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SHORT TERM EFFECT OF DOSE DEPENDENT CAMEL MILK IN ALLOXAN INDUCED DIABETES IN FEMALE ALBINO RATS

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ABSTRACT

Current project was designed to evaluate the antidiabetic effect of camel milk on hematology, serum profile and histology of selected organs. Forty female albino rats were divided into 4 groups (n=10): Group 1 as placebo. Diabetes was induced by Alloxan® in remaining groups. Group 2 served as diabetic control while group 3 and 4 were offered camel milk orally @ 20 and 40ml/kg/day, respectively, for 60 days. Weekly blood glucose was measured. Animals were slaughtered on day 60 to collect: blood for hematology and tissue for histology. Microscopy was done for degenerative changes in uterus (epithelial height, gland area, thickness of endometrium and myometrium), liver and kidneys. Diabetes revealed significant ($P<0.05$) adverse effect on all parameters. Camel milk exhibited more significant ($P<0.05$) mitigating influence on diabetic altered hematology and histology of uterus, liver and kidney @ 40ml/kg compared to 20 ml/kg. Camel milk @ 20 ml/kg significantly ($P<0.05$) reduced blood glucose in 3rd week and remained constant in trial while this reduction was significant ($P<0.05$) at 2nd week and became more significant ($P<0.01$) in last two weeks @ 40 ml/kg. Hence, camel milk has potential to recover elevated blood glucose, hematological parameters and degenerative changes in uterus, liver and kidneys.

Keywords: camel milk, diabetes, uterus, hematology, microscopy, liver function test, kidney.

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder diagnosed by elevated blood glucose concentration and lipedemia, and is associated with high prevalence of microvascular complication that poses substantial threat worldwide in 21st century. The dramatic change in its expending prevalence is due to obesity and changes in lifestyle. It is stated that in 2000 its prevalence was 171 million and this figure will reach up to 360 million in 2030. The hyperglycemia disturbs the carbohydrate, protein and fat metabolism (Khan *et al*., 2013; Baragob, 2015). In chronic cases hypertension, neuropathy, nephropathy, hepatopathy, retinopathy and diabetic foot ulcers which can lead to amputation, are the major complications observed (Oyedemi *et al*., 2009).

DM type 1 represents the destruction of β cells of islets of Langerhans in pancreas and results in low/no insulin production (Rahimi *et al*., 2011). This kind of DM develops in the autoimmune disease condition in which immune system reacts against its own body cells and destroys pancreatic beta cells (Notkins and Lemmark, 2001), hence, named insulin dependent DM. This metabolic disorder showed genetic involvement in its transmission (Khan *et al*., 2013).

Effect of DM has been extensively studied on reproductive system of males, but these studies have recently received attention in females albeit the prevalence of sexual dysfunction seems to be lower. Type 1 DM has perturbative impact on the ovarian steriogensis, folliculogensis and ovulation. There is decrease in vaginal secretion, orgasmic dysfunction and low arousability (Ramalho-Santos *et al*., 2008). Pathological changes in the reproductive system consequence in severe hypogonadism and low fertility (Ramalho-Santos *et al*., 2008; Codner *et al*., 2012).

Histological studies on the uterus of non-pregnant diabetic albino rats revealed that there is a decline in smooth muscle cells and vanished contractive response of myometrium to oxytocin. There is observed decreased uterine weight, atrophy of uterine myometrium and endometrium and altered uterine functions in DM (Favaro *et al*., 2010).

The chronic elevated concentration of blood glucose causes long term dysfunction of liver and kidneys by damaging their cellular structures. Hyperlipidemia and fatty liver inductions are sequelae of insulin insufficiency which accelerates the disintegration of lipids in adipose tissue (Goodman *et al.,* 2006; Manal and Moussa, 2014). DM causes cirrhosis and carcinoma of hepatic cells (Ragavan and Krishnakumari, 2006).

Traditionally, natural products possessing antidiabetic effect are preferred because synthetic drugs have side effects on liver and kidneys and are not safe in pregnancy (Agrawal *et al*., 2011; Baragob, 2015). Camel milk (CM) holds many properties to normalize insulin action and improves insulin sensitivity. The antihyperglycemic action of CM is mainly due to the presence of insulin like protein which ranges from 45-128

IU/ liter of milk. Insulin present in CM is encapsulated and can tolerate stomach environment (Agrawal *et al*., 2005). It contains high amount of zinc which assists in insulin secretory activity of pancreatic beta cells and vitamin C is 5 times higher in camel milk as compared to cow milk which function as antioxidant (Rahimi *et al*., 2011; Mullaicharam, 2014). Therefore, the present study was conducted to elucidate the short-term dose dependent CM therapy on blood glucose concentration, hematochemical parameters and histometry of uterus, liver and kidneys in non-pregnant diabetic rats.

MATERIALS AND METHODS

Collection of animals: A total of 40 adult healthy female albino rats weighing about 160 $\pm$ 13 g body weight were subjected to this study. The rats were kept for two weeks in the animal house of Institute of Microbiology, University of Agriculture, Faisalabad for adaptation under optimally maintained environmental room condition in a 12 hr light/dark cycle. The rats were offered standard commercial feed and water *Ad libitum*. The experiment was carried out in accordance with the guidelines of the Directorate of Graduate Studies and Institutional Animal Ethical Committee.

Induction of diabetes: Diabetes was induced by administrating Alloxan® intraperitonealy @ 150 mg/kg of body weight to the 12 hour fasting rats (Hassan and Bayoumi, 2010). The blood glucose level was measured using an On Call EZ II® blood glucose monitor 4-5 days' post administration of Alloxan to confirm the induction of diabetes. Rats having fasting blood glucose >250mg/dL were declared as diabetic and used for the present study.

Collection of camel milk: Fresh raw camel milk (CM) was used in this study. CM was collected in the sterile bottles on daily basis from a local camel market of Faisalabad. The bottles were kept in cold container and transported to laboratory.

Research Design: All experimental animals were randomly divided into 4 groups: each having ten rats. Group 1 was considered as placebo. Diabetes was induced in rest of the groups such as Group 2 kept as diabetic control while CM was administered orally to group 3 and 4 @ 20 and 40ml/kg/day respectively for a period of 60 days.

Collection of samples: Fasting blood glucose concentration was measured on weekly basis with the help of blood glucose monitoring system (On Call® EZ II, Acon® Laboratories, Inc. USA). Collection of samples was done on day 60 after euthanizing the animals. Blood sample (2ml) was taken from heart before slaughter and collected in two vacutainers: one containing EDTA for hematology and second without EDTA for the estimation of liver and kidney function tests. Serum was separated by centrifugation at 1500 rpm for 15 minutes and stored at -20°C for its further analysis. Samples of uterus, liver and kidneys were collected immediately after the slaughtering. Uterus was fixed in Bouin's fluid while liver and kidneys were fixed in 10% neutral buffered formalin after washing with normal saline.

Microscopic analysis: Tissues were cut into thin slices and processed by paraffin preparation technique. Sections were cut at 5 µm and subjected to Hematoxylin and Eosin (H&E) staining procedure of Bancroft *et al*. (2013). Microscopic slides were examined at 100X to measure the uterine height (µm) of epithelium, endometrial glands area and thickness (µm) of endometrium and myometrium using automated image analysis system image J®. Vacuolar and degenerative changes in tubules of kidneys and radial arrangement of hepatocytes around the central vein along with the necrosis of hepatocytes were also observed.

Statistical Analysis: Descriptive statistics of each parameter under study was calculated with the help of computer software Microsoft Excel®. The means of parameters were compared with one-way analysis of variance (ANOVA) except fasting blood glucose for which repeated measurement ANOVA under Complete Randomize Design (CRD) was performed by SAS®. The group means were compared with help of the Least Significance Difference (LSD) test. The level of significance was kept at 5 percent.

RESULTS

Multiple mean comparison of fasting blood glucose concentration and live weight gain of all groups of rats is given in Table 1. Alloxan® caused significant ($P<0.05$) rise in the blood glucose concentration. Following the oral therapy of CM @ 20 and 40ml/kg/day, the blood glucose concentration reduced significantly ($P<0.05$). The live weight gain was significantly ($P<0.05$) high in CM @ 40 group as compared to other groups.

Table 2 described that diabetes caused significant ($P<0.05$) decrease in hematological parameters including RBCs, leucocytes, platelets, hemoglobin, MCV, MCH and lymphocytes. Effect of CM @ 20 ml/kg remained non-significant ($P>0.05$) except for hemoglobin. CM @ 40ml/kg revealed significant ($P<0.05$) increase in these parameters especially in platelets, hemoglobin, MCV and MCH which was near to the placebo.

The significant ($P<0.05$) reduction was seen in the uterine histometry including epithelial height, endometrium thickness and its glands area, inner circular and outer longitudinal smooth muscle thickness of myometrium in the diabetic rats. Oral administration of

CM showed significant (P<0.05) recovery towards normal in these parameters especially @ 40 ml/kg (Table 3, Figure 1).

Micrograph of hepatic tissue, in placebo rats, showed radial arrangement of hepatocytes around the central vein along with the portal triad with bile duct, portal vein and hepatic artery. Hyperglycemic rats showed the disrupted radial arrangements of hepatocytes around central vein along with the necrosis of hepatocytes. Oral administration of CM recovered the radial arrangement of hepatocytes and reduced the necrosis of hepatocytes with less hemorrhages but best results were displayed in group treatment with CM @ 40 ml/kg (Figure 2).

Histological examination of kidney from placebo rats showed normal glomerular structure along with renal tubules while diabetic kidneys showed glomerular damage, excessive tubular degeneration and hemorrhages. CM @ 20 ml/kg showed no improvement in the cellular structures of damaged glomerulus and renal tubules. Nephroprotective effect was observed in the rats treated with CM @ 40ml/kg with less hemorrhages and tubular degeneration and nearly normal glomerular structure (Figure 3).

Diabetes caused marked (P<0.05) increase in the Aspartate transaminase (AST), Alanine transaminase (ALT), serum urea and creatinine level as compared to the placebo (Figure 4). It was observed that long term CM treatment significantly (P<0.05) decrease diabetic AST level at both doses while significant (P<0.05) reduction in ALT level was only observed in group treated with CM @ 40ml/kg. CM therapy significantly (P<0.05) decrease the serum urea level but more significant results were observed by CM @ 40ml/kg. CM treatment was seen no more significant (P>0.05) on the creatinine level (Figure 5).

Table 1. Comparison of dose dependent effect of camel milk in different groups on fasting blood glucose and live weight gain.

Groups	Blood glucose (Mean±SE) mg/dL						
	W-1	W-2	W-3	W-4	W-5	W-6	W-7
Placebo	95.6±21.22^{C}	120±11.84^{C}	119.3±1.74^{C}	132.3±21.92^{C}	125.75±21.34^{C}	132.8±13.84^{C}	130.5±11.84^{C}
Diabetic control	495.86±21.74^{A}	408.57±7.75^{A}	457.57±20.8^{A}	419.00±21.30^{A}	457.57±20.79^{A}	486.86±22.45^{A}	491.00±20.4^{A}
CM @20	503.67±14.25^{A}	399.00±7.64^{A}	406.00±6.66^{AB}	333.67±20.90^{B}	305.67±18.70^{B}	315.33±21.40^{B}	306.33±18.9^{B}
CM @40	482.25±19.98^{A}	407.38±7.16^{A}	342.63±15.4^{B}	291.88±18.45^{B}	251.00±16.30^{B}	241.67±10.00^{C}	226.00±7.48^{C}
	Live Weight Gain (Mean±SE) grams						
Placebo	95.00±11.58^{A}	120.00±6.36^{A}	119.00±2.08^{A}	123.30±11.2^{A}	125.74±12.4 ^{A}	132.8±8.2^{A}	130.5±10.4^{A}
Diabetic control	164.00±3.91^{A}	155.57±11.58^{A}	168.14±12.64^{A}	158.14±11.6^{B}	156.57±11.2^{B}	151.14±10.0^{B}	147.57±9.33^{B}
CM @20	153.00±1.53^{A}	156.00±2.08^{A}	181.33±6.36^{A}	181.00±4.51^{AB}	179.33±4.98^{AB}	180.00±3.61^{AB}	176.67±3.33^{AB}
CM @40	160.75±4.60^{A}	169.13±6.08^{A}	187.13±5.73^{A}	192.38±5.41^{A}	197.17±6.59^{A}	198.83±6.55^{A}	211.50±10.2^{A}

Values with superscript ^{A,B,C,D} are significantly different at P<0.05

Table 2. Dose dependent effect of camel milk on hematological parameters in Alloxan induced diabetic female albino rats.

Groups	Hematology (Mean±SE)						
	RBCs (10^{12}/L)	PLT (10^{9}/L)	WBC (10^{9}/L)	MCV (fl)	Hb (g/dl)	Lymphocyte (%)	MCH (pg)
Placebo	8.94±0.12 ^{A}	851±15 ^{A}	17.20±1.05 ^{A}	55.63±5.41 ^{A}	15.03±0.45 ^{A}	65.20±2.03 ^{A}	16.93±1.78^{A}
Diabetic control	4.81±0.38 ^{C}	398±179 ^{B}	5.63±1.18 ^{C}	51.65±1.47 ^{B}	11.00±0.53 ^{C}	45.87±1.61 ^{B}	12.63±0.85 ^{B}
CM @20	4.88±0.32 ^{C}	455±39 ^{B}	7.17±0.58 ^{C}	51.87±1.27 ^{B}	12.60±0.42 ^{B}	46.23±2.13 ^{B}	14.23±0.41 ^{B}
CM @40	6.09±0.42 ^{B}	751±104 ^{A}	10.43±2.51 ^{B}	56.52±1.05 ^{A}	14.72±0.49 ^{A}	60.32±2.83 ^{A}	16.55±0.78 ^{A}

Means sharing different superscript are statistically significantly different in a column at P<0.05

Table 3. Effect of different doses of camel milk on histometry of uterus in Alloxan induced diabetic female albino rats.

Groups	Epithelial height (µm)	Endometrium thickness(µm)	Endometrium glands (µm^2)	Inner circular smooth muscle layer (µm)	outer longitudinal smooth muscle layer (µm)	myometrium thickness (µm)
Placebo	103.95±3.07^{AB}	200.24±18.44^{A}	31.883±9.3^{A}	277.02±07.22^{A}	396.26±26.03^{A}	673.28±23.75^{A}
Diabetic control	87.86±5.18^{C}	152.95±13.05^{B}	25.837±4.5^{B}	161.70±09.01^{C}	121.03±05.06^{C}	282.73±10.99^{C}
CM @20	95.79±3.12^{BC}	184.70±13.72^{AB}	30.114±10.0^{C}	140.61±10.94^{C}	168.25±23.59^{C}	304.69±27.04^{C}
CM @40	113.09±3.99^{A}	229.96±18.95^{A}	31.617±9.2^{C}	227.05±15.48^{B}	240.06±20.03^{B}	467.11±21.18^{B}

Means sharing different superscript are statistically significantly different at (P<0.05) in a column

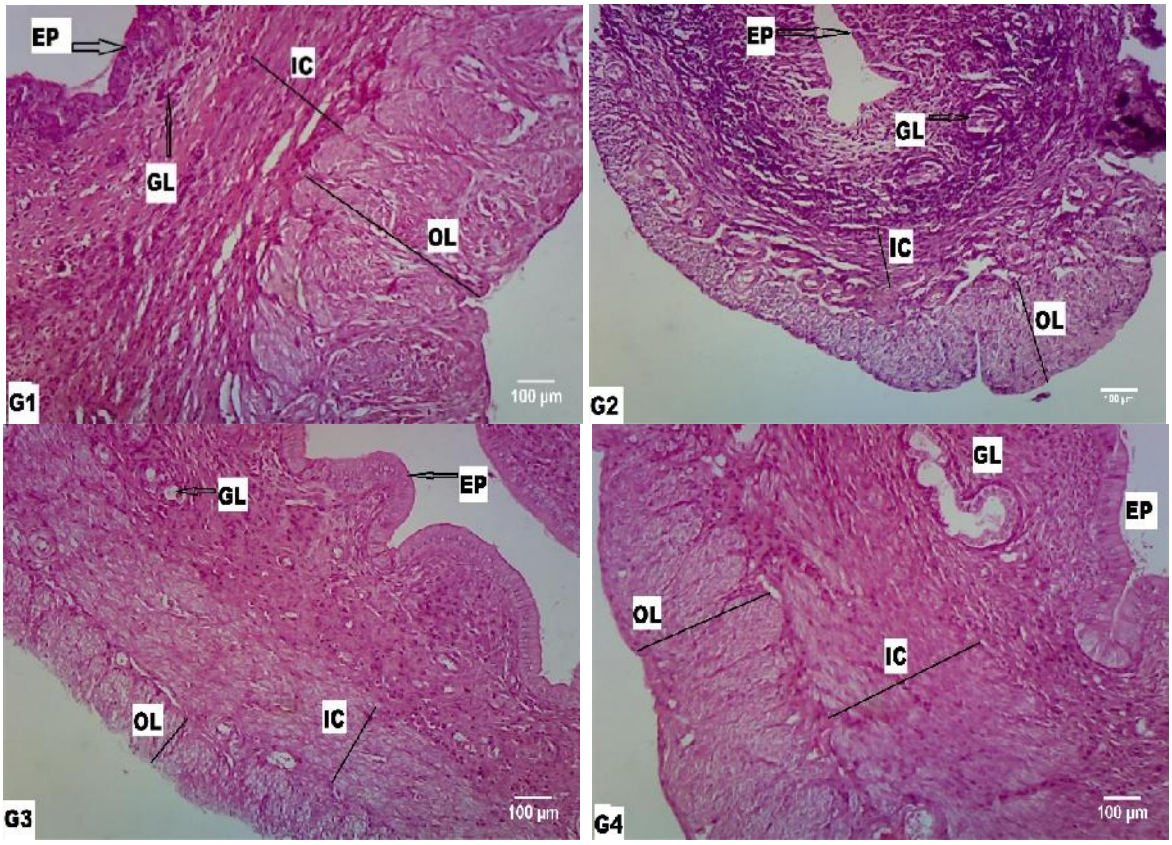

Figure 1: Histological examination of uterus at day 60: placebo (G1), diabetic control (G2), CM @20 (G3) and CM @40 (G4). G1 showed normal histology of endometrium (epithelium height (EP) and uterine glands (GL) and myometrium (inner circular (IC), outer longitudinal (OL) smooth muscles). G2 showed decreased thickness of these parameters. G3 showing minor improvements in the thickness of different uterine layers. G4 showing improvement near to placebo. Hematoxylin and Eosin (H&E) at 100X.

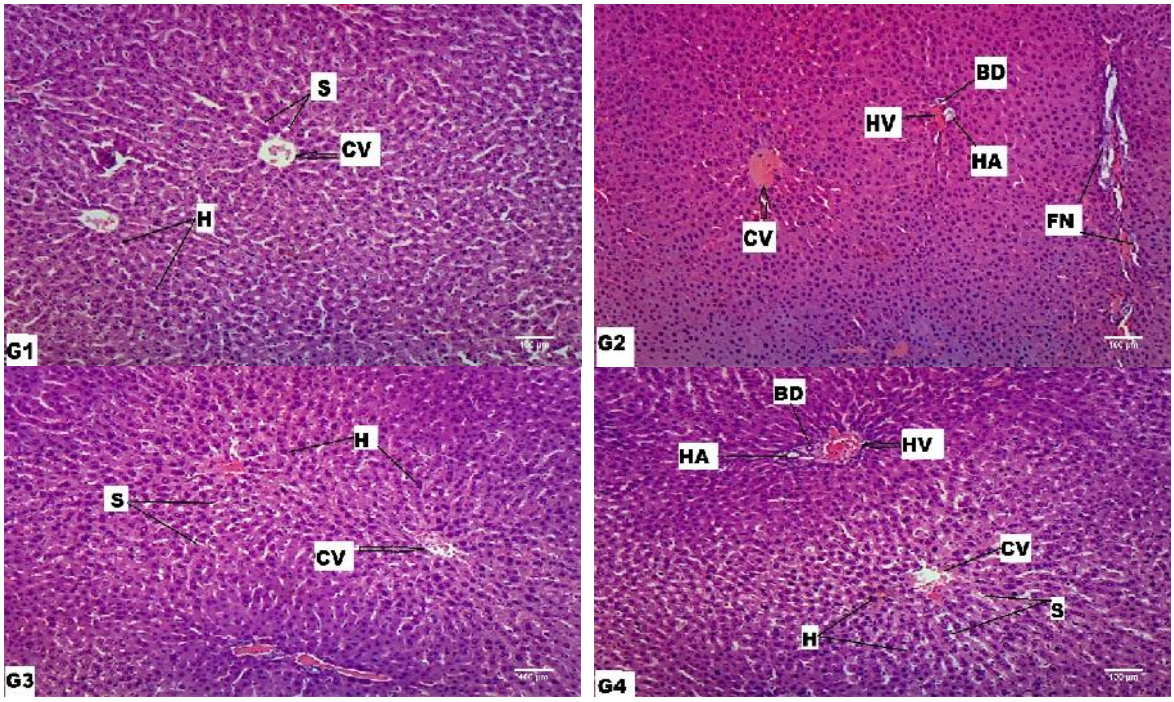

Figure 2: Histological examination of liver at day 60: placebo (G1), diabetic control (G2), CM @20 (G3) and CM @40 (G4). G1 showed normal radial arrangement of hepatocytes (H) along with sinusoidal cords (S) around the central vein (CV). G2 liver showed: fat necrosis (FN), hemorrhages in hepatic artery (HA), hepatic vein (HV) and distorted radial arrangement of H. G3 showed improvement in H and S arrangements around CV. G4 showed near to normal CV, H and S arrangements. Haematoxylin and Eosin (H&E) at 100X.

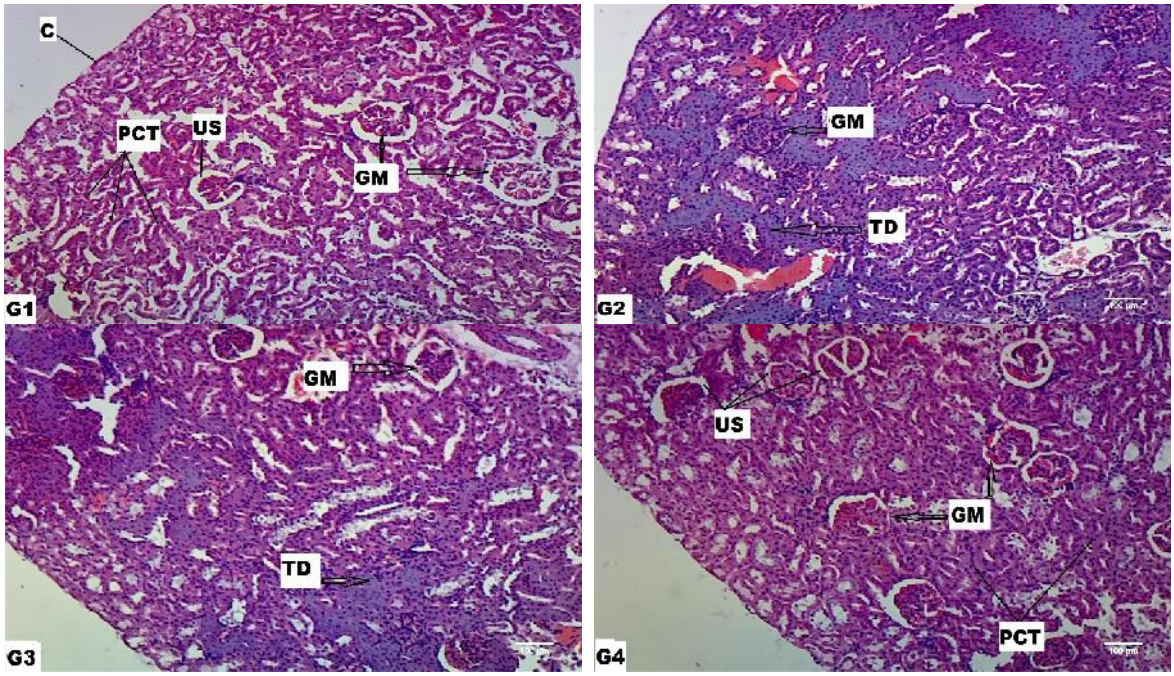

Figure 3: Histological examination of kidney at day 60: placebo (G1), diabetic control (G2), CM @20 (G3) and CM @40 (G4). G1 kidneys showed normal glomeruli (GM), proximal convoluted tubules (PCT) and urinary space (US). G2 showed tubular degenerations (TD) and damaged glomeruli (GM). G3 showed no improvement in TD and GM. G4 showing improvement in GM along with PCT and US. Haematoxylin and Eosin (H&E) at 100X.

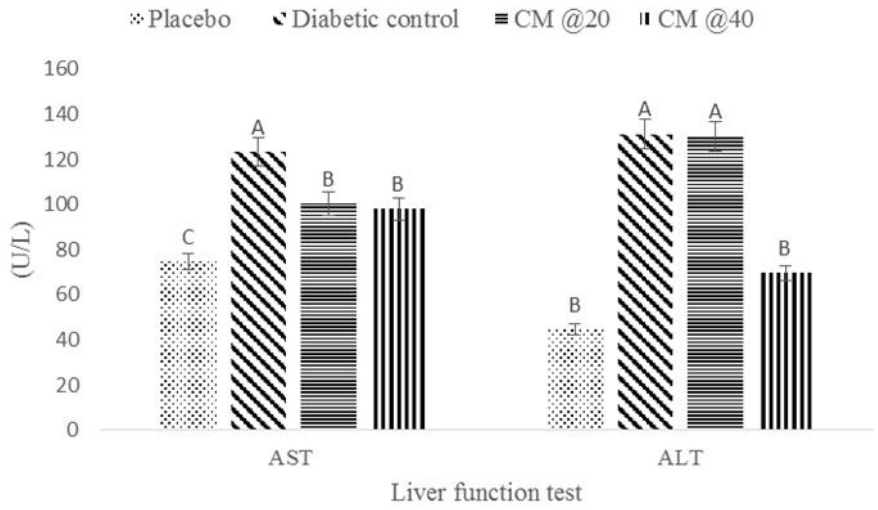

Figure 4: Comparison of AST and ALT (Mean ± SE) in placebo, diabetic control, CM @20 and CM @40. Superscripts $^{A, B, C}$ represent significant (P<0.05) difference in different test groups

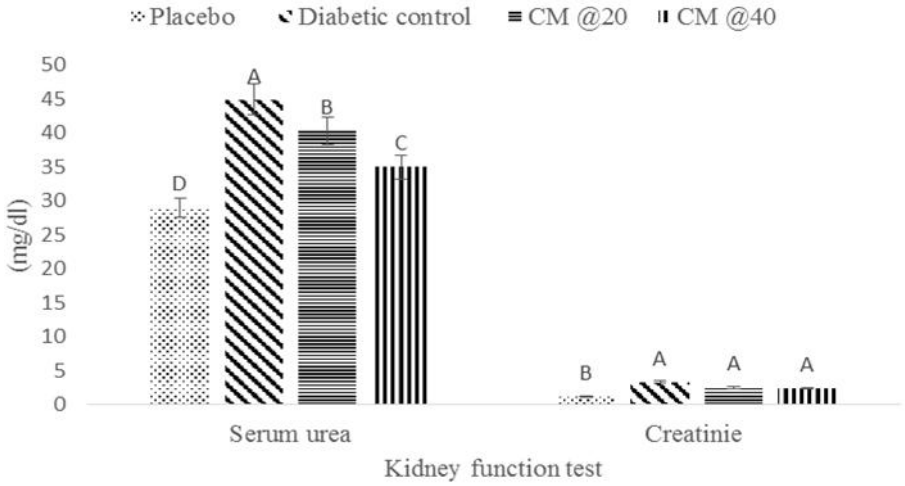

Figure 5: Comparison of serum urea and creatinine (Mean ± SE) in placebo, diabetic control, CM @20 and CM @40. Superscripts $^{A, B, C}$ represent significant (P<0.05) difference in different test groups.

DISCUSSION

Diabetes mellitus (DM) has been recognized as the most common metabolic disorder that impairs blood glucose level which leads to high microvascular complications, angiopathy, nephropathy, retinopathy, hepatopathy and neurological defects (Sharma *et al*., 2010; Khan *et al.,* 2013). The prevalence of this disorder has been increasing day by day and becoming a major threat to the global health. Health departments of all over the world are utilizing their sources to combat this threat (Marx, 2002; Baragob, 2015).

Camel milk (CM) has many qualities to normalize blood glucose level and restore body functions. This action of camel milk may be due to the presence of insulin like protein (45-128 IU/ L), high amount of zinc and vitamin C (Rahimi *et al*., 2011; Mullaicharam, 2014: Ali *et al.,* 2017).

DM can be induced by synthetic drugs like Alloxan® and Streptozotocin® in rabbits and rats (Alam *et al.,* 2005; Hassan and Bayoumi, 2010). Alloxan® monohydrate solution can be prepared in normal saline having pH 7 and citrate buffer having pH 4.5 (Ajiboye and Ojo, 2014). In the present study, Alloxan® (prepared in the normal saline) was administered intraperitonealy @ 150mg/kg b.w. to overnight fasted rats. DM was confirmed by measuring blood glucose level after 3 days. This result was according to Doss *et al*. (2009) and Ali *et al.* (2017).

In the present study, Alloxan® administration induced an elevated blood glucose level in rats as observed by Hassan and Emam (2012). Both the treatments of CM @ 20 and 40 ml/kg bw significantly (P<0.05) decreased this elevated blood glucose level. However, multiple comparison showed highly significant (P<0.01) in reduction in CM @ 40ml/kg bw. This anti-

hyperglycemic effect may be due to the presence of high concentration of insulin like protein that can tolerate the stomach acidic pH (Agrawal *et al*., 2005; Mullaicharam, 2014).

DM alters the uterine histology and causes atrophy of endometrium and myometrium which hampers its normal function. DM lowers the number of myofibrils which results in thinning of myometrium (McMurtrie *et al*., 1985). In present study, DM caused a significant (P<0.05) decrease in endometrium (epithelial height, endometrium thickness and glands area). Similarly, a significant (P<0.05) decrease was found in myometrium thickness (inner circular and outer longitudinal muscles). These results were in accordance to the Tatewaki *et al*. (1989) and Favaro *et al*. (2010). The histological changes in the myometrium smooth muscle layer depend upon the duration of diabetes. Short duration (7-8 weeks) of hyperglycemia had not developed significant abnormal alterations in myometrium (Favaro *et al.*, 2010). CM @ 20ml/kg bw significantly (P<0.05) increased the epithelial height, endometrium thickness and glands area while its effect remained non-significant (P>0.05) on diabetic myometrium. CM @ 40ml/kg bw significantly (P<0.05) improved both the endometrium and myometrium thickness thus restored the histology of uterus towards normal.

In the present study, DM significantly (P<0.05) decreased the hematological parameters (RBCs, Hb, MCH, MCV). This decrease could be attributed to high level of non-enzymatic glycosylation of the cell membranes of RBCs which caused lysis of RBCs and ultimately resulted in anemia (Oyedemi *et al*., 2011a; Oyedemi *et al*., 2011b; Basker *et al.,* 2006). CM showed significant (P<0.05) increase in RBCs, Hb, MCH and MCV @ 40ml/kg bw and its effect remained non-significant (P>0.05) @ 20ml/kg bw. This antihyperglycemic effect of CM may be due to presence of high level of antioxidant and some compounds that favor the erythropoietin production.

Blood clotting mechanism affected in DM is mainly due to poor glycemic control and insulin deficiency. DM caused a decrease in platelets count which consequents in internal and external blood loss and leads to death (Jarald *et al.,* 2008; Oyedemi *et al.,* 2010). CM treatment caused a significant (P<0.05) increase in platelets count @ 40ml/kg bw but this effect was found to be non-significant (P>0.05) @ 20ml/kg bw This antidiabetic therapy of CM which showed an increase in the platelets count may be due to high level of insulin present in it.

Alloxan® suppresses the immunity of animals by damaging and/or decreasing the WBCs count (Erukainure *et al.,* 2013). This suppression may be due to poor leukocytosis in the bone marrow (Torell *et al.,* 1986; Oydemi *et al.,* 2011). In this trial, diabetes significantly (P<0.05) decreased WBCs count but CM treatment caused a significant (P<0.05) increase in WBCs count @ 40ml/kg bw as compared to 20 ml/kg bw. This effect of CM could be due to the presence of some immune booster components like zinc which improves and stimulates neutrophils and phagocytic activity.

Alloxan® stimulates the production of reactive oxygen species which target the pancreatic beta cells and ultimately lead to the development of hyperglycemia.

Alloxan® damaged the cellular structure of liver and kidney and altered their normal histology. These microscopic degenerative changes in liver and kidney are mainly due to oxidative stress and absence of insulin (Ragavan and Krishnakumari, 2006; Aboonabi *et al.,* 2014). CM @ 40ml/kg bw potentially restored the histology of liver and kidney towards normal but this effect was not found significant (P>0.05) by CM @ 20 ml/kg bw. The restoration of histological structures toward normal may be due to the presence of higher levels of antioxidant and insulin (Mullaicharam, 2014).

A significance (P<0.05) increase was observed in the liver enzymes (AST and ALT) in the diabetic rats at the end of trial. These findings are similar to that of khan *et al*. (2013). The elevated level of liver enzymes reflects the necrosis and damaging of hepatocytes which results in the leakage of AST and ALT from hepatocytes (Manal and Moussa, 2014). In present study, camel milk significantly (P<0.05) decreased these diabetogenic values of liver enzymes and these results were supported by the findings of Khan *et al.* (2013) and Manal and Moussa (2014). Creatinine and serum urea are the two kidney function markers. Data analysis of present study showed that diabetes caused significant (P<0.05) increased in these markers as compared to placebo. The elevated level of these parameters could be due to the diabetic alterations in the structure of the kidney tubules. Sunil *et al*. (2011) observed the same trend in kidney function markers. Therapy of camel milk significantly (P<0.05) recovered the serum urea level of diabetic rats.

Therapeutic activity of fresh raw camel milk was found significant in Alloxan® induced female diabetic rats. Based on this study, results showed that camel milk has potential to improve diabetes related reproductive and hematological complications especially @ 40 ml/kg bw. This result may have implications in the clinical management of diabetes mellitus in human.

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