Nat. Volatiles & Essent. Oils, 2021; 8(4): 16166-16193

NVEO
Natural Volatiles &
Essential Oils

Clinico-Pathological Profile In Streptozotocin Treated Non-Diabetic Rabbits

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ABSTRACT

Purpose: The present study aimed at investigating clinic-pathological profiling in the low doses streptozotocin intoxicated normoglycemic rabbits.

Method: New Zealand bred white rabbits weighing about 1-1.5 kg were given STZ @65mg/kg b.w, as a single intravenous dose followed by glucose therapy after 9 hours. Haemato-biochemical investigations were carried out fortnightly from days 0 to 60 except for glucose which was recorded on weekly basis.

Results: Streptozotocin intoxicatedrabbits revealed polyuria, polydypsia, dullness, lethargy, and appeared more apprehensive, which were more prominent during first week. Short durations of increased activity, and feeding were followed by complete inactivity. From 2nd week onwards individual variation in feed intake was observed ranging from normal to reduced feed intake with preference for green fodder. Rabbits showed decreased body weight gain and body temperature. Haematology revealed significantly decreased Hb, MCH and MCHC, where as PCV, TEC and MCV were not altered significantly; indicating normocytic hypochromic anemia. TLC was significantly decreased without any alteration in DLC, indicating suppressed myelopoiesis. Serum biochemistry revealed that the plasma protein levels were not altered while AST and ALT showed a non-significant but progressive increase, indicating low grade but persistent liver damage. Kidney function test revealed significant alteration in plasma chloride levels while BUN and creatinine showed a progressively non-significant increase. Total plasma cholesterol increased significantly whereas plasma triglyceride showed non-significant increase.

Conclusion: STZ cause prolonged haemato-biochemical alterations characteristic of multiple organ pathology without persistent glycemic change.Such toxic impacts should be considered in development of STZ induced diabetic model using higher drug doses.

Keywords; diabetes, streptozotocin, hematological indices, biochemical profile

INTRODUCTION

Streptozotocin (STZ) is an N-methyl-N-nitrosoureido D-glucosamine derivative which is specifically toxic to pancreatic beta-cells (Szkudelski, 2001; Lenzen, 2008) is used for induction of diabetes (T1DM and T2DM). Diabetes is a metabolic disorder that is associated with chronic hyperglycemia with altered deficiency in secretion and action of insulin. Globally diabetes is one of the most commonly known disease with large percentage of population being affected. A number of compounds have been used for inducing diabetes, however alloxan is more preferred due to its specific action and being a potent β-cytotoxic agent. The half-life of alloxan is longer (15 minutes) and for longer period it produces prolonged hyperglycemia with well featured complications and few ketosis incidences and decreased mortality (Srinivasan and Ramarao, 2007).The hexose substitution makes STZ less lipophilic and rather highly hydrophilic preventing its free entry into the cells as well as access to the brain via the blood-brain barrier. It has been postulated that the sugar moiety facilitates its selective uptake and accumulation in pancreatic β-cells via the low-affinity GLUT2 glucose transporter selectively expressed in pancreatic islets (Karunanayake et al., 1976; Tjalve et al., 1976; Elsneret al., 2000) and has been confirmed overexpression experimental research studies with colorimetric derivatives of STZ(Schnedlet al., 1994; Ran et al., 2007). The glucose transporter that is not expressed by insulin-producing cells have been found to be resistant to STZ while it is more toxic in comparison to N-methyl-N-nitrosourea in cells that express GLUT2, although both compounds to similar level alkylate DNA (Ledoux and Wilson, 1984;Schnedl et al., 1994; Elsneret al., 2000). The diabetogenic function of STZ is prevented by reduced GLUT2 expression (Schnedlet al., 1994; Thulesenet al., 1997). When multiple doses of STZ are administered invivo and invitro studies, GLUT2 expression is restricted itself (Wang and Gleichmann, 1995; Wang and Gleichmann, 1998). In this procedure, significance of GLUT2 is drawn from the fact that organs that express this glucose transporter ae damaged by STZ, preferably liver and kidney (Rerup, 1970; Weiss, 1982; Thorenset al., 1988).With respect to nutritional status, sex, strain and species, STZ sensitivity varies(Okamato, 1981; Honjoet al., 1986; Kramer et al., 2009). For inducing diabetes mellitus in animal models (mice and rat), STZ is mostly used (Lei et al., 2005; Sharma et al., 2006; Patel et al., 2006) and in all those species its function has been well characterized (Szkudelski, 2001). Many animal species such as guinea pigs (Losertet al., 1971) and marmoset (Kramer et al., 2009) have found to have lower sensitivity whereas cats (Hatchellet al., 1986) and human pancreatic beta-cells (Yang and Wright, 2002) have found to be resistant to the diabetogenic action of STZ.

Rabbits are frequently used as animal models in biomedical studies. STZ has been used to develop diabetic rabbit models for screening of hypoglycemic drugs (Sharma et al., 2006). In our previous studies we observed that STZ induces typical multiphasic immediate response associated with beta-cytolysis in rabbits (Mir et al., 2015) but failed to induce significant and sustained hyperglycemia (Mir et al., 2016). STZ has various biological actions, including the production of acute and chronic cellular injury, carcinogenesis, teratogenesis and mutagenesis (Magee and Swann, 1969). Besides being diabetogenic, it is hepatotoxic, nephrotoxic and also causes gastric ulceration (Piyachaturawatet al., 1988 & 1990). The

incidence and severity of lesions produced by STZ in different organs has been observed to increase progressively with time (Piyachaturawatet al., 1988). Besides direct effects of STZ, the disturbances in various tissues have been associated with the diabetic complications (Guet al., 1997; Arkkilaet al., 2001; Zafar et al., 2009b).Hence, the present study focused at studying STZ induced clinico-pathological effects in normoglycemic STZ treated rabbits.

MATERIALS AND METHODS

Experimental Animals

New Zealand bred white rabbits were procured from Laboratory Animal Resource and reared in cage system under standard living conditions. In present study, rabbits weighing 1-1.5 kg and of the age group (3 months) were used. In this study, all the experimental procedures were performed as per the guidelines approved by the Institutional Animal Ethics Committee. For a duration of 7 days, all the animals used for experimental purposes were acclimatized. Equal random allocation was followed for constitution of experimental groups. Feed and water adlibtumwas given to rabbits. Commercially available feed and greens were given twice a day to all the animals (morning and evening).

Development of Diabetic Model

Rabbits were fed in the morning and then fasted for 18 hours providing only water during the period. Their fasting blood glucose level was determined using glucometer (Accu-Chek, Roche diagnostics India Pvt. Ltd., Mumbai). The beta-cytotoxic drug streptozotocin (Sigma-Aldrich) was administered @35mg/kg body weight in 1ml freshly prepared citrate buffer, pH 4.6 as slow intravenous injection through ear vein using insulin syringe. Freshly prepared solutions of the calculated dose of drugs were used. At 9 hours post alloxan administration, rabbits were given intraperitoneally 5ml of 25% dextros e and 10% glucose in drinking water up to 24 hours post-treatment, followed by normal management.

Collection of blood and plasma

Using the standard techniques, blood samples were withdrawn from the auricular artery by using heparin as anticoagulant. Samples (5 mL from each rabbit) were collected early in the morning prior to watering and feeding. 1 mL aliquots were taken for haematology. For biochemical investigations, plasma was collected following centrifugation at 5000rpm for 5 min, and stored in multiple aliquots, at -40°C until used. The samples were divided into sufficient number of aliquots to avoid freezing and thawing effects during multiple analysis.

Haematology

In this study, haematological indices studied were haemoglobin (Hb), packed cell volume (PCV), total erythrocyte count (TEC) and total leukocyte count (TLC). Using Wrights-Giemsa stain, fresh blood smears were stained for differential leukocyte count (DLC). Further, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH) and mean corpuscular haemoglobin concentration (MCHC) were studied (Benjamin, 1985; Jain 1986).

Biochemical studies

The biochemical studies included blood glucose (Glucometer method). Biochemical estimation of plasma proteins (total protein, albumin), liver enzymes (as partate transaminase (AST) and alanine transaminase (ALT), kidney function test (KFT) (blood urea nitrogen (BUN), creatinine and chloride) and plasma proteins (total cholesterol and triglycerides) was performed using diagnostic kits (Aspen Laboratories Pvt. Ltd, Rapid Diagnostic Group of Companies, Karnal Road Industrial Area, Delhi, India) and semi-automatic blood chemistry analyzer (model ERBA CHEM-PRO).

Statistical Analysis

Data was analyzed by t-test, one-way ANOVA followed by Dunnet's test. A value of $P<0.05$ was considered to be statistically significant (Snedecor and Cochran, 1989).

RESULTS

Clinical effects

General observation: These rabbits though non-hyperglycemic yet they showed polyuria and polydypsia which was more prominent during first week. They were dull and lethargic and often appeared more apprehensive. Increased activity was noted for short durations followed by complete inactivity with a tendency to lie down. Frequency of feeding, in small amounts at a time, increased during first week. Subsequent to each feeding a comparatively a longer period of inactivity and reluctance to move was observed. From 2nd week onwards individual variation in feed intake was observed ranging from normal to reduced feed intake with preference for green fodder. After 4 weeks, feed intake was further reduced and the rabbits appeared weak and anemic.

One of 10(10%) rabbits died during 8th which was emaciated, dull and depressed prior to death. Muscular weakness made the rabbit to rest on its sternum followed by wry-neck and lateral recumbency. Paddling of limbs occurred frequently associated with marked turning of head and rolling movements on longitudinal axis. Postural abnormality, along the long axis with the body plan at lumbar and thoracic region rotating in the direction that of rotation of head, was observed.

Body weight: The mean body weights from 0 to 60 days at fortnightly intervals are presented in Table 1 and Fig. 1(a). The body weight of control rabbits revealed a consistent and significant ($P\leq0.05$) increase throughout the period of study. STZ treated rabbits showed the significant ($P\leq0.05$) increase in body weight only at 45 and 60. However, during the initial periods up to day 30 the weights were lower when compared with controls.

Temperature: The body temperature recorded from day 15 to 60 was significantly ($P\leq0.05$) lower when compared with baseline values in STZ group. It was also lower than age matched control group with significant ($P\leq0.05$) difference at day 60. (Table1 and Fig. 1(b).

Heart rate: Marked fluctuations were recorded in heart rate and at times differed significantly ($P\leq0.05$) from the baseline values as well as from that of age matched control rabbits. It did not differ significantly ($P\geq0.05$) in control rabbits (Table 1 and Fig. 1(c).

Haematology

Erythrocytic Attributes

Haemoglobin (Hb): Hb values were significantly (P≤0.05) lower compared to baseline values from day 30 and onwards. Similarly they were lower than that of control at day 30 and 45. The value at day 60 was significantly (P≤0.05) higher than at day 30 and did not differ significantly (P≥0.05) from the age matched control (Table 2; Fig. 2(a).

Packed cell volume (PCV): No significant changes were seen in PCV. (Table 2; Fig. 2(b).

Total erythrocyte count (TEC): No significant changes were seen in total erythrocyte count. (Table 2; Fig. 2(c).

MCV, MCH and MCHC: MCV did not differ significantly (P≥0.05) but a marked decrease was observed in MCH and MCHC values. MCH was significantly reduced at day 30 and 45, while at day 30 and onwards MCHC was similarly found decreased. (Table2; Fig. 2(d-f).

Leukocytic attributes

Total leukocyte count (TLC): TLC revealed a significant (P≤0.05) decrease on day 15 and onwards (Table3; Fig. 2(g).

Differential leukocyte count (DLC): No marked changes in different cell counts during the period of study. The mean per cent counts for heterophils, lymphocytes, monocytes and basophils, observed from 0 to 60 days did not differ significantly (P≥0.05) from the base line values or those observed in age matched control rabbits at any point in time. However, eosinophil counts at day 45 and 60 were significantly (P≤0.05) lower than baseline value but did not differ significantly (P≥0.05) from those observed in age matched control rabbits (Table 3; Fig. 2(h-l).

Biochemical analysis

Blood glucose: The blood glucose dropped to significantly (P≤0.05) at 1 week. Thereafter, the levels were higher than that week 1 but the values did not show any significant variation from the base value or that of control (Table 4; Fig. 3(a).

Plasma proteins: No significant variation was seen in total proteins, albumin, globulin or albumin: globulin ratios when compared with either baseline values or those of control rabbits. (Table 5; Fig. 3(a-e).

Plasma enzymology: Serum Alanine Aminotransferase (ALT/SGPT) and Serum Aspartate Aminotransferase (AST/SGOT) showed a non-significant increase from the base values and in relation to the age-matched controls. AST:ALT ratio was significantly (P≤0.05) higher than base level from day 15. However, the values did not differ significantly from those of age

matched controls which showed fluctuations with significantly (P≤0.05) higher values, when compared with base values, at days 15 and 60. (Table 6; Fig. 4(a-c).

Kidney function test (KFT): Non-significant increase in BUN levels was observed. Both, STZ treated and control rabbits, revealed a progressive and significant (P≤0.05) increase in plasma creatinine levels. Although, the mean values in control rabbits were slightly lower, the two groups did not differ significantly (P≥0.05) at any point in time. The plasma chloride levels were progressively and significantly (P≤0.05) decreased from days 15. (Table 7; Fig. 5(a-c).

Plasma lipids: Total plasma cholesterol level was significantly (P≤0.05) higher at day 60. Non-significant increase in plasma triglyceride levels was noted but the values differed significantly (P≤0.05) only at day 45 from the control (Table8; Fig. 6(a-b).

DISCUSSION

The behavioural alterations observed during first week following STZ treatment may be attributed to altered glycemic state concomitant with changes in insulin levels. The rabbits were mildly hyperglycemic up to day-5. Various workers have reported polydypsia, polyurea, weight loss; decreased physical activities associated with STZ induced hyperglycemia in rabbits (Calabresi and Chabner, 1985; Shenoy and Ramesh, 2002; Mir, 2007). In present study, persistence of polyuria and polydypsia without hyperglycemia may be attributed to altered kidney function as evidenced by pathoanatomical alterations. However, CNS disturbances, caused by antecedent hypoglycemia and hyperglycemia, leading to altered hypothalamic control, cannot be ruled out and warrants tailored investigations. Interestingly, polyuria and polydypsia was associated with decreased feed intake where as polyphagia or hyperphagia has been observed as a prominent feature in diabetes (Havel et al., 2000). STZ has been found to cause selective destruction of glucose monitoring (GM) neurons of the hypothalamus causing severe deficits of feeding and metabolism (Telkeset al., 2011). Oyedemi et al.(2011a) reported increased feed intake in STZ-diabetic rats. The preference for greens may be associated with increased thirst. During present study only one rabbit died over a period of 60 days. STZ has been preferred over Alloxan as a diabetogenic agent for associated lower mortality.

Decrease in body weight gain, observed in present study, may be directly attributed to decreased feed intake. However, role of subclinical metabolic disturbances and stress due to CNS mediated effects and organotoxic effects, of STZ need to be evaluated. This is supported by consistently observed lowered body temperature in the STZ treated rabbits.

Haematological evaluations revealed that STZ caused normocytic hypochromic anemia. Significant decrease in the levels of RBC, Hb, PCV, MCH, MCV, RCDW and MCHC have been reported in STZ-diabetic rats (Oyedemi et al., 2011a). The occurrence of anemia in diabetes mellitus has been associated with glucotoxicity and increased non-enzymatic glycosylation of RBC membrane proteins leading to hemolysis (Arun and Ramesh, 2002; Oyedemi et al., 2011b). Although the erythrocytic parameters observed depict hemolyticanemia, it occurred without hyperglycemia.

STZ has been reported to cause immunosuppression and intraperitoneal injection of STZ into rats has been found to cause significant reduction in WBC count and its

differentials such as basophils, monocytes, eosinophils, lymphocytes and neutrophils (Oyedemi 2010 & 2011a). In present study STZ caused leukocytopenia without any changes in differential counts indicating suppressed myelopoiesis. Direct effects of STZ causing irreversible damage to bone marrow cell subpopulations or other important T-cell precursor populations has been evidenced by the observation that bone marrow cells from STZ-diabetic mice were unable to reconstitute gamma-irradiated normal syngeneic mice (Nichols et al., 1981).

Although, mild hyperglycemia was noted upto day-5 following STZ administration, significant drop in the fasting blood glucose levels was noted at 1-week which had recovered to the normal by 2nd week and did not differ till end of the experiment. This observation is contrary to earlier report of sustained hyperglycemia, albeit mild, by Mir et al. (2008) who observed blood glucose levels of >150mg/dL up to 15 days in rabbits given similar doses of STZ. The observed discrepancy may be attributed to the sensitivity to STZ that varies with species, strain, sex and nutritional state, and also, there are batch differences in activity (Okamato, 1981). Spontaneous recovery from high blood glucose levels in STZ models has been considered as one of the limiting factors (Etuk, 2010). It has been associated with development of functional insulinoma (Steiner et al., 1970; Yamagamiet al., 1985; Iwase et al., 1991). Histopathologically, changes in pancreas were suggestive of progressive β-cell regeneration. Arora et al. (2009) reported that i.p. administration of 100mg/kg STZ failed to induce diabetes in Swiss albino mice, where as higher single dose (@180 mg/kg) as well as multiple low doses (@40 mg/kg x5) resulted in T1DM and T2DM, respectively. The authors suggested that over secretion of insulin from the β-cells escaping from the attack of STZ might be responsible for maintaining normoglycemia.

Measurement of serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) reflects the concentrations of intracellular AST and ALT that have leaked into the general circulation and thus, serves as an indicator of hepatotoxicity along with plasma protein and bilirubin levels (Elizabeth and Harris, 2005; Senior, 2009). In present study, the plasma protein levels were not altered while plasma enzymes including AST and ALT revealed a non-significant but progressive increase, indicating low grade but persistent liver toxicity. Experimental studies have shown that subtle membrane changes are sufficient to allow passage of intracellular enzymes to the extracellular space (Garella, 1997). The toxic effects may be either direct or mediated by some metabolic disturbance which needs detailed investigation.

Kidney function test revealed significant alteration in plasma chloride levels while BUN and creatinine showed a progressively non-significant increase. This correlates well with the observed histopathological alterations. The incidence and severity of lesions produced by STZ in different organs has been observed to increase progressively with time (Piyachaturawatet al., 1988). Altered KFT has been reported by different workers but has been frequently associated with STZ induced hyperglycaemia (Alderson et al., 2004; Mir et al., 2008). In present study, changes in KFT, although mild, were progressive and without development of hyperglycaemia. Following i.v. administration, plasma levels of STZ decrease rapidly (within 15 minutes) and the drug concentrates in the liver and kidneys. Twenty percent of the drug is metabolized and/or excreted by the kidneys (Sicor Pharmaceuticals, 2003).

Hypercholesterolemia and hypertriglyceridemia has been reported in STZ (@65 mg/kg i.v) induced diabetic models including rabbits and has been associated with impaired insulin action (Kedar and Chakrabarti, 1983; Iwasaki et al., 2005). Significant increase in total plasma cholesterol level associated with non-significant increase in plasma triglyceride levels indicate STZ induced altered metabolism without change in glycemic state or persistence of early induced-metabolic disturbances even after resumption of normoglycemia.

Conclusion:

STZ cause prolonged haemato-biochemical alterations characteristic of multiple organ pathology without persistent glycemic change. Such toxic impacts should be considered in development of STZ induced diabetic model using higher drug doses.

References

Alderson, N.L., Chachich, M.E., Frizzell, N., Canning, P., Metz, T.O. and Januszewski, A.S. 2004. Effect of antioxidants and ACE inhibition on chemical modification of proteins and progression of nephropathy in streptozotocin diabetic rat. Diabetologia**47:**1385-1395.

Arkkila, P.E., Koskinen, P.J., Kantola, I.M., Ronnemaa, T., Seppanen, E. and Viikari, J.S. 2001. Diabetic complications are associated with liver enzyme activities in people with type-1 diabetes. Diabetes Research and Clinical Practice**52(2):**113-118.

Arora, S., Ojha, S.K. and Vohora, D. 2009. Characterisation of streptozotocin induced diabetes mellitus in swiss albino mice. Global Journal of Pharmacology**3 (2):**81-84.

Arun, G.S. and Ramesh, K.G. 2002. Improvement of insulin sensitivity by perindopril in spontaneously hypertensive and streptozotocindiabetic rats. Indian Journal of Pharmacology**34:**156-164.

Benjamin, M.M. 1985. Outline of veterinary clinical pathology.3rd Ed. Iowa State University Press, Iowa.

Calabresi, P. and Chabner, B.A. 1985. Antineoplastic agentspp1209-1263.**In:** The pharmacological basis of therapeutics (Eds. Goodman, A., Rall, J.W.) Pergmann Press, New York.

Elizabeth, H. and Harris, M.D. 2005. Elevated liver function tests in type 2 diabetes. Clinical Diabetes **23:**115-119.

Elsner, M., Guldbakke, B., Tiedge, M., Munday, R. and Lenzen, S. 2000. Relative importance of transport andalkylation for pancreatic beta-cell toxicity of streptozotocin. Diabetologia**43:**1528-1533.

Etuk, E.U. 2010. Animal models for studying diabetes mellitus. Agriculture and Biology Journal of North America**1(2):**130-134.

Garella, S. 1997. The cost of dialysis in the USA. Nephrology Dialysis Transplantation**12:**10-12.

Gu, D., Arnush, M. and Sarvetnic, N. 1997. Endocrine/exocrine intermediate cells in

Streptozotocin treated Ins-IFNgamma transgenic mice. Pancreas**15(3):**246-250.

Hatchell, D.L., Reiser, H.J., Bresnahan, J.F. and Withworth, U.G. 1986. Resitence of cats to the diabetogenic effect of alloxan. Laboratory Animal Science**36:**37-41.

Havel, P.J., Hahn, T.M., Sindelar, D.K., Baskin, D.G., Dallman, M.F., Weigle, D.S. and Schwartz, M.W. 2000. Effects of streptozotocin-induced diabetes and insulin treatment on the hypothalamic melanocortin system and muscle uncoupling protein 3 expression in rats. Diabetes**49:**244–252.

Honjo, K. Doi, K., Doi, C. and Mitsuoka, T. 1986. Histopathology of streptozotocin-induced diabetic DBA/2N and CD-1 mice. Laboratory animals**20:**298-303.

Iwasaki, T., Takahashi, S., Takahashi, M., Zenimaru, Y., Kujiraoka, T., Ishihara, M., Nagano, M., Suzuki, J., Miyamori, I., Naiki, H., Sakai, J., Fujino, T., Miller, N.E., Yamamoto, T.T. and Hattori, H. 2005. Deficiency of the very low-density lipoprotein (VLDL) receptors in streptozotocin-induced diabetic rats: insulin dependency of the VLDL receptor. Endocrinology**146(8):**3286-3294.

Iwase, M., Nnunoi, K., Wakisaka, M., Kikuchi, M., Maki, Y., Sadoshima, S. and Fujishima, M. 1991. Spontaneous recovery from non insulin-dependent diabetes mellitus induced by neonatal streptozotocin treatment in spontaneously hypertensive rats. Metabolism**40:**10-14.

Jain, N.C. 1986. Schalm's Veterinary Haematology.4th Ed. Lea and Febiger, Philadelphia, USA.

Karunanayake, E.H., Baker, J.R., Christian, R.A., Hearse, D.J. and Mellows, G. 1976. Autoradiographic study of the distribution and cellular uptake of (14C)-streptozotocin in the rat. Diabetologia**12:**123–128.

Kedar, P. and Chakrabarti, C.H. 1983. Effects of Jambolan seed treatment on blood sugar, lipids and urea in streptozotocin induced diabetes in rabbits. Indian Journal of Pharmacol**27:**135-140.

Kramer, J., Moeller, E.L., Hachey, A., Mansfield, K.G. and Wachtman, L.M. 2009. Differential expression of GLUT2 in pancreatic islets and kidneys of New and Old World nonhuman primates. American Journal of Physiology- Regulatory. Integrative and Comparative Physiology**296(3):** R786–R793.

Ledoux, S.P. and Wilson, G.L. 1984. Effects of streptozotocin on a clonal isolate of rat insulinoma cells. BiochimicaetBiophysicaActa**804:**387–392.

Lei, Y.C., Hwang, J.S., Chan, C.C., Lee, C.T. and Cheng, T.J. 2005. Enhanced oxidative stress and endothelial dysfunction in streptozotocin-diabetic rats exposed to fine particles. Environmental Research **99:**335–343.

Lenzen, S. 2008. The mechanisms of alloxan- and streptozotocin-induced diabetes. Diabetologia**51:**216–226.

Losert, W., Rilke, A., Loge, O. and Richter, K.D. 1971. Vergleichendebiochemischeuntersuchungenuber die diabetogenewirkung von streptozotocin beimausen, ratten, chinesischenstreifen-hamstern und meerschweinchen. ArzneimForsch**21:**1643-1653.

Magee, P. N. and Swann, P.F. 1969. Nitroso compounds. British Medical Bulletin**25:** 240-244.

Mir, M.S., Darzi, M.M., Baba, O.K., Khan, H.M., Kamil, S.A., Sofi, A.H. and Wani, S.A. 2015. Streptozotocin Induced Acute Clinical Effects in rabbits(Oryctolaguscuniculas). Iranian Journal of Pathology, **10(3)**: 206-213

Mir, M.S., Darzi, M.M., Baba, O.K., Shah, A.A., Qureshi, S. and Khan, H.M., 2016. Comparative evaluation of diabetogenic potentials of alloxan, streptozotocin and their cocktail in rabbits(Oryctolaguscuniculas). Applied Biological Research, **18**: 61-65; DOI: 10.5958/0974-4517.2016.00009.4

Mir, S.H. 2007. Biochemical, histopathological and therapeutic studies in alloxan- and streptozotocin-induced diabetes mellitus in rabbits. PhD thesis submitted to Postgraduate Department of Zoology, University of Kashmir, Srinagar(J&K) India.

Mir, S.H., Baqui, A., Bhagat, R.C., Darzi, M.M. and Shah, A.W. 2008. Biochemical and histomorphological study of streptozotocin-induced diabetes mellitus in rabbits. Pakistan Journal of Nutrition**7(2):**359-364.

Nichols, W.K., Vann, L.L and Spellman, J.B. 1981. Streptozotocin effects on T lymphocytes and bone marrow cells.Clinical and Experimental Immunology**46(3):**627–632.

Okamato, H. 1981. Regulation of proinsulin synthesis in pancreatic islets and a new aspect to insulin dependent diabetes. Molecular and Cellular Biochemistry**37:**43-61.

Oyedemi, S.O., Adewusi, E.A., Aiyegoro, O.A. and Akinpelu, D.A. 2011a. Antidiabetic and haematological effect of aqueous extract of stem bark of Afzeliaafricana (Smith) on streptozotocin-induced diabetic Wistar rats. Asian Pacific Journal of Tropical Biomedicine**2011:**353-358.

Oyedemi, S.O., Yakubu, M.T. and Afolayan, A.J. 2010. Effect of aqueous extract of Leonotisleonurus (L)R. Br leaves in male Wistar rats. Human and Experimental Toxicology**29:**377-384.

Oyedemi, S.O., Yakubu, M.T. and Afolayan, A.J. 2011b. Antidiabetic activities of aqueous leaves extract of Leonotisleonurus in streptozotocin induced diabetic rats. Journal of Medicinal Plants Research**5(1):**119-125.

Patel, R., Shervington, A., Pariente, J.A., Martinez-Burgos, M.A., Salido, G.M., Adeghate, E. and Singh, J. 2006. Mechanism of exocrine pancreatic insufficiency in streptozotocin-induced type 1 diabetes mellitus. Annals of the New York Academy of Sciences**1084:**71–88.

Piyachaturawat, P., Poprasit, J. and Glinsukon, T. 1990. Gastric mucosal secretions and lesions by different doses of Streptozotocin in rats. Toxicology Letters **55:**21-29.

Piyachaturawat, P., Poprasit, J., Glinsukon, T. and Warichanon, C. 1988. Gastric mucosal lesions in Streptozotocin diabetic rats. Cell Biology International Reports**12(1):**53-63.

Ran, C., Pantazopoulos, P., Medarova, Z. and Moore, A. 2007. Synthesis and testing of β-cell-specific streptozotocin-derived near-infrared imaging probes Angewandte Chemie-International Edition In English **46:**8998–9001.

Rerup, C.C. 1970. Drugs producing diabetes through damage of the insulin secreting cells. Pharmacological Reviews**22 (4):**485-518.

Schnedl, W.J., Ferber, S., Johnson, J.H. and Newgard, C.B. 1994. STZ transport and cytotoxicity. Specific enhancement in GLUT2- expressing cells. Diabetes**43:**1326–1333.

Senior, J.R. 2009. Monitoring for hepatotoxicity: what is the predictive value of liver "function" tests? Clinical Pharmacology and Therapeutics **85:**331-334.

Sharma, S.B., Nasir, A., Prabhu, K.M., Murthy, P.S. 2006. Antihyperglycemic effect of the fruit-pulp of Eugenia jambolana in experimental diabetes mellitus. Journal of Ethnopharmacology**104:**367–373.

Shenoy, A.G. and Ramesh, K.G. 2002. Improvement of insulin sensitivity by perindopril in spontaneously hypertensive and streptozotocin-diabetic rats. Indian Journal of Pharmacology**34:**156-164.

Sicor Pharmaceuticals. 2003. Material Safety Data Sheet.Sicor Pharmaceuticals Inc. Irvine CA.

Snedecor, G.W. and Cochran, W.G. 1989.,Statistical Methods, 8th Ed., Iowa State University Press.

Srinivasan, K. and Ramarao, P. 2007. Animal models in type 2 diabetes research: An overview. Indian Journal of Medical Research **125**:451-472.

Steiner, H., Oelz, O., Zahnd, G. and Froesch, E.R. 1970. Studies on islet cell regeneration, hyperplasia and intraminsular cellular interrelations in long lasting streptozotocin diabetes in rats. Diabetologia**6:**558-564.

Szkudelski, T. 2001. The mechanism of alloxan and streptozotocin action in β-cells of the rat pancreas. Physiological Research **50:**536-546.

Telkes, I., Szalay, C., Lénárd, L. and Karádi, Z. 2011.Deficits of hypothalamic GLUT2 immunolabeling after streptozotocin microinjection into the ventromedial hypothalamic nucleus of the rat. abstract in 13th conference of the Hungarian Neuroscience Society (MITT), EötvösLoránd University (ELTE), Lágymányos Campus, Northern Building, H-1117, Budapest, Pázmány Pétersétány 1/A, Budapest, Hungary. Abst. P2.31.

Thorens, B., Sarkar, H.K., Kaback, H.R. and Lodish, H.F. 1988. Cloning and functional expression in bacteria of a novel glucose transporter present in liver, intestine, kidney, and beta-pancreatic islet cells. Cell**55:**281-290.

Thulesen, J., Orskov, C., Holst, J.J. and Poulsen, S.S. 1997. Short term insulin treatment prevents the diabetogenic action of streptozotocin in rats. Endocrinology**138(1):**62-68.

Tjälve, H., Wilander, E. and Johansson, E.B. 1976. Distribution of labelled streptozotocin in mice: uptake and retention in pancreatic islets. Journal of Endocrinology**69:**455–456.

Wang, Z. and Gleichmann, H. 1995. Glucose transporter 2 expression: prevention of streptozotocin-induced reduction in beta-cells with 5-thio-D-glucose. Experimental and Clinical Endocrinology and Diabetes **103:**83-97.

Wang, Z. and Gleichmann, H. 1998. GLUT2 in pancreatic islets: crucial target molecule in diabetes induced with multiple low doses of streptozotocin in mice. Diabetes**47:**50–56.

Weiss, R.B. 1982. Streptozocin: a review of its pharmacology, efficacy, and toxicity. Cancer Treatment Reports **66:**427–438.

Yamagami, T., Miwa, A., Takasawa, S. and Yamamoto, H. 1985. Introduction of rats pancreatic β-cell tumour by the combined administration of streptozotocin or alloxan and poly(adenosine diphosphate ribose) synthetase inhibitors. Cancer Research**45:**1845-1849.

Yang, H. and Wright, J.R. Jr. 2002. Human beta cells are exceedingly resistant to streptozotocin in vivo. Endocrinology**143(7):**2491-2495.

Zafar, M., Naqvi, S.N.H., Ahmed, M. and Kaimkhani, Z.A. 2009b. Altered liver morphology and enzymes in streptozotocin induced diabetic rats. International Journal of Morphology**27(3):**719-725.

Table - 1. Changes in body weight (kg), body temperature (°F) and heart rate (beats/min) in rabbits administered with single intravenous dose of Streptozotocin @ 65 mg/kg b.w (Mean ± SE).

Parameter	Treatment	Days of treatment				
		0day	15day	30day	45day	60day
Number	STZ	10	10	8	6	4
	Control	6	6	6	6	6
Body weight (kg)	STZ	1.43^{aA} ± 0.072 (1.21 - 1.84)	1.56^{aA} ± 0.071 (1.32 - 1.90)	1.68^{aA} ± 0.077 (1.50 - 2.07)	1.97^{bA} ± 0.093 (1.77 - 2.32)	2.20^{bA} ± 0.109 (1.95 - 2.47)
	Control	1.415^{aA} ± 0.035 (1.33 – 1.52)	1.580^{bA}± 0.041 (1.40 – 1.67)	1.737^{cA}± 0.039 (1.57 – 1.82)	1.858^{dA}± 0.04 (1.70 – 1.97)	2.030^{eA}± 0.05 (1.85 – 2.15)
Body Temperature (°F)	STZ	101.55^{aA} ± 0.30705 (99.90 - 103.20)	100.63^{bA} ± 0.204 (99.80 - 101.50)	100.61^{bA} ± 0.214 (99.80 - 101.60)	100.45^{bA} ± 0.285 (99.70 - 101.50)	100.43^{bA} ± 0.193 (100.00 - 100.80)
	Control	101.55^{aA} ± 0.29 (100.50 - 102.50)	101.40^{aA} ± 0.27 (100.40 - 102.30)	101.20^{aA} ± 0.33 (99.90 - 102.50)	101.15^{aA} ± 0.46 (99.90 - 103.10)	102.23^{aB} ± 0.32 (100.90 - 103.20)
Heart Rate (beats/min)	STZ	244.30^{abA} ± 2.526 (229.00 - 255.00)	224.40^{aA} ± 9.318 (142.00 - 243.00)	243.63^{abA} ± 3.877 (229.00 - 258.00)	245.67^{bA} ± 3.018 (238.00 - 256.00)	241.00^{abA} ± 5.612 (228.00 - 255.00)
	Control	247.17^{aA} ± 3.64 (235 – 258)	246.50^{aB} ± 2.92 (239 – 260)	248.50^{aA} ± 3.63 (233 – 259)	249.00^{aA} ± 2.68 (238 – 257)	240.17^{aA} ± 2.94 (231 – 249)

Means for a parameter in different columns bearing at least one common 'lowercase alphabet' superscript, and in different rows bearing at least one common 'uppercase alphabet' superscript does not differ significantly (P≤ 0.05).

Table - 2. Effect of single intravenous dose of Streptozotocin @ 65 mg/kg b.w on erythrocytic attributes of rabbits (Mean ± SE).

Parameter	Treatment	Days of treatment				
		0day	15day	30day	45day	60day
Number	STZ	10	10	8	6	4
	Control	6	6	6	6	6
Haemoglobin (gm/dl)	STZ	12.08^{aA} ± 0.182 (11.20 - 13.40)	11.71^{aA} ± 0.426 (9.20 - 14.20)	9.10^{bA} ± 0.201 (8.40 - 10.00)	9.17^{bcA} ± 0.255 (8.50 - 10.30)	10.15^{cA} ± 0.501 (9.20 - 11.40)
	Control	12.00^{aA} ± .339 (10.80 - 13.20)	12.10^{aA} ± .282 (11.20 - 13.20)	11.77^{aB} ± .201 (11.00 - 12.50)	11.77^{aB} ± .267 (10.80 - 12.60)	11.30^{aA} ± .375 (9.90 - 12.50)
PCV (%)	STZ	42.00^{abcA} ± 0.667 (38.00 - 45.00)	44.25^{aA} ± 1.172 (37.50 - 50.00)	43.79^{acA} ± 1.010 (40.00 - 47.61)	40.30^{bA} ± 0.587 (38.20 - 42.50)	40.85^{bcA} ± 0.492 (40.00 - 41.80)
	Control	41.87^{aA} ± 1.031 (38.00 - 44.80)	41.63^{aA} ± .545 (40.00 - 43.00)	41.23^{aA} ± .561 (39.40 - 43.00)	41.28^{aA} ± .620 (38.80 - 43.20)	40.25^{aA} ± .670 (37.90 - 42.40)
TEC (10^6/cmm)	STZ	6.49^{aA} ± 0.210 (5.10 - 7.06)	6.16^{aA} ± 0.226 (4.95 - 7.34)	5.93^{aA} ± 0.191 (4.90 - 6.60)	6.13^{aA} ± 0.105 (5.80 - 6.50)	6.08^{aA} ± 0.085 (5.90 - 6.30)
	Control	6.41^{aA} ± .308 (5.20 - 7.20)	6.28^{aA} ± .215 (5.60 - 7.00)	6.25^{aA} ± .138 (5.80 - 6.60)	6.13^{aA} ± .186 (5.40 - 6.60)	6.02^{aA} ± .210 (5.30 - 6.80)
MCV (fL)	STZ	65.26^{aA} ± 1.942 (58.07 - 76.36)	72.78^{aA} ± 3.589 (57.89 - 91.37)	74.57^{aA} ± 3.358 (60.61 - 91.84)	65.75^{aA} ± 0.860 (62.62 - 68.45)	67.25^{aA} ± 0.442 (66.35 - 68.20)
	Control	65.82^{aA} ± 2.026 (58.33 - 73.08)	66.69^{aA} ± 2.423 (57.71 - 73.10)	66.06^{aA} ± .966 (63.49 - 69.32)	67.50^{aA} ± 1.321 (63.18 - 71.85)	67.15^{aA} ± 1.587 (62.35 - 71.51)
MCH (pg)	STZ	18.78^{aA} ± 0.584 (17.00 - 23.14)	19.29^{aA} ± 1.128 (13.31 - 26.74)	15.49^{bA} ± .712 (13.94 - 20.00)	14.94^{bA} ± 0.277 (14.35 - 15.85)	16.69^{abA} ± 0.608 (15.33 - 18.10)
	Control	18.86^{aA} ± .609 (16.67 - 20.77)	19.35^{aA} ± .635 (16.57 - 20.69)	18.85^{aB} ± .262 (18.18 - 20.00)	19.22^{aB} ± .289 (18.33 - 20.00)	18.81^{aB} ± 457 (17.54 - 20.88)

MCHC (%)	**STZ**	28.79^{aA} ± 0.407 (26.67 - 31.05)	26.65^{adA} ± 1.289 (22.00 - 35.20)	20.84^{bA} ± 0.548 (18.48 - 23.00)	22.73^{bcA} ± 0.404 (21.41 - 24.24)	24.82^{cdA} ± 0.942 (23.00 - 27.27)
	Control	28.65^{aA} ± .225 (27.83 - 29.46)	29.05^{aA} ± .410 (28.00 - 30.70)	28.54^{aB} ± .358 (27.55 - 29.76)	28.49^{aB} ± .319 (27.74 - 29.79)	28.04^{aB} ± .527 (26.12 - 29.48)

Means for a parameter in different columns bearing at least one common 'lowercase alphabet' superscript, and in different rows bearing at least one common 'uppercase alphabet' superscript does not differ significantly (P≤ 0.05).

Table - 3. Effect of single intravenous dose of Streptozotocin @ 65 mg/kg b.w on leukocytic attributes of rabbits (Mean ± SE).

Parameter	**Treatment**	**Days of treatment**				
		0day	**15day**	**30day**	**45day**	**60day**
Number	**STZ**	10	10	8	6	4
	Control	6	6	6	6	6
TLC (10^3/cmm)	**STZ**	9.16^{aA} ± 0.109 (8.75 – 9.80)	7.35^{bA} ± 0.485 (4.85 – 10.25)	7.39^{bA} ± 0.391 (5.70 – 9.10)	7.63^{bA} ± 0.336 (6.50 – 8.78)	7.05^{bA} ± 0.401 (5.90 – 7.60)
	Control	9.18^{aA} ± .453 (8.30 – 11.30)	9.24^{aB} ± .241 (8.35 – 9.90)	8.99^{aB} ± .107 (8.70 – 9.40)	9.08^{aB} ± .113 (8.75 – 9.55)	8.98^{aB} ± .092 (8.70 – 9.30)
Heterophils (%)	**STZ**	30.50^{aA} ± 1.655 (21.00 – 38.00)	30.20^{aA} ± 0.952 (25.00 – 35.00)	31.25^{aA} ± 1.031 (27.00 – 36.00)	30.50^{aA} ± 1.118 (27.00 – 35.00)	31.50^{aA} ± 1.323 (29.00 – 35.00)
	Control	30.00^{aA} ± 1.713 (25.00 – 35.00)	29.67^{aA} ± 2.362 (23.00 – 37.00)	31.33^{aA} ± 2.140 (25.00 – 37.00)	30.83^{aA} ± 1.957 (26.00 – 37.00)	30.67^{aA} ± 1.961 (23.00 – 35.00)
Lymphocytes (%)	**STZ**	61.60^{aA} ± 1.586 (56.00 – 71.00)	61.00^{aA} ± 0.803 (57.00 – 65.00)	61.50^{aA} ± 1.476 (54.00 – 68.00)	63.17^{aA} ± 0.910 (60.00 – 66.00)	63.00^{aA} ± 2.041 (59.00 – 67.00)
	Control	62.67^{aA} ± 1.606 (58.00 – 68.00)	62.33^{aA} ± 1.764 (56.00 – 68.00)	61.83^{aA} ± 2.482 (56.00 – 71.00)	63.17^{aA} ± 2.272 (55.00 – 70.00)	63.33^{aA} ± 2.261 (56.00 – 72.00)

Monocytes (%)	**STZ**	5.00^{aA} ± 0.394 (3.00 - 7.00)	5.80^{aA} ± 0.554 (2.00 - 8.00)	5.25^{aA} ± 0.620 (3.00 - 8.00)	5.00^{aA} ± 0.577 (3.00 - 7.00)	4.25^{aA} ± 0.854 (2.00 - 6.00)
	Control	5.67^{aA} ± 0.715 (3.00 - 8.00)	5.50^{aA} ± 0.922 (3.00 - 9.00)	4.83^{aA} ± 0.401 (3.00 - 6.00)	4.00^{aA} ± 0.365 (3.00 - 5.00)	4.33^{aA} ± 0.494 (3.00 - 6.00)
Eosinophils (%)	**STZ**	2.20^{aA} ± 0.249 (1.00 - 3.00)	2.60^{aA} ± 0.400 (1.00 - 5.00)	1.63^{abA} ± 0.263 (1.00 - 3.00)	1.00^{bA} ± 0.258 (0.00 - 2.00)	0.75^{bA} ± 0.479 (0.00 - 2.00)
	Control	1.67^{aA} ± 0.211 (1.00 - 2.00)	1.83^{aA} ± 0.307 (1.00 - 3.00)	1.50^{aA} ± 0.224 (1.00 - 2.00)	1.50^{aA} ± 0.224 (1.00 - 2.00)	1.17^{aA} ± 0.307 (0.00 - 2.00)
Basophils (%)	**STZ**	0.70^{aA} ± 0.153 (0.00 - 1.00)	0.40^{aA} ± 0.163 (0.00 - 1.00)	0.38^{aA} ± 0.183 (0.00 - 1.00)	0.33^{aA} ± 0.211 (0.00 - 1.00)	0.50^{aA} ± 0.289 (0.00 - 1.00)
	Control	0.83^{aA} ± 0.167 (0.00 - 1.00)	0.67^{aA} ± 0.333 (0.00 - 2.00)	0.50^{aA} ± 0.224 (0.00 - 1.00)	0.50^{aA} ± 0.224 (0.00 - 1.00)	0.50^{aA} ± 0.224 (0.00 - 1.00)

Means for a parameter in different columns bearing at least one common 'lowercase alphabet' superscript, and in different rows bearing at least one common 'uppercase alphabet' superscript does not differ significantly ($P \leq 0.05$).

Table - 4. Effect of single intravenous dose of Streptozotocin @ 65 mg/kg b.w on blood glucose level (mg/dL) of rabbits (Mean ± SE).

Weeks post-treatment	STZ			CONTROL		
	N	Mean ± S.E.	Range	N	Mean ± S.E.	Range
0 day	10	113.90^{aA} ± 2.877	97.00 - 125.00	6	113.00^{aA} ± 7.165	98.00 - 145.00
1 week	10	95.40^{bA} ± 3.449	81.00 - 118.00	6	111.50^{aA} ± 5.271	98.00 - 135.00
2 week	10	100.10^{abA} ± 2.822	90.00 - 120.00	6	117.17^{aA} ± 6.882	102.00 - 140.00
3 week	8	106.25^{abA} ± 3.697	95.00 - 121.00	6	113.83^{aA} ± 3.400	99.00 - 122.00
4 week	8	109.75^{abA} ± 6.053	79.00 - 131.00	6	114.67^{aA} ± 6.637	100.00 - 145.00
5 week	6	103.00^{abA} ± 3.804	91.00 - 117.00	6	118.17^{aA} ± 6.348	100.00 - 143.00
6 week	6	101.17^{abA} ± 5.868	89.00 - 129.00	6	117.83^{aA} ± 6.332	97.00 - 138.00
7 week	4	102.50^{abA} ± 3.969	92.00 - 110.00	6	111.00^{aA} ± 4.524	101.00 - 125.00
8 week	3	101.33^{abA} ± 6.691	89.00 - 112.00	6	120.67^{aA} ± 6.020	108.00 - 148.00

Means in different rows bearing at least one common 'lowercase alphabet' superscript, and in different columns bearing at least one common 'uppercase alphabet' superscript does not differ significantly ($P \leq 0.05$).

Table - 5. Effect of single intravenous dose of Streptozotocin @ 65 mg/kg b.w on plasma protein levels of rabbits (Mean ± SE).

Parameter	Treatment	Days of treatment				
		0day	15day	30day	45day	60day
Number	STZ	10	10	8	6	4
	Control	6	6	6	6	6
Total Protein (gm/dL)	STZ	5.70^{aA} ± 0.305 (4.57 - 7.63)	5.64^{aA} ± 0.196 (4.95 - 6.58)	5.85^{aA} ± 0.231 (5.12 - 7.03)	5.91^{aA} ± 0.261 (5.32 - 7.12)	5.71^{aA} ± 0.105 (5.55 - 6.00)
	Control	5.71^{aA} ± 0.348 (4.62 - 7.05)	5.81^{aA} ± 0.400 (4.53 - 7.34)	5.98^{aA} ± 0.287 (4.99 - 6.74)	5.99^{aA} ± 0.310 (5.25 - 6.99)	5.90^{aA} ± 0.214 (5.32 - 6.69)
Albumin (gm/dL)	STZ	3.98^{aA} ± 0.225 (3.25 - 5.20)	3.96^{aA} ± 0.141 (3.51 - 4.65)	3.85^{aA} ± 0.103 (3.41 - 4.23)	4.01^{aA} ± 0.145 (3.52 - 4.58)	3.86^{aA} ± 0.171 (3.58 - 4.36)
	Control	3.89^{aA} ± 0.385 (2.68 - 5.34)	3.80^{aA} ± 0.387 (2.82 - 5.25)	3.98^{aA} ± 0.186 (3.26 - 4.47)	3.94^{aA} ± 0.108 (3.54 - 4.35)	3.91^{aA} ± 0.128 (3.58 - 4.45)
Globulin (gm/dL)	STZ	1.72^{aA} ± 0.132 (1.15 - 2.43)	1.68^{aA} ± 0.069 (1.30 - 2.03)	2.00^{aA} ± 0.175 (1.40 - 2.92)	1.90^{aA} ± 0.151 (1.49 - 2.54)	1.85^{aA} ± 0.078 (1.64 - 1.97)
	Control	1.82^{aA} ± 0.118 (1.56 - 2.36)	2.02^{aB} ± 0.144 (1.64 - 2.64)	2.00^{aA} ± 0.132 (1.57 - 2.37)	2.06^{aA} ± 0.238 (1.36 - 2.96)	1.99^{aA} ± 0.105 (1.70 - 2.37)
Albumin : Globulin Ratio	STZ	2.40^{aA} ± 0.165 (1.49 - 3.08)	2.38^{aA} ± 0.077 (2.04 - 2.81)	2.02^{aA} ± 0.156 (1.41 - 2.66)	2.16^{aA} ± 0.138 (1.70 - 2.57)	2.12^{aA} ± 0.188 (1.82 - 2.66)
	Control	2.20^{aA} ± 0.291 (1.38 - 3.13)	1.93^{aA} ± 0.243 (1.27 - 2.79)	2.01^{aA} ± 0.106 (1.64 - 2.42)	2.03^{aA} ± 0.210 (1.36 - 2.91)	1.98^{aA} ± 0.071 (1.68 - 2.16)

Means for a parameter in different columns bearing at least one common 'lowercase alphabet' superscript, and in different rows bearing at least one common 'uppercase alphabet' superscript does not differ significantly (P≤ 0.05).

Table - 6. Effect of single intravenous dose of Streptozotocin @ 65 mg/kg b.won plasma enzyme levels of rabbits (Mean ± SE).

Parameter	Treatment	Days of treatment				
		0day	15day	30day	45day	60day
Number	STZ	10	10	8	6	4
	Control	6	6	6	6	6
SGOT /AST (IU/L)	STZ	15.82^{aA} ± 2.684 (4.09 - 27.67)	18.87^{aA} ± 2.655 (8.23 - 30.12)	22.55^{aA} ± 3.016 (9.76 - 30.78)	22.82^{aA} ± 3.331 (12.23 - 34.21)	22.89^{aA} ± 4.370 (15.22 - 33.65)
	Control	14.85^{aA} ± 3.416 (4.05 - 28.25)	15.50^{aA} ± 3.966 (7.40 - 33.30)	14.71^{aA} ± 3.536 (5.98 - 30.35)	14.79^{aA} ± 3.210 (7.32 - 27.85)	15.17^{aA} ± 2.794 (6.45 - 23.34)
SGPT/ ALT (IU/L)	STZ	18.43^{aA} ± 2.937 (5.96 - 30.32)	20.52^{aA} ± 2.675 (9.56 - 31.04)	24.56^{aA} ± 3.095 (11.53 - 33.43)	24.60^{aA} ± 3.408 (14.65 - 35.65)	24.76^{aA} ± 4.858 (16.23 - 36.65)
	Control	17.98^{aA} ± 3.839 (5.91 - 32.80)	16.55^{aA} ± 4.246 (8.35 - 35.56)	17.18^{aA} ± 4.233 (7.54 - 36.32)	16.66^{aA} ± 3.527 (9.20 - 30.43)	15.63^{aA} ± 2.952 (6.87 - 25.47)
AST:ALT Ratio	STZ	0.84^{aA} ± 0.020 (0.69 - 0.91)	0.91^{bA} ± 0.014 (0.84 - 0.97)	0.91^{bA} ± 0.016 (0.84 - 0.96)	0.92^{bA} ± 0.025 (0.83 - 1.01)	0.93^{bA} ± 0.006 (0.92 - 0.94)
	Control	0.81^{aA} ± 0.031 (0.69 - 0.90)	0.94^{bcA} ± 0.020 (0.89 - 1.03)	0.86^{abA} ± 0.026 (0.79 - 0.98)	0.89^{abA} ± 0.027 (0.79 - 0.96)	0.97^{cA} ± 0.037 (0.92 - 1.16)

Means for a parameter in different columns bearing at least one common 'lowercase alphabet' superscript, and in different rows bearing at least one common 'uppercase alphabet' superscript does not differ significantly (P≤ 0.05).

Table - 7. Effect of single intravenous dose of Streptozotocin @ 65 mg/kg b.w on kidney function test of rabbits (Mean ± SE).

Parameter	Treatment	Days of treatment				
		0day	15day	30day	45day	60day
Number	STZ	10	10	8	6	4
	Control	6	6	6	6	6
Blood Urea Nitrogen (mg/dL)	STZ	31.15^{aA} ± 2.160 (20.34 - 40.33)	32.98^{aA} ± 2.154 (22.15 - 42.35)	34.37^{aA} ± 2.944 (25.32 - 45.76)	36.99^{aA} ± 3.220 (28.33 - 46.66)	37.55^{aA} ± 3.077 (32.33 - 46.33)
	Control	29.97^{aA} ± 3.064 (21.10 - 42.56)	30.79^{aA} ± 3.416 (19.37 - 38.96)	28.68^{aA} ± 2.654 (22.47 - 40.54)	30.23^{aA} ± 2.785 (23.78 - 41.17)	30.01^{aA} ± 2.489 (22.32 - 38.82)
Creatinine (mg/dL)	STZ	0.89^{aA} ± 0.057 (0.59 - 1.23)	1.04^{abA} ± 0.061 (0.78 - 1.35)	1.12^{bcA} ± 0.062 (0.90 - 1.42)	1.16^{bcA} ± 0.095 (0.88 - 1.52)	1.33^{cA} ± 0.063 (1.23 - 1.50)
	Control	0.89^{aA} ± 0.050 (0.67 - 0.99)	0.98^{abA} ± 0.050 (0.76 - 1.12	1.04^{bcA} ± 0.048 (0.88 - 1.21	1.14^{cdA} ± 0.030 (1.03 - 1.23	1.20^{dA} ± 0.034 (1.12 - 1.35
Chloride (mmol/L)	STZ	115.90^{aA} ± 1.935 (103.50 - 122.50)	96.06^{bA} ± 1.031 (91.50 - 102.30)	90.39^{cA} ± 1.187 (85.40 - 94.40)	88.08^{cA} ± 1.140 (84.30 - 91.40)	85.68^{cA} ± 2.072 (81.20 - 91.20)
	Control	116.03^{aA} ± 3.309 (102.70 - 123.30	114.90^{aB} ± 1.353 (109.80 - 118.50	116.27^{aB} ± 2.843 (107.50 - 124.50	114.13^{aB} ± 2.774 (105.90 - 122.40	113.75^{aB} ± 2.531 (105.80 - 122.50

Means for a parameter in different columns bearing at least one common 'lowercase alphabet' superscript, and in different rows bearing at least one common 'uppercase alphabet' superscript does not differ significantly (P≤ 0.05).

Table - 8. Effect of single intravenous dose of Streptozotocin @ 65 mg/kg b.w on plasma lipids of rabbits (Mean ± SE).

Parameter	Treatment	Days of treatment				
		0day	15day	30day	45day	60day
Number	STZ	10	10	8	6	4
	Control	6	6	6	6	6
Total Cholesterol (mg/dL)	STZ	40.99^{aA} ± 1.910 (30.50 - 47.20)	41.32^{aA} ± 1.216 (33.80 - 45.70)	43.05^{aA} ± 1.282 (37.60 - 48.50)	45.33^{aA} ± 1.449 (40.30 - 50.30)	51.98^{bA} ± 1.780 (48.10 - 56.30)
	Control	39.30^{aA} ± 2.053 (31.90 - 46.20	39.28^{aA} ± 1.705 (33.80 - 43.80)	39.38^{aA} ± 1.244 (34.50 - 42.80)	41.08^{aA} ± 2.224 (33.80 - 48.10)	41.33^{aB} ± 1.377 (37.50 - 46.30)
Triglyceride (mg/dL)	STZ	59.40^{aA} ± 4.743 (37.17 - 80.16)	64.68^{aA} ± 4.229 (46.22 - 82.13)	69.17^{aA} ± 4.937 (49.57 - 83.22)	73.84^{aA} ± 4.470 (55.78 - 85.89)	75.58^{aA} ± 6.393 (64.33 - 91.23)
	Control	56.52^{aA} ± 8.919 (25.70 - 83.09)	60.35^{aA} ± 6.791 (33.65 - 78.23)	65.46^{aA} ± 5.498 (46.72 - 82.57)	57.80^{aB} ± 4.059 (43.67 - 70.33)	64.03^{aA} ± 4.266 (50.43 - 76.23)

Means for a parameter in different columns bearing at least one common 'lowercase alphabet' superscript, and in different rows bearing at least one common 'uppercase alphabet' superscript does not differ significantly (P≤ 0.05).

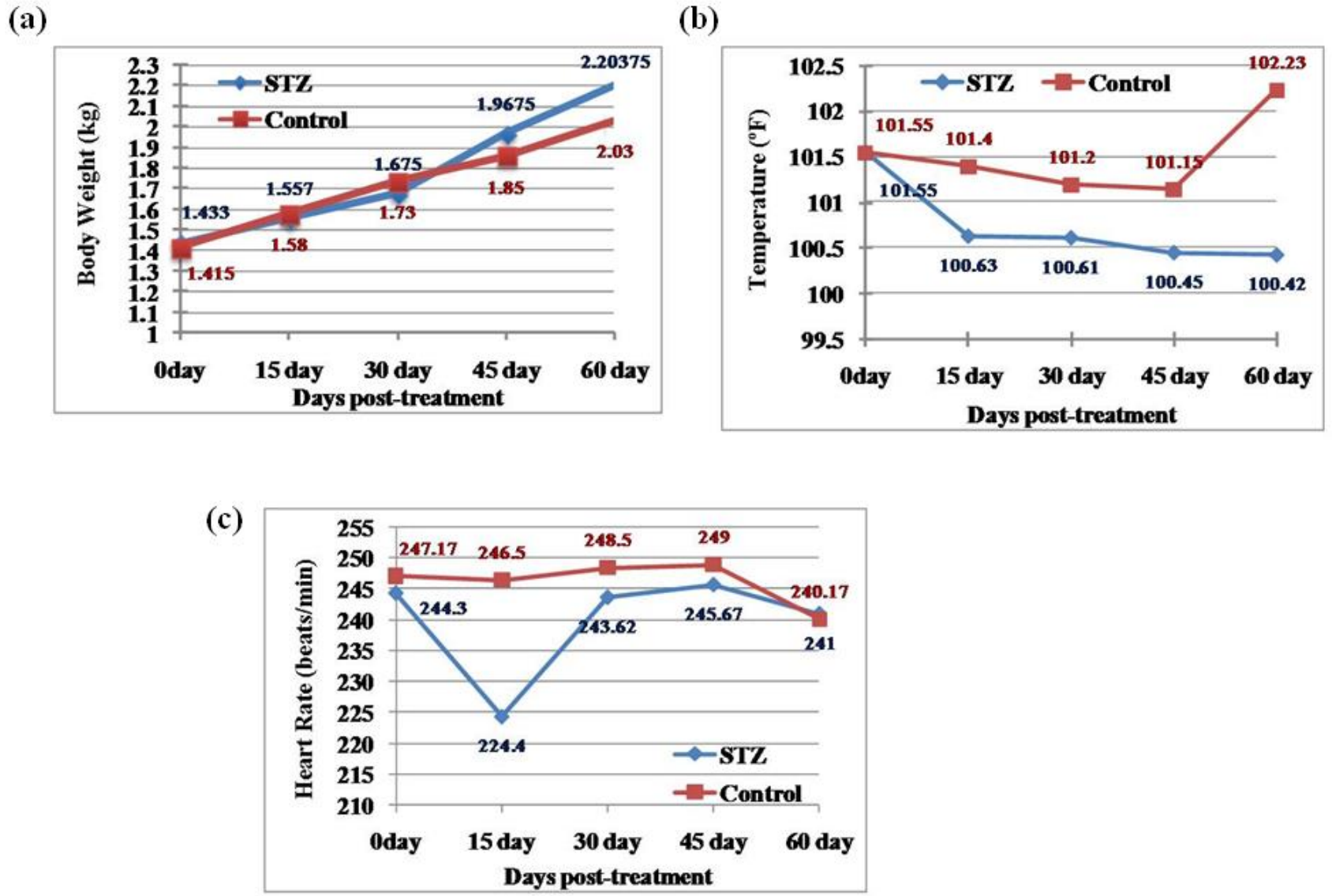

Fig. 1: Graphical representation of: (a) Body weight; (b) Body temperature; (c) Heart rate

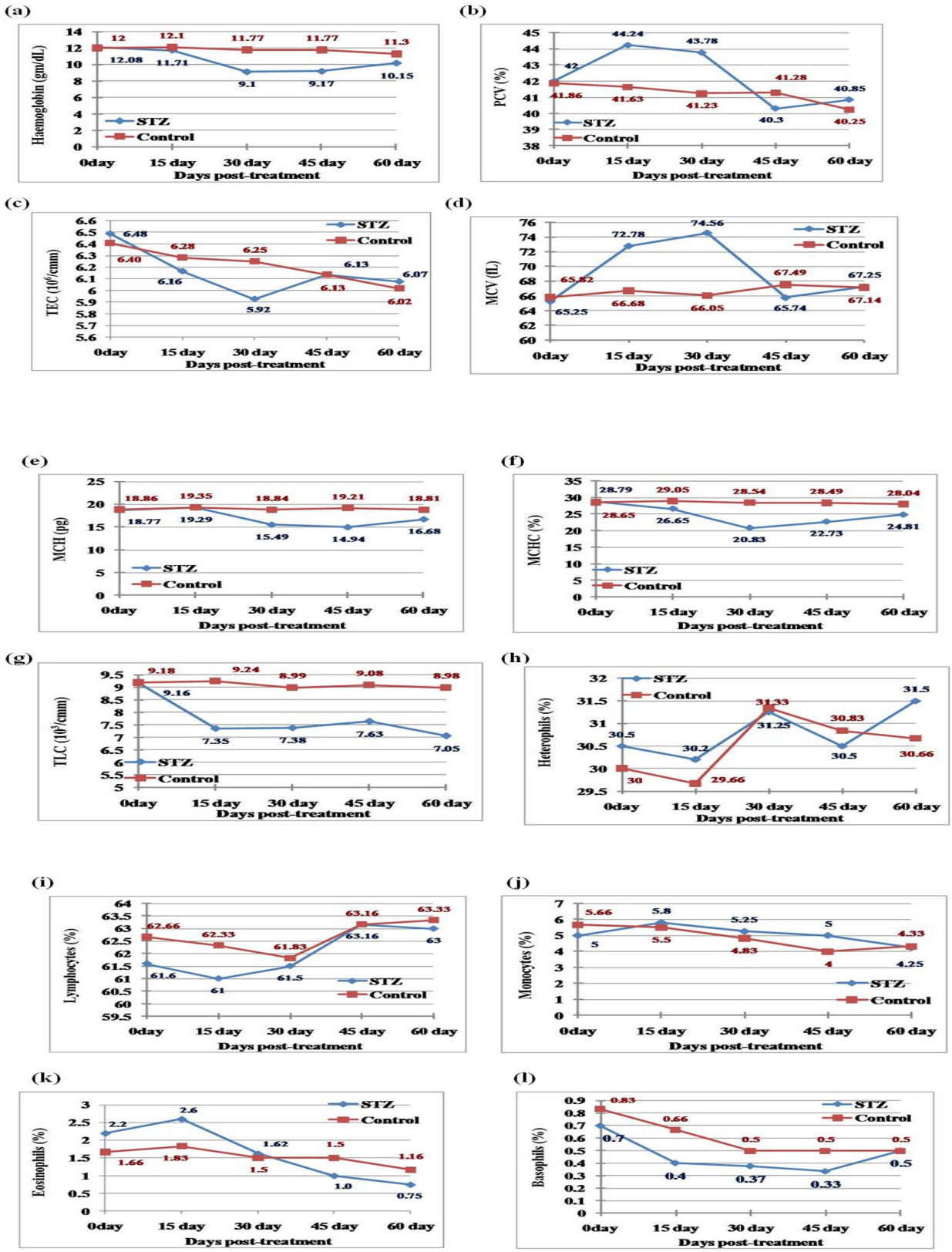

Fig. 2: Haematological profile in Streptozotocin treated non-diabetic rabbits

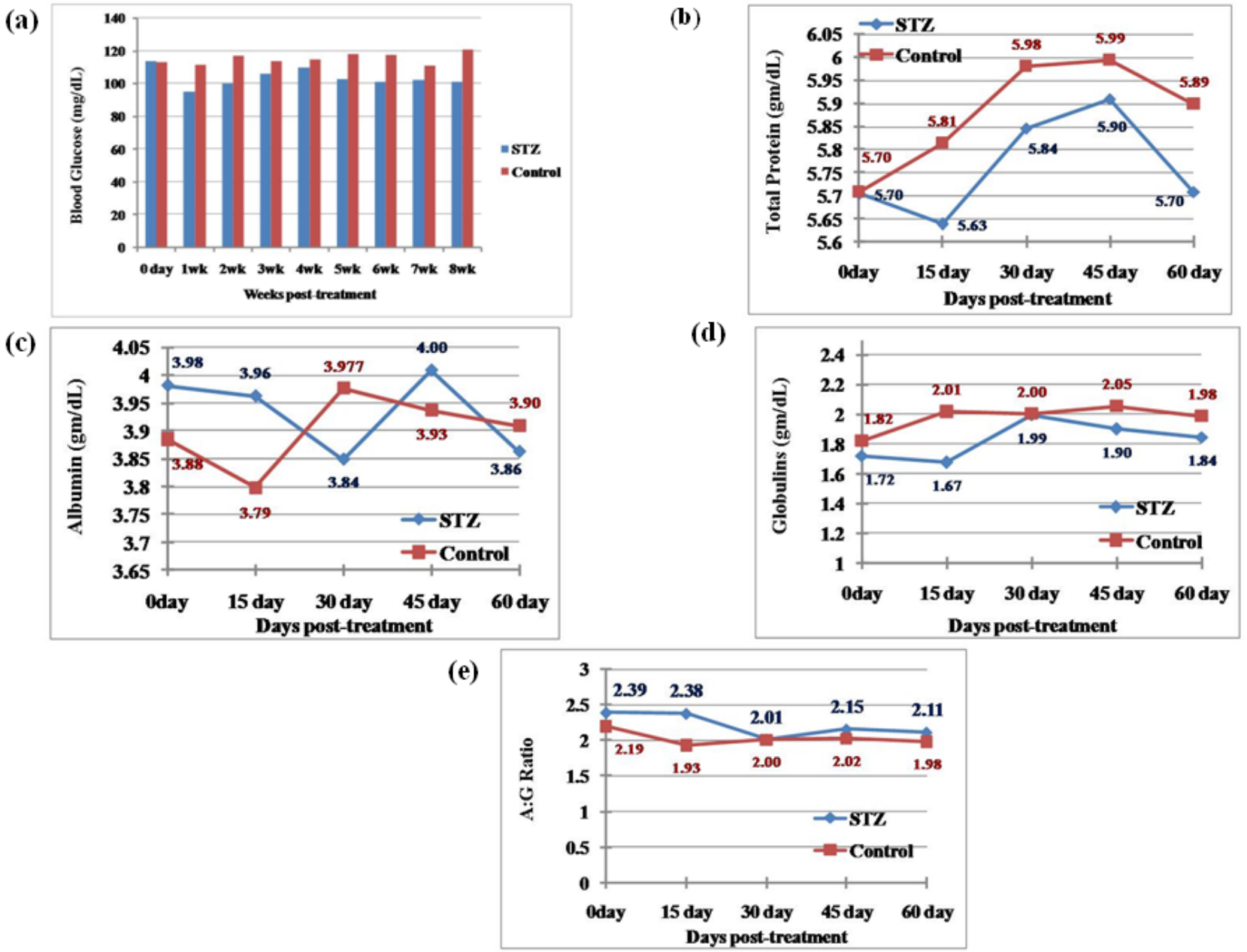

Fig. 3: Biochemical indices in Streptozotocin treated non-diabetic rabbits

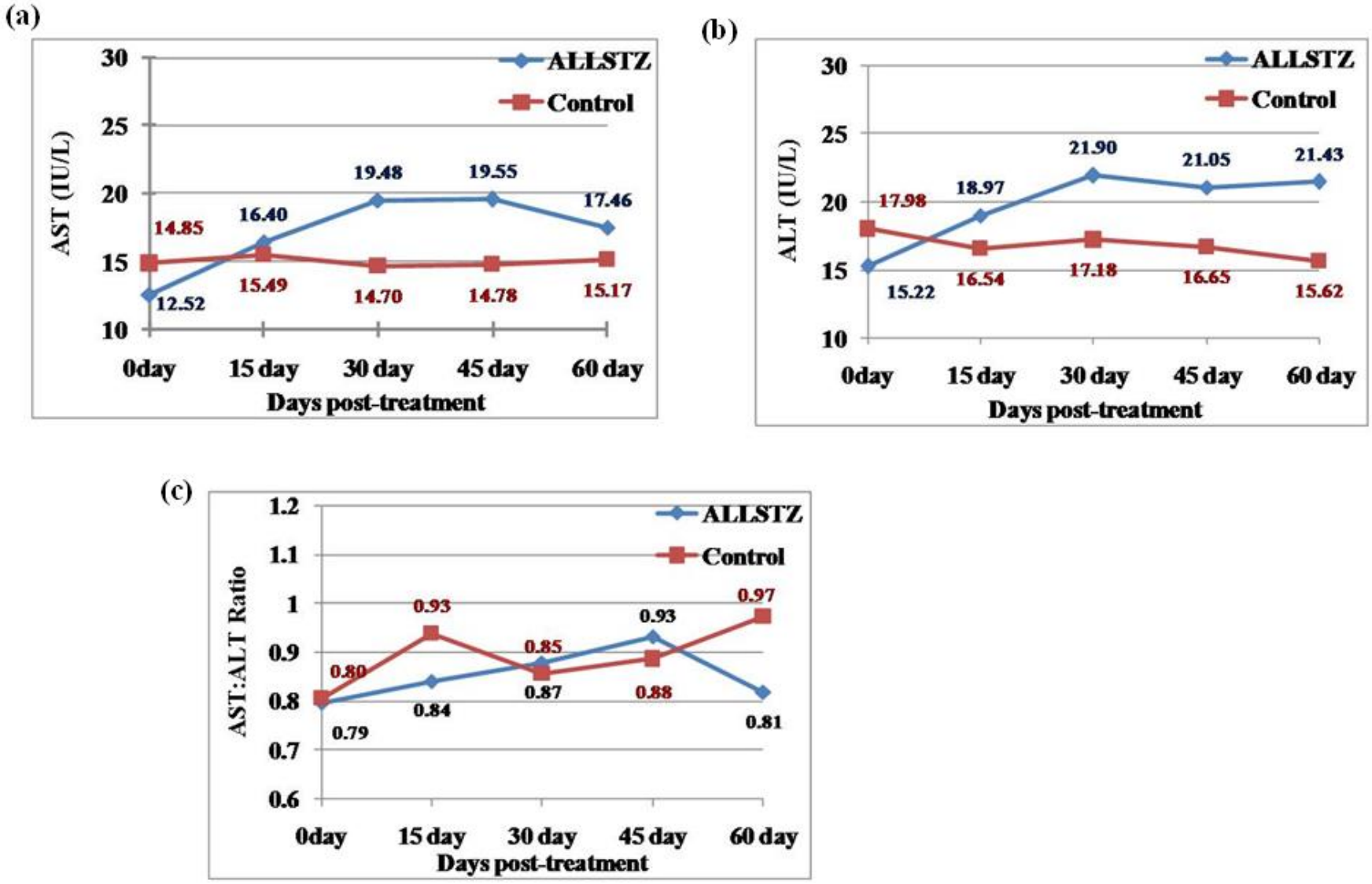

Fig. 4: Estimation of plasma liver enzymes in Streptozotocin treated non-diabetic rabbits

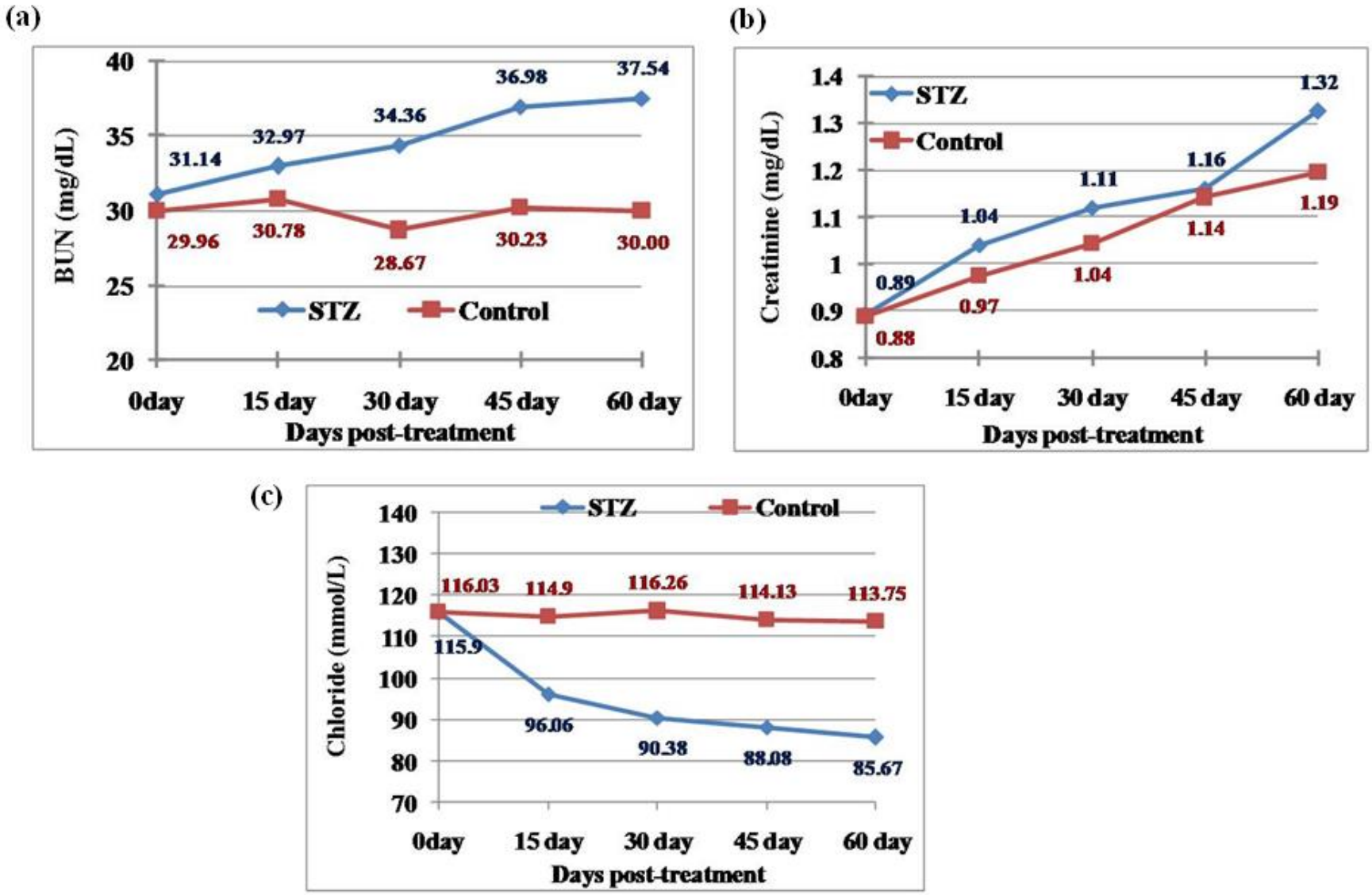

Fig. 5: Estimation of Kidney function test in Streptozotocin treated non-diabetic rabbits

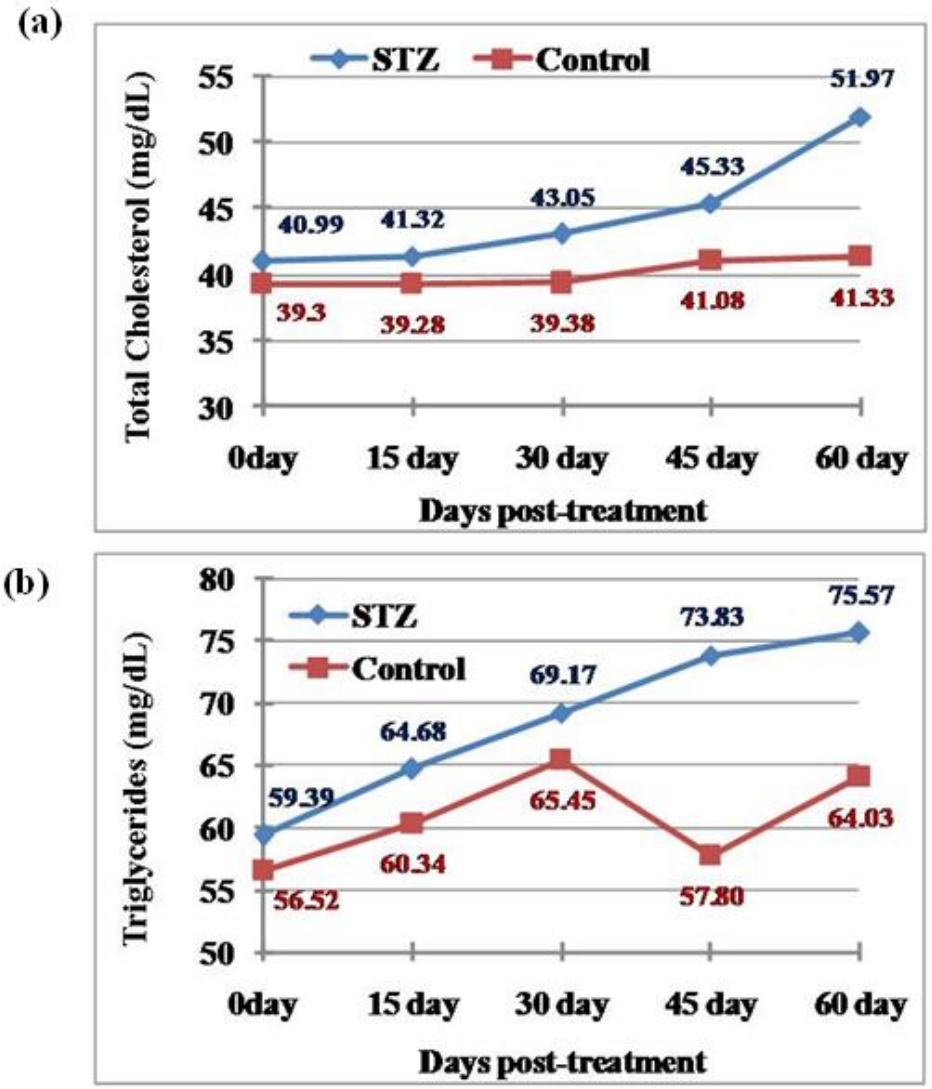

Fig. 6: Estimation of plasma lipids in Streptozotocin treated non-diabetic rabbits