A Study on the Effect of Female Camel (*Camelus Dromedarius*) Milk on Glycemic Control of Streptozotocin (STZ) Induced Diabetes Mellitus in Rats

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Abstract: It is known that camel milk have multiple benefits on the body functions and treatment of some diseases. This study was designed to investigate the effect of camel milk on diabetes mellitus induced by streptozotocin in rats. Thirty healthy adult male albino rats were used for this study. The rats were divided into three equal groups. Group 1 non diabetic control group, group 2 diabetic rats in which diabetes mellitus was induced intraperitoneal injection of Streptozotocin (65mg/kg body weight) and group 3 diabetic and treated with camel milk given orally at a dose of (40ml/day) for each rat daily for four weeks. Glucose, insulin, glycosylated hemoglobin HbA_{1C}, lipids profile, ketone body, pH, bicarbonate, creatinine, urea and atherogenic index of plasma (AIP) were estimated. Obtained results revealed that there was a significant decrease in glucose, HbA_{1C}, total cholesterol, triglyceride, Low density lipoproteins (LDL), very low density lipoproteins (VLDL), atherogenic index of plasma (AIP), creatinin, urea and acetoacetic acid keton and a significant increase in insulin, High density lipoproteins (HDL), pH, Bicarbonate and final body weight in group 3 when compared with group 2. In conclusion, camel's milk has hypoglycemic effect on experimental diabetic rats.

1. Introduction

Diabetes is a metabolic disorder that is known to produce various dysfunctions in the body including the central nervous system. The sustained hyperglycemia leads to a further impairment of insulin production by β-cells, so called glucose toxicity (**Del-Prato & Marchetti, 2004**). The elevated serum triacylglycerol and its accumulation in pancreatic islets during the development of diabetes have been associated with impaired β-cells secretory responses (**Ishikawa *et al.*, 2008**).

Camel milk differs from other ruminant milk as it is low in cholesterol, sugar and protein but high in minerals (sodium, potassium, iron, copper, zinc and magnesium), vitamins A, B2, C and E and contains a high concentration of insulin and immunoglobulins (**Kamal *et al.*, 2007 and Al-Hashem, 2009**). It has no allergic properties and lactase-deficient individuals and those with a weakened immune system (**Yateem *et al.*, 2008**). A reduction in daily insulin dose required by patients with type I diabetes was observed by treatment with camel milk (**Agrawal *et al.*, 2002**). Camel milk does seem to contain high levels of insulin (**Singh, 2001**) or an insulin-like protein which appears to be able to pass through the stomach without being destroyed (**Agrawal *et al.*, 2004**). Camel milk does not form coagulum in acidic environment (**Hassan & Bayoumi, 2010**).

The present study was aimed to investigate the effect of camel milk on streptozotocin (STZ) induced diabetic rats as an experimental model of insulin dependent diabetes mellitus (IDDM).

2. Materials and Methods

Thirty healthy adult male albino rats weighing 200-225 gm were obtained from experimental animal house in Faculty of Medicine of Zagazig University. Animals were housed under hygienic conditions in steel wire cages (5 rats per cage). Animals had free access to water (tap water adlibitum), kept at room temperature (21-23 °C with relative humidity 60-65%) and were maintained on a 12 hr light/ 12 hr dark cycle. All animals were bred in the animal house and are fed the same type of food elements on experiments. Rats were acclimatized under laboratory conditions for two weeks before the experiments going on. Rats were divided into three equal groups. Group 1 normal non diabetic control group in which rats were injected with saline (1ml / rat), group 2 experimental diabetes was induced by intraperitoneal injection of streptozotocin (STZ, 65mg/kg body weight) dissolved in saline (1ml / rat) (**Karen *et al.*, 2008**). Three days later, diabetes induction was confirmed through measurement of blood glucose level from tail vein Blood Glucose Meter (*Elegance CT-X[10] meters*, Convergent Technologies, Germany) (**Yves & Theo, 2007**). Group

3 diabetic and treated with 40ml/day of camel milk for each rat daily by oral cannula (**Agrawal *et al.*, 2005**) for 4 weeks. The weight of each rat was measured at the start and the end of experiment.

Blood samples were obtained from sinus orbitus vein (orbital venous plexus). A total amount of blood drowns per rat was divided to three tubes. Tube (A) Blood was clot and centrifuging for 10 minutes at 3000 rpm and the separated serum was used for determination of glucose, insulin, Acetoacetic acid ketone, Creatinine, Urea, lipids profile and Atherogenic index of Plasma (AIP). Tube (B) containing the anticoagulant ethylene diamine tetra-acetic acid (EDTA) for determination of plasma glycosylated hemoglobin (HBA$_{1C}$). Tube (C) hepranized tube [containing 200 IU/mL blood insulin as an anticoagulant] for determination pH and bicarbonate.

Measurement of glucose, insulin, HbA$_{1C}$:

Serum glucose was estimated by enzymatic oxidation in the presence of glucose oxidase (**Tietz, 1995**) with commercially available kit Glucose – Liquizyme GOD – PAP [Spectrum-The Creative Approach to Bioscience, Egyptian Company for Biotechnology (S.A.E) Obour city industrial area. block 20008 piece 19 A. Cairo. Egypt.]. Insulin was estimated by Enzyme Amplified Sensitivity Immunoassay (EASIA) (**Temple *et al.*, 1992**) by kits: INS-EASIA, KAP1251 (BioSource Europe S.A.-Rue de Iʹ Industrie, 8-B- 1400 Nivelles-Belgium). HbA$_{1C}$ was estimated by quantitative colorimetric method (**Geiger & Binder, 1986**) by A STANBIO kit: (San Antonio, Texas).

Measurement of lipids profile and atherogenic index of plasma:

Total cholesterol (TC) and triglycerides (TG) were estimated by enzymatic colorimetric method (**Tietz, 1995**) by cholesterol and triglycerides CHOD – POD, Enzymatic colorimetric kits [SPINREACT, S.A. ctra. Santa Coloma 7E – 17176 SANT ESTEVE DE BAS (GI) SPAIN] kits. High density lipoproteins (HDL) estimated by precipitating reagent method (**Tietz, 1995**) by HDL precipitating reagent kits [SPINREACT, S.A Ctra Coloma, 7E – 17176 SANT ESTEVE DE BAS (GI) SPAIN]. Low density lipoproteins (LDL), very low density lipoproteins (VLDL) estimated by **Friedewald *et al.* (1972)** formula and atherogenic index of plasma (AIP) estimated by **Dobiášová & Frohlich (2001)** formula.

$$LDL = TC - HDL - \left(\frac{TG}{5}\right) \qquad VLDL = \frac{TG}{5} \qquad AIP = \log\left(\frac{TG}{HDL}\right)$$

In case of AIP calculate based on mmol/L.

Measurement of Acetoacetic Acid (ketone body), creatinine and urea:

Acetoacetic Acid (AcAc) ketone estimated by quantitative colorimetric determination (**Nuwayhid *et al.,* 1988**) by using Enzychrom™ ketone body Assay

kit (EKBD-100) [BioAssay Systems, 3423 Investment Boulevard, Suit 11, Hayward, CA 94595, USA]. Urea estimated by Enzymatic, colorimetric method (urease) modified Berthelot reaction (**Tietz, 1990**) and Creatinine estimated by colorimetric method Jaffé reaction (**Jaffé, 1886**) by UREA/BUN (UREASE) and CREATININE (Colorimetric) kit [Vitro Scient, Inshas Industrial Zone, Belbis, Sharkia Egypt].

Measurement of pH, bicarbonate:

PH and bicarbonate estimated directly by blood gas analyzer [GemPremier 3000 series IL US Instrumentation Laboratory Worldwide Headquarters180 Hartwell Road Bedford, MA 01730].

Statistical Analysis:

All data were expressed as mean and standard error (mean ± SE). Unpaired student's t-test was used to compare means of different groups. Differences were considered significant if P < 0.05 (**Kirkwood, 1989**).

3. Results

As shown in table (1) it was found that there was a significant (p<0.001) increase in glucose, HbA$_{1C}$, total cholesterol, triglyceride, LDL, VLDL, AIP, acetoacetic acid keton, creatinin and urea and a significant (p<0.001) decrease in insulin, pH, Bicarbonate and final body weight and a significant (p<0.01) decrease in HDL in diabetic group compared with the control group. However, a significant (p<0.001) reduction in glucose, HbA$_{1C}$, total cholesterol, triglyceride, LDL, VLDL, AIP and creatinin and a significant (p<0.01) decrease in urea and acetoacetic acid keton and a significant (p<0.001) increase in insulin, HDL, pH, Bicarbonate and a significant (p<0.01) increase final body weight in diabetic treated with camel milk group compared with diabetic group [Fig. 1 to 15].

4. Discussion

The present study revealed that all animals given streptozotocin (STZ) 65mg/kg single intraperitoneal (i.p.) injection developed overt diabetes with plasma and glucose levels increasing progressively and These findings are in line with those of many investigators who showed that with lower doses (<40 mg/kg) of this diabetogenic chemical diabetes did not develop and plasma glucose level remained below 200 mg/dl (**Lev-Ran *et al.*, 1986 and Bailey & Flatt, 1997**) and agreement with those of **Akpan (1989)** who demonstrated that both alloxan (AL) and streptozotocin (STZ) administration were associated with hyperglycemia and glucosuria which were improved in the presence of phenazine monosulfate or nicotinamide. Hyperglycemia can be considered as a direct reflex to the marked hypoinsulinemia caused by the selective destructive cytotoxic effect of STZ on the β-cells of the pancreas (**Bolaffi *et al.*, 1986**).

Table 1: The mean values ± SE of all parameters studied and its comparison in different groups.

Parameters	Group 1(n=10) Control	Group 2 (n=10) Diabetic	Group 3 (n=10) Diabetic with camel milk
	Mean ± SE	Mean ± SE	Mean ± SE
Initial body weight (gm)	271.1 ± 4.398	280.4 ± 3.253	277.6 ± 3.697
Final body weight (gm)	338.5 ± 7.853	215.7 ± 5.621 [A*]	242.4 ± 4.554 [B+]
Glucose (mg/dl)	86.4 ± 1.839	411.8 ± 9.737 [A*]	207.2 ± 2.871 [B*]
Insulin (µU/ml)	25.145 ± 0.544	2.620 ± 0.286 [A*]	14.180 ± 1.256 [B*]
HbA$_{1C}$ (%)	5.01 ± 0.102	10.87 ± 0.579 [A*]	7.26 ± 0.228 [B*]
Total cholesterol (mg/dl)	69.148 ± 1.792	99.715 ± 1.272 [A*]	85.969 ± 1.027 [B*]
Triglyceride (mg/dl)	86.62 ± 2.391	183.89 ± 3.566 [A*]	127.42 ± 3.015 [B*]
HDL (mg/dl)	35.934 ± 1.312	28.723 ± 1.393 [A+]	40.462 ± 1.034 [B*]
LDL (mg/dl)	15.89 ± 0.366	34.216 ± 1.938 [A*]	20.023 ± 1.323 [B*]
VLDL (mg/dl)	17.324 ± 0.478	36.776 ± 0.713 [A*]	25.484 ± 0.603 [B*]
AIP	0.0231 ± 0.0152	0.4505 ± 0.0229 [A*]	0.1384 ± 0.01503 [B*]
AcAc Keton (mmol/l)	0.78 ± 0.057	3.94 ± 0.274 [A*]	2.65 ± 0.154 [B+]
Creatinin (mg/dl)	0.856 ± 0.045	1.752 ± 0.089 [A*]	1.094 ± 0.054 [B*]
Urea (mg/dl)	25.83 ± 1.856	51.64 ± 3.617 [A*]	35.14 ± 2.163 [B+]
pH	7.393 ± 0.01044	7.1013 ± 0.03605 [A*]	7.3242 ± 0.00871 [B*]
Bicarbonate (meq/l)	25.62 ± 0.447	18.2 ± 1.223 [A*]	23.67 ± 0.286 [B*]

[#] p<0.05 [+] p<0.01 * p<0.001 significant values.
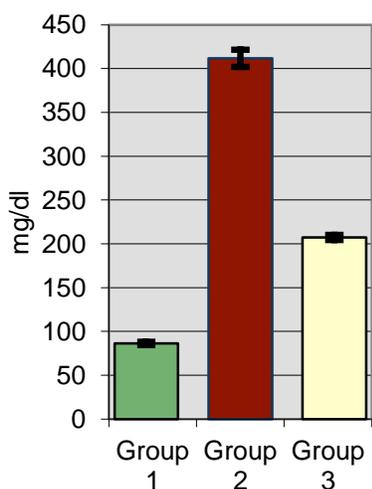[A] in significant compare with group1 and [B] in significant compare with group 2.

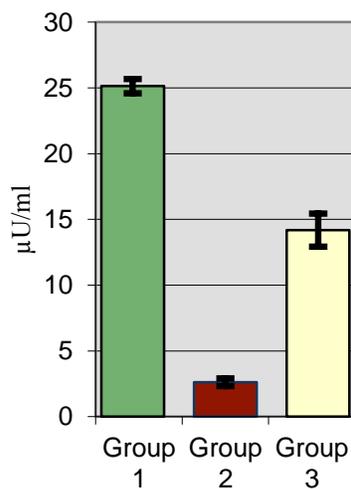Fig 1: Glucose levels (mg/dl) in studied groups

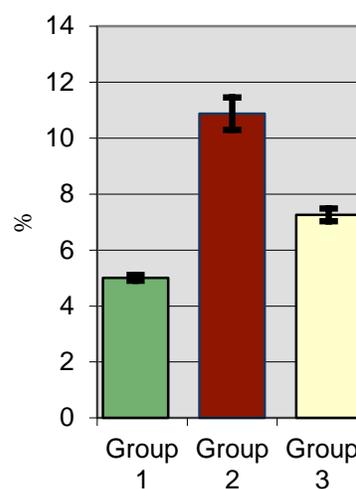Fig 2: Insulin (µU/ml) in studied groups

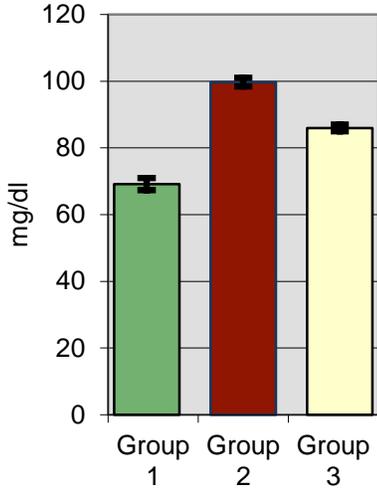Fig 3: HbA$_{1C}$ (%) in studied groups

Fig 4: Total cholesterol (mg/dl)
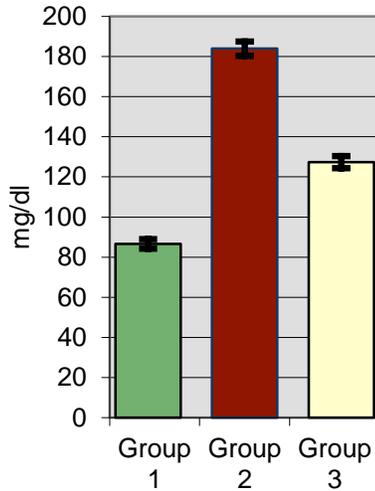in studied groups
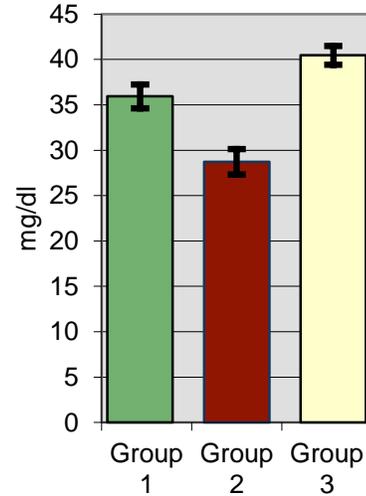
Fig 5: Triglyceridel (mg/dl)
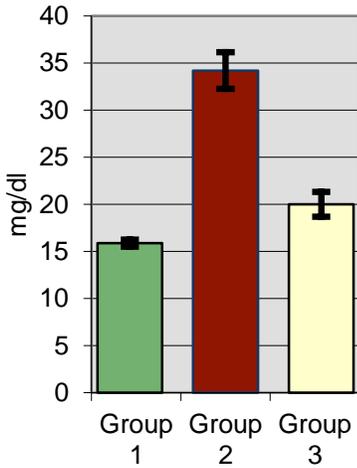in studied groups

Fig 6: HDL (mg/dl)
in studied groups

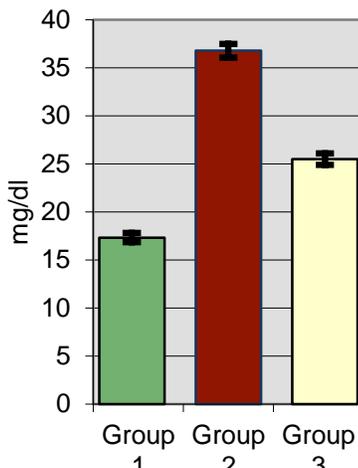Fig 7: LDL (mg/dl)
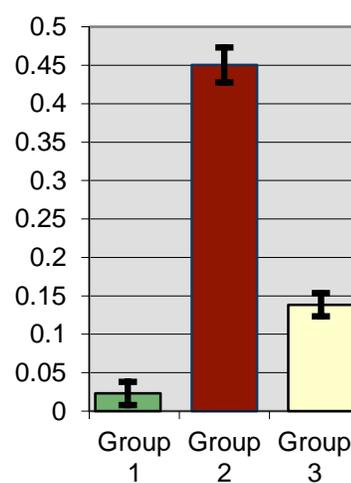in studied groups

Fig 8: VLDL (mg/dl)
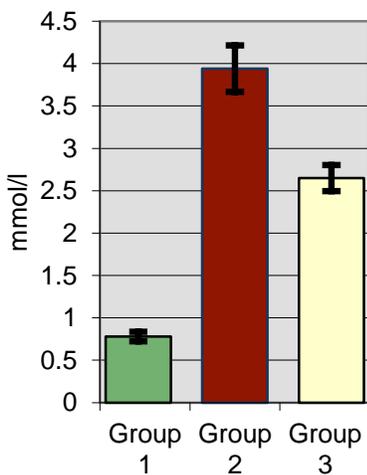in studied groups

Fig 9: AIP in studied
groups

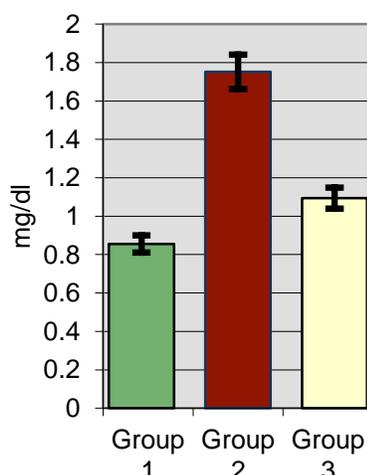Fig 10: AcAc Keton (mmol/l)
in studied groups

Fig 11: Creatinin (mg/dl)
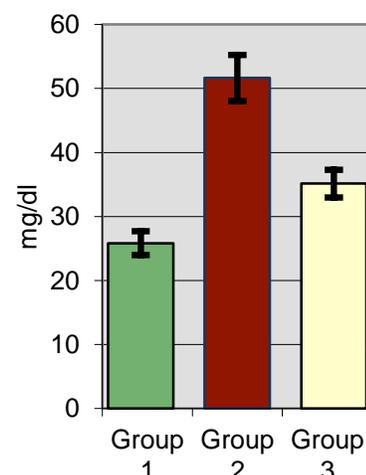in studied groups

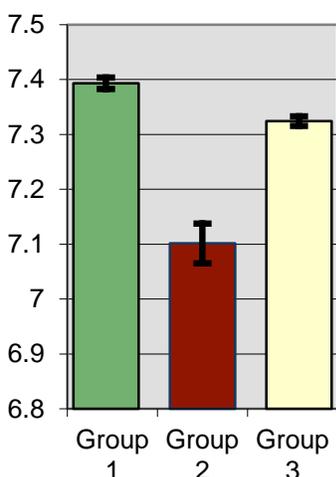Fig 12: Urea (mg/dl)
in studied groups
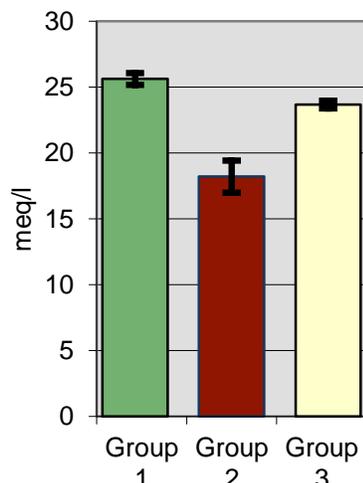
Fig 13: pH in studied groups
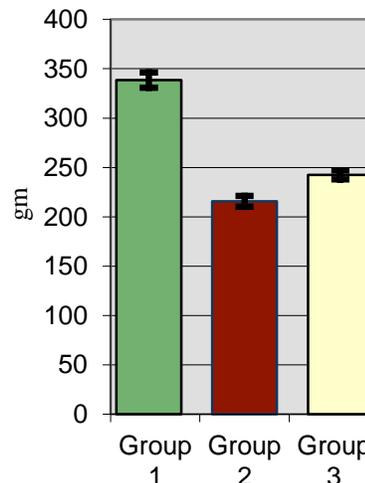
Fig 14: Bicarbonate (meq/l) in studied groups

Fig 15: the final body weight (gm) of the studied groups.

The changes in blood glucose and insulin concentrations reflect abnormalities in β-cell function. STZ impairs glucose oxidation (**Bedoya *et al.*, 1996**) and decreases insulin biosynthesis and secretion (**Nukatsuka *et al.*, 1990**).

Glycosylated hemoglobin is formed by the attachment of a glucose group to the terminal amino acids 'valine' in each β-chain of the hemoglobin molecule and used as a supplement to blood glucose estimations the degree of diabetic control because the quantity in blood increases in poorly controlled diabetes mellitus (**Alberti & Krall, 1985**).

Destroyed pancreatic β-cells, leading to inhibited insulin secretion, increased plasma glucose levels, increased production of triglycerides and LDL-cholesterol occurred in association with reduced levels of HDL-cholesterol and plasma uric acid (**Abdel-Rahman, 2011**). The effects of change in the lipid composition of lipoproteins could further contribute to atherosclerosis (**Bagdade *et al.*, 1993 and Serdyuk & Morton, 1997**). Insulin deficiency, resulting in spontaneous ketosis and ketonuria and death if insulin is not given (**Bone & Gwilliam, 1997**). There is some evidence that in severe diabetes the rate of ketone utilization may also decline making the ketosis worse and insulin is said to increase ketone uptake in muscles (**Keen & Jarrett, 1982**). ketone bodies are acids which dissociate almost completely at physiological pH, releasing hydrogen ions into the body fluids. The fall in pH is countered by the buffers of the blood, the most important being bicarbonate (HCO_3^-). The dissociation of carbonic acid is reduced, the ratio of bicarbonate ions to carbonic ions fall, and measurement of plasma bicarbonate will show lower values than normal (metabolic acidosis) and The rise in hydrogen ion concentration in the arterial blood stimulates the respiratory center producing rapid deep respiration so that clinically hyperpnea "air hunger" is observed and the urine becomes acidic (**Creutzfeldt & Lefebvre, 1988**).

A significant weight gain and a significant improvement in all biochemical parameters were observed in the present study. The therapeutic efficacy of camel milk observed in the current study is consistent with earlier clinical trials [camel milk + insulin therapy] (**Agrawal *et al.*, 2003**). The hypoglycemic activity of camel milk may be because of high concentrations of insulin / insulin like proteins in camel milk. It found that amino acid sequence of some of the camel milk proteins is rich in half- cystine, which has superficial similarity with insulin family of peptides (**Beg *et al.,* 1986**). **Breitling (2002)** reported that camel milk had an antidiabetic activity possibly because of insulin – like activity, regulatory and immunomodulatory functions on beta-cells. Camel milk was found to contain approximately 52 units / liter insulin and it may be the reason for a lesser requirement of insulin in diabetic patients receiving camel milk (**Singh, 2001**). The potential benefits of oral delivery of insulin include control of plasma glucose levels without peripheral hyperinsulinemia and restoration of the peripheral pathway of endogenous insulin (**Agrawal *et al.*, 2005**). The lack of coagulum formation of camel milk may act as an effective vehicle to take the milk insulin unchanged to the intestine, and from there it can be absorbed even if some amount is destroyed in the passage (**Agrawal *et al.*, 2004**).

It has been reported that camel milk contains high levels of vitamins A, B2, C and E and is very rich in magnesium (Mg) and other trace elements (**Al-Humaid *et al.*, 2010**). These vitamins act as

antioxidants that have been found to be useful in preventing tissue injury caused by toxic agents. High mineral content in camel milk (sodium, potassium, iron, zinc, copper and magnesium) as well as a high vitamin C intake may act as antioxidant, thereby removing free radicals, which may provide a stress free situation to the animals. The vitamin C levels in camel milk are two-three times that of cow milk and one and a-half time that of human milk (**Al-Attas, 2008**). Vitamins E and C play an important role in glucose metabolism (**Martini *et al.*, 2010**). Vitamin C was found to significantly decrease the elevated levels of blood hydroperoxide, glucose, cholesterol, triglycerides and low-density lipoprotein (LDL) in diabetic rats (**Badr *et al.*, 2011**). Also Camel's milk may have a direct effect on liver or an indirect effect through thyroid hormones which affect lipid metabolism (**AL-Hashem, 2009**).

Conclusion

Impaired biochemical parameters in STZ – induced diabetes mellitus could by improved by oral administration of camel milk. However, further studies are required to demonstrate whether camel milk can be used alone or as an adjuvant to insulin for proper control of diabetes mellitus and its complications in human beings.

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