GARLIC (*ALLIUM SATIVUM*) SUPPLEMENTATION WITH STANDARD ANTIDIABETIC AGENT PROVIDES BETTER DIABETIC CONTROL IN TYPE 2 DIABETES PATIENTS

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ABSTRACT
Garlic has been used safely since ancient times as both food and medicine in human populations, but studies of its efficacy in the management of diabetes have yielded conflicting results. This study has evaluated the potential hypoglycemic effects of garlic in type 2 diabetic patients. The study was conducted in diagnosed type 2 diabetic patients (n=60) with fasting blood sugar level above 126 mg/dl to evaluate the effects of adding garlic tablets with standard antidiabetic therapy on blood sugar. Patients were divided randomly into 2 groups. Group 1 (n=30) was given tablet Garlic (KWAI) 300 mg thrice daily + Metformin 500 mg twice daily and Group 2 (n=30) was given Placebo+Metformin 500 mg twice daily respectively for 24 weeks. Serum lipids and fasting blood glucose were measured at week 0, 12 and week 24.
Group1 showed significant reduction in fasting blood sugar at week 24 with a percentage decrease of (-3.12 percent) (P = <0.005) as compared to group 2 (0.59 percent). At the end of week 24, GR1 group also showed considerable decrease in mean total cholesterol (6.2 mg/dl, -2.82%, P=<0.005), LDL-C (-3 mg/dl, 2.18% P=<0.005), triglycerides (-5.2 mg/dl, 3.12%, P<0.005) while HDL cholesterol was significantly increased (2.36 mg/dl, 6.72%, P<0.005) as compared to GR2 group. Combination of garlic with typical antidiabetic remedy has shown to improve glycemic control in addition to antihyperlipidemic activity. Garlic may be a good addition in the management of patients with diabetes and hyperlipidemia.

Keywords: *Allium sativum*, blood glucose, diabetes, garlic.

INTRODUCTION

The pervasiveness of type 2 diabetes mellitus (T2DM) is rising globally almost approaching epidemic proportions (Zimmet *et al*., 2001). According to WHO, the incidence of diabetes was 4.0% in 1995 which by the year 2025 is estimated to mount to 5.4%. This will lead to raise in the number of diabetic patients from 135 million in 1995 to 300 million in 2025. Greater increase will be in developing countries where the number of patients afflicted with diabetes will rise to about 170% from 84 million to 228 million as compared to the developed countries where the number of patients will go up 42%, from 51 million to 72 million (King *et al*., 1998). In Pakistan, no of patients afflicted with diabetes are estimated to increase from 4.3 million in 1995 to 14.5 million in 2025. It is expected that more than 75% of diabetic populace will be from developing countries by the year 2025 (Shera *et al*., 2007).

In patients with T2DM, a common pharmacological treatment approach is less well accepted. Usually treatment started with an oral antidiabetic agent but due to the progressive character of the illness, patients ultimately need one or more supplementary antidiabetic agents (DeFronzo, 1999). Selection of particular drug depends upon on individual patient status and the presence of other cardiovascular risk factors like dyslipidemia and hypertension (Nathan DM *et al*., 2009).

Owing to the worldwide rise in the incidence and socioeconomic burden of diabetes**,** it is quite important to discover pharmacological preparation that not only provide good glycemic control but also proved to be safe and cost effective. The utilization of natural substances has increased for various diseases amongst general public over last few years not only because of their easy availability without prescription, cost and appointment to the health care professionals, but also owing to the belief that natural substances has less adverse effects as compared to synthetic medicines. Numerous natural substances have been investigated for their potential antidiabetic effects (Fujita *et al*., 2001; Park *et al*., 2006; Youn *et al.,* 2004). Garlic is one of such natural substances which have been considered for long time to provide protective effects on various cardiovascular disease risk factors (Steiner *et al*., 2001). Although blood glucose lowering effect of different garlic preparations has been comprehensively reported in animal models of diabetes (Anwar *et al*., 2003; Duncan, 1999; Liu *et al*., 2005; Liu *et al*., 2006), studies reporting hypoglycemic effects of garlic in humans are scarce and conflicting (Bordia *et al*., 1998; Jain *et al*., 1993; Zhang *et al.,* 2001). Keeping in mind the lack of scientific evidence regarding hypoglycemic effects of garlic from human studies and inconsistent data from animal studies and increasing

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prevalence of diabetes mellitus worldwide and growing curiosity in natural remedies, we designed a study to substantiate the blood glucose lowering potential of garlic in type 2 diabetic patients.

MATERIALS AND METHODS

This was a 24 weeks, single-blind and placebo controlled study. Study was done simultaneously in different primary health care centers in Karachi, Pakistan in cooperation with registered medical practioners. Patients with diagnosed type 2 diabetes mellitus (n=60) were recruited and were divided into 2 groups, each comprised of 30 patients. Patients in group 1 (GR1) were given garlic tablets (odor-free, commercial preparations, Kwai, Lichtwer Pharmaceuticals, Berlin, Germany that provides 0.6% allicin) at a dose of 300 mg three times per day while patients in group 2 (GR2) were given placebo. Both the groups received metformin in addition to garlic and placebo respectively at a dose of 500 mg twice daily. All patients in the study were selected according to following criteria.

Inclusion criteria

Patients of either sex, aged between 25-70 years, with recently diagnosed type 2 diabetes mellitus with fasting blood sugar levels between 100 to 130 mg/dl.

Exclusion criteria

Patients having record of allergy to garlic, ischemic heart disease, angina, impaired hepatic or renal dysfunction, bleeding disorders and pregnant or lactating women.

The patient's previous record and recent blood glucose levels were evaluated at the time of presentation in OPD and those having a profile that fulfilled our inclusion criteria were counseled those who were ready to participate and follow study protocol were enrolled after taking informed and written consent (tables 1 and 2). All the necessary credentials of patient's, record of follow up visits and laboratory analysis data of each patient were documented on special proforma intended for this study. The patients were advised to come for follow-up fortnightly. Patients were advised to come with 12 hours fasting for lipid profile and fasting blood sugar analysis at week 0, week 12 and week 24 respectively. At each visit, all patients were fully inquired about drug compliance and side effects of drugs. Patients were motivated to keep their nutritional plan, physical activity, and general life style as constant as possible throughout the study period. The patients were forbidden to take any other medication during the study period. Statistical analysis was done with one-way analysis of variance (ANOVA) followed by Tukey post-hoc test. Statistical P value less than 0.05 was considered significant.

RESULTS

The present study demonstrated significant reduction in fasting blood sugar levels in group 1 (GR2=Garlic ±metformin) as compared to group 2 (GR2=Placebo ±metformin).

The demographic data of the study population is shown in table 1. The patients were male (56%) and females (40%). The mean age was 40 years in garlic treated group and 35 years in placebo treated group (range 25-60 years) (table 1). Measurements of fasting blood glucose and lipid profile were done at 12 week intervals i.e. at week 0, week 12 and week 24 (table 1 and 2, figs. 1 and 2). Out of 60 patients initially enrolled in the study, fifty-four patients completed the study protocol till week 24. One patient in the garlic added group (GR1) reported heart burn in the first week of study and say no to follow the study protocol. Two patient in GR1 and three patients in placebo group (GR2) were dropped out as they did not come back for follow up due to unknown reasons. Seventeen patients in GR1 and eighteen patients in GR2 were found to have concurrent dyslipidemia.

Table 1: Demographic Data of GR1 and GR2 Group

	GR1 Garlic + Metformin	GR2 Placebo+ Metformin
Men	17	16
Women	13	14
Age (years)	40 ± 5.04	35 ± 4.58
Body weight (Kg)	68.2 ± 10.45	69.1 ± 7.58
Height (cm)	165.2 ± 8.81	166.4 ± 6.58
Average duration of type 2 diabetes mellitus	Recently diagnosed	Recently diagnosed
Co-morbid disease	None	None

Table 2: Changes in Fasting Blood Glucose from week 0 to week 12 & week 24 of treatment with GR1 and GR2 in patients with type 2 diabetes mellitus

	Drugs	Week 0 (mg/dl)	Week 12 (mg/dl)	Week 24 (mg/dl)
Fasting Blood Glucose	GR1	128.3 ± 0.311 (n=30)	126.9 ± 0.369* (n=27)	124.8 ± 0.330** (n=27)
	GR2	112.9 ± 0.542 (n=30)	111.7 ± 0.540 (n=27)	110.2 ± 0.520 (n=27)

GR1 = (Garlic+ Metformin), GR2 = (Placebo + Metformin)
*Significant P value <0.05 as compared to placebo
**Highly significant P value <0.005 as compared to placebo.
Values are in mean ± SEM
All observations were measured in mg/dl.
Figures in Parenthesis indicate number of patients.

At the end of week 24, the changes in fasting blood glucose levels from week 0 to week 24 were significantly

divergent between GR1 and GR2 groups (table 2 and fig. 1). The GR1 group has shown significant reduction in mean glucose levels. The garlic treated GR1 group had a mean fasting blood glucose of 128.3 ± 0.311 mg/dl at week 0 which was reduced to 126.9 ± 0.369* mg/dl (P<0.05) at week 12 and to 124.8 ± 0.330** mg/dl (P<0.005) at week 24. The percentage change in fasting blood glucose from week 0 to week 24 in GR1 showed a greater decreasing trend (3.12 %) (P=<0.005) as compared to GR2 which showed a decrease of 1.78%.

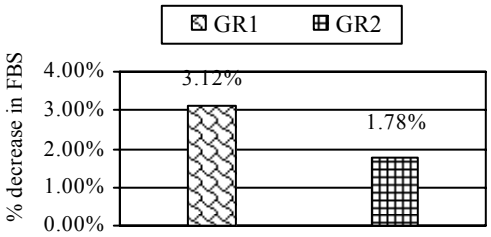

Fig. 1: % change in FBS from week 0 to week 24 with GR1 and GR2:
GR1 = Garlic + Metformin, GR2 = Placebo + Metformin
FBS= Fasting blood sugar

The changes observed in total cholesterol, HDL-cholesterol, and LDL-cholesterol and triglycerides were appreciably dissimilar when compared between GR1 and GR2 groups (table 3 and fig. 2). The garlic treated group had a significant reduction in mean total cholesterol as compared to the placebo treated group. At the end of week 24, GR1 group showed considerable decrease in mean total cholesterol (6.2 mg/dl, -2.82%, P=<0.005), LDL–C (-3 mg/dl, 2.18 % P=<0.005), triglycerides (-5.2 mg/dl, 3.12%, P<0.005) while HDL cholesterol was significantly increased (2.36 mg/dl, 6.72%, P<0.005) as compared to GR2 group. The changes in lipid profile were appeared to be duration dependent as the significant increase in HDL was seen after 12 weeks of study.

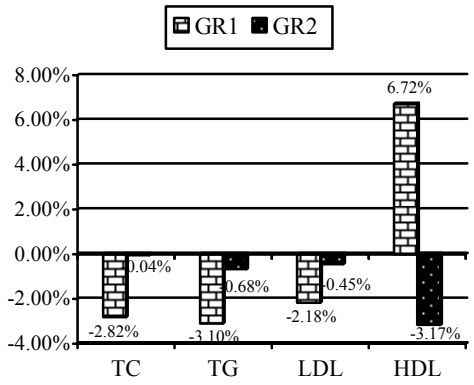

Fig. 2: % changes in Lipid Profile with GR1 and GR2 from week 0 to week 24.
GR1 = Garlic + Metformin, GR2 = Placebo + Metformin
(-) indicates decrease in percentage, T. Chol. = Total Cholesterol, TG. = Triglyceride, HDL = High

DISCUSSION

The present study was focused to monitor the effects of addition of garlic to antidiabetic agent metformin on fasting blood glucose levels in patients with type 2 diabetes mellitus; metformin was selected in this study since it is recognized as a first-line antidiabetic agent for the management of type 2 diabetes (Esposito *et al*., 2011). It is suitable irrespective of age, body weight, severity of hyperglycemia and provides a convenient pharmacological base for combined therapy with other antidiabetic agents (Scarpello and Howlett, 2008). Metformin has a lower mortality and cardiovascular risk as compared with most insulin secreting agents such as glimepiride, glibenclamide, glipizide, and tolbutamide in patients with type 2 diabetes mellitus (Schramm T *et al*., 2011). Another benefit of metformin is that it does not produce hypoglycemia because it does not stimulate insulin secretion when it is given alone in patients with type diabetes mellitus (Wright *et al*., 2006). Metformin is also renowned to facilitate modest weight loss in type 2 diabetic patients (Golay, 2008). The garlic was added to antidiabetic agent metformin with the hypothesis that it will not only provide better glycemic control but will also helps in improving lipid profile which is a frequent occurrence in patients with type 2 diabetes mellitus. The results observed in the present study demonstrate statistical significant decrease in fasting blood glucose and serum lipids when compared from baseline values at week 0 to week 12 and week 24 in garlic treated group as compared to placebo treated group.

Our study confirms the earlier hypoglycemic effects of garlic observed in previous preclinical trials. Numerous trials in animal models of diabetes (Al-Qattan *et al*., 2008; Eidi *et al*., 2006; Sheila *et al*., 1992; Chang *et al.,* 1980; Jeloder *et al*., 2005, Banerjee *et al*., 2003) has demonstrated the blood glucose lowering as well as antioxidant effects of garlic (Lee *et al*., 2009). Insulin levels were found to be increased in diabetic rats when given garlic oil (Devaki *et al.,* 1992; Venmahdi *et al*., 1992). Garlic was also found to be effective in preventing adrenal hypertrophy, elevation of corticosterone and increased blood glucose in diabetic mice (Kasuga *et al*., 1999). S-allyl cysteine sulfoxide (alliin), a sulfur containing amino acid in garlic has been reported to have comparative efficacy with standard antidiabetic agents like glibenclamide and insulin in controlling hyperglycemia in diabetic animals (Sheela *et al*., 1995; Sheela *et al*., 1992). The changes observed in present study are in accordance with the findings of Eidia *et al*., 2006 who reported that administration of the both garlic extract and glibenclamide tend to bring serum glucose and insulin appreciably toward normal values.

Although many of the previous trials in animal models showed considerable hypoglycemic effects of garlic,

human studies are inadequate and showed conflicting results. Some of the clinical trials on garlic showed hypoglycemic effects in humans (Zhang *et al*., 2001; Kiesewetter *et al*., 1991; Bordia *et al*., 1998; Jain *et al*., 1993; Ali *et al*., 1995), but were done in normal healthy individuals. The present study is unique from previous clinical trials because hypoglycemic effects of garlic have been observed in patients with type 2 diabetes mellitus in combination with a standard antidiabetic agent metformin. The present study is in accordance with a previous clinical trial by Sobenin *et al*., 2008 who also reported hypoglycemic potential of garlic in patients with type 2 diabetes mellitus although the preparation used was different from that used in the present study. Our study contradicts with the study of Afkhami-Ardekani *et al*., 2006 who reported that garlic has no hypoglycemic and antilipidemic effects. The hypoglycemic effects observed in this study are also in agreement with the earlier clinical trial by Li *et al*., 2000 that reported discernible reduction in blood sugar levels in patients with hyperglycemia. Mahmodi *et al*., 2006 also reported hypoglycemic effects of garlic similar to that found in our study. Although the precise mechanism for hypoglycemic effects of garlic is not apparent, however it has been proposed in some studies that garlic acts as an insulin secretagogue. It has also been proposed that allylepropyldisulphide or diallyle disulphide present in garlic are responsible for hypoglycemic effect of garlic (Jain *et al*., 1973; Chang *et al*., 1980; Jain *et al*., 1974; Jain *et al*., 1975). Antioxidant effects of garlic are another possible mechanism that makes it a contender as antidiabetic agent (Queiroz *et al*., 2009; Lee *et al*., 2009). Antioxidant effect of S-allyl cysteine sulfoxide, isolated product from garlic, is considered to possess antiglycation properties.

Garlic was also found to produce hypoglycemic effects by sparing insulin inactivation from sulphydryl group (Banerjee *et al.,* 2002). Patients with diabetes frequently have coexisting hyperlipidemia commonly known as diabetic dyslipidemia that is known to increase the risk for cardiovascular disease many fold. Patients with diabetes commonly require combination of antidiabetic and antilipidemic agents to prevent the patients against morbidity associated with cardiovascular disease. We found significant antilipidemic effects of garlic on all the lipid parameters as compared to placebo group. The change observed in lipid profile in the present study is in accordance with previous clinical trials (Steiner *et al*., 1996; Tohidi *et al*., 2000; Ashraf *et al*., 2005; Jabbar *et al.*, 2005; Kannar *et al*., 2001).

The proposed mechanism for antilipidemic effects of garlic is inhibition of hydroxymethylglutaryl-CoA reductase (HMG-CoA reductase), by allicin (Siegel *et al*., 1999; Adler *et al*., 1997). Garlic is supposed to reduce total cholesterol largely owing to decrease in LDL-C levels. The present study contradicts with some previous trials (Tanamai *et al*., 2004; Turner *et al*., 2004; Peleg *et al*., 2003) which showed garlic to be ineffective. The most probable reason for this contradiction may be attributed to difference in garlic preparation, dose and duration of study.

Although garlic was assumed safe and recommended for many common ailments since ancient times, too much utilization of garlic can cause problems. Garlic breath and infrequent allergic response are predictable adverse effects. Reports have also revealed gastrointestinal side effects like nausea and diarrhea (Sieger *et al*., 1992; Desai *et al*., 1990) associated with raw garlic and garlic powder preparations. In the present study, garlic did not produce any considerable problem in patients with type 2 diabetes mellitus and only one patient has complained of gastric discomfort, the possible reasons for this good tolerance might be enteric coated, odorless garlic tablet preparation used in this study.

CONCLUSION

The present study has demonstrated significant hypoglycemic and hypolipidemic effects of garlic when added with standard antidiabetic agent. Comprehensive clinical studies are desirable to verify the effectiveness of garlic either alone or in combination with other antidiabetic or antihyperlipidemic agents in the treatment and prevention of diabetes and other cardiovascular risk factors.

Disclosure statement

The authors do not have any competing financial interests.

REFERENCES

Adler AJ and Holub BJ (1997). Effect of garlic and fresh oil supplementation on serumlipids and lipoproteins concentration in hypercholesterolemic men. *Am. J. Clin. Nut.,* **65**: 445-450.

Afkhami-Ardekani M, Kamali-Ardekani A and Shojaoddiny-Ardekani A (2006). Effects of garlic on serum lipids and blood glucose of type 2 diabetic patients. *Int. J. Diab. Dev. Ctries.,* **26**: 86-88.

Ali M and Thomson M (1995). Consumption of garlic clove a day could be beneficial in preventing thrombosis. *Prostaglandins Leukot Essent Fatty Acids*, **53**: 211-212.

Al-Qattan K, Thomson M and Ali M (2008). Garlic (*Allium sativum*) and ginger (*Zingiber officinale*) attenuate structural nephropathy progression in streptozotocin-induced diabetic rats. *Eur E J Clin Nutr Metab*, 3: e62-e71.

Anwar MM and Meki AR (2003). Oxidative stress in streptozotocin-induced diabetic rats: effects of garlic oil and melatonin. *Comp. Biochem. Physiol., Part A Mol. Integr. Physiol.,* **135**: 539-547.

Ashraf R, Aamir K, Shaikh RA and Ahmed T (2005). Effects of garlic on dyslipidemia in patients with type 2 diabetes mellitus. *J. Ayub. Med. Coll*., **17**(3): 60-64.

Banerjee SK, Mukherjee PK and Maulik SK (2003). Garlic as an antioxidant: The good, the bad and the ugly. *Phytother Res.,* **17**: 97-106.

Banerjee SK and Maulik SK (2002). Effect of Garlic on cardiovascular disorders; review. *Nutr J.,* **1**: 4.

Bordia A, Verma SK and Srivastava KC (1998). Effect of garlic (Allium Sativum) on blood lipids, blood sugar, fibrinogen, and fibrinolytic activity in patients with coronary artery disease *Prostaglandins Leukot Essent Fatty Acids*, **58**: 257-263.

Chang MW and Johnson MA (1980). Effect of garlic on carbohydrate metabolism and lipid synthesis in rats. *J. Nutr*., **110**: 931-936.

Defronzo RA (1997). Pathogenesis of diabetes. *Diabetes, Rev*., **5**: 177.

Desai HG, Kalro RH and Choksi AP (1990). Effect of ginger and garlic on DNA content of gastric aspirate. *Indian J. Med*., **92**: 139-141.

Devaki T, Venmahdi S and Govindaraju P (1992). Alterations in protein metabolism in ethanol-ingested rats treated with garlic. *Med. Sci. Res*., **20**: 725-727.

Duncan MG (1999). The effects of nutritional supplements on the treatment of depression, diabetes, and hypercholesterolemia in the renal patient. *J. Ren. Nutr*., **9**: 58-62.

Eidi A, Eidi M and Esmaeili E (2006). Antidiabetic effect of garlic (*Allium sativum* L.) in normal and streptozotocin-induced diabetic rats. *Phytomedicine,* **13**: 624-629.

Esposito K, Bellastella G and Giugliano D (2011). When metformin fails in Type 2 diabetes mellitus. *Arch. Intern. Med.*, **171**(4): 365-366.

Fujita H, Yamagami T and Ohshima K (2001). Long-term ingestion of a fermented soybean-derived *Touchi*-extract with alpha-glucosidase inhibitory activity is safe and effective in humans with borderline and mild type-2 diabetes. *J. Nutr*., **131**: 2105-2108.

Golay A (2008). Metformin and body weight. *Int. J. Obes*., **32**: 61-72.

Jabbar A, Argani H, Ghorbanihaghjo A and Mahdavi R (2005). Comparison between swallowing and chewing of Garlic on levels of serum lipids, cycloserine, creatinine and lipid peroxidation in renal transplant recipients. *Lipids Health Dis.,* **4**: 11.

Jain AK Jain AK, Vargar R, Gotzkowsky S and McMahon FG (1993). Can garlic reduce levels of serum lipids? A controlled clinical study. *Am. J. Med*., **94**: 632-635.

Jain RC and Vyas CR (1975). Garlic in alloxan-induced diabetic rabbit. *Am. J. Clin. Nutr*., **28**: 684-685.

Jain RC and Vyas CR (1974). Hypoglycemic action of onion on rabbits. *Br. Med. J.,* **2**: 730.

Jain RC and Vyas CR (1973). Hypoglycemic action of onion and garlic. *Lancet,* **2**: 1491.

Jelodar GA, Maleki M, Motadayen MH and Sirus S (2005). Effect of fenugreek, onion and garlic on blood glucose and histopathology of pancreas of alloxan induced diabetic rats. *Indian J. Med. Sci*., **59**(2): 64-69.

Kannar D, Wattanapenpaiboon N, Savige GS and Wahlqvist ML (2001). Hypocholesterolemic effect of an enteric coated garlic supplement. *J. Am. Coll. Nutr*., **20**: 225-231.

Kasuga S, Ushijima M, Morihara N, Itakura Y and Nakata Y (1999). Effect of aged garlic extract (AGE) on hyperglycemia induced by immobilization stress in mice. *Nippon Yakurigaku Zassh*., **114**: 191-197.

Kiesewetter H, Jung F, Pindur G, Jung EM, Mrowietz C and Wenzel E (1991). Effect of garlic on thrombocyte aggregation, microcirculation, and other risk factors. Int. *J. Clin. Pharmacol. Ther. Toxicol*., **29**: 151-155.

King H, Aubert RE and Herman WH (1998). Global burden of diabetes, 1995-2025: Prevalence, numerical estimates, and projections. *Diabetes Care,* **21**: 1414-1431.

Lee YM, Gweon OC, Seo YJ, Im J, Kang MJ, Kim MJ, Kim JI (2009). Antioxidant effect of garlic and aged black garlic in animal model of type 2 diabetes mellitus. *Nutr Res Pract.*, **3**:156-61.

Liu CT, Hse H, Lii CK, Chen PS and Sheen LY (2005). Effects of garlic oil and diallyl trisulfide on glycemic control in diabetic rats. *Eur. J. Pharmacol*., **516**: 165-173.

Liu CT, Wong PL, Lii CK, Hse H and Sheen LY (2006). Antidiabetic effect of garlic oil but not diallyl disulfide in rats with streptozotocin-induced diabetes. *Food Chem. Toxicol.,* **44**: 1377-1384.

Li G, Shi Z, Jia H, Ju J, Wang X, Xia Z, Qin L, Ge C, Xu Y, Cheng L, Chen P and Yuan GA (2000). Clinical investigation on garlicin injection for treatment of unstable angina pectoris and its actions on plasma endothelin and blood sugar levels. *J. Tradit. Chin. Med.,* **20**(4): 243-246.

Mahmoodi M, Islami MR, Asadi Karam GR, Khaksari M, Sahebghadam Lotfi A, Hajizadeh MR and Mirzaee MR (2006). 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.,* **19**(4): 295-298.

Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R and Zinman B (2009). Medical management of hyperglycemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy: A consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*, **32**: 193-203.

Park SA, Choi MS, Jung UJ, Kim MJ, Kim DJ, Park HM, Park YB and Lee MK (2006). *Eucommia ulmoides* Oliver leaf extract increases endogenous antioxidant activity in type 2 diabetic mice. *J. Med. Food,* **9**: 474-479.

Peleg A, Hershcocivi T, Lipa R, Anbar R, Redler M and Beigel Y (2003). Effect of Garlic on lipid profile and psychopathologic parameters in people with mildtomoderate hypercholesterolemia. *Isr. Med. Assoc. J*., **5**(9): 637-640.

Queiroz YS, Ishimoto EY, Bastos DH, Sampaio GR and Torres EA (2009). Garlic (*Allium sativum* L.) and ready-to-eat garlic products: *In vitro* antioxidant activity. *Food Chem.,* **115**: 371-374.

Scarpello JHB and Howlett HC (2008). Metformin therapy and clinical uses. *Diabetes Vasc. Dis. Res.*, **5**: 157-167.

Schramm TK, Gislason GH, Vaag A, Rasmussen JN, Folke F, Hansen ML, Fosbøl EL, Køber L, Norgaard ML, Madsen M, Hansen PR and Torp-Pedersen C (2011). Mortality and cardiovascular risk associated with different insulin secretagogues compared with metformin in type 2 diabetes, with or without a previous myocardial infarction: a nationwide study. *Eur. Heart J.*, epub 6 April 2001, doi:10.1093/ eurheartj/ehr077

Siegel G, Walter A, Engel S, Walper A and Michel F (1999). Pleiotropic effects of Garlic. *Wien. Med. Wochenschr*., **149**: 217-224.

Siegers CP (1992). *Allium sativum. In*: Adverse effects of herbal drugs (DeSmet PAGM, Keller K, Hansell R and Chandler R F eds). *Springer-Verlag.* Berlin, Germany, pp.73-77.

Sheela CG and Augusti KT (1992). Anti-diabetic effects of S-allyl cysteine sulphoxide isolated from garlic Allium Sativum L. *Indian J. Exp. Biol.,* **30**: 523-526.

Sheela CG, Kumud K and Augusti KT (1995). Anti-diabetic effect of onion and garlic sulfoxide amino acids in rats. *Planta Medica*., **61**: 356-357.

Sheela CG and Augusti KT (1992). Anti-diabetic effects of S-allyl cysteine sulphoxide isolated from garlic *Allium sativum* Linn. *Indian J. Exp. Biol*., **30**: 523-526.

Shera AS, Jawad F and Maqsood A (2007). Prevalence of diabetes in Pakistan. Diabetes Res Clin Pr., **76**: 219-222.

Sobenin IA, Nedosugova LV, Filatova LV, Balabolkin M I, Gorchakova T V and Alexander N. Orekhov (2008). Metabolic effects of time-released garlic powder tablets in type 2 diabetes mellitus: the results of double-blinded placebo-controlled study. Acta Diabetol., **45**:1-6.

Steiner M and Li W (2001). Recent advances on the nutritional effects associated with use of garlic as a supplement. Aged garlic extract, a modulator of cardiovascular risk factors. A dose finding study on the effects of AGE on platelet functions. *J. Nutr*., **131**: 980S-984S.

Steiner M, Khan AH, Holbert D and Lin RI (1996). 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*., **64**: 866-870.

Tanamai J, Veeramanomai S and Indrakosas N (2004). The efficacy of cholesterol-lowering action and side effects of garlic enteric coated tablets in man. *J. Med. Assoc. Thai*., **87**(10): 1156-1161.

Tohidi M and Rahbani M (2000). Evaluation of the effects of garlic powder on blood pressure, serum lipids and lipoproteins. *Pharmacy journal of Tabriz Univ Med. Sci.,* **4**: 16-20.

Turner B, Molgaard C and Markmann P (2004). Effect of Garlic (Allium Sativum) powder tablet on serum lipid, blood pressure and arterial stiffness in normolipidemic volunteers: A randomized double blind, placebo controlled trial. *Br. J. Nutr*., **92**: 701-706.

Venmahdi S and Devaki T (1992). Studies on some liver enzymes in rats ingesting ethanol and treated with garlic oil. *Med. Sci. Res*., **20**: 729-731.

Wright AD, Cull CA, Macleod KM and Holman RR (2006). Hypoglycemia in Type 2 diabetic patients randomized to and maintained on monotherapy with diet, sulphonylurea, metformin, or insulin for 6 years from diagnosis: UKPDS73. J Diabetes Complications., **20**: 395-401.

Youn JY, Park HY and Cho KH (2004). Anti-hyperglycemic activity of *Commelina communis* L. inhibition of α-glucosidase. *Diabetes Res. Clin. Pract.,* **66S**: S149-S155.

Zhang Xh, Lowe D, Giles P, Fell S, Connock MJ and Maslin DJ (2001). Gender may affect the action of garlic oil on plasma cholesterol and glucose levels of normal subjects. *J. Nutr.,* **131**: 1471-1478.

Zimmet P, Alberti KG and Shaw J (2001). Global and societal implications of the diabetes epidemic. *Nature,* **414**: 782-787.