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Tinospora cordifolia regulates lipid metabolism in allaxon induced diabetes in rats

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Abstract

The present study was carried out to investigate the antidyslipidemic activity of *Tinospora cordifolia* stem extract in alloxan-induced (150 mg/kg body wt.) diabetic rats. There was significant increase in plasma markers of diabetic-dyslipidemia namely: the levels of glucose, glycosylated hemoglobin(Hb_{A1c}) lipid peroxide, total lipid and free fatty acids (FFA).The abnormalities with lipid metabolism was .accompanied with increase in the lipids and apoprotein levels of serum very low density lipoprotein (VLDL) and low density lipoprotein (LDL) following decrease in high density lipoprotein (HDL) and diminution of plasma lecithin cholesterol acyltransferase(LCAT) and post-heparin lipolytic activity (PHLA).The alteration in lipoprotein pattern was associated with inhibition of hepatic lipolytic (LPL) and antioxidant enzymes; superoxide desmutase(SOD) and catalase as well as decreased excretion of bile acids through feces of diabetic rats. Oral administration of Tinospora cordifolia stem extract (500 mg/kg body weight) for 15 days in dyslipidemic animals resulted in significant decrease in plasma glucose, Hb_{A1c} lipid peroxide, total lipid and FFA. The decrease in the plasma level of lipid peroxide and lipid and apoprotein components of VLDL and LDL were also accompanied by stimulation of plasma PHLA, LCAT and hepatic LPL, SOD and catalase activities. Lipid and apoprotein level of HDL were also recovered partially by the treatment with root extract. Although anti diabetic effect of *T. cordifolia* was less than glibenclamide, however, its anti dyslipidemic activity was more pronounced in above test model .The result of present study leads to research and development of a potent antidyslipidemic drug from *Tinospora cordifolia.*

Key-Words: *Tinospora cordifolia*, Alloxan, Antidyslipidemic drug, Anti oxidant enzymes, Lipid peroxide, Lipid metabolism

Introduction

Tinospora cordifolia (*T. cordifolia*): family Menispermaceae, Hindi name: Giloya ; Gurch or Tinospora in English, is a perennial twiner with succulent stem and papery bark that climb over the highest trees. It grows throughout India in deciduous as well as dry forests. *Tinospora cordifolia* has a long history of use in the traditional medicine of India. Its stem is one of the constituents of several ayurvedic preparations used in general debility, dyspepsia, fever, skin and urinary diseases. The root and stem of *T. cordifolia* in combination with other drugs used as an anti-dote to snake bite and scorpion sting.

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Dry barks of *T. cordifolia have* anti-spasmodic, anti-pyretic, anti-allergic, anti-inflammatory and anti-leprotic properties. The scientific evidences in term of modern medicine reported that *T. cordifolia* have immunomodulatory, antipyretic, anti-diabetic,antiallergic, anti-inflammatory, cholesterol lowering ,hepatoprotective and antioxidant activities(1 , 2). *T. cordifolia has* also shown some promising speed in healing the diabetic foot ulcers (3) and inhibitory effect on experimental metastasis and anti obesity activity in rats (4).

Diabetes mellitus is a chronic disease caused by inherited and/or acquired deficiency in production of insulin by β-cell of pancreas or by the ineffectiveness of the insulin produced, which leads to hyperglycemia

and later on the disorders of lipid and lipoprotein metabolism in patients. Apart from hyperglycemia, disorders of lipid metabolism following oxidative stress are the prime risk factors for initiation and progression of diabetic complications including cardiovascular diseases (CVD), cerebrovescular diseases, atherosclerosis, coronary heart disease (5).These secondary complications in diabetic patients accounts for more than 70% of all deaths in individuals with diabetes(6).Thus there is an urgent need for a simultaneous treatment of diabetic -dyslipidemia (7).The known lipid lowering drugs such as fibrates, statins, almost inefficient to regulate lipid metabolism and also cause many side effects in diabetic patients (8). Herbal formulations are preferred due to lesser side effects and their low cost. Thus, a drug having multi-fold properties such as antidiabetic, lipid lowering and antioxidant activities is in great demand. There are reports that *T. cordifolia leaf*; but not root exerts lipid lowering action in alloxan induced dyslipidemia in rats. However, such work has not so far been done to investigate lipid lowering action of cardifolia stem in experimental dyslipidemia.Therefore, the present study was designed to study the mechanism of action of *T. cordifolia* stem extract to act as a lipid lowering agent in alloxan induced diabetic-dyslpidemia in rats.

Material and Methods

Preparation of plant extract

T. cordifolia stem was collected from local area of Lucknow and identified taxonomically by the Department of Pharmacology, Era's Lucknow Medical College & Hospital, Lucknow and a voucher specimen was also submitted (TC-001/06). Stem was dried under shade and made into fine powder using laboratory mill. Powder (1000g) was extracted thrice with 3x2000 ml portions of 95% ethyl alcohol in a laboratory percolator at room temperature. Time allowed for each extraction was 8 hr. The extract obtained after third extraction was colorless. All the extracts were mixed; alcohol was distilled out at reduced temperature (20^{o}C) and reduced pressure (100 psi) in a rotor evaporator. This yielded 20g (2% w/w) of crude extract, which was used for in vivo study. Alloxan monohydrate and standard antidiabetic drug: glibenclamide were procured from Sigma Chemical Company St. Louis, MO, USA.

Preparation of doses

A quantity of 50 mg of *T. cordifolia stem* extract was suspended /ml tripled distilled water (TDW) containing 2 % (w/v) gum acacia. The suspension was given in a volume of 1ml/100g animal bw (500 mg drug /kg bw) by oral intubation. Similarly suspension of glibenclamide (6 mg /dl in TDW containing 2 % (w/v) gum acacia) was prepared and fed in a volume of 1ml/100g animal bw (0.6 mg drug /kg bw) as above.

Lipid lowering activity in alloxan induced diabetic rats

Animals: Animal study was performed with the approval of Animal Care Committee of Division of Laboratory Animal; Central Drug Research Institute, Lucknow, India and confirmed to the guideline for Care and Use of Laboratory Animals of the institute. Male adult rats of Charles Foster strain (200-225g) bred in the animal house of the Institute were used. The animals were kept in controlled conditions; temperature 24 -25˚C, relative humidity 50-60% and 12/12 hrs light / dark cycle (light from 08:00 AM to 08:00PM), fed with standard pellet diet (Lipton India Ltd.), and water ad libitum. One group of normal rats without treatment with alloxan was used to serve as control. In remaining animals, diabetes was induced by a single intraperitonial injection of alloxan monohydrate (150 mg/kg b.w.) freshly prepared in normal saline (9). After three days of injection, diabetes was confirmed by glucometer (10). The rats with blood glucose level 300-350 mg/dl were taken for the study.

Experimental design: The rats were divided in four groups having six animals in each as follows: Group 1: control rats (on 2% aqueous gum acacia); Group 2, Alloxan treated diabetic rats (on 2% aqueous gum acacia); Group 3, Alloxan treated diabetic rats + *T. cordifolia* (500mg/kg b.w) (9); Group 4, Alloxan treated diabetic rats + glibenclamide (0.6 mg/kg b.w) (11). After 15 days of feeding, rats were fasted overnight, anaesthetized with thiopental solution, and injected (ip) with 1ml/kg bw of 10mg/ml solution of heparin. After 15 min blood was withdrawn from the retro-orbital plexus and collected in EDTA coated tubes. Thereafter rats were sacrificed; their liver and adipose tissue (abdominal fat pad) were excised promptly.

Biochemical analysis of blood and plasma lipoproteins: The blood was centrifuged and plasma was separated. The glycosylated hemoglobin (HbA1C) in RBC and plasma total lipid were assayed by standard spectrophotometric methods (12,13).Plasma was also used for the assay of lecithin cholesterol acyl transferase activity(14) (LCAT), post heparin lipolytic activity (15)(PHLA), glucose(10), free fatty acid (16)(FFA)and lipid peroxide(17) (LPO) A portion of plasma was fractionated into very low density lipoprotein (VLDL), low density lipoprotein (LDL) and high density lipoprotein (HDL) by polyanionic precipitation methods (18).Plasma as well as lipoproteins were measured for their total cholesterol

(19)(TC), phospholipids(20) (PL), triglyceride (21) (TG) and apoprotein (22) by standard spectrophotometric methods.

Biochemical analysis of adipose tissue and liver: Adipose tissue and liver were homogenized (10% w/v) in cold 100 mM phosphate buffer pH 7.2 and used for the assay of lipoprotein lipase activity (15) (LPL) as well as TC, PL , TG and lipid peroxide content in them. Liver homogenate was also used for the assay SOD (23) and catalase (24) enzymes, reduced glutathione (GSH) (25).

Biochemical analysis of feces: The rats faces spilling from all groups over 15 days were collected and measured for the cholic and deoxycholic acid content (26).

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.

Results and Discussion

Effect of *T. cordifolia stem* extract on alloxan-induced induced diabetic–dyslipidemia: The present work represents a detailed report on the mechanism of action of *T. cordifolia to* act as an antidyslipidemic agent in alloxan induced diabetes in rats. Alloxan caused reversible damage to insulin-producing β-cells and caused a significant increase in both diabetogenic and dyslipidemia parameters, that is why this animal model have been used for primary screening of drugs to treat diabetic- dyslipidemia(27).We found that challenge with alloxan caused a significant increase in blood levels of glucose, 287%; Hb_{A1C}, 35%; total lipid, 38% and lipid peroxide 82% in rats (Table 1). Treatment with *T. cordifolia* and glibenclamide for 15 days caused reversal, but with varying extents, in the levels of these biochemical parameters of diabetic-dyslipidemia. The antidyslipidemic effect of *T. cordifolia* was more than gliblenclamide.

Effect of *T. cordifolia in* alloxan induced lipid changes in adipose, liver and fecal excretion of bile acids in diabetic rats: The data in table 2 show that induction of diabetes in rats caused stimulation in LPL activity (77%) following depletion of TC (29%), PL (20%) and TG (45%) in adipose tissue. However, in case of liver, the situation was just opposite, where diabetes caused diminution of LPL activity (44%), which was accompanied with marked accumulation of TC, PL and TG by 55, 50 and 80 % respectively.

In diabetes mellitus decreased bioavailability of insulin or its resistance to adipocytes, provokes lipolysis of fat depots through activation of hormone sensitive lipase and causes an increase in FFA flux which is very likely the initial step in development of dyslipidemia. The ensuing increase in fatty acid transport to liver, has been shown to stimulate secretion of VLDL (28).Furthermore, decreased bioavailability of insulin produces hyperglycemia and also effects on liver apoprotein production and VLDL secretion, regulation of LPL, actions of cholesteryl ester transfer protein (CETP), and peripheral actions on adipose and muscle. All these complications are likely to be responsible for diabetic- dyslipidemia. Treatment with *T. cordifolia and* glibenclamide caused reversal in altered levels of adipose and hepatic LPL activity as well as the levels of TC, PL and TG in these tissues. Further more diabetic animals were observed with decreased excretion of cholic acid (30%) and deoxycholic acid (38%) through their faces, which was also found to be recovered in T.cardifolia treated rats. This improvement may thus contribute to prevent accumulation of lipids in their liver. The treatment with glibenclamide was less effective to produce regulation of lipids in adipose tissue or liver and excretion of bile acids through faeces in diabetic rats.

Effect of *T. cordifolia* on some hepatic oxidative and antioxidative parameters in diabetic rats: The data in table 3 show that challenge with alloxan in rats caused increase in hepatic level of lipid peroxide (57%) following diminution of enzyme activity of SOD (24%) and catalase (P25%) and depletion of glutathione (35%). The involvement of hyperglycemia causes a variety of pathologic changes that may affect the synthesis, also cause structural modifications such as glycosylation and oxidative degradation as well as functional changes in proteins including enzymes and lipids at any situation (29). Increased oxidative stress plays a critical role in oxidative modification of LDL (30). Oxidized LDL is also a cytotoxic agent and it may cause endothelial dysfunction and may be actively involved in the etiology of atherosclerosis in diabetes (31)**.**Treatment with *T. cordifolia* stem extract stimulated antioxidant enzymes, recovered GSH and caused decrease in level of lipid peroxide in treated animals .These effects were comparable to glibenclamide.

Effect of *T. cordifolia stem* extract on alloxan-induced induced alterations in lipid and apoprotein composition of plasma lipoprotein in diabetic rats: The effect of *T. cordifolia treatment* on abnormalities with lipid metabolism in diabetic rats are shown in table 4and 5. In these animals, there was increase in

their plasma levels of TC, PL and TG by 40, 49 and 78% respectively, following diminution of PHLA (37%) and LCAT activity (33%). In diabetes mellitus, enhanced lipolysis of TG and consequently increase in FFA release and its transport to the liver, has been shown to produced hyperlipidemia (28).To that of glibenclamide and some antidiabetic medicinal plants, which act as initiator of insulin release, *T. cordifolia* treatment could normalize these changes showing that insulin secretion would have been corrected either by stimulation or by repair of β-cells.(32).The analysis of lipid and apoprotein components of β-lipoproteins showed that administration of alloxan in rats caused significant increase in TC, PL, TG and apoprotein components of VLDL by 50, 52,89 and 84 % as well as of LDL by 27, 55, 29 and 35%, respectively (Table 4). It is well documented that hyperglycemia induced pathologic changes also suppresses the synthesis of glucosominaglycons in capillary endothelium surface that lead to defect in LPL binding and consequent poor clearance of VLDL in diabetics (33). This may be true; the diminution of capillary endothelial and hepatic lipases had been involved to produce hyper β-lipoproteinemia; and their reactivation by the treatment with *T. cordifolia had* played a significant role in regulation of lipoprotein metabolism in diabetic rats. Further more, structural modifications in lipoproteins would have made them a defective substrate for their catabolism through LPL and hepatic LDL receptors. The treatment with *T. cordifolia* and glibenclamide might also improved antioxidative status in animals following inhibition of oxidative changes in body biomolecules including to that of LDL, facilitating its catabolism through hepatic receptors. Induction of diabetes adversely affects on HDL, as it caused decrease in levels of lipids and apoprotein components of this lipoprotein by 24-27% (Table 5). Hyperglycemia also interferes with function of CETP and LCAT, which are reported to be responsible for abnormalities with HDL metabolism and appearance of high atherogenic sd-LDL particles in diabetics **(**28). In the present study, we found that treatment with *T. cordifolia but* not glibenclamide could stimulated LCAT enzyme and partially recovered the level of HDL in diabetic rats.

Earlier studies have shown that feeding with *T. cordifolia* root alcoholic-extract caused lowering in blood sugar levels, serum and tissue lipids in alloxan induced diabetic rats (34). However, the alcoholic extract of leaves of this plant, though showed hypoglycemic activity but failed to exert lipid lowering action in above model(35)The chemical constituents reported from stem of this shrub belong to different classes such as alkaloids, diterpenoid lactones, glycosides, steroids, sesquiterpenoid, phenolics, aliphatic compounds and polysaccharides, root contains alkaloids, however, the leaf contains only steroids (36). Furthermore, stem as well as roots both contain alkaloids; Berberine. Palmatine, Tembetarine, Magnoflorine, Choline, Tinosporin Isocolubin, Palmatine, Tetrahydropalmatine, Magnoflorine. Therefore, to that of root (34) antidiabetic and antidyslipidemic activities of *T. cordifolia stem* may be partly due to presence of these typical alkaloids.

In conclusion, *T. cordifolia might* suppress hyperglycemia induced alterations in biochemical pathways that are responsible to cause abnormities with lipid metabolism in diabetic rats. Besides its antidiabetic and antilipoperoxidative effects, *T. cordifolia may* have regulated functioning of various enzymes and metabolites to afford a normal lipid metabolism in dyslipidemic animals. This may be due to reactivation of PHLA, LCAT and tissue LPL enzymes. Treatment caused beneficial effect on HDL synthesis that may also contributed to regulate lipid metabolism. *T. cordifolia enhanced* excretion of bile acids through faeces and thus contributed to regress the hepatic cholestesteosis in diabetic rats. The study reveals that *T. cordifolia* is a better drug as a natural product to regress diabetic-dyslipidemia and oxidative stress in diabetes. Further work to assess the antidyslipidemic activity of different fractions of *T. cordifolia* stem in alloxan induced diabetic rats is under progress to substantiate the present findings.

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Table 1: Effect of *T. cordifolia* stem extract on blood diabetogenic and dyslipidemic parameters in Alloxan-induced diabetic rats

Experimental schedule	Glucose (mg/dl)	Glycosylated Hemoglobin (g%)	Total Lipid (mg/dl)	Free Fatty Acid (µ mol/L)	Lipid Peroxide (n mole MDA/ml)
Control	80.20 ±10.50	1.38±0.17	324.75±30.55	1.68± .17	2.73± 0.49
Alloxan-treated	310.65*** ±35.00 (+287)	1.86** ±0.20 (+35)	446.80**±47.00 (+38)	2.56*** ±0.30 (+52)	4.98*** ±0.60 (+82)
Alloxan + *T. cordifolia* (500 mg /kg b.w.)	232.00**±29.30 (-25)	1.60 ^{NS}±0.18 (-14)	353.00*±34.60 (-21)	1.88**±0.29 (-27)	3.80 **± 0.46 (-24)
Alloxan + Glibenclamide (0.6 mg/kg b.w.)	180.30***±20.45 (-42)	1.45*±0.18 (-22)	364.50*±35.70 (-18)	2.00*±0.24 (-22)	3.15 ***± 0.99 (-37)

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

Table 2: Effect of *T. cordifolia* on the level of adipose and liver lipids and fecal excretion of bile acids in Alloxan induced diabetic rats

Experimental Schedule	Adipose				Liver				Faeces	
	TC (mg/dl)	PL (mg/dl)	TG (mg/dl)	LPL (n mol FFA released/hr/mg protein)	TC (mg/dl)	PL (mg/dl)	TG (mg/dl)	LPL (n mol FFA released/hr/mg protein)	Cholic Acid (µg/g feces)	Deoxycholic Acid (µg/g feces)
Control	4.20 ±0.40	6.38 ± 0.50	421.50 ±45.60	78.25 ±9.98	4.68 ±0.55	13.40 ±1.48	10.25 ±1.20	122.60 ±13.85	76.30 ±6.86	56.76 ±7.36
Alloxan treated	3.00** ±0.32 (-29)	5.10 ** ±0.45 (-20)	230.70*** ±25.40 (-45)	138.30*** ±15.37 (+77)	7.25*** ±0.86 (+55)	20.10*** ±2.58 (+50)	18.45*** ± 2.15 (+80)	68.72*** ±10.35 (-44)	53.68 ** ± 6.49 (-30)	35.34** ±3 .83 (-38)
Alloxan + *T. cordifolia* (500mg/kg	3.60** ±0.40* (+20)	6.12** ±0.62 (+20)	330.00*** ±35.15 (+43)	90.20** ±13.00 (-35)	5.00** ±0.65 (-31)	15.25** ±2.20 (-24)	13.10** ± 1.85 (-29)	92.30** ±12.20 (+ 34)	68.00** ±9.00 (+27)	48.85** ± 5.00 (+38)

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Alloxan+ Glibenclamide (0.6mg/kg b.w)	3.35^{NS} ±0.55 (+12)	5.86^{NS} ±0.60 (+15)	295.20* ±30.50 (+28)	98.85* ±11.75 (-28)	5.22* ±0.70 (-28)	15.80* ±1.95 (-21)	14.00* ±1.40 (-24)	85.80 * ±10.28 (+25)	61.70^{NS} ± 8.80 (+15)	42.30* ± 8.36 (+20)

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

Table 3: Effect of *T. cordifolia* stem extract on some hepatic Oxidative and Antioxidative parameters in Alloxan induced diabetic rats

Experimental schedule	Lipid peroxide nmole/g	Reduced glutathione µmoleGSH/g	SOD (Unit /min /mg protein)	CAT (Unit /min /mg protein)
Control	172.50±25.10	4.25±0.58	2.80±0.20	3847±248.17
Alloxan treated	270.65***±45.35 (+57)	2.75**±0.32 (-35)	2.14±0.16** (-24)	2873±402.08*** (-25)
Alloxan + T.cordifolia(500 mg/kg bw)	156.78***±18.20 (-42)	3.70***±0.48 (-35)	2.68±0.13** (+25)	3563±504.59* (+24)
Alloxan + Glibenclamide (0.6 mg/kg b.w.)	148.00***±16.95 (-45)	3.84***±0.50 (-40)	2.70±0.13** (+26)	3625±482.02** (+26)

Values are expressed as mean ± SD of 6 animals. Values in the parenthesis are % change. Alloxan-treated group was compared with control, alloxan and drug-treated group with alloxan. **P<0.01-More significant, ***P<0.001- Most significant

Table 4: Effect of *T. cordifolia* stem extract on plasma lipids and enzyme activities of PHLA and LCAT in Alloxan-induced diabetic rats

Experimental schedule	Total cholesterol (mg/dl)	Phospholipids (mg/dl)	Triglyceride (mg/dl)	PHLA (n mole FFA formed/h/l)	LCAT Activity (n mol Cholesterol released/hr/l)
Control	84.20± 10.66	76.76± 11.30	97.70± 11.54	15.20±1.90	61.57±4.92
Alloxan-treated	118.15**± 16.80 (+40)	114.75**± 14.60 (+49)	173.80***±13.60 (+78)	9.60**± 0.98 (-37)	41.00**±3.76 (-33)
Alloxan + *T. cordifolia* (500 mg /kg b.w.)	90.80**± 12.36 (-23)	82.98**± 7.22 (-28)	114.82 **± 6.07 (-34)	13.00**± 1.90 (+35)	56..50**± 4..92 (+38)
Alloxan + Glibenclamide (0.6 mg/kg b.w.)	98.00*± 10.85 (-17)	97.45^{NS}± 11.65 (-15)	125.78**± 11.24 (-28)	11.85**± 1.16 (+23)	43.00^{NS}± 5.23 (+5)

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

Table 5: Effect of *T. cordifolia* stem 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 ±1.00	16.43 ±1.99	39.10 ±4.25	6.85 ±1.04	17.07 ±1.78	16.48 ±2.11	20.12 ±1.11	17.13 ±1.61	51.53 ±6.80	39.95 ±5.35	14.45 ±1.43	173.80 ±18.34
Alloxan treated	12.10*** ±1.20 (+50)	24.92*** ±2.48 (+52)	73.76*** ±8.70 (-89)	13.00*** ±1.50 (+84)	28.68*** ±3.15 (+68)	24.00*** ±3.43 (+46)	27.21*** ±6.29 (+35)	24.55*** ±1.46 (+43)	38.71** ±3.75 (-25)	30.52** ±2.27 (-24)	10.55** ±1.28 (-27)	127.42** ±12.33 (-27)
Alloxan + T. cordifolia(500 mg /kg b.w.)	9.32** ±1.20 (-23)	18.18** ±2.10 (-27)	44.29*** ±4.85 (-40)	7.36*** ±6.80 (-43)	20.50** ±3.46 (-28)	17.40** ±2.20 (-28)	20.66** ±4.28 (-24)	18.70** ±2.40 (-24)	46.52** ±4.41 (+20)	36.80* ±2.90 (+21)	13.25** ±1.25 (+26)	158.80** ±13.27 (+25)
Alloxan+ glibenclamide (0.6 mg/kg b.w.)	10.04* ±0.96 (-14)	20.30 * ±2.39 (-19)	56.02** ±6.60 (-24)	9.20** ±1.15 (-29)	22.33* ±3.80 (-22)	19.45* ±2.40 (-19)	22.24* ±4.36 (-18)	18.90 * ±2.52 (-23)	41.00^{NS} ±4.22 (+6)	32.12^{NS} ±3.55 (+5)	11.50^{NS} ±1.28 (+9)	141.15^{NS} ±16.41 (+11)

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