.

**Garlic and Hyperhomocysteinemia**

Consumption of about 2 cloves of garlic/meal are known to release sufficient H$_2$S to maintain vascular health. Hyperhomocysteinemia is a known culprit for endothelial dysfunction and cardiovascular disorders. Hyperhomocysteinemia is a risk factor for cardiovascular and cerebrovascular diseases. Homocysteine thiolacone, a highly active free radical is formed in this condition which thiolates LDL. These thiolated LDL particals get aggregated and endocytosed by macrophages resulting in to enhanced atherogenesis. Increased homocysteine levels may be a consequence of decreased endothelial production of H$_2$S. Increased levels of homocysteine were found in people having low dietary intake of protein and sulfur containing aminoacids which might be regarded as biomarker of sulfur deficiency. Garlic containing high sulfur compounds like SAC can correct sulfur deficiencies caused by low protein diet. Budoff MJ studied the effect of garlic in patients with atherosclerosis and found the garlic’s potential in reduction of homocysteine levels. H$_2$S deficiency is known to contribute to vascular dysfunction, including hypertension. H$_2$S is a vascular gaseous signal transmitter present in various mammalian tissues like vascular smooth muscle cells, heart, brain and nervous system. Hyperhomocystenemia results in decreased production of NO and H$_2$S and results in vascular dysfunction.

**Diabetes, dementia, alzheimer’s and role of garlic**

Risk factors for cardiovascular diseases like hypertension, hyperlipidemia, hypercholesteroine asma also pose a risk for dementia like Alzheimer’s disease (AD). A hallmark of AD has been correlated with high cholesterol level. Oxidative damage is also a strong risk factor for both AD and CV disease. The neuroprotective effects of garlic may be due to its antioxidant, antiatherogenic and antiapoptotic property. There is a clear negative correlation between hyperhomocystenemia and brain and cognitive functions. Garlic is known to correct hyperhomocystenemia. AGE which is rich in antioxidants has been tried in both the diseases. AGE scavenges oxygen radicals and inhibits lipid peroxidation and inflammatory prostaglandins. It increases levels of superoxide dismutase, catalase, glutathione peroxidase and glutathione. AGE is a known inhibitor of HMG-co A reductase resulting in decreased cholesterol synthesis. It also decreases the LDL oxidation, reduces homocysteine levels, prevents platelet aggregation, reduces BP, enhances microcirculation and prevents arterial plaque formation. Thus, it helps in reducing the risk of dementia. AGE and SAC also protect the neurons from A beta neurotoxicity, apoptosis, prevents neuronal death and degeneration of frontal lobe of brain reflecting into improved cognition, learning and memory. Elevated homocysteine levels damage blood vessel endothelial cells and trigger thrombosis. It breaks the DNA, induces apoptosis and causes neuronal death and dementia. Preclinical studies have proved that consumption of AGE reduces homocysteine levels. AGE is also known to have additional anti-aging effect.

**Diabetes, nephropathy and protective role of garlic**

Proteinuria is the predictor of glomerular injury and increased protein excretion suggests progressive nephropathy. Diabetic rats who presented with nephropathy related proteinuria when treated with garlic showed lowered protein excretion compared to control group. Garlic extract protects against tubular injury by modulation of oxidative stress on the tubules and correcting biochemical alterations. Elevated serum urea and creatinine suggest nephropathy and renal dysfunction in diabetics. A study done by Almadal et al, showed that garlic extract decreased serum urea and creatinine in diabetic rats. El-Demerdash et al also observed the alleviating effect of garlic on renal damage. Hence it can be concluded that garlic offers renoprotection in diabetics in experimental condition which needs to be translated in human beings.

**Antimicrobial effect of garlic**

Antifungal property of garlic

Schmidt and Marquardt in 1936 confirmed the antifungal property of garlic. It reduces the synthesis of lipids, proteins, nucleic acids and inhibit the growth of organisms and also damage the membrane. When used locally garlic treated denture stomatitis better than nystatin. Allicin, DATS and ajoene have shown antifungal activity against Cryptococcus and aspargillus. Inhibition of succinate dehydrogenase by garlic resulted into respiratory inhibition Garlic extract also reduced the adhesion of candida.

Antibacterial property of garlic

Garlic has been proven to be effective against Salmonella, klebsiella, pseudomonas, proteus and Staphylococcus aureus, clostridium, helicobactor pylori and mycobacterium. Garlic has been suggested for treatment of multidrug resistant tuberculosis. Garlic extract was found to be effective against human dental plaque microbiota in vitro study. Allicin a form of garlic bears antibacterial property due to inhibition of sulphhydryl enzyme as it modifies sulphhydryl activity. Some vancomycin resistant Enterococci were found to be sensitive for garlic as allicin modifies sulphhydryl group of the TN1546 transposon which encodes vancomycin resistance. In rat model of chronic bacterial prostatitis, garlic was given with ciprofloxacin. Garlic group showed statistically significant decrease in bacterial growth and improvement in prostatic inflammation as compared to only ciprofloxacin group.
and antimicrobial effects of garlic and synergistic effect between garlic and ciprofloxacin in chronic bacterial prostatitis rat model-international journal of antimicrobial agents.

**Antiprotosozial property of garlic**

Garlic extract was observed to be effective against tinea pedis, entamoeba histolytica, trypanosoma, leishmania. Clinical trial conducted with garlic on patients with giardiasis resulted into elimination of infection within 3 days.

**Antiviral property of garlic**

In vitro studies done with garlic extract showed its activity against influenza A and B rhinovirus, herpes simplex virus 1 and herpes simplex virus 2. Allicin, DATS and ajone all bear antiviral potential.

**Hepatoprotective effect of garlic**

Hepatotoxic effect of anti TB drugs (isoniazid, rifampicin, ethambutol and pyrazinamide) indicated by rise in liver enzymes was decreased in experimental animals when supplemented with garlic homogenate. Aged black garlic extracts in experimental animals protected liver against hepatic injury by carbon tetrachloride. Garlic derived S allyl mercaptocysteine (SAMC) has therapeutic effect in diabetes and non alcoholic fatty liver disease due to the regulation of lipogenesis and glucose metabolism. SAMC can prevent inflammation induced by nonalcoholic fatty liver disease (NAFLD) by reducing pro inflammatory mediators, chemokine signaling and chemokine. Study concludes that garlic or garlic derivatives could be considered as potent agents in prevention of fatty liver disease. These studies done in animals need to be confirmed and applied in treatment of fatty liver disorders in diabetic patients.

**CONCLUSION**

Diabetes is becoming a global menace. It is a metabolic syndrome arising out of hyperglycemia and its complications. It is known to induce cardiovascular, cerebrovascular, renal and hepatic complications. In various experimental and clinical studies garlic was found to correct hyperglycemia, hyperlipidemia, hypertension. It has antiplatelet, antioxidant and fibrinolytic properties along with generation of NO and H2S which contribute to its cardioprotective and cerebroprotective and antiatherosclerotic properties. Garlic is proved to be neuroprotective, cardioprotective and hepatoprotective. Plethora of experimental evidence should be utilized to initiate various clinical trials to confirm and utilize the efficacy of garlic in diabetes and its complications.

**REFERENCES**


18. Lawson LD. The composition and chemistry of garlic cloves and processed garlic. In Koch HP, Lawson LD, editors. Garlic the science and therapeutic application...


124. Almadal TP. Strict insulin treatment normalizes the organic nitrogen contents and the capacity of urea-N.


164. Xiao J, Ching YP, Liong EC, Nanji AA, Fung ML, Tiope GL. Garlic-derived S-allylmercaptocysteine is a hepato-protective agent in non-alcoholic fatty liver...