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INFLUENCE OF TETRAHYDROCURCUMIN AND GALLIC ACID ON GLYCOPROTEIN COMPONENTS IN STREPTOZOTOCIN INDUCED DIABETIC RATS

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ABSTRACT

Hyperglycemia associated with diabetes induces considerable metabolic changes, resulting in heightened levels of serum glycoprotein components - namely sialic acid, hexosamine, hexose, and fucose - which serve as indicators for vascular complications. The increase in these components is due to enhanced glycation or modified synthesis, leading to structural impairment in the kidneys and liver. Tetrahydrocurcumin (THC) is a significant, colorless, and highly potent metabolite of curcuminoids, which are the active compounds present in turmeric (*Curcuma longa*). It is frequently regarded as a "superior" variant of curcumin, providing enhanced bioavailability, stability, and antioxidant properties in comparison to its precursor, curcumin. Gallic acid (GA) is a naturally occurring phenolic compound present in tea, fruits, and herbs, which provides substantial, scientifically validated antioxidant and anti-

inflammatory advantages for diabetes management. Studies indicate that it enhances insulin sensitivity, decreases blood glucose levels, addresses obesity-related type 2 diabetes, and mitigates complications like kidney and brain deterioration by influencing metabolic pathways. The oral administration of a combination of THC at 60 mg/kg body weight and GA at 15 mg/kg body weight to diabetic rats over a period of 45 days led to a significant decrease in blood glucose and leptin levels, alongside a notable increase in plasma insulin levels. Furthermore, the oral administration of the THC and GA combination to diabetic rats resulted in a reduction in plasma glycoprotein levels. The treatment resulted in elevated plasma insulin and tissue sialic acid levels, whereas the levels of tissue hexose, hexosamine, and fucose remained nearly normal in the diabetic rats treated with the THC and GA combination. This study demonstrates that the THC and GA combination has a notable positive impact on the glycoprotein moiety, in addition to its antidiabetic properties. Furthermore, the combination of THC and GA exhibited greater potency compared to treatment with THC or GA alone in the rats.

Keywords: blood glucose, curcumin, diabetes mellitus, glycoproteins components, tetrahydrocurcumin, gallic acid

INTRODUCTION

Chronic hyperglycemia and insulin deficiency are distinctive characteristics of diabetes mellitus, which modifies glycoprotein levels in different tissues, resulting in disrupted metabolism of glycoproteins that significantly contribute to the development of diabetic complications. Glycoproteins are organic molecules composed of proteins and carbohydrates, present in various regions of living organisms, including cell membranes. Additionally, the disrupted metabolism of glycoprotein constituents is a key factor in the development of diabetes mellitus **[1]**. These compounds, which consist of protein and carbohydrate components, are found in several crucial forms, including hormones, enzymes, membranes, and antibodies. In recent years, there has been a growing interest in glycoproteins due to their biological relevance, as they have been shown to play a role, either directly or indirectly, in various disease conditions, such as diabetes mellitus. The carbohydrate moiety of glycoproteins has several biological functions such as cell adhesion, development, immune responses, trafficking, host-pathogen interactions and signaling **[2]**.

Glycoproteins are carbohydrate linked protein macromolecules found in the cell

surface, which form the principal component of animal cells. Hexose, hexosamine, fucose and sialic acid are the basic components of the glycoproteins **[3]**. They play an important role in membrane transport, cell differentiation and recognition, the adhesion of macromolecules to the cell surface, and the secretion and absorption of macromolecules. Impaired metabolism of glycoproteins plays a major role in the pathogenesis of diabetes mellitus **[4]**.

The glycosylation of proteins is a significant factor among the aforementioned possibilities that warrant considerable interest. All mechanisms were triggered by a singular upstream event involving the excessive production of reactive oxygen species (ROS) by the mitochondria, resulting in oxidative stress. The ROS produced due to elevated glucose levels is causally associated with increased glucose and various metabolic irregularities. Both oxidative stress and oxidative damage to tissues are prevalent endpoints in complications related to diabetes. The rise in glycoxidation products found in plasma and tissue proteins indicates an escalation of oxidative stress in diabetes, which encompasses the autooxidation of glucose, alterations in redox balances, and an abnormal increase in the concentrations of glycoproteins in plasma and tissues. In recent times, many traditionally important medicinal plant phytochemicals have been tested for their efficacy against impaired glycoprotein levels in diabetes **[4]**.

Medicinal plants and their bioactive compounds are fundamental to modern pharmacology, serving as the foundation for foundational antidiabetic medications like metformin. These botanical elements naturally mitigate insulin resistance and oxidative stress. However, capitalizing on this potential requires rigorous standardization and careful management of botanical risks **[5]**.

Tetrahydrocurcumin (THC), a highly effective active metabolite derived from curcumin, demonstrates considerable potential in diabetes research **[6]**. Preclinical investigations indicate that it significantly reduces blood glucose levels, enhances insulin secretion, safeguards pancreatic islet cells, and addresses diabetic complications—often exhibiting superior efficacy compared to curcumin **[7-9]**. Gallic acid (GA) is a naturally occurring phenolic acid present in a variety of plants, fruits (such as grapes and berries), nuts, tea, and oak bark **[10]**. Recognized for its antioxidant, antimicrobial, and anti-inflammatory characteristics, it is extensively utilized in the pharmaceutical, food, and cosmetic sectors **[11]**. Recent

studies indicate that it may assist in managing diabetes and its complications by enhancing insulin sensitivity, regulating blood sugar metabolism, and combating the oxidative stress that contributes to tissue damage **[13]**.

GA and THC are powerful phenolic compounds recognized for their significant synergistic therapeutic benefits **[14, 15]**. Research conducted on animal models has demonstrated that their combination effectively improves lipid profiles **[16]**, markedly reduces blood glucose levels **[17]**, and boosts insulin sensitivity in individuals with diabetes **[18]**. This study expands upon earlier research by comprehensively investigating the antidiabetic effects resulting from the combined and comparative actions of THC and GA in diabetic rats induced by streptozotocin (STZ). Of all existing animal models for diabetes, the STZ-induced diabetic model has been the most extensively characterized and has demonstrated all the alterations observed in patients with diabetes mellitus.

To the best of our knowledge, no other biochemical studies have been conducted regarding the combined effects of THC and GA on plasma and tissue glycoproteins in experimental diabetic rats. Therefore, this investigation was undertaken to examine the combined effects of THC and GA on plasma and tissue glycoproteins in rats with diabetes induced by STZ.

MATERIALS AND METHODS

Animals

Male albino Wistar rats, weighing between 180 and 220 grams, were sourced from the Central Animal House at J.J College of Arts and Science in Pudukkottai, which is affiliated with Bharathidasan University in Tiruchirappalli. These rats were housed in polypropylene cages within a pathogen-free environment, maintained at an ambient temperature of 28±2°C and a relative humidity of 45–55%, with a 12-hour cycle of light and dark. The rats were provided with a pellet diet from Hindustan Lever Ltd., India, and had access to water *ad libitum*. The care of the animals adhered to the guidelines set forth by the National Institute of Nutrition, Indian Council of Medical Research, Hyderabad, India, and received approval from the Institutional Animal Ethical Committee at J.J College of Arts and Science in Pudukkottai (JJC/BC/AH/002/2025).

Drugs and Chemicals

THC was a gift provided by Sabinsa Corporation, USA. GA was purchased from Sigma Chemical Company, St. Louis, MO, USA, and all other chemicals

utilized were of analytical grade sourced from Himedia, Mumbai, India.

Induction of diabetes

Adult male albino Wistar rats (8 weeks), weighing 180-220 g bred in the Central Animal House, J.J College of Arts and Science in Pudukkottai, affiliated with Bharathidasan University, Tiruchirappalli, India, were used. All animal experiments were approved by the ethical committee (JJC/BC/AH/002/2025), at J.J College of Arts and Science and were maintained in accordance with the guidelines of the National Institute of Nutrition, Indian Council of Medical Research, Hyderabad, India. During the experimental period, the animals were fed with a balanced commercial diet (Lipton India Ltd., India) and water *ad libitum*.

Drugs and chemicals

THC was a gift provided by Sabinsa Corporation, USA. GA was obtained from Sigma Chemicals Corporation, St.

Induction of diabetes

Experimental animals were administered a freshly prepared solution of STZ (55 mg/kg) in 0.1 M citrate buffer at pH 4.5, delivered intraperitoneally in a volume of 1 ml/kg **[19]**. Normal rats were given 1 ml of citrate buffer as a vehicle. The animals were permitted to consume a 20% glucose solution overnight to counteract drug-induced hypoglycemia. Control rats received the same volume of isotonic saline. After 72 hours, plasma glucose levels were measured, and those rats exhibiting fasting glucose levels exceeding 250 mg/dL were classified as diabetic rats and utilized in the current study.

Experimental design

The animals were randomly divided into five groups of six animals in each group (24 diabetic surviving and 6 normal). Group I: Normal rats. Group II: Diabetic control rats. Group III: Diabetic rats given THC (60 mg/kg body weight) and GA (15 mg/kg body weight) in aqueous solution daily using an intragastric tube for 45 days **[15]**. Group IV: Diabetic rats given THC (80 mg/kg body weight) in aqueous solution daily using an intragastric tube for 45 days **[20]**. Group V: Diabetic rats given GA (20 mg/kg body weight) in aqueous solution daily using an intragastric tube for 45 days **[13]**.

At the end of the experimental period, all the animals were fasted overnight, anaesthetized and sacrificed by cervical dislocation. Blood samples were gathered in tubes that contained a mixture of potassium oxalate and sodium fluoride in a 3:1 ratio for the purpose of estimating fasting plasma

glucose levels. The liver and kidney were carefully dissected, rinsed in ice-cold saline, and subsequently stored at -80°C until required for analysis. The weights of the liver and kidney were recorded, and a 10% tissue homogenate was prepared using 0.1 M Tris–HCl buffer at pH 7.4. Following centrifugation, the clear supernatant was collected and utilized for biochemical assays.

Analytical methods

Measurement of blood glucose and plasma insulin

The efficacy of the automated colorimetric glucose oxidase method, known as Trinder's method, was assessed for measuring blood glucose levels using glucose **[21]**. Plasma insulin levels were determined through standard semi-automated immunoassay techniques, as evaluated by Boehringer Mannheim **[22]**.

Extraction of glycoprotein components

To 0.1 mL of plasma, 5.0 mL of methanol was added, thoroughly mixed, and then centrifuged for 10 minutes at 3000×g. The supernatant was decanted, and the precipitate was washed again with 5.0 mL of 95% ethanol, followed by another centrifugation, after which the supernatant was decanted to isolate the precipitate of glycoprotein components. This precipitate was utilized for the estimation of hexose, hexosamine, fucose, and sialic acid in plasma. For the extraction of glycoprotein components from tissues such as the liver or kidney, a known weight of the tissue was homogenized in 7.0 mL of methanol. The mixture was filtered and then homogenized with 14 mL of chloroform. This was filtered again, and the residue was subsequently homogenized in a chloroform: methanol mixture (2:1 v/v), with filtration occurring after each extraction. The residue, referred to as defatted tissues, was collected, and the filtrate was decanted. A measured amount of the defatted tissue was suspended in 3.0 mL of 2 N HCl and heated at 90°C for 4 hours. After cooling, the sample was neutralized with 3.0 mL of 2 N NaOH. Portions of this sample were then used for the estimation of hexose, hexosamine, sialic acid, and fucose in the tissues **[23]**.

Determination of levels of glycoproteins components

Hexose estimation was conducted following the method described by Niebes **[24]**. The reaction mixture consisted of 0.5 ml of aliquot/plasma, 0.5 ml of 5% phenol, and 2.5 ml of concentrated H_2SO_4, which was boiled for 20 minutes, and the absorbance was measured at 490 nm.

Hexosamine was quantified using the Elson and Morgan method **[25]**, with minor

adjustments made by Niebes **[24]**. In summary, the reaction mixture consisted of 0.5 ml of plasma and 1.0 ml of aliquot, combined with 2.5 ml of 3 M HCl, and was boiled for 6 hours before being neutralized with 6 M NaOH. To 0.8 ml of the neutralized sample, 0.6 ml of acetyl acetone reagent was added, followed by boiling for 30 minutes. Subsequently, the mixture was treated with 2.0 ml of Ehrlich's reagent, and the absorbance was measured at 540 nm.

Sialic acid was quantified using the method described by Warren **[26]**. In summary, 0.5 ml of plasma aliquot was mixed with 0.5 ml of water and 0.25 ml of periodic acid, then incubated at 37°C for 30 minutes. Following this, 0.2 ml of sodium meta arsenate and 2.0 ml of thiobarbituric acid were introduced into the reaction mixture, which was then heated for 6 minutes before adding 5.0 ml of acidified butanol. The absorbance was measured at 540 nm.

Fucose was quantified using the method described by Winzler **[27]**. In summary, 1.0 ml of glycoprotein precipitate from the platelet membrane and 1.0 ml of processed serum were combined with 1 ml of 0.1 M NaOH and placed in an ice bath. Subsequently, 4.5 ml of cold H2SO4 was added and thoroughly mixed. The tubes were then heated in a boiling water bath for 3 minutes, cooled, and 0.1 ml of 3% cysteine was added and mixed immediately. The tubes were allowed to sit at room temperature for 60–90 minutes. The absorbance of the solution was measured at 396 and 430 nm using a spectrophotometer, and the difference in absorbance values was used for calculations.

Statistical assessment

All data were expressed as mean ± SD for six rats in each group. The statistical analysis was conducted using one-way analysis of variance (ANOVA), followed by Duncan's Multiple Range Test (DMRT), utilizing SPSS (Statistical Program for Social Sciences, SPSS Corporation, Chicago, IL). A p-value of less than 0.05 was considered significant and included in the study **[28]**.

RESULTS

Table 1 presents the blood glucose levels and plasma insulin concentrations across different experimental groups. The diabetic control rats showed a significant increase in blood glucose, leptin along with a marked decrease in plasma insulin levels. The oral administration of a combination of THC and GA to diabetic rats effectively reversed the aforementioned biochemical changes. In normal rats, the administration of THC and GA had a

considerable effect on blood glucose, leptin and plasma insulin levels. The combination therapy of THC and GA proved to be more effective than either THC or GA administered alone.

The concentrations of plasma and tissue glycoproteins in both normal and experimental rats are presented in **Table 2**. A notable increase in plasma glycoprotein levels was observed in diabetic rats. In the liver and kidneys of diabetic rats, the levels of hexose, hexosamine, and fucose were significantly elevated, while the level of sialic acid was significantly reduced. The oral administration combination of THC and GA significantly counteracted the alterations in plasma, liver, and kidney glycoproteins in diabetic rats. The combination effect of THC and GA was better when compared with that of THC or GA alone.

DISCUSSION

Diabetes is a progressive condition, and the biochemical mechanisms underlying its progression and associated complications remain inadequately understood. In individuals with diabetes, glucose is diverted through insulin-independent pathways, leading to an increased synthesis of carbohydrate components in glycoproteins. Consequently, there is a rise in the concentrations of protein-bound hexose, hexosamine, fucose, and sialic acid in the plasma of diabetic animals **[29]**.

Glycoproteins are carbohydrate linked protein macromolecules found in the cell surface, which form the principle components of animal cells. They play an imporatant role in membrane transport, cell differentiation and recognition, the adhesion of macromolecules to cell surface and the excretion and absorption of macromolecules **[4]**. Prolonged elevation of blood glucose in diabetes may result in structural and functional alteration of both circulating and membrane bound proteins **[30, 31]**. Alterations in the diabetic state of the composition of the carbohydrate components of glycoproteins, especially serum glyloproteins and glycoproteins of the capillary basement membrane have been reported.

Glycation is defined as a spontaneous, non-enzymatic reaction where reducing sugars, like glucose, or reactive metabolic byproducts bond with proteins, nucleotides, and lipids. Unlike the enzyme-driven process of glycosylation, this uncontrolled chemical reaction gradually alters molecular structures and significantly influences the aging process and complications related to diabetes. The non-enzymatic glycation, known as the Maillard reaction, is a spontaneous sequence

that occurs without enzymes, wherein reducing sugars create covalent bonds with the amino groups of proteins, lipids, or nucleic acids. This occurrence has a substantial impact on biological aging, metabolic disorders, and food chemistry **[33]**. The non-enzymatic attachment of sugars to proteins leads to a permanent alteration of their macromolecular structure, which directly contradicts the body's natural systems for protein degradation and renewal **[34]**. Advanced Glycation End-products (AGEs) and their receptor interactions trigger a pathological cascade that is crucial to numerous age-related and metabolic diseases, including diabetes, atherosclerosis, and neurodegeneration. This molecular pathway modifies the cellular microenvironment by fostering inflammation, oxidative stress, and structural tissue remodeling **[35]**.

In a diabetic state, it is common to observe abnormalities in glycoprotein metabolism **[36]**. In our study, we observed elevated levels of hexose, hexosamine, fucose, and sialic acid in the plasma and tissues (liver and kidney) of rats induced with streptozotocin diabetes. The secretion or shedding of glycoconjugates from cell membranes into the bloodstream contributes to the increased levels of plasma glycoprotein components. Furthermore, insulin deficiency and elevated plasma glucose levels in diabetic conditions may lead to enhanced synthesis of glycoprotein components **[4]**. Treatment with THC and GA in STZ-induced diabetic rats significantly reduced plasma glycoprotein components to levels close to normal, owing to their antihyperglycaemic effects. The combined treatment of THC and GA proved to be more effective than administering either THC or GA alone.

Elevated levels of glycoprotein hexose (protein-bound hexose) are a well-documented metabolic change associated with diabetes mellitus, which is directly related to hyperglycemia and the management of glycemic levels. Increased glucose concentrations promote the non-enzymatic glycosylation of proteins, resulting in heightened amounts of glycoprotein constituents—namely hexose, hexosamine, fucose, and sialic acid—in serum and different tissues **[37]**. An overabundance of flux within the hexosamine biosynthesis pathway results in elevated concentrations of glycoprotein-associated hexosamines, which plays a vital role in the mechanisms underlying insulin resistance related to diabetes and the complications associated with chronic hyperglycemia **[38]**.

Increased levels of serum sialic acid are being recognized as a significant biomarker for diabetes. This biomarker consistently reflects the existence of chronic, subclinical inflammation and extensive vascular damage linked to type 2 diabetes **[39]**. Similarly, heightened serum fucose levels act as an essential biomarker for metabolic stress and changes in protein glycosylation in diabetes mellitus. These elevated levels are closely associated with the initiation and advancement of diabetic microvascular complications, such as nephropathy, retinopathy, and cardiovascular disease.

Several workers have suggested that elevated levels of plasma glycoprotein components in diabetic rats could be a consequence of abnormal carbohydrate metabolism. Insulin deficiency and high levels of plasma glucose in diabetic condition may result in an increase of glycoproteins synthesis **[4, 37, 40, 41]**. The requirement of insulin for the biosynthesis of the carbohydrate moiety of mucoproteins from glucose is thus evident **[42]**.

This phenomenon describes glucotoxicity in diabetes. When insulin is deficient or cells become resistant, glucose cannot enter insulin-dependent pathways (like glycolysis in muscle and adipose tissue). This excess blood glucose is instead shunted into insulin-independent pathways and the hexosamine biosynthesis pathway **[43]**. Glycoproteins consist of a protein core with carbohydrate chains (glycans) covalently attached, where terminal sugars like fucose and sialic acid play critical roles in cellular recognition, adhesion, and signaling. When the biosynthesis of glycoproteins increases or their metabolism (breakdown) decreases, these abnormal glycan-rich materials can abnormally accumulate in the basement membrane and extracellular matrix **[44]**. The basement membrane proteins consist of glycoprotein components and basement membrane thickening may be influenced by insulin deficiency. Thickening of capillary basement membrane is accompanied by the disruption of glycemic control in the diabetes mellitus **[45, 46]**. Alterations of those functional glycoconjugates could induce abnormal cellular behavior, as it is frequently described in diabetic microvascular complications **[47, 48]**. The hypothesis describes a metabolic shift in diabetes where sialic acid is drawn away from tissue stores to synthesize fibronectin. This glycoprotein—which contains sialic acid residues—is markedly overproduced during diabetes, contributing to basement membrane thickening, fibrosis, and

microvascular complications in both patients and animal models **[49]**.

Cytokines (IL-6 and TNF-α) released by inflammatory cells and damaged endothelia due to angiopathy-associated tissue injury could elicit an acute-phase response, resulting in increased hepatic production of sialylated glycoproteins and other glycoproteins, leading to a rise in acute phase proteins with sialic acid. The synthesized glycoproteins are made to circulate in blood. Alternatively, a systemic cytokine response to atherosclerosis could directly cause vasculopathy in diabetes mellitus **[50]**. In our study, a significant elevation in plasma hexose, hexosamine, sialic acid and fucose with a fall in hepatic and renal tissues was observed in diabetic control rats. Oral administration of THC and GA to diabetic treated rats significantly restored the levels of glycoprotein components in plasma, hepatic and renal tissues to near normal.

CONCLUSION

The combination of THC and GA improved the glycoprotein components in STZ induced diabetic rats. Through its insulinotropic effect on the remaining pancreatic β-cells, THC and GA restored the altered glycoprotein levels in the plasma, liver, and kidney tissues of diabetic rats, thereby positioning itself as a promising agent for the management of diabetes mellitus. The combined effect of THC and GA was more significant than the effects observed with THC or GA used individually.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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Table 1: Effect of THC and GA on hormone and glucose index parameters in normal and experimental animals.

Parameters	Normal	Diabetic control	Diabetic + THC and GA	Diabetic + THC	Diabetic + GA
Glucose (mg/dl)	89.57±4.68^{a}	279.55±4.52^{b}	91.55±4.55^{a}	105.69±4.25^{c}	108.45±4.51^{c}
Leptin (ng/ml)	0.59±0.02^{a}	1.93±0.03^{b}	0.63±0.03^{a}	0.79±0.02^{c}	0.81±0.03^{c}
Insulin (µU/ml)	12.31 ± 0.72^{a}	3.94 ± 0.22^{b}	11.18 ± 0.52^{a}	8.58 ± 0.45^{c}	8.32 ± 0.45^{c}

Values are expressed as Mean ± SD for 6 rats.
Statistical analysis of one-way ANOVA, post-hoc followed by DMRT test using SPSS ver. 24.
Mean values are within the row followed by different letters, superscript (homogeneous subsets) are mentioned as statistically significant (*P*<0.05) while same letter was statistically non-significant (*P*>0.05) from each other groups

Table 2: Effect of THC and GA on changes in the levels of plasma and tissue hexose, hexosamine, sialic acid and fucose in normal and experimental rats

Group	Normal	Diabetic control	Diabetic + THC and GA	Diabetic + THC	Diabetic + GA
Hexose					
Plasma (mg/dl)	97.51 ±6.53^{a}	141.72 ±7.44^{b}	101.55 ±6.15^{a}	112.21 ±5.94^{c}	113.45 ±5.54^{c}
Liver (mg/g defatted tissue)	31.49±2.81^{a}	61.42±3.09^{b}	32.51±2.23^{a}	45.72±2.79^{c}	43.29±2.60^{c}
Kidney (mg/g defatted tissue)	24.62 ±1.55^{a}	45.13 ±2.32^{b}	25.42 ±2.14^{a}	31.15 ±1.77^{c}	32.05 ±1.82^{c}
Hexosamine					
Plasma (mg/dl)	78.45 ±5.32^{a}	99.35 ±5.45^{b}	79.87 ±3.55^{a}	86.21 ±4.47^{c}	87.12 ±4.64^{c}
Liver (mg/g defatted tissue)	18.72±2.02^{a}	35.67±1.69^{b}	19.32±1.82^{a}	27.13±1.91^{c}	25.67±1.33^{c}
Kidney (mg/g defatted tissue)	15.54 ±1.30^{a}	31.21 ±2.45^{b}	16.21 ±1.02^{a}	20.91 ±1.4^{c}	20.78 ±1.41^{c}
Sialic acid					
Plasma (mg/dl)	56.21 ±4.24^{a}	71.32±4.19^{b}	57.31 ±2.47^{a}	62.20 ±3.55^{c}	63.20 ±3.65^{c}
Liver (mg/g defatted tissue)	12.09±0.59^{a}	22.79±0.42^{b}	13.47±0.65^{a}	19.63±0.99^{c}	18.15±0.84^{c}
Kidney (mg/g defatted tissue)	8.55 ±0.41^{a}	4.21 ±0.22^{b}	7.31 ±0.45^{a}	5.77 ±0.44^{c}	5.68 ±0.40^{c}
Fucose					
Plasma (mg/dl)	29.76 ±1.70^{a}	43.66±2.12^{b}	30.87 ±1.77^{a}	35.54 ±2.77^{c}	35.54 ±2.8^{c}
Liver (mg/g defatted tissue)	7.15±0.44^{a}	15.92±0.59^{b}	7.63±0.40^{a}	12.95±0.65^{c}	12.47±0.69^{c}
Kidney (mg/g defatted tissue)	34.55 ±0.65^{a}	25.32 ±1.77^{b}	33.22 ±0.97^{a}	28.32±1.16^{c}	29.30±1.15^{c}

Values are expressed as Mean ± SD for 6 rats. Statistical analysis of one-way ANOVA, post-hoc followed by DMRT test using SPSS ver. 24. Mean values within the rows followed by different superscript (homogeneous subsets) letters indicate statistically significant (*P*<0.05) while same letters indicate statistically non-significant (*P*>0.05) from each other groups