

Analysis of dose and duration dependent effects of *Allium sativum* Linn and other hypocholesterolemic agents exhibited on dyslipidemia in patients with essential hypertension

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Abstract: Globally, cardiovascular diseases (CVD) are one of the most significant cause of organ failure, mortality and substantial escalation of health care cost. Dyslipidemia and hypertension poses significant risks in cardiovascular diseases and morbidity and mortality can be minimized by altering risks factors. Dyslipidemia is one of the major leading cause of rise of global incidences and socioeconomic burden which necessitates to explore the pharmacological options of significant antilipemic activity with minimal untoward effects at affordable price. *Allium Sativum* (Garlic) proved medicinally effective in different clinical trials, but further investigations are required to investigate its effects on diabetes, hypertension and dyslipidemia based on variable doses and duration. In this study dose and duration dependent effects of Garlic were evaluated on hypertensive patients with dyslipidemia. Study was randomized, single blind and placebo controlled. Effects of tablets of garlic (KWAJ) 300 mg in doses of daily 0.3g, 0.6g, 0.9g, 1.2g and 1.5g for 24 weeks were compared in humans. Each tablet contains 1.3 percent of alliin and 0.6 % of alliin. Results showed remarkable improvements in different serum lipid levels (Cholesterol, Triglycerides, Low density lipoproteins and High density lipoproteins) based on different doses and duration as compared to placebo and standard Lipid-lowering agent simvastatin.

Keywords: Hypertension, dyslipidemia, garlic, simvastatin.

INTRODUCTION

Globally, cardiovascular diseases are considered not only a leading cause of disability and early death but also play an important role in rising health care costs and is among the leading causes of global mortality, representing 31% of all global deaths (Roth *et al.*, 2020). Hypertension, dyslipidemia, diabetes mellitus, smoking, lack of physical activities and obesity are well established risks of cardiovascular diseases (CVD) (Tran *et al.*, 2021). It is evident from different studies that these risks are continuously escalating in developing countries (Ruan *et al.*, 2018). Recently it was found that impaired lipid profile and high blood pressure are major contributors in CVD (Ayoadea *et al.*, 2020). Morbidity and mortality of cardiovascular patients can be reduced by managing these risk factors (Yusuf *et al.*, 2020). Dyslipidemia is a known amendable risk factor in coronary artery disease and atherosclerosis (Hedayatnia *et al.*, 2020). Pakistan has an almost equal rate of incidences as that of developed countries (Talpur *et al.*, 2020; Zaid 2018; Liaquat 2018; Khan 2016). Epidemiological studies of previous years have shown that, incidence of hypertension is constantly increasing. Approximately more than a billion are suffering from hypertension, which is projected to be 1.5

billion by 2025 (Nawi, 2020).

Multiple studies proved the coexistence of high blood pressure with dyslipidemia, which is termed as 'Lipitension' by one author (Dalal, 2012). It is defined as raised blood pressure and serum lipids as a part of metabolic syndrome referred by National Cholesterol Education Program guidelines (Onat *et al.*, 2005). The risk of CVD will be multiplied in hypertensive patients with dyslipidemia as compared to the other collective risk factors (Ariyanti and Besral, 2019).

Garlic is well known for its lipid lowering effects with some controversial reports for its efficacy (Sun *et al.*, 2018). Enormous studies have been conducted to verify the beneficial effects of garlic on serum levels of normal and raised cholesterol (Ansary *et al.*, 2020; Limbu, 2019). These studies have shown some limitations in methodologies, but the results of different meta-analyses found reduction of serum cholesterol, low density lipoprotein and triglycerides up to 6-12% as compared to placebo (Alam, 2018; Alder *et al.*, 2003, Stevinson, 2000). Whereas some studies and meta analyses didn't find any significant effects of garlic on lipid profile (Khoo & Aziz, 2009; Gardner *et al.*, 2007; Zhang *et al.*, 2006; Van Doorn *et al.*, 2006; Turner, 2004; Kannar *et al.*,

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2001; McCrindle *et al.*, 1998; Berthold *et al.*, 1998; Neil *et al.*, 1996).

Keeping the rise in global incidence and socioeconomic burden of CVD risks in different populations in view, it is deemed necessary to explore the other pharmacotherapeutic agents with notable improvement in dyslipidemia with minimal toxicity at an affordable price (Gyawali, 2021).

Besides the variable therapeutic advantages of garlic proved in multiple trials, its efficacy based on different doses and duration in a range of comorbid conditions is still unexplored

MATERIAL AND METHODS

Purpose of study

Recent inclination of masses towards complementary and alternative therapies for hypertension, diabetes and especially hyperlipidemia demands clinical trials on efficacy of herbal drugs especially *Allium sativum* (Garlic), in these conditions to prevent and reduce cardiovascular risk factors. This study was planned to determine the dose and duration dependent effects of *Allium sativum* (Garlic) in hypertensive patients having dyslipidemia.

The study design was single blind, randomized, placebo controlled to compare the range of beneficial effects of *Allium sativum* (garlic) tablets (KWAI) 300 mg in different doses (1, 2, 3, 4 and 5 tablets) per day. Different health care centers of Karachi were selected for study in collaboration of legally qualified physicians with the direct involvement of the principal investigator. Every patient was given treatment for 24 weeks unless withdrawn from study. The study protocol was approved by Board of Advanced Studies and Research, University of Karachi vide letter No.1172/2260-A/Sc.

Selection and recruitment of patients

Patients of essential hypertension with dyslipidemia (n=210) were selected and classified in seven groups designated from A to G, having 30 participants in each group. Patients of group A-E were given 1, 2, 3, 4 and 5 garlic tablets respectively per day for 24 weeks. Patients

of group F received the standard lipid lowering agent Simvastatin at a dose of 20 mg per day; on the other hand, group G was placebo.

Before recruitment of patients, a thorough medical examination was conducted on each patient keeping inclusion and exclusion criteria in mind. A proper written consent was obtained from every patient. Patients were instructed to keep their usual garlic or onion intake unaltered for the entire study duration. They were also advised to carry on with their usual physical activities and lifestyle.

Patients were not allowed to take any medicine without consulting a physician or investigator and were asked to visit a concerned physician for follow-up at two weeks' interval. Patients of each group were observed for the entire period of study.

Parameters monitored during the study

Blood pressure and fasting lipid profile (Cholesterol, TG, HDL & LDL) were recorded on week 0, week 12 and 24. Blood pressure and physical checkup were also performed during each visit.

Inclusion criteria

Patients were included based on ATP III classification and diagnosed with dyslipidemia. Patients having cholesterol 200-239 mg/dl, TG 150-199 mg/dl, LDL 130-159 mg/dl and HDL cholesterol < 40 mg/dl.

Exclusion criteria

We have excluded from the study patients having allergies to garlic, breast feeding, pregnancy, diabetes mellitus of type 1, history of heart attack, bypass heart surgery, coronary artery disease, unstable angina, heart failure, liver or renal impairment.

STATISTICAL ANALYSIS

Data was reported as mean ± standard error to the mean. Statistical analysis was carried out using one-way analysis of variance (ANOVA) followed by Tukey post-hoc test using SPSS version 21. Paired-t test was used for comparisons of the effects of Garlic, Simvastatin and Placebo on lipid profile from the baseline (week 0) and

Table 1: Demographic data of patients enrolled in hyperlipidemic group

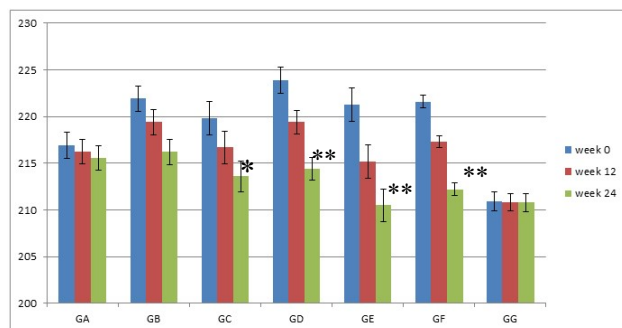
	Garlic treated group GR1	Simvastatin treated group GR2	Placebo treated group GR3
Men	100	16	19
Women	50	14	11
Mean Age (years)	40 ± 5.04	50 ± 5.80	45 ± 4.58
Body weight (Kg)	68.2 ± 10.45	65.4 ± 9.80	69.1 ± 7.58
Height (cm)	165.2 ± 8.81	167.60 ± 9.20	166.4 ± 6.58
Co-morbid disease	Hypertension	Hypertension	Hypertension

the follow-up (week 12 and week 24). Values of $P < 0.05$ were considered as significant and $P < 0.005$ as highly significant.

RESULTS

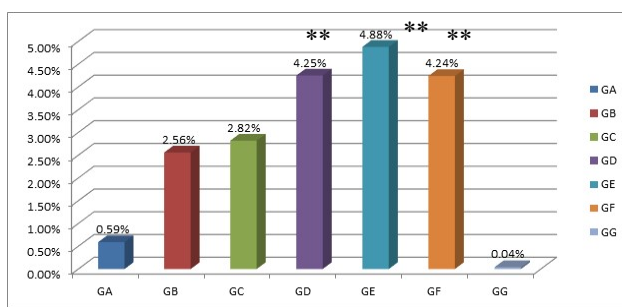
Demographic characteristics of enrolled patients are depicted in table 1. Male preponderance is evident in this table (65% Male vs 35% female). The mean age was from 25-70 years in different groups i.e., 40 years in garlic, 50 years in simvastatin and 45 in placebo treated groups.

Comparison of garlic with simvastatin and placebo is given in table 2 for variable duration. Initially, 210 patients were enrolled and 195 continued for the entire period of study. The results of the study are evident in table 2 and figs. 1-8, statistical significant effects of garlic were found on the lipid profile of patients at different doses for variable duration in comparison with simvastatin and placebo.



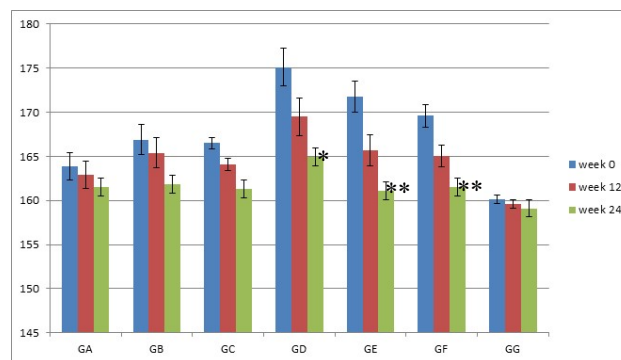
GA = Garlic 0.3g, GB= Garlic 0.6 g, GC=Garlic 0.9g, GD= Garlic 1.2g, GE= Garlic 1.5g, GF= Simvastatin, GG = Placebo
Asterisk denotes significant p values.
* Significant $p < 0.05$, ** Highly significant $p < 0.005$

Fig. 1: Duration dependent Changes in mean Serum Total Cholesterol from week 0 to week 12 and 24 with Allium sativum (Garlic) different doses, Simvastatin and Placebo



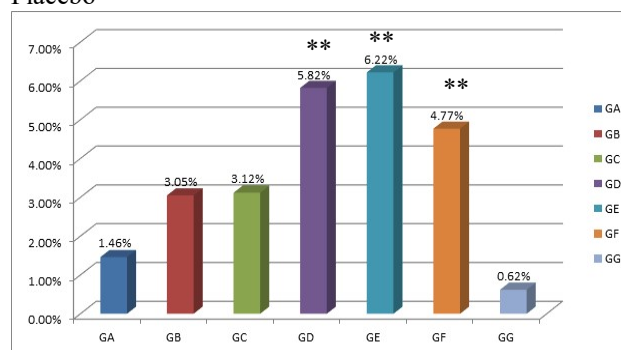
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Asterisk denotes significant p values.
* Significant $p < 0.05$, ** Highly significant $p < 0.005$

Fig. 2: % Decrease in serum Total Cholesterol levels at week 24 with Allium sativum (Garlic) different doses, Simvastatin and Placebo



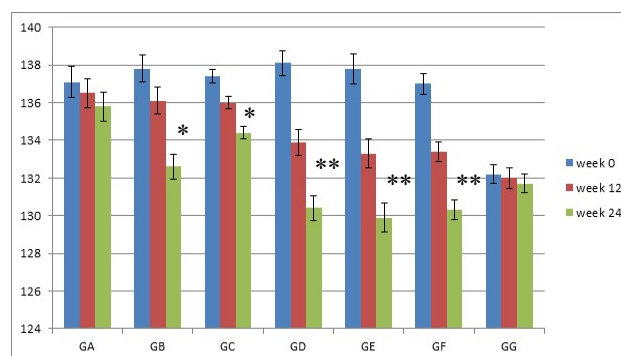
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Asterisk denotes significant p values.
* Significant $p < 0.05$, ** Highly significant $p < 0.005$

Fig. 3: Duration dependent Changes in mean Serum Triglycerides levels from week 0 to week 12 and 24 with Allium sativum (Garlic) different doses, Simvastatin and Placebo



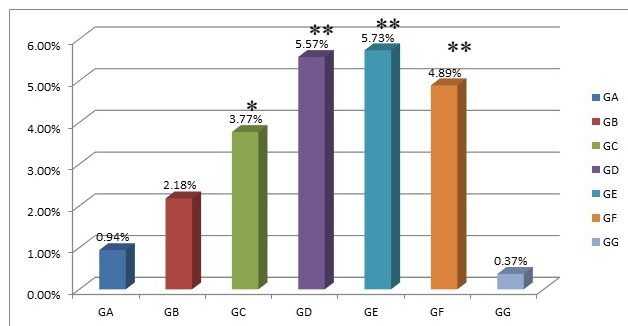
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Asterisk denotes significant p values.
* Significant $p < 0.05$, ** Highly significant $p < 0.005$

Fig. 4: % Decrease in serum Triglycerides levels at week 24 with Allium sativum (Garlic) different doses, Simvastatin and Placebo



GA = Garlic 0.3g, GB= Garlic 0.6 g, GC=Garlic 0.9g, GD= Garlic 1.2g, GE= Garlic 1.5g, GF= Simvastatin, GG = Placebo
Asterisk denotes significant p values.
* Significant $p < 0.05$, ** Highly significant $p < 0.005$

Fig. 5: Duration dependent Changes in mean Serum LDL levels from week 0 to week 12 and 24 with Allium sativum (Garlic) different doses, Simvastatin and Placebo.



GA = Garlic 0.3g, GB= Garlic 0.6 g, GC=Garlic 0.9g, GD= Garlic 1.2g, GE= Garlic 1.5g, GF= Simvastatin, GG = Placebo

Asterisk denotes significant *p* values.

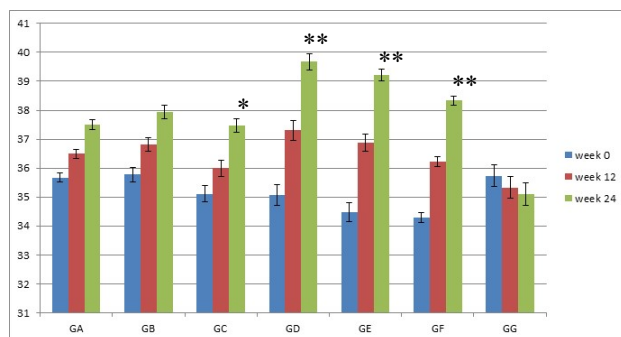
* Significant $p < 0.05$, ** Highly significant $p < 0.005$

Fig. 6: % Decrease in serum LDL levels at week 24 with *Allium sativum* (Garlic) different doses, Simvastatin and Placebo

Dose and Duration dependent effects of Garlic on Lipid profile

Garlic vs Placebo

Serum Cholesterol level was significantly decreased in patients with garlic treatment after the middle (12 weeks) and the end of the study (24 weeks) period in comparison with placebo control. There was a statistically significant ($p < 0.005$) difference in garlic treated patients in doses of 0.6, 0.9, 1.2, 1.5 grams when compared with placebo in both middle and the end of study period shown in figs. 1-8. When the mean of all doses was compared in 12 and 24 weeks there was a noticeable decrease in cholesterol level was found.



GA = Garlic 0.3g, GB= Garlic 0.6 g, GC=Garlic 0.9g, GD= Garlic 1.2g, GE= Garlic 1.5g, GF= Simvastatin, GG = Placebo

Asterisk denotes significant *p* values.

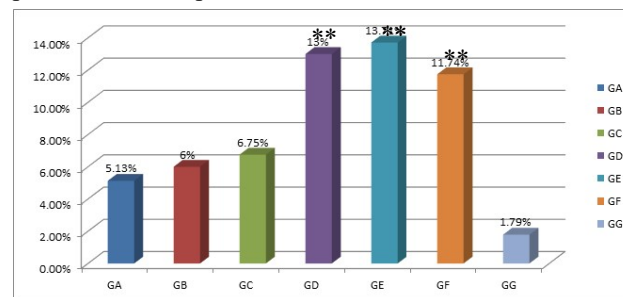
* Significant $p < 0.05$, ** Highly significant $p < 0.005$

Fig. 7: Duration dependent Changes in mean Serum HDL levels from week 0 to week 12 and 24 with *Allium sativum* (Garlic) different doses, Simvastatin and Placebo.

Garlic 0.3g vs 0.6, 0.9, 1.2 and 1.5 g

Garlic at different doses (0.3, 0.6, 0.9, 1.2 and 1.5g) reduced the serum cholesterol (1.3, 5.7, 6.2, 9.5 and 10.8 mg/dl) respectively. There was a marked reduction in TG levels with high doses (1.2 & 1.5g) in comparison with lower doses, i.e., 0.3, 0.6 and 0.9g of garlic, but the

reduction was not statistically significant when the difference between 12 and 24 weeks of garlic treated patients was compared.



GA = Garlic 0.3g, GB= Garlic 0.6 g, GC=Garlic 0.9g, GD= Garlic 1.2g, GE= Garlic 1.5g, GF= Simvastatin, GG = Placebo

Asterisk denotes significant *p* values.

* Significant $p < 0.05$, ** Highly significant $p < 0.005$

Fig. 8: % Increase in serum HDL levels at week 24 with *Allium sativum* (Garlic) different doses, Simvastatin and Placebo

Garlic vs Simvastatin

There was no significant difference found when garlic treated groups were compared with simvastatin treated patients. After 24 weeks of treatment, higher doses of garlic (1.2 & 1.5g) were found to reduce TG levels of 4.24 percent (9.5mg/dl) and 4.88 percent (10.8mg/dl) respectively, almost similar to simvastatin i.e., 4.24 percent (9.4mg/dl) which was statistically non-significant.

DISCUSSION

It was estimated that cardiovascular diseases caused 17.9 million deaths globally in 2019, which is approximately 32 percent of the global mortality rate (Rehman *et al.*, 2020). Different models have projected the rapid escalation of CVDs specifically in Asia by 2020 onwards as compared to other regions of the world (Prasad *et al.*, 2010). Like in other developing south Asian countries, pervasiveness of dyslipidemia has been reported to be on the rise in Pakistan.

According to the survey conducted from February 2016 to August 2017 by NDSP (national diabetes survey of Pakistan), incidences of hypercholesterolemia, hypertriglyceridemia and higher low density lipoprotein-C levels are 39, 49 and 40 percent respectively in the adult population of age 20 and higher. Whereas more than 90 percent of women and 84 percent of men had lower high density lipoprotein levels. It was also found that the level of cholesterol and TG was very high in patients of 50-60 years and high levels of LDL and low levels of HDL were predominant in the age group of 40-50 years (Basit *et al.*, 2020). Multiple studies proved that diabetes and hypertension are important factors for dyslipidemia (Gazzaz *et al.*, 2020), which necessitates the regular

screening and aggressive lifestyle modifications with significant reduction in lipid intake in order to reduce the CVD incidences (Opoku, 2019). Based on the cultural and economic factors of Pakistan it is imperative to explore better treatment options in herbal drugs to reduce and manage lipid levels with minimum adverse and toxic effects (Kirichenko, 2020, Shaito, 2020).

The current study was designed to investigate the optimum dose and duration of 'garlic' in different doses with varied duration in comparison of placebo and standard lipid lowering drug simvastatin for better outcomes.

Results of this study showed statistical significant reduction in total cholesterol, TG and LDL levels and increased HDL levels in both 12 and 24 weeks of treatment with garlic at higher doses. The changes in lipid levels were significant as compared to placebo and almost equivalent to simvastatin. The highest reduction in lipid levels was found after 24 weeks.

This study is distinct from other clinical trials in terms of its comparative efficacy with a standard lipid lowering agent simvastatin in both dose and duration dependent manner in hypertensive patients simultaneously affected by dyslipidemia. Although the lipid lowering potentials of garlic in this study was consistent with previously conducted clinical and pre-clinical trials to determine the beneficial effects of different garlic preparations on lipid levels, but none of the previous studies were designed to investigate dyslipidemia with other comorbidities like essential hypertension (Rido *et al.*, 2020; Lachhramka, 2016; Ackermann *et al.*, 2001). A multitude of meta-analyses proved the moderate reduction (6-12%) of total cholesterol, LDL and TG levels when compared to placebo (Maisaroh *et al.*, 2020; Ansary *et al.*, 2020; Sun *et al.*, 2018; Stevinson *et al.*, 2000; Ackermann *et al.*, 2001; Alder *et al.*, 2003).

In contrast, several studies reported no significant effects of garlic on the lipid profile of patients of dyslipidemia (Kannar *et al.*, 2001; Turner *et al.*, 2004; Zhang *et al.*, 2006; van Doorn *et al.*, 2006; Gardner *et al.*, 2007; Khoo & Aziz, 2009). Earlier reports (Kojuri *et al.*, 2007) of significant lipid lowering properties of garlic on cholesterol and LDL and favorable action on HDL supports present study to improve lipid profile of patients. Another study conducted by Adler & Holub (1997) reported significant reduction in cholesterol and LDL-C levels by 12 and 14 percent respectively, by administration of 0.9g of garlic tablets per day is consistent in this study with the exception of TG levels. However, in this study, TG level is reduced by 3.2, 5.8 and 6.0 percent, by 0.9, 1.2 and 1.5g doses of garlic respectively, after 24 weeks in dyslipidemia patients. It is believed that reduction of cholesterol is mediated via

lowering of LDL-C level through inhibition of cholesterol biosynthesis in the liver. Another important study conducted by Ackermann *et al.* (2001), reported significant reduction in cholesterol, LDL and TG levels but non-significant effect on HDL, whereas this study showed similar reduction of total cholesterol, LDL and TG levels, but in contrast to Ackermann *et al.* (2001) this study showed increased HDL levels after 24 weeks.

In this study, chronic use of garlic i.e., 12-24 weeks produced more prominent lipid lowering activity than previous clinical trials (Superko *et al.*, 2000; Berthold *et al.*, 1998; Isaacsohn *et al.*, 1998). A possible explanation of this contradiction might be due to the non-availability of standardized preparation of garlic, multiple population factors, variation in doses and duration. Another investigator, Berthold HK used oil of garlic prepared by distillation for 12 weeks with placebocontrol and failed to find any significant activity of garlic in his trial. Results of this study are in accordance with a study conducted by Sobenin *et al.*, 2008, in which slow released tablets of garlic Allicor, 600mg in a double-blinded placebo-controlled trial reduced the cholesterol 8% and LDL-C 12% and raised HDL levels up to 12 percent after 12 weeks. Chronic use of garlic was found to reduce ultra-structural changes by inhibition of oxidative stress (Banerjee *et al.*, 2002). *In vitro*, garlic, oxidizes human LDL through inhibition of reactive oxygen species and lipid peroxidases and aged garlic extract is known to prevent depletion of intracellular glutathione in endothelial cells raised with oxidized low density lipoproteins (Rahman & Lowe, 2006). In another placebo controlled randomized double blinded study 0.6g of garlic for 15 days reduced the *ex-vivo* ability of lipoproteins consisting apo-B for oxidation by 34 percent (Lampe, 1999). A large number of sulfur containing active ingredients are found in garlic, specifically glutamyl cysteine, S-allyl cysteine, alliin, allicin and ajoene reported to inhibit the synthesis of cholesterol in humans (Yeh & Liu, 2001). Among various organic sulfur constituents of garlic, allicin is the major compound known for its anticholesterol activity (McRae, 2005). Garlic compounds are known to inhibit a number of key enzymes for cholesterol biosynthesis like squalene monooxygenase and 3-hydroxy-3-methyl-glutaryl-coenzymeA reductase (Gupta & Porter, 2001; Augusti *et al.*, 2005). Other sulfur containing constituents of garlic, such as S-allylcysteine and ajoene were also reported for their inhibitory effects on HMG-CoA reductase responsible for cholesterol biosynthesis (Ferri *et al.*, 2003; Liu & Yeh, 2002).

Another enzyme, sterol 4-alpha-methyl oxidase, involved in cholesterol synthesis, is inhibited by various compounds of garlic (Singh & Porter, 2006). Aged garlic extract is famous for strong antioxidant and radical scavenging activities by its main ingredient, S-allyl

Table 2: Dose & Duration dependent changes in Lipid Profile with *Allium sativum* (Garlic) different doses, Simvastatin and Placebo from week 0 to week 12 and week 24

Groups	Triglycerides			Total Cholesterol			HDL Cholesterol			LDL Cholesterol		
	WEEK 0	WEEK 12	WEEK 24	WEEK 0	WEEK 12	WEEK 24	WEEK 0	WEEK 12	WEEK 24	WEEK 0	WEEK 12	WEEK 24
	PLACEBO	160.1± 0.498	159.6± 0.509	159.1± 0.480	210.9± 0.987	210.8± 0.915	210.8± 0.957	35.74± 0.379	35.33± 0.374	35.10± 0.378	132.2± 0.504	132.0± 0.539
<i>Allium sativum</i> (GARLIC) Group A 0.3 g	163.9± 1.539	162.9± 1.563	161.5± 1.536	216.9± 1.404	216.2± 1.319	215.6± 1.307	35.67± 0.160	36.49± 0.151**	37.50± 0.184***	137.1± 0.823	136.5± 0.748	135.8± 0.766
<i>Allium sativum</i> (GARLIC) Group B 0.6 g	166.9± 1.739	165.4± 1.693	161.8± 1.710	221.9± 1.346	219.4± 1.336	216.2± 1.345***	35.78± 0.252	36.81± 0.238**	37.93± 0.232***	136.0± 0.363	136.0± 0.339**	134.4± 0.342***
<i>Allium sativum</i> (GARLIC) Group C 0.9 g	166.5± 0.665	164.1± 0.681**	161.3± 0.712***	219.8± 1.764	216.7± 1.759	213.6± 1.633**	35.11± 0.279	36.00± 0.282	37.48± 0.228***	137.8± 0.716	136.1± 0.710	132.6± 0.681***
<i>Allium sativum</i> (GARLIC) Group D 1.2 g	175.1± 2.130	169.5± 2.121	164.9± 2.130***	223.9± 1.402	219.4± 1.279**	214.4± 1.243***	35.07± 0.365	37.30± 0.332***	39.67± 0.277***	138.1± 0.656	133.9± 0.695***	130.4± 0.682***
<i>Allium sativum</i> (GARLIC) Group E 1.5 g	171.8± 1.767	165.7± 1.787**	161.1± 1.775***	221.3± 1.808	215.2± 1.773**	210.5± 1.742***	34.49± 0.329	36.87± 0.289***	39.22± 0.209***	137.8± 0.790	133.3± 0.785***	129.9± 0.747***
Simvastatin 20 mg OD	169.6± 1.255	165.0± 1.214**	161.5± 1.270***	221.6± 0.663	217.3± 0.583**	212.2± 0.667**	34.30± 0.175	36.22± 0.179***	38.33± 0.160***	137.0± 0.535	133.4± 0.523***	130.3± 0.519***

Data are presented as Mean ± SEM. Asterisk denotes significant p values. * Significant p<0.05. **Highly significant p<0.005

cysteine. It is also known for inhibiting hydrogen peroxide and LDL oxidation in cells, which minimizes oxidized LDL mediated cell injury (Banerjee *et al.*,2003).A potent antioxidant Tetrahydro-b-Carboline (THbCs), found in aged garlic extract prevents the disease associated oxidative damage (Ichikawa *et al.*,2006).

CONCLUSION

Long term dose and duration dependent clinical trials in diabetic dyslipidemic patients are required for substantiation of the findings of the present study.

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