Available online on www.ijppr.com
International Journal of Pharmacognosy and Phytochemical Research 2016; 8(7); 1227-1237

ISSN: 0975-4873

Research Article

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

Patil T. R[1*], Patil S[2], Patil A[3], Patil ST[4]

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

Available Online: 12th July, 2016

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, antiathlerosclerotic and cardioprotective benefits. Its antiplatelet, fibrinolytic, antioxidant, NO and H_2S 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[1]. 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[2]. 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[3]. Similar findings have been reported in the ancient Vedas[4] and Hippocrates documents[5]. 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[6-8], hypolipidemic[9], antioxidant[10], antimicrobial[11], hypotensive[12-14] and hypoglycemic properties[15-17]. 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[18], 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[19]. The common preparations of garlic which are investigated for therapeutic purposes are raw garlic, garlic powder, tablets, oil of oil- macerated garlic, oil of steam distilled garlic, ether extracted oil of garlic and aged garlic extracts (AGE)[20]. 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[21,22]. Recent evidence points towards diabetes being an inflammatory disorder[23]. Increased platelet aggregation and enhanced thrombosis along with endothelial dysfunction forms the basis for vascular complications. Plethora of allopathic drugs like sulphonyulreas, 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[21,22].
- Hyperglycemia induced increased concentration of asymmetric dimethyl arginine (ADMA), a NO synthesis inhibitor[24]
- Induction of non enzymatic glycation of proteins on the platelet surface decreasing its membrane fluidity[25].
- Hyperglycemia induced osmotic effect and activation of protein kinase C[26].
- Overexpression of surface glycoproteins Ib, IIb/ IIIa[27] and increased circulating levels of von Willebrand factor (vWF)[28]
- 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)[29].
- Hyperglycemia induced shear stress resulting into platelet activation[30].
- DM related enhanced systemic inflammation, oxidative stress, excessive superoxide generation and ROS resulting into increased intraplatelet calcium[31,32].
- Inhibition of NO by superoxides and impairment of endothelial function[33].
- Promotion of collagen induced platelet activation by reactive oxygen species[34].
- Hyperglycemia related reduced production of prostacyclin, a known platelet anti- aggregator[35].
- Inflammation induced increased expression of Fcγ receptor type IIa (FcγIIa) resulting into increased platelet activation in response to collagen[36,37].
- DM related Hypercholestrolemia increasing cholesterol/phospholipid ratio in platelets, thromboxane A2 synthesis, platelet alpha adrenergic receptor density and cytosolic Ca^{++} accumulation in platelets[38-40].
- High LDL or oxidized LDL on their own or by platelet aggregation agonists[41].
- High lipid content increasing expression of fibrinogen binding sites on platelets and secretion of dense granules[41].
- 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[42].

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[30]. 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 A 23187 in dose dependent manner. It also reduced the formation of thromboxane from exogenous AA, inhibited phospholipase activity and lipooxygenase 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[43]. In vitro studies, as reported by Rahman K, garlic reduced cyclo-oxygenase activity with subsequent reduction of thromboxane A2. Decreased mobilization of intra platelet calcium and increased intraplatelet cAMP and cGMP by garlic contributes to platelet's anti-aggregatory action. A strong antioxidant property of 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[44]. Garlic also inhibited ADP and PAF along with suppression of calcium mobilization and inhibition of cyclo-oxygenase activity[45]. Garlic enhances fibrinolytic activity along with inhibition of platelet aggregation[3]. In human studies Bordia et al consistently showed fibrinolytic activity of garlic in healthy persons and in patients of acute myocardial infarction[46,47]. 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[48]. 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[49]. Organosulfides like diallylsulfide (DADS) and diallyltrisulfides (DATS) from garlic, scavenge reactive oxygen species like superoxide radicals(O_2^-), hydrogen peroxide (H_2O_2) and other oxidases along with peroxinitrite ($ONOO^-$), which are responsible for platelet aggregation, thus preventing their action[50,51]. Allicin is also a good scavenger against O_2^-, OH and $ONOO^-$[52,53]. Fresh garlic homogenates, garlic oil, DADS, DATS, SAC, SACS and allicin 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[54,55].

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[56]. LDL oxidation and oxidative stress form the important mechanisms for development of atherosclerosis and endothelial dysfunction[57,58]. Garlic constituents inhibit human squalene monooxygenase and 3-hydroxy-3-methyl glutaryl coenzyme A[HMG CoA] reductase enzymes responsible for cholesterol synthesis[59,60]. Garlic acts as an antiplatelet agent by various mechanisms[6-8,61,62]. In hypertensive patients garlic reduced blood pressure and also reduced vascular tone[63,64]. Dietary organosulphur compounds like garlic are precursors of hydrogen sulfide[H2S].After nitric oxide[NO] and carbon monoxide [CO] H2S is the newest gasotransmitter and gaseous signal molecule for various physiological and pathological conditions[65,66]. H2S induces vascular smooth muscle relaxation and vasodilatation as result of kATP activation[67]. By reducing oxidative stress, preserving mitochondrial function and by enhancing myocardial vascular density it prevents heart failure[68]. H2S also protects against myocardial ischemia reperfusion injury[69]. It inhibits adhesion molecule expression and smooth muscle proliferation and prevents atherosclerosis[70]. Sulfur atoms in dietary organosulfides like garlic are good oxidant scavengers. AGE and garlic oil contain high amount of organosulfides and prevent oxidative damage[71,72]. 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.JNK ½. AKT, NF-kB and SMADS signalling[73-75]. L-arginine is a substrate for NO production and tetrahydrobiopterin (BH_4) acts as a cofactor. BH_4 levels were found lowered with ageing and cardiovascular disease. Lack of BH_4 causes eNOS uncoupling resulting into generation of excess of superoxide (O_2^-) and low levels of NO[76]. AGE is known to prevent the fall in BH_4 levels and normalizes NO output from endothelial cells. This prevents NO uncoupling and superoxide generation and improves endothelial function[77].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[78,79]. Garlic contains functional sulphur containing bioactive compounds like Alliin, Allicin, DADS, DATS, ajoene and SAC[80,81]. Allicin is volatile, unstable and destroyed by cooking[82,83]. DADS and DATS are the contents of garlic's essential oil[82]. SAC is the stable main active component of aged garlic extract[84]. 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 angiotension converting enzyme, expression of nuclear factor kappa β and proliferation of vascular smooth muscles[85]. eNOS derived NO induces relaxation of vascular smooth muscle cells leading to vasodilatation via guanylyl cyclase dependent mechanism[76]. BP reduction through H_2S 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[86]. 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[83]. Hence generation of NO and H_2S by garlic predominates the mechanism of lowering the BP[87].

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[88]. 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[89]. Study done by S. Mirunalini et al 2011 in diabetic patients with raw garlic (3.6 grams for 30 days on fasting) resulted into significant decrease in fasting hyperglycemia and lipid levels[90]. Hypoglycemia induced by garlic may be due to increase in insulin release from pancreatic beta cells, enhanced insulin sensitivity and release of bound insulin[91]. Allicin in garlic can combine with cysteine and spare insulin from SH group reaction and prevent insulin inactivation[92]. Antioxidant effect of SACS may contribute to beneficial effect in diabetes[93].

Hypolipidemic effect of garlic

Administration of ethylic extract of garlic or fresh garlic was found to reduce serum cholesterol[94]. Cholesterol lowering effect of garlic was also confirmed by using primary hepatocyte cultures where garlic reduced hepatic synthesis of cholesterol and triglycerides[95]. 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[96]. In animal studies garlic depressed hepatic activity of choletserogenic and lipogenic enzymes like HMG CoA reductase, glucose 6 phosphate dehydrogenase and malic enzyme[97-99]. Garlic was also found to enhance hepatic degradation of cholesterol to bile acids[100]. Various clinical trials conducted on hyperlipidemic patients for a duration ranging from 4weeks to 11 months showed decrease in total cholesterol level[101-104]. Meta-analysis conducted by zeng et al in 2012[105] and Ried et al in 2013[106] 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][107]. Peroxinitrite [$ONOO^{--}$] 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 [oxLDL][108].ROS is also responsible for platelet aggregation, monocyte adhesion, vascular smooth muscle

apoptosis, inflammatory gene expression, proliferation and migration of adhesion cells and for defective endothelial function and vasorelaxation[51]. Sulfur atoms in dietary organosulfides like AGE and garlic oil are good ROS scavangers[71,72]. [110,112,~~113~~/gto].and prevent ROS induced damage. SAC is the major watersoluble organosulfide compound in AGE and scavenges peroxinitrite[50]Allicin, DADS, and DATS are good scavangers of O2, H2O2, and ONOO[50,109]. Likewise DADS and DATS are reported to reduce cellular peroxide levels in oxLDL[110].

Garlic and Hyperhomocystinemia

Consumption of about 2 cloves of garlic/ meal are known to release sufficient H_2S to maintain vascular health[111]. Hyperhomocysteinemia is a known culprit for endothelial dysfunction and cardiovascular disorders[112,113]. Hyperhomocysteinemia is a risk factor for cardiovascular and cerebrovascular diseses. Homocysteine thiolactone, 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[114]. Increase homocysteine levels may be a consequence of decreased endothelial production of H_2S[115]. 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[116]. Garlic containing high sulfur compounds like SAC can correct sulfur deficiencies caused by low protein diet[87]. Budoff MJ studied the effect of garlic in patients with atherosclerosis and found the garlic's potential in reduction of homocysteine levels[117]. H_2S deficiency is known to contribute to vascular dysfunction, including hypertension[111,118]. H_2S is a vascular gaseous signal transmitter present in various mammalian tissues like vascular smooth muscle cells, heart, brain and nervous system[111]. Hyperhomocystenemia results in decreased production of NO and H2S and results in vascular dysfunction.

Diabetes, dementia, alzheimer's and role of garlic

Risk factors for cardiovascular diseases like hypertension, hyperlipidemia, hyperchomocysteinemia also pose a risk for dementia like Alzheimer's disease (AD)[119]. B amyloid is a hallmark of AD which has been correlated with high cholesterol level[120]. Oxidative damage is also a strong risk factor for both AD and CV disease[121]. The neuroprotective effects of garlic may be due to its antoxidant, antiatherogenic and antiapoptotic property[119]. There is a clear negative correlation between hyperhomocystenemia and brain and cognitive functions[122,123]. Garlic is known to correct hyperhomocystenemia[117]. AGE which is rich in antioxidants has been tried in both the diseases. AGE scavenges oxidants and inhibits lipid peroxidation and inflammatory prostaglandins[124]. It increases levels of superoxide dismutase, catalase, glutathione peroxidase and glutathione[125]. AGE is a known inhibitor of HMG-co A reductase resulting in decreased cholesterol synthesis[126]. 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[127,128]. B amyloid peptides are associated with production of free radicals in cerebral small vessel diseases[129]. Elevated homocysteine levels damage blood vessel endothelial cells and trigger thrombosis. It breaks the DNA, induces apoptosis and causes neuronal death and dementia[114]. Preclinical studies have proved that consumption of AGE reduces homocysteine levels[117,130]. AGE is also known to have additional anti-aging effect[128,131].

Diabetes, nephropathy and protective role of garlic

Proteinuria is the predictor of glomerular injury and increased protein excretion suggests progressive nephropathy[132]. Diabetic rats who presented with nephropathy related proteinuria when treated with garlic showed lowered protein excretion compared to control group[89]. Garlic extract protects against tubular injury by modulation of oxidative stress on the tubules and correcting biochemical alterations[133]. Elevated serum urea and creatinine suggest nephropathy and renal dysfunction in diabetics[132]. A study done by Almadal et al, showed that garlic extract decreased serum urea and creatinine in diabetic rats[134]. El-Demerdash et al also observed the alleviating effect of garlic on renal damage[135]. 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 l936 confirmed the antifungal property of garlic[136]. It reduces the synthesis of lipids, proteins, nucleic acids and inhibit the growth of organism[137] and also damage the membrane[138]. When used locally garlic treated denture stomatitis better than nystatin[139] Allicin[140], DATS[141] and ajone[142] 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[143].

Antibacterial property of garlic

Garlic has been proved to be effective against Salmonella[144,145] and e coli[145], klebsiella[146], pseudomonas, proteus and Staphylococcus aureus[147], clostridium[148], helicobactor pylori[149] and mycobacterium[150].Garlic has been suggested for treatment of multidrug resistant tuberculosis[151]. Garlic extract was found to be effective against human dental plaque microbiota in vitro study[152]. Allicin a form of garlic bears antibacterial property due to inhibition of sulfhydryl enzyme as it modifies sulfhydryl activity[153]. Some vancomycin resistant Enterococci were found to be sensitive for garlic as allicin modifies sulfhydryl group of the TN1546 transposon which encodes vancomycin resistance[154]. 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. [anti-inflammatory

and antimicrobial effects of garlic and synergistic effect between garlic and ciprofloxacin in chronic bacterial prostatitis rat model-international journal of antimicrobial agents[155].

Antiprotozoal property of garlic

Garlic extract was observed to be effective against tinea pedis, entamoeba hystolytica, trypanosoma, leishmania[156]. Clinical trial conducted with garlic on patients with giardiasis resulted into elimination of infection within 3days[157].

Antiviral property of garlic

In vitro studies done with garlic extract showed its activity against influenza A and B[158] rhinovirus, herpes simplex virus 1[159], herpes simplex virus 2[160] Allicin, DATS and ajone all bear antiviral potential[160].

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[161]. Aged black garlic extracts in experimental animals protected liver against hepatic injury by carbon tetrachloride[162]. 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[163]. 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[164]. These studies done in animals need to be confirmed and applied in treatment of fatty liver disorders in diabetic patients. S. Mirunalini administered 2 small sized raw garlic cloves in 20 alcoholic patients for 45 days and observed the hepatoprotective effect of garlic. There was significant improvement in liver enzymes as result of antioxidant effect of garlic[165].

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 fibrinolyitc properties along with generation of NO and H_2S 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

1. King H, Aubert RE, Herman WH. Global burden of diabetes, 1995–2025: prevalence, numerical estimates, and projections. Diabetes Care 1998; 21: 1414–1431.
2. Ernst E. Complementary medicine: common misconceptions. Journal of the Royal Society of Medicine 1995; 88: 244–247.
3. Rahman K. Historical perspective on garlic and cardiovascular disease. *J Nutr*.2001;**131**: 977S–9S.
4. Petrovska BB, Cekovska S. Extracts from the history and medical properties of garlic. *Pharmacogn Rev*. 2010; 4: 106.
5. Moyers SB. *Garlic in Health, History, and World Cuisine*. St Petersburg: Suncoast Press; 1996.
6. Thomson M, Mustafa T, Ali M. Thromboxane-B2 levels in serum of rabbits receiving a single intravenous dose of aqueous extract of garlic and onion. Prostaglandins Leukot Essent Fatty Acids 2000; 63: 217-221.
7. Bordia T, Mohammed N, Thomson M, Ali M. An evaluation of garlic and onion as antithrombotic agents. Prostaglandins Leukot Essent Fatty Acids 1996; 54: 183-186.
8. Kiesewetter H, Jung F, Pindur G, et al. Effect of garlic on thrombocyte aggregation, microcirculation, and other risk factors. Int Clin Pharmacol Ther Toxicol 1991; 29: 151-155.
9. Ali M, Al-Qattan KK, Al-Enezi F, Khanafer RM, Mustafa T. Effect of allicin from garlic powder on serum lipids and blood pressure in rats fed with a high cholesterol diet. Prostaglandins Leukot Essent Fatty Acids. 2000; 62: 253-259.
10. Anwar MM, Meki AR. Oxidative stress in streptozotocin-induced diabetic rats: effects of garlic oil and melatonin. Comp Biochem Physiol A Mol Integr Physiol 2003; 135: 539-547.
11. Rees LP, Minney SF, Plummer NT, Slater JH, Skyrme DA. A quantitative assessment of the antimicrobial activity of garlic (*Allium sativum*.) World J Microbiol Biotechnol 1993; 9: 303-307.
12. Silagy CA, Neil HAW. A meta-analysis of the effect of garlic on blood pressure. *Journal of Hypertension*. 1994;12: 463–468.
13. Dhawan V, Jain S. Effect of garlic supplementation on oxidised low density lipoproteins and lipid peroxidation in patients of essential hypertension. Mol Cell Biochem. 2004; 266:109–115.
14. Banerjee SK, Maulik SK. Effect of garlic on cardiovascular disorders: a review. Nutr J. 2002; 1: 4–14.
15. Jelodar GA, Maleki M, Motadayen MH, Sirus S. Effect of fenugreek, onion and garlic on blood glucose and histopathology of pancreas of alloxan-induced diabetic rats. Indian J Med Sci 2005; 59: 64-69.
16. Liu CT, Hse H, Lii CK, Chen PS, Sheen LY. Effects of garlic oil and diallyl trisulfide on glycemic control in diabetic rats. Eur J Pharmacol 2005; 516: 165-173.
17. Sheela CG, Kumud K, Augusti KT. Anti-diabetic effects of onion and garlic sulfoxide amino acids in rats. Planta Med 1995; 61: 356-357.
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

of *Allium sativum L* and related species. Baltimore: Williams & Wilkins; 1996. p. 37–107.
19. Vinson JA, Su X, Zubik L, Bose P. Phenol antioxidant quantity and quality in foods: fruits. *J Agric Food Chem.* 2001; 49: 5315–5321.
20. Banerjee SK, Mukherjee PK, Maulik SK. Garlic as an antioxidant: the good, the bad and the ugly. *Phytother Res.* 2003; 17: 97–106.
21. Cerriello A. Oxidative stress and glycemic regulation. Metabolism. 2000; 49:27-29.
22. Bonnefont-Rousselot D1. Glucose and reactive oxygen species. Curr Opin Clin Nutr Metab Care. 2002; 5:561-568.
23. Donath MY, Shoelson SE. Type 2 diabetes as an inflammatory disease. Nature Reviews Immunology. 2011; 11:98–107.
24. Lin KY, Ito A, Asagami T, Tsao PS, Adimoolam S, Kimoto M, Tsuji H, Reaven GM, Cooke JP. Impaired nitric oxide synthase pathway in diabetes mellitus: role of asymmetric dimethylarginine and dimethylarginine dimethylaminohydrolase. Circulation. 2002; 106: 987-992.
25. Winocour PD, Watala C, Kinlough-Rathbone RL. Membrane fluidity is related to the extent of glycation of proteins, but not to alterations in the cholesterol to phospholipid molar ratio in isolated platelet membranes from diabetic and control subjects. *Thromb Haemost 1992;* 67: 567– 571.
26. Assert R, Scherk G, Bumbure A, Pirags V, Schatz H, Pfeiffer AF.: Regulation of protein kinase C by short term hyperglycaemia in human platelets in vivo and in vitro. Diabetologia 2001; 44: 188– 195.
27. Tschoepe D, Roesen P, Kaufmann L, Schauseil S, Kehrel B, Ostermann H, Gries FA. Evidence for abnormal platelet glycoprotein expression in diabetes mellitus. *Eur J Clin Invest* 1990; 20: 166–170.
28. Gresele P, Guglielmini G, De Angelis M, Ciferri S, Ciofetta M, Falcinelli E, Lalli C, Ciabattoni G, Davì G, Bolli GB. Acute, short-term hyperglycemia enhances shear stress–induced platelet activation in patients with type II diabetes mellitus. J Am Coll Cardiol 2003; 41: 1013–1020.
29. Westerbacka J, Yki-Järvinen H, Turpeinen A, Rissanen A, Vehkavaara S, Syrjälä M, Lassila R.: Inhibition of platelet-collagen interaction: an in vivo action of insulin abolished by insulin resistance in obesity. *Arterioscler Thromb Vasc Biol 2002;* 22: 167–172.
30. Gresele P, Marzotti S, Guglielmini G, Momi S, Giannini S, Minuz P, Lucidi P, Bolli G. Hyperglycemia-Induced Platelet Activation in Type 2 Diabetes Is Resistant to Aspirin but Not to a Nitric Oxide–Donating Agent. Diabetes Care. 2010; 33: 1262–1268.
31. Handin RI, Karabin R, Boxer GJ. Enhancement of platelet function by superoxide anion. *J Clin Invest 1977;* 59: 959– 965.
32. Schaeffer G, Wascher TC, Kostner GM, Graier WF. Alterations in platelet Ca2+ signalling in diabetic patients is due to increased formation of superoxide anions and reduced nitric oxide production. Diabetologia 1999; 42: 167– 176.
33. Spinetti G, Kraenkel N, Emanueli C, Madeddu P. Diabetes and vessel wall remodelling: from mechanistic insights to regenerative therapies. *Cardiovasc Res 2008;* 78: 265– 273.
34. Caccese D1, Praticò D, Ghiselli A, Natoli S, Pignatelli P, Sanguigni V, Iuliano L, Violi F. Superoxide anion and hydroxyl radical release by collagen-induced platelet aggregation--role of arachidonic acid metabolism. Thromb Haemost. 2000; 83: 485-490.
35. Schäfer A, Bauersachs J. Endothelial dysfunction, impaired endogenous platelet inhibition and platelet activation in diabetes and atherosclerosis. *Curr Vasc Pharmacol* 2008; 6: 52–60.
36. Calverley DC, Hacker MR, Loda KA, Brass E, Buchanan TA, Tsao-Wei DD, Groshen S. Increased platelet Fc receptor expression as a potential contributing cause of platelet hypersensitivity to collagen in diabetes mellitus. *Br J Haematol* 2003; 121: 139–142.
37. Belostocki K, Pricop L, Redecha PB, Aydin A, Leff L, Harrison MJ, Salmon JE.: Infliximab treatment shifts the balance between stimulatory and inhibitory Fcgamma receptor type II isoforms on neutrophils in patients with rheumatoid arthritis. *Arthritis Rheum* 2008; 58: 384– 388.
38. Ravindran R, Krishnan LK. Increased platelet cholesterol and decreased percentage volume of platelets as a secondary risk factor for coronary artery disease. Pathophysiol Haemost Thromb. 2007; 36: 45-51.
39. Sikora J, Kostka B, Marczyk I, Krajewska U, Chałubiński M, Broncel M. Effect of statins on platelet function in patients with hyperlipidemia. Arch Med Sci. 2013; 9: 622–628.
40. Hackeng C, Huigsloot M, Pladet M, Nieuwenhuis K, van Rijn H, Akkerman J. Low-Density Lipoprotein Enhances Platelet Secretion Via Integrin-αIIbβ3–Mediated Signaling. Arterioscler Thromb Vasc Biol. 1999; 19: 239-247.
41. Van Willigen G, Gorter G, Akkerman JW. LDLs increase the exposure of fibrinogen binding sites on platelets and secretion of dense granules. Arterioscler Thromb. 1994;14: 41-46.
42. Tretjakovs P, Kalnins U, Dabina I, Dinne I, Erglis A, Kumsars I, Jurka A. Plasma HDL-cholesterol has an effect on nitric oxide production and arachidonic acid metabolism in the platelet membranes of coronary heart disease patients without LDL-hypercholesterolemia. Med Sci Monit. 2000; 6: 507-511.
43. Srivastava KC. Evidence for the mechanism by which garlic inhibits platelet aggregation. Prostaglandins Leukot Med 1986; 22: 313-321.
44. Rahman K. Effects of garlic on platelet biochemistry and physiology. Mol Nutr Food Res. 2007; 51: 1335-1344.

45. Rahman K, Lowe GM. Garlic and cardiovascular disease: a critical review. J Nutr. 2006; 136: 736S-740S.
46. Bordia AK, Sodhya SK, Rathore AS, Bhu N. Essential oil of garlic on blood lipids and fibrinolytic activity in patients with coronary artery disease. J. Assoc. Phys.Ind. 1978; 26: 327–333.
47. Chutani SK, Bordia AK. The effect of fried versus raw garlic on fibrinolytic activity in man. Atherosclerosis. 1988; 38: 417–421.
48. Steiner M, Li W. Aged garlic extract, a modulator of cardiovascular risk factors: a dose-finding study on the effects of AGE on platelet functions. J Nutr. 2001; 131: 980S-984S.
49. Allison GL, Lowe GM, Rahman K. Aged garlic extract inhibits platelet activation by increasing intracellular cAMP and reducing the interaction of GPIIb/IIIa receptor with fibrinogen. Life Sci. 2012; 91: 1275-1280.
50. Kim JM, Chang HJ, Kim WK, Chang N, Chun HS. Structure-activity relationship of neuroprotective and reactive oxygen species scavenging activities for *Allium* organosulfur compounds. J Agric Food Chem 2006; 54: 6547–6553.
51. Papaharalambus CA, Griendling KK. Basic mechanisms of oxidative stress and reactive oxygen species in cardiovascular injury. Trends Cardiovasc Med 2007; 17: 48–54.
52. Chung LY. The antioxidant properties of garlic compounds: allyl cysteine, alliin, allicin, and allyl disulfide. J Med Food 2006; 9: 205–213.
53. Arguello-Garcia R, Medina-Campos ON, Perez-Hernandez N, Pedraza-Chaverri J, Ortega-Pierres G. Hypochlorous acid scavenging activities of thioallyl compounds from garlic. J Agric Food Chem 2010; 58:11226–11233.
54. Lei YP, Liu CT, Sheen LY, Chen HW, Lii CK. Diallyl disulfide and diallyl trisulfide protect endothelial nitric oxide synthase against damage by oxidized low density lipoprotein. Mol Nutr Food Res 2010; 54: S42–52.
55. Dimmeler S, Fleming I, Fisslthaler B, Hermann C, Busse R, Zeiher AM. Activation of nitric oxide synthase in endothelial cells by Akt-dependent phosphorylation. Nature 1999; 399: 601–615.
56. Wood D. Established and emerging cardiovascular risk factors. *Am Heart J.*2001; 141: S49–57.
57. Dhawan V, Jain S. Effect of garlic supplementation on oxidised low density lipoproteins and lipid peroxidation in patients of essential hypertension. *Mol Cell Biochem.* 2004; 266: 109–115.
58. Keaney JF. Atherosclerosis: from lesion formation to plaque activation and endothelial dysfunction. *Mol Aspects Med*. 2000; 21: 99–166.
59. Gebhardt R. Multiple inhibitory effects of garlic extracts on cholesterol biosynthesis in hepatocytes. *Lipids*. 1993; 28: 613–619.
60. Gupta N, Porter TD. Garlic and garlic derived compounds inhibit human squalene monooxygenase. *J Nutr*. 2001; 131: 1662–1667.
61. Ali M, Thomson M, Alnaqeeb MA. Antithrombotic activity of garlic: its inhibition of the synthesis of thromboxane-TXB2 during infusion of arachidonic acid and collagen in rabbits. Prostaglandins Leukot Essent Fatty Acids 1990; 41: 95–99.
62. Ali M, Thomson M. Consumption of a garlic clove a day could be beneficial in preventing thrombosis. Prostaglandins Leukot Essent Fatty Acids 1995; 53: 211-212.
63. Kim-Park S, Ku DD. Garlic elicits a nitric oxide-dependent relaxation and inhibits hypoxic pulmonary vasoconstriction in rats. *Clin Exp Pharmacol Physiol*.2000; 27: 780–786.
64. Sendl A, Elbl G, Steinke B, Redl K, Breu W, Wagner H. Comparative pharmacological investigations of *Allium ursinum* and *Allium sativum. Planta Med*. 1992; 58: 1–7.
65. Mancardi D, Penna C, Merlino A, Del Soldato P, Wink DA, Pagliaro P. Physiological and pharmacological features of the novel gasotransmitter: hydrogen sulfide. Biochim Biophys Acta 2009; 1787: 864–872.
66. Li L, Rose P, Moore PK. Hydrogen sulfide and cell signaling. Annu Rev Pharmacol Toxicol 2011; 51: 169–187.
67. Zhao W, Zhang J, Lu Y, Wang R. The vasorelaxant effect of H_2S as a novel endogenous gaseous KATP channel opener. EMBO J 2001; 20: 6008–6016.
68. Kondo K, Bhushan S, King AL, Prabhu SD, Hamid T, Koenig S. H_2S protects against pressure overload-induced heart failure via upregulation of endothelial nitric oxide synthase. Circulation 2013; 127: 1116–1127.
69. Johansen D, Ytrehus K, Baxter GF. Exogenous hydrogen sulfide (H_2S) protects against regional myocardial ischemia-reperfusion injury – Evidence for a role of K ATP channels. Basic Res Cardiol 2006; 101: 53–60.
70. Mani S, Li H, Untereiner A, Wu L, Yang G, Austin RC. Decreased endogenous production of hydrogen sulfide accelerates atherosclerosis. Circulation 2013; 127:2523–2534.
71. Imai J, Ide N, Nagae S, Moriguchi T, Matsuura H, Itakura Y. Antioxidant and radical scavenging effects of aged garlic extract and its constituents. Planta Med 1994; 60: 417–420.
72. Borek C. Antioxidant health effects of aged garlic extract. J Nutr 2001; 131:1010S–1015S.
73. Ide N, Lau BH. Garlic compounds minimize intracellular oxidative stress and inhibit nuclear factor-kappa b activation. J Nutr. 2001; 131: 1020S-1026S.
74. Liu C, Cao F, Tang QZ, Yan L, Dong YG, Zhu LH, Wang L, Bian ZY, Li H. Allicin protects against cardiac hypertrophy and fibrosis via attenuating reactive oxygen species-dependent signaling pathways. J Nutr Biochem. 2010; 21: 1238-1250.
75. Kim SR, Jung YR, An HJ, Kim DH, Jang EJ, Choi YJ, Moon KM, Park MH, Park CH, Chung KW, Bae HR, Choi YW, Kim ND, Chung HY. Anti-wrinkle and

anti-inflammatory effects of active garlic components and the inhibition of MMPs via NF-κB signaling. PLoS One. 2013; 8: e73877
76. Förstermann U, Sessa WC. Nitric oxide synthases: regulation and function. Eur Heart J. 2012; 33: 829–837.
77. Weiss N, Papatheodorou L, Morihara N, Hilge R, Ide N. Aged garlic extract restores nitric oxide bioavailability in cultured human endothelial cells even under conditions of homocysteine elevation. J Ethnopharmacol. 2013; 145: 162–167.
78. Zhang XH, Lowe D, Giles P. A randomized trial of the effects of garlic oil upon coronary heart disease risk factors in trained male runners. *Blood Coagulation and Fibrinolysis*. 2001; 12: 67–74.
79. Turner B, Molgaard C, Marckmann P. Effect of garlic (*Allium sativum*) powder tablets on serum lipids, blood pressure and arterial stiffness in normo-lipidaemic volunteers: a randomised, double-blind, placebo-controlled trial. Br J Nutr. 2004; 92: 701–716.
80. Amagase H. Clarifying the real bioactive constituents of garlic. J Nutr. 2006; 136: 716S–725S.
81. Yun HM, Ban JO, Park KR, et al. Potential therapeutic effects of functionally active compounds isolated from garlic. Pharmacol Ther. 2014; 142: 183–195.
82. Amagase H, Petesch BL, Matsuura H, Kasuga S, Itakura Y. Intake of garlic and its bioactive components. J Nutr. 2001; 131: 955S–962S.
83. Lawson LD, Gardner CD. Composition, stability, and bioavailability of garlic products used in a clinical trial. J Agric Food Chem. 2005; 53: 6254–6261.
84. Hoshino T, Kashimoto N, Kasuga S. Effects of garlic preparations on the gastrointestinal mucosa. J Nutr.2001; 131: 1109S–1113S.
85. Shouk R, Abdou A, Shetty K, Sarkar D, Eid A. Mechanisms underlying the antihypertensive effects of garlic bioactives. Nutr Res. 2014; 34: 106–115.
86. Jiang B, Tang G, Cao K, Wu L, Wang R. Molecular mechanism for H2S-induced activation of KATP channels. Antioxid Redox Signal. 2010; 12: 1167–1178.
87. Ried K, Fakler P. Potential of garlic (*Allium sativum*) in lowering high blood pressure: mechanisms of action and clinical relevance. Integrated Blood Press Control. 2014; 7: 71–82.
88. Kumar R, Chhatwal S, Arora S, Sharma S, Singh J, Singh N, Bhandari V, Khurana A. Antihyperglycemic, antihyperlipidemic, anti-inflammatory and adenosine deaminase- lowering effects of garlic in patients with type 2 diabetes mellitus with obesity. Diabetes Metab Syndr Obes. 2013; 6: 49-56.
89. Thomson M, Al-Amin Z, Al-Qattan K, Shaban L, Ali M. Anti-diabetic and hypolipidaemic properties of garlic (Allium sativum) in streptozotocin-induced diabetic rats. Int J Diabetes & Metabolism 2007; 15: 108-115.
90. Mirunalini S, Krishnaveni M, Ambily V. Effects of Raw Garlic (Allium Sativum) On Hyperglycemia In Patients With Type 2 Diabetes Mellitus. Pharmacologyonline 2011; 2: 968-974.
91. Jain RC, Vyas CR. Hypoglycemic action of onion and garlic. Am j nutr 1975; 28: 684-685.
92. Mathew PT, Augusti KT. Studies on the effect of allicin (diallyl disulphide-oxide) on alloxan diabetes. I. Hypoglycaemic action and enhancement of serum insulin effect and glycogen synthesis. Indian J Biochem Biophys. 1973;10: 209-212.
93. Augusti KT, Sheela CG. Antiperoxide effect of S-allyl cysteine sulfoxide, an insulin secretagogue, in diabetic rats. Experientia. 1996; 52: 115-120.
94. Kleijnen J, Knipschild P, Riet G. Garlic, onions and cardiovascular risk factors - A review of the evidence from human experiments with emphasis on commercially available preparations. Br J Clin Pharmacol. 1989; 28: 535–544.
95. Yeh YY, Yeh SM. Garlic reduces plasma lipids by inhibiting hepatic cholesterol and triacylglycerol synthesis. Lipids. 1994; 29:189-193.
96. Chi MS, Koh ET, Stewart TJ. Effects of garlic on lipid metabolism in rats fed cholesterol or lard. J Nutr. 1982; 112: 241-248.
97. Mathew BC, Daniel RS, Augusti KT. Hypolipidemic effect of garlic protein substituted for casein in diet of rats compared to those of garlic oil. Indian J Exp Biol. 1996; 34: 337-340.
98. Gebhardt R. Inhibition of cholesterol biosynthesis by a water-soluble garlic extract in primary cultures of rat hepatocytes. Arzneimittelforschung. 1991; 41: 800-804.
99. Gebhardt R, Beck H. Differential inhibitory effects of garlic-derived organosulfur compounds on cholesterol biosynthesis in primary rat hepatocyte cultures. Lipids. 1996; 31: 1269-1276.
100. Rajasree CR, Rajamohan T, Augusti KT. Biochemical effects of garlic protein on lipid metabolism in alcohol fed rats. Indian J Exp Biol. 1999; 37: 243-247.
101. Mader FH. Treatment of hyperlipidaemia with garlic-powder tablets. Evidence from the German Association of General Practitioners' multicentric placebo-controlled double-blind study. Arzneimittelforschung. 1990; 40:1111-1116.
102. Steiner M, Khan AH, Holbert D, Lin RI. A double-blind crossover study in moderately hypercholesterolemic men that compared the effect of aged garlic extract and placebo administration on blood lipids. Am J Clin Nutr. 1996; 64: 866-870.
103. Mahmoodi M, Islami MR, Asadi Karam GR, Khaksari M, Sahebghadam Lotfi A, Hajizadeh MR, Mirzaee MR. Study of the effects of raw garlic consumption on the level of lipids and other blood biochemical factors in hyperlipidemic individuals. Pak J Pharm Sci. 2006; 19: 295-298.
104. Sobenin IA, Andrianova IV, Demidova ON, Gorchakova T, Orekhov AN. Lipid-lowering effects of time-released garlic powder tablets in double-blinded placebo-controlled randomized study. J Atheroscler Thromb. 2008; 15: 334-338.

105. Zeng T, Guo FF, Zhang CL, Song FY, Zhao XL, Xie KQ. A meta-analysis of randomized, double-blind, placebo-controlled trials for the effects of garlic on serum lipid profiles. J Sci Food Agric. 2012; 92: 1892-1902.
106. Ried K, Toben C, Fakler P. Effect of garlic on serum lipids: an updated meta-analysis. Nutr Rev. 2013; 71: 282-299.
107. Cai H, Griendling KK, Harrison DG. The vascular NAD(P)H oxidases as therapeutic targets in cardiovascular diseases. Trends Pharmacol Sci. 2003; 24: 471-478.
108. Witztum JL, Steinberg D. Role of oxidized low density lipoprotein in atherogenesis. J Clin Invest. 1991; 88: 1785–1792.
109. Argüello-García R, Medina-Campos ON, Pérez-Hernández N, Pedraza-Chaverrí J, Ortega-Pierres G. Hypochlorous acid scavenging activities of thioallyl compounds from garlic. J Agric Food Chem. 2010; 58: 11226-11233.
110. Lei YP, Chen HW, Sheen LY, Lii CK. Diallyl disulfide and diallyl trisulfide suppress oxidized LDL-induced vascular cell adhesion molecule and E-selectin expression through protein kinase A- and B-dependent signaling pathways. J Nutr. 2008; 138: 996-1003.
111. Wang R. Physiological implications of hydrogen sulfide: a whiff exploration that blossomed. Physiol Rev. 2012; 92: 791-896.
112. Schalinske KL, Smazal A. Homocysteine imbalance: a pathological metabolic marker. Adv Nutr. 2012; 3: 755-762.
113. Moat SJ, McDowell IF. Homocysteine and endothelial function in human studies. Semin Vasc Med. 2005; 5:172-182.
114. Seshadri S, Beiser A, Selhub J, Jacques PF, Rosenberg IH, D'Agostino RB, Wilson PW, Wolf PA. Plasma homocysteine as a risk factor for dementia and Alzheimer's disease. N Engl J Med. 2002; 346: 476-483.
115. Beard RS Jr, Bearden SE. Vascular complications of cystathionine β-synthase deficiency: future directions for homocysteine-to-hydrogen sulfide research. Am J Physiol Heart Circ Physiol. 2011; 300: H13-26.
116. Ingenbleek Y, McCully KS. Vegetarianism produces subclinical malnutrition, hyperhomocysteinemia and atherogenesis. Nutrition. 2012; 28: 148-153.
117. Budoff MJ, Takasu J, Flores FR, Niihara Y, Lu B, Lau BH, Rosen RT, Amagase H. Inhibiting progression of coronary calcification using Aged Garlic Extract in patients receiving statin therapy: a preliminary study. Prev Med. 2004; 39: 985-991.
118. Kashfia K, Olsonb K. Biology and therapeutic potential of hydrogen sulfide and hydrogen sulfide-releasing chimeras. Biochemical Pharmacology 2013; 85: 689–703.
119. Mathew BC, Augusti KT. Biochemical effects of garlic protein diet and garlic oil on glycosaminoglycan metabolism in cholesterol fed rats. Indian J Exp Biol. 1996; 34: 346-350.
120. Patil T, Patil S, Patil S, Patil A. Berberine- A Neuropsychiatric Pharmacotherapy. International Journal of Pharmacognosy and Phytochemical Research 2015; 7; 1059-1065.
121. Borek C. Dietary antioxidants and human cancer. Integr Cancer Ther. 2004; 3: 333-341.
122. Smith AD. The worldwide challenge of the dementias: a role for B vitamins and homocysteine? Food Nutr Bull. 2008; 29: S143-172.
123. Smith AD, Smith SM, de Jager CA, Whitbread P, Johnston C, Agacinski G, Oulhaj A, Bradley KM, Jacoby R, Refsum H. Homocysteine-lowering by B vitamins slows the rate of accelerated brain atrophy in mild cognitive impairment: a randomized controlled trial. PLoS One. 2010; 5: e12244.
124. Borek C. Garlic Reduces Dementia and Heart-Disease Risk. J. Nutr. 2006; 136: 810S-812S.
125. Liu L, Yeh YY. S-alk(en)yl cysteines of garlic inhibit cholesterol synthesis by deactivating HMG-CoA reductase in cultured rat hepatocytes. J Nutr. 2002; 132: 1129-1134.
126. Okuhara C. Clinical study of aged garlic extract on peripheral circulation. Jou pharmacol ther 1994; 228: 3695- 3701.
127. Griffin B, Selassie M, Gwebu ET. Effect of Aged Garlic Extract on the Cytotoxicity of Alzheimer β-Amyloid Peptide in Neuronal PC12 Cells. Article in Nutritional Neuroscience 2000; 3: 139-142.
128. Moriguchi T, Saito H, Nishiyama N. Anti-ageing effect of aged garlic extract in the inbred brain atrophy mouse model. Clin Exp Pharmacol Physiol. 1997; 24: 235-242.
129. Yao M, Nguyen TV, Pike CJ. Beta-amyloid-induced neuronal apoptosis involves c-Jun N-terminal kinase-dependent downregulation of Bcl-w. J Neurosci. 2005; 25: 1149-1158.
130. Yeh YY, Lim H, Yeh S, Picciano M. Garlic extract attenuates hyperhomocysteinemia caused by folic acid deficiency in the rat. Nutrition research 2005; 25: 92-102.
131. Nishiyama N, Moriguchi T, Katsuki H, Saito H. Effects of aged garlic extract on senescence accelerated mouse and cultured brain cells. In: Preclinical and clinical strategies for the treatment of neurodegenrative, cerebrovascular and mental disorders. Int Acad Drug Res. Basel Karger 1996; 11: 253–258.
132. Keane WF, Eknoyan G. Proteinuria, albuminuria, risk, assessment, detection, elimination (PARADE): a position paper of the National Kidney Foundation. Am J Kidney Dis. 1999; 33: 1004-1010.
133. Rafieian-Kopaei M, Baradaran A, Merrikhi A, Nematbakhsh M, Madihi Y, Nasri H. Efficacy of Co-administration of Garlic Extract and Metformin for Prevention of Gentamicin-Renal Toxicity in Wistar Rats: A Biochemical Study. Int J Prev Med. 2013; 4: 258-264.
134. Almadal TP. Strict insulin treatment normalizes the organic nitrogen contents and the capacity of urea-N

synthesis in experimental diabetes in rats. Diabetologia 1988; 31: 114-118.
135. El-Demerdash FM, Yousef MI, El-Naga NI. Biochemical study on the hypoglycemic effects of onion and garlic in alloxan-induced diabetic rats. Food Chem Toxicol. 2005; 43: 57-63.
136. Lemar KM, Turner MP, Lloyd D. Garlic (Allium sativum) as an anti-Candida agent: a comparison of the efficacy of fresh garlic and freeze-dried extracts. J Appl Microbiol. 2002; 93: 398-405.
137. M Adetumbi, G T Javor, and B H Lau. Allium sativum (garlic) inhibits lipid synthesis by Candida albicans. Antimicrob Agents Chemother. 1986; 30: 499–501.
138. Ghannoum MA. Studies on the anticandidal mode of action of Allium sativum (garlic). J Gen Microbiol. 1988; 134: 2917-2924.
139. Bakhshi M, Taheri JB, Shabestari SB, Tanik A, Pahlevan R. Comparison of therapeutic effect of aqueous extract of garlic and nystatin mouthwash in denture stomatitis. Gerodontology. 2012; 29: e680-684.
140. Bronwyn G. Hughes and Larry D. Lawson. Antimicrobial effects of Allium sativum L. (garlic), Allium ampeloprasum L. (elephant garlic), and Allium cepa L. (onion), garlic compounds and commercial garlic supplement products. Phytotherapy Research 1991; 5: 154–158
141. Cai Y. Anticryptococcal and antiviral properties of garlic. Cardiol Pract. 1991;9: ll.
142. Yoshida S, Kasuga S, Hayashi N, Ushiroguchi T, Matsuura H, Nakagawa S. Antifungal activity of ajoene derived from garlic. Appl Environ Microbiol. 1987; 53: 615–617.
143. Ghannoum MA. Inhibition of Candida adhesion to buccal epithelial cells by an aqueous extract of Allium sativum (garlic). J Appl Bacteriol. 1990; 68:163-169.
144. Johnson M, Vaughn R. Death of Salmonella typhimurium and Escherichia coli in the Presence of Freshly Reconstituted Dehydrated Garlic and Onion. Appl Microbiol. 1969; 17: 903–905.
145. Adler BB, Beuchat LR. Death of Salmonella, Escherichia coli O157:H7, and Listeria monocytogenes in garlic butter as affected by storage temperature. J Food Prot. 2002; 65: 1976-1980.
146. Jezowa L, Rafinski T, Wrocinski T. Investigations on the antibiotic activity of Allium sativum L. Herba Pol. 1966;12: 3–13.
147. Cavallito C, Bailey J. Allicin, the Antibacterial Principle of Allium sativum. I. Isolation, Physical Properties and Antibacterial Action. J. Am. Chem. Soc. 1944; 66: 1950–1951.
148. Jacora C, Notermans S, Gorin N, Kampelmacher EH. Effect of garlic oil or onion oil on toxin production by Cl. botulinum in meat slurry. Journal of Food Protection 1979; 3: 196-276.
149. O'Gara EA, Hill DJ, Maslin DJ. Activities of garlic oil, garlic powder, and their diallyl constituents against Helicobacter pylori. Appl Environ Microbiol. 2000; 66: 2269-2273.
150. Delaha EC, Garagusi VF. Inhibition of mycobacteria by garlic extract (Allium sativum). Antimicrob Agents Chemother. 1985; 27: 485–486.
151. Dini C, Fabbri A, Geraci A. The potential role of garlic (Allium sativum) against the multi-drug resistant tuberculosis pandemic: a review. Ann Ist Super Sanita 2011; 47: 465-73.
152. Houshmand B, Mahjour F, Dianat O. Antibacterial effect of different concentrations of garlic (Allium sativum) extract on dental plaque bacteria. Indian J Dent Res. 2013; 24: 71-75.
153. Wills ED. Enzyme inhibition by allicin, the active principle of garlic. Biochem J. 1956; 63: 514–520.
154. Jonkers D, Sluimer J, Stobberingh E. Effect of Garlic on Vancomycin-Resistant Enterococci. Antimicrob Agents Chemother. 1999; 43: 3045.
155. Sohn DW, Han CH, Jung YS, Kim SI, Kim SW, Cho YH. Anti-inflammatory and antimicrobial effects of garlic and synergistic effect between garlic and ciprofloxacin in chronic bacterial prostatitis rat model. International journal of antimicrobial agents 2009; 34: 215-219.
156. Reuter HD, Koch HP, Lawson LD. Garlic: The science and therapeutic application of Allium sativum L. and Related Species. In: Koch, HP, LD Lawson, editors. Therapeutic effects and applications of garlic and its preparations. Baltimore: Williams and Wilkins 1966: 135–213.
157. Soffar SA, Mokhtar GM. Evaluation of the antiparasitic effect of aqueous garlic (Allium sativum) extract in hymenolepiasis nana and giardiasis. J Egypt Soc Parasitol. 1991;21: 497–502.
158. Fenwick GR, Hanley AB. Allium species poisoning. Vet Rec. 1985;116: 28.
159. Tsai Y, Cole LL, Davis LE, Lockwood SJ, Simmons V, Wild GC. Antiviral properties of garlic: in vitro effects on influenza B, herpes simplex and coxsackie viruses. Planta Med. 1985;5: 460–461.
160. Weber ND, Andersen DO, North JA, Murray BK, Lawson LD, Hughes BG. In vitro virucidal effects of Allium sativum (garlic) extract and compounds. Planta Med. 1992; 58: 417–423.
161. Nasiru A, Hafsat IG, Sabo AA. Effect of Anti-tuberculosis Drugs Co-administered with Garlic Homogenate on Rat Liver Enzymes. International Journal of Bioscience, Biochemistry and Bioinformatics 2012; 2: 354-357.
162. Shin JH, Lee CW, Oh SJ, Yun J, Kang MR, Han S, Park H, Jung J, Chung YH, Kang JS. Hepatoprotective Effect of Aged Black Garlic Extract in Rodents. Toxicol Res. 2014 Mar; 30(1): 49–54
163. Takemura S, Minamiyama Y, Kodai S, Shinkawa H, Tsukioka T, Okada S, Azuma H, Kubo S S-Allyl cysteine improves nonalcoholic fatty liver disease in type 2 diabetes Otsuka Long-Evans Tokushima Fatty rats via regulation of hepatic lipogenesis and glucose metabolism. J Clin Biochem Nutr. 2013; 53 :94-101.
164. Xiao J, Ching YP, Liong EC, Nanji AA, Fung ML, Tipoe GL. Garlic-derived S-allylmercaptocysteine is a hepato-protective agent in non-alcoholic fatty liver

disease in vivo animal model. Eur J Nutr. 2013; 52: 179-91.
165. Mirunalini S, Arulmozhi V, Arulmozhi T. Curative Effect of Garlic on Alcoholic Liver Diseased Patients. Jordan Journal of Biological Sciences 2010; 3: 147 – 152.