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ALLIUM SATIVUM REGULATES LIPID METABOLISM IN ALLOXAN INDUCED DIABETIC RATS

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ABSTRACT: *Allium sativum* (*A. sativum*), commonly known as garlic, is a species in the onion genus, Allium. The hypolipidemic activity of *A. Sativum* (Family: Amaryllidaceae) extract have been studied in alloxan-induced diabetic rats. In this model oral administration of extract (500mg/kg bw., p.o.) for 15 days in diabetic-dyslipidemic rats exerted significant lipid lowering effect as assessed by the reversal of serum levels of total cholesterol, phospholipids, triglyceride, free fatty acids, protein and lipid peroxide. The decrease of lipids and apoprotein levels of Very Low Density Lipoprotein and Low Density Lipoprotein were followed by stimulation of plasma post-heparin lipolytic activity as well as lecithin cholesterol acyltransferase, hepatic superoxide dismutase, catalase, triglyceride lipase and lipoprotein lipase activities with increase in reduced glutathione. Lipid and apoprotein level of High Density Lipoprotein were also recovered partially on treatment with *A. sativum* extract. The results of the present study demonstrated antidyslipidemic and antioxidant activities in *A. sativum* extract which could be used in prevention of diabetic dyslipidemia and related complications. The hypolipidemic activity of *A. sativum* was compared with a standard drug glibenclamide (600 µg/kg b.w./day, p.o.).

INTRODUCTION: *Allium Sativum* (Lat.), (Eng: Garlic, Urdu: '*Lahsan*') is widely distributed in all parts of the world and used not only as spice but also as a popular remedy for prevention and treatment of a variety of diseases like rheumatism, dermatitis, abdominal disorders and diabetes mellitus.

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Effect of garlic in cardiovascular diseases was more encouraging in experimental studies, which prompted several clinical trials. Dietary factors play a key role in the development of various human diseases, including cardiovascular disease. Garlic has attracted particular attention of modern medicine because of its widespread health use around the world, and the cherished belief that it helps in maintaining good health warding off illnesses and providing more vigor.

To date, many favorable experimental and clinical effects of garlic preparations, including garlic extract, have been reported. These biological responses have been largely attributed to reduction

of risk factors for cardiovascular diseases, cancer and stimulation of immune functions, enhanced detoxification of foreign compound, hepatoprotective, antimicrobial effect and antioxidant effect.[1] Garlic is reported to prevent cardiovascular disease by multiple effects, one of which is the decrease total cholesterol and triglycerides [2], LDLc, VLDLc, while increase HDLc [3] and suppression of the cholesterol biosynthesis [4]. Studies prior to 1995 consistently concluded hypolipidemic action of garlic [5, 6]. However, studies after 1995 using enteric-coated preparation of raw garlic did not manifest any hypolipidemic effect [7–9]. These paradoxical observation warrant a systemic study to resolve the controversy.

It is a remarkable plant, which has multiple beneficial effects such as antimicrobial, antithrombotic, hypolipidemic, antiarthritic, hypoglycemic and antitumor activity. Additionally, garlic has known hypoglycemic properties, which have been demonstrated in alloxan induced diabetic rats and rabbits. The extract of garlic and its component, S-allylcysteine sulfoxide, significantly decreased blood glucose concentration. Its activity appears to be in part due to stimulation of insulin secretion from β-cell in the pancreas[10].

Cardiovascular diseases are leading cause of death in both industrialized and developing nations [11]. Disorders of lipid metabolism following oxidative stress are the prime risk factors for initiation and progression of heart diseases [12]. The current therapies used for controlling hyperlipidemia; fibrates, stains and bile acid sequestraints are almost inefficient to regulate lipid metabolism. Furthermore, these drugs also cause a number of serious adverse effects in patients. Currently available treatment for hyperlipidemia in modern medicine, fibrats, statins or bile acids sequestraints and their combinations do not regulate lipid metabolism up to a appreciable mark, also have several adverse effects in patients [13].

Therefore, there is a need to develop safe and effective treatment modalities for hyperlipidemia. Furthermore medicinal plants play an important role in the treatment of lipid disorders, especially due to their lesser toxicity, side effects and cost effectiveness. Therefore, the research and development of hypoglycemic and lipid lowering drugs from natural products are the best option and also are in great demand. In view of the above considerations, the present study was designed to investigate antidyslipoproteinemic activity of *A. sativum* in hyperglycemic rats.

MATERIAL AND METHODS:

Preparation of *A. sativum* extract:

A. sativum were collected from local area of Lucknow and identified taxonomically by Department of Pharmacology, Era's Lucknow Medical College Lucknow. A voucher specimen (AS-005/10) was also submitted. The bulbs of garlic (*A. sativum*) were cut into small pieces and extracted with alcohol. The alcohol content was evaporated to dryness. The final yield of 20.0 gms of crude extract (concentrate) was added with 50 ml of triple distilled water and was used for *in vivo* studies. A dose of 400 mg/kg was administered to rats orally, daily for 15 days [14].

Animals:

In vivo experiments were conducted as per CPCSEA guidelines provided by Animal Ethics Committee of the institute (IAEC/PV/08/14). Male adult rats of Charles Foster strain (200-225g) bred in animal house of the Institute were used. The animals were housed in polypropylene cages and kept in uniform hygienic conditions, temperature 25-26 °C, relative humidity 50-60% and 12/12 h light/dark cycle (light from 8:00 a m to 8:00 p m) and provided with standard rat pellet diet and *water ad libitum*.

Alloxan induced hyperglycemia:

Rats were divided into four groups having six animals in each as follows: control, hyperglycemic, hyperglycemic treated with *A. sativum* and hyperglycemic treated with glibenclamide. Diabetes was induced in rats by a single intraperitonial injection of alloxan monohydrate 150 mg/kg b.w. in 18 animals. After two weeks of diabetes induction, rats with serum glucose level 280-367 mg/dl were taken for the study.

A. sativum extract and glibenclamide were macerated with aqueous gum acacia (1 % w/v) suspension and fed orally at the doses of 500 and 600 µg/kg, b.w., respectively. Control animals received same amount of vehicle.

After 15 days of feeding rats were fasted overnight and blood was withdrawn from the retro-orbital pluxes. A group of normal rats without treatment with alloxan was also included to serve as control. Animals were kept in controlled conditions. Temperature 25-26˚C, relative humidity 60-70% and 12/12 h light/dark cycle (light from 08:00 AM to 08:00PM), provided with standard pellet diet (Lipton India Ltd.), and water *ad libitum* [15].

Biochemical analysis of plasma:
Serum from above rats was fractionated into very low density lipoprotein (VLDL), low density lipoprotein (LDL) and high density lipoprotein (HDL) by polyanionic precipitation method [16]. Serums as well as lipoproteins were analyzed for their total cholesterol: TC [17], triglyceride: TG [18], phospholipids: PL[19] and apoprotein: Apo [20] by standard procedures reported earlier, serum lipid peroxide (LPO) [21], free fatty acid: FFA [22], plasma protein [23], Plasma lecithin cholesterol acyl transferase: LCAT activity [24] and post heparin lipolytic activity: PHLA [25] were also estimated.

Biochemical analysis of liver:
Liver homogenized (10% w/v) in cold 1 M phosphate buffer (pH7.2) was used for the assay of lipoprotein lipase: LPL [25], and triglyceride lipase: TGL [26] activities. Liver homogenate 10% w/v in 0.15 M KCl was also used for the estimation of superoxide dismutase: SOD [27], catalase: CAT [28] and reduced glutathione: GSH [29]. The lipid extract of each homogenate was used for the estimation of TC, PL and TG by above- mentioned methods.

Biochemical analysis of feces:
Feces spilling of Rats from all groups over 15 days was collected and analysed for the cholic and deoxycholic acid [30].

Statistical analysis: One-way-analysis of variance (ANOVA-Newman's student test) was performed by comparison of values for alloxan-treated group with control, alloxan and drug-treated with alloxan only. All hypothesis testing were two-tailed. $P<0.05$ was considered statistically significant and the results were expressed as mean ± SD. The Graph pad INSTAT 3.0 software was used to carried out the statistical analysis [31].

RESULTS:

Effect of *A. sativum* extract on serum lipid, FFA, LPO and plasma protein in alloxan induced diabetic rats: In the present study we observed that acute administration of alloxan markedly increased in the plasma; TC, TG and PL levels 76%, 98% and 29%, FFA 52%, LPO, 228% and decreased plasma protein 31%. However, treatment with *C. tora* seed extract caused reversal in the levels; TC 35%, TG 34%, PL 38%, FFA 14%, LPO 32% and protein by 25%. Glibenclamide reversed the levels; TC 18.0%, TG 24.0%, PL 4.0%, FFA 27%, LPO 38% and Protein 15.0% (**Table 1**).

TABLE 1: EFFECT OF *A. SATIVUM* EXTRACT ON SERUM LIPID, PROTEIN, LIPID PEROXIDE AND FFA IN ALLOXAN-INDUCED DIABETIC RATS

Experimental schedule	Total cholesterol (mg/dl)	Triglycerides (mg/dl)	Phospholipids (mg/dl)	Protein (g/dl)	Serum lipid peroxide (n mol MDA/ml plasma	Serum free fatty acid (μ mol/L)
Control	84.23± 10.66	87.72± 7.54	96.76± 11.30	7.13± 0.45	2.73± 0.49	1.68± 0.17
Alloxan-treated	148.15± 26.80 ** (+ 76)	173.81± 13.60 ** (+ 98)	124.88± 14.68 ** (+ 29)	4.94± 0.36 ** (- 31)	8.98± 1.40** (+ 228)	2.56± 0.30** (+ 52)
Alloxan + *A. sativum* extract (500 mg /kg b.w.)	96.11 ± 12.36 *** (-35)	115.12 ±6.07*** (-34)	77.28 ± 7.22*** (-38)	6.22 ± 0.39** (+25)	6.10 ± 0.46*** (-32)	2.20 ± 0.24* (-14)
Alloxan + Glibenclamide (600 μg/kg b.w.)	122.18± 18.86* (-18)	131.78± 11.24** (-24)	119.45± 11.67 NS (-4)	5.67± 0.69 * (+15)	5.55± 0.99*** (-38)	1.88± 0.29** (-27)

Values are expressed as mean ± SD of 6 animals.
Values in the paranthesis indicate percent change.
Alloxan-treated group was compared with control, alloxan and drug-treated groups with alloxan.
***p<0.001, **p<0.01, *p<0.05, NS= Non significant.

Effect of *A. sativum* extract on serum lipoprotein profile in alloxan-induced diabetic rats:

Analysis of hyperglycemic serum (**Table 2**) showed marked increase in the levels of lipids and apoprotein constituting β-lipoproteins (VLDL and LDL) and these effects were pronounced for VLDL-TC, PL and TG 50%, 27% and 89% respectively and apoprotein 17%. There was increase in LDL-TC, PL, TG 302%, 45%, 85% respectively and apoprotein 20%. The decrease in HDL-TC, PL, TG and Apoprotein 25%, 24%, 13% and 27% respectively. Our data demonstrates that treatment with *A. sativum* extract for 15 days significantly reversed the level VLDL-TC 17% and PL, 14 %,TG 26% and Apoprotein 8% and decrease in LDL-TC 29%, PL, TG 19%, 23 % and apoprotein 8%. At the same time *A. sativum* extract increased in the levels of HDL-TC, PL, TG 9%, 7%, 5% respectively, and apoprotein 7%. Glibenclamide decreased VLDL-TC, Apoprotein 17%, 11% respectively PL 3 % and TG 29 % and LDL-TC, TG 38%, 24% respectively, PL 1.0 % and apoprotein 12 % respectively with simultaneously increase in HDL-TC, PL, TG, Apoprotein 9 %, 8 %, 6 %, 11% respectively (**Table 2**).

TABLE 2: EFFECT OF *A. SATIVUM* EXTRACT ON LIPOPROTEIN PROFILE IN ALLOXAN-INDUCED DIABETIC RATS

Experimental schedule	VLDL				LDL				HDL			
	TC (mg/dl)	PL (mg/dl)	TG (mg/dl)	Apo-protein (mg/dl)	TC (mg/dl)	PL (mg/dl)	TG (mg/dl)	Apo-protein (mg/dl)	TC (mg/dl)	PL (mg/dl)	TG (mg/dl)	Apo-protein (mg/dl)
Control	8.08	16.43	39.10	6.85	17.07	11.48	20.12	17.13	51.53	39.97	14.47	173.83
	±0.63	±1.99	±3.95	±1.04	±1.78	±1.11	±1.11	±1.61	±3.80	±3.35	±1.43	±11.34
Alloxan	12.09***	20.92***	73.76***	8.00*	68.68***	16.59***	37.21***	20.55*	38.71***	30.52***	12.55*	127.42***
treated	±1.20	±2.48	±5.70	±0.57	±8.65	±1.43	±6.29	±1.46	±3.75	±2.27	±1.28	±12.33
	(+50)	(+27)	(+89)	(+17)	(+302)	(+45)	(+85)	(+20)	(-25)	(-24)	(-13)	(-27)
Alloxan + *A.*	8.52***	17.98*	54.29***	7.36^{NS}	40.51***	13.41*	28.66**	18.80^{NS}	42.52^{NS}	32.82^{NS}	13.25^{NS}	136.80^{NS}
sativum	±0.99	±1.51	±4.85	±6.80	±3.46	±0.90	±4.28	±1.44	±4.41	±2.90	±1.25	±13.27
extract	(-29)	(-14)	(-26)	(-8.0)	(-41)	(-19)	(-23)	(-12)	(+9.0)	(+7.0)	(+6.0)	(+7.0)
Alloxan+	10.04	20.30^{NS}	52.02***	7.20^{NS}	42.33***	16.44^{NS}	28.24**	18.70^{NS}	41.00^{NS}	31.12^{NS}	13.50^{NS}	141.16^{NS}
glibenclamide	±0.96*	±2.39	±5.62	±0.86	±3.80	±1.40	±4.36	±1.52	±4.22	±1.55	±1.28	±12.41
	(-17)	(-3.0)	(-29)	(-8.0)	(-38)	(-1.0)	(-24)	(-12)	(+ 9.0)	(+8.0)	(+6.0)	(+11)

Values are expressed as mean ± SD of 6 animals, Values in the parenthesis indicate percent change.
Alloxan-treated group was compared with control, alloxan and drug-treated groups with alloxan.
***p<0.001, **p<0.01, *p<0.05, NS= Non significant.

Effect of *A. sativum* extract on hepatic SOD, CAT, TGL, LPL and reduced GSH in alloxan-induced diabetic rats: Table 3 illustrates that administration of alloxan in rats decreases the levels of SOD 24%, CAT 25%, TGL 20% and LPL 23% and depletion of GSH 35% respectively. Treatment with *A. sativum* for 15 days reactivates SOD 21%, CAT 24 %, TGL 17%, LPL 21% and recovered GSH 35%. Glibenclamide increases the levels of SOD 26%, CAT 9%, TGL 17 %, LPL 23% and recovered GSH 40%, respectively (**Table 3**).

TABLE 3: EFFECT OF *A. SATIVUM* EXTRACT ON HEPATIC SOD, CAT, TGL, LPL AND GSH IN ALLOXAN-INDUCED DIABETIC RATS

Experimental schedule	SOD (Unit /min /mg protein)	CAT (Unit /min /mg protein)	TGL (n mol FFA released/hr/mg protein)	LPL (n mol FFA released/hr/mg protein)	Reduced glutathione (µmole GSH/g)
Control	2.80 ± 0.20	3847 ± 248.17	74.11 ± 5.78	85.69 ± 7.71	4.25 ± 0.58
Alloxan treated	2.14 ± 0.16**	2873 ± 402.08**	59.63 ± 4.62**	66.36 ± 5.46**	2.75 ± 0.32***
	(-24)	(-25)	(-20)	(-23)	(-35)
Alloxan + *A.*	3.58 ± 0.13**	3560 ± 504.59**	69.71 ± 4.88*	80.34 ± 9.79**	3.70 ± 0.48***
sativum extract	(+21)	(+24)	(+17)	(+21)	(+35)
Alloxan +	2.70 ± 0.13***	2625 ± 482.02^{NS}	69.85 ± 7.08*	81.89 ± 8.68**	3.84 ± 0.50***
Glibenclamide	(+26)	(+9)	(+17)	(+23)	(+40)

Values are expressed as mean ± SD of 6 animals, Values in the parenthesis indicate percent change.
Alloxan-treated group was compared with control, alloxan and drug-treated groups with alloxan.
***p<0.001, **p<0.01, *p<0.05, NS= Non significant.

Effect of *A. sativum* extract on faecal bile acids, plasma LCAT, PHLA in alloxan induced diabetic rats: Administration of alloxan in rats markedly decreased in the levels of cholic acid 30% and deoxycholic acid 38% in feces, as well as LCAT 33% and PHLA 29%, in plasma. The treatment with *A. sativum* for 15 days increased the levels of cholic acid 27% and deoxycholic acid 33% in feces and LCAT 22.0 % and PHLA 19 % in plasma of alloxan induced diabetic rats. Glibenclamide decreased the levels of cholic acid 28% and deoxycholic acid 27% in feces and also LCAT 29% and PHLA 25% in plasma (**Table 4).**

TABLE 4: EFFECT OF *A. SATIVUM* EXTRACT ON FAECAL BILE ACIDS, PLASMA LECITHIN CHOLESTEROL ACYLTRANSFERASE AND PLASMA POST-HEPARIN LIPOLYTIC ACTIVITIES IN ALLOXAN-INDUCED DIABETIC RATS

Experimental schedule	Faecal bile acids		Plasma lecithin cholesterol acyl transferase activity (n mol Cholesterol released/hr/l)	Plasma post -heparin lipolytic activity (n mol FFA formed/h/l)
	Cholic acid (µg/g feces)	Deoxycholic acid (µg/g feces)		
Control	76.31 ± 6.86	56.76 ± 11.36	61.57 ± 4.92	15.19 ± 1.9
Alloxan-treated	53.68 ± 6.49*** (- 30)	35.34 ± 7.83*** (- 38)	41.04 ± 3.76*** (- 33)	10.96 ± 0.98** (-29)
Alloxan + *A. sativum* extract (500 mg/kg b.w.)	67.08 ± 1.76** (+27)	57.36 ± 11.36*** (+33)	62.17 ± 4.92** (+22)	15.19 ± 1.19* (+18.6)
Alloxan + Glibenclamide (600 µg/kg b.w.)	68.69 ± 3.81** (+28)	44.81 ± 2.08** (+27)	53.00 ± 1.23** (+29)	13.75 ± 1.16** (+25)

Values are expressed as mean ± SD of 6 animals.
Values in the paranthesis indicate percent change.
Alloxan-treated group was compared with control, alloxan and drug-treated groups with alloxan.
***p<0.001, **p<0.01, *p<0.05.

DISCUSSION: In the present study, *A. sativum* were tested for their anti-dyslipidemic and antioxidant activities in alloxan induded diabetic rats. Alloxan causes reversible damage to insulin producing β-cells found in the pancreas, and that is why this animal model have been used for primary screening of test drug for anti dyslipoproteineic activity [32].

In the present study we found that, intoxication with alloxan caused increased levels of TC, PL, TG, FFA, LPO as well as decrease in protein. The analysis of the lipid and apoprotein components of β lipoproteins showed that alloxan intoxication in rats also caused significant increase in TC, PL, TG and Apoproteins components of VLDL and LDL. On the other hand levels of TC, PL, TG and Apoproteins components were decreased in HDL. Due to alloxan intoxication levels of SOD, CAT, TGL, LPL and GSH were also decreased. Fecal bile acids, LCAT, PHLA were also decreases by alloxan. Similar observations were reported by others. Lipases play a significant role in lipoprotein metabolism and decreased lipoprotein lipases activities in diabetes are main cause of atherosclerosis [33]. However, treatment with *A. sativum* for 15 days reversed these effects.

The abnormal high concentration of serum lipid in diabetes is mainly due to the increase in the mobilization of free fatty acid from the peripheral depots, since insulin inhibits the hormone sensitive lipase [34]. On the other hand, glucagons, catecholamine and other hormones enhance lipolysis. The marked hyperlipidemia that characterizes the diabetic state may, therefore, be regarded because of the unregulated actions of lipolytic hormones on the fat depots [35]. *A. sativum* and glibenclamide both caused a significant decrease in the plasma levels of TC, TG, PL and FFA in alloxan-induced hyperglycemia. In alloxan induced diabetic rats, *A. sativum* could increased the level of HDL by increasing the activity of LCAT, which might contribute to the regulation of blood lipids. LCAT play a key role in lipoprotein metabolism and most of the lipoprotein changes are the outcome of primary abnormality owing to the diseases related with lipid metabolism [32]. *A. sativum* extract enhanced the excretion of bile acids through feces and this contributed to regress the

cholestesteosis in liver damage. In conclusion, the lipid lowering activity of *A. sativum* might be due to inhibition of hepatic cholesterol biosynthesis, activation of tissue lipases, SOD, CAT and these beneficial effects may be due the extract of garlic and its bioactive compounds like typical alkaloids, S-allylcysteine sulfoxide, significantly decreased blood glucose concentration [36].

CONCLUSION: Type 2 diabetes is by far the most prevalent endocrine disorder of the world characterized by chronic hyperglycemia and associated complications. Although insulin is one of the important therapeutic agents known to medicine and, technological breakthroughs have improved its access and availability, there is an increased focus on finding insulin substitutes, secretagogues or sensitizer from synthetic or plant source for the treatment of diabetes. It should be pointed out here that plant derived natural compounds have established a proven platform for developing new drug synthesis with fewer side effects. A strong antioxidative and antidiabetic activity of *C. tora* seeds extract in our study not only validates its use in diabetes management but also demands a wider role, application and research in insulin alternative strategies for diabetes management for it.

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CONFLICT OF INTEREST: Authors declare no conflict of interest.

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