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RESEARCH OPINIONS IN ANIMAL & VETERINARY SCIENCES

Hypoglycemic effect of *Aloe vera* on streptozotocin-induced diabetic mice

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Abstract

In the present study, an attempt was made to evaluate the effects of hydro-alcoholic extract of *Aloe vera* in streptozotocin-induced diabetic mice. A total 48 white lab mice were divided into four groups (n=12). One group served as control which was neither diabetic nor treated with *Aloe vera*. Second group was normal and treated with *Aloe vera* orally at the dose rate of 300 mg/kg. Third group was diabetic and in fourth group was also diabetic but treated with *Aloe vera*. The glucose analogue, streptozotocin was used to induce diabetes. After a week treatment of *Aloe vera*, the glucose level returned to normal. Histologically, the islet of Langerhens in pancreas was damaged in diabetic mice which were restored by feeding *Aloe vera.* The hepatocytes of diabetic rats were swollen. These degenerative changes were repaired by supplementation of *Aloe vera.* Similarly, in the kidney and small intestines, the degenerative changes were restored by the addition of *Aloe vera* in the feed. The present study demonstrated that *Aloe vera* have a beneficial effects in treatment of diabetes.

Keywords: *Aloe vera*; diabetes; streptozotocin; pancreas

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Introduction

Diabetes mellitus is the one of the most common endocrine disorder and one of the leading causes of death in the world (Ogbonnia et al., 2008). Diabetes is associated with increased risk of disease such as neuropathy and cardiovascular disorders. *Diabetes mellitus* is classified into two major subtypes: type I (insulin dependent *diabetes mellitus*, IDDM) and type II (non-insulin dependent *diabetes mellitus*, NIDDM). IDDM results from a cellular mediated autoimmune destruction of the β cells of the pancreas (Takeshi et al., 2002) However, NIDDM results from the development of insulin resistance and the affected individuals usually have insulin deficiency (De Fronzo et al., 1997).

In experimental diabetes models where certain chemical agents are used to induce type 1diabetes, the pancreatic β cells of the subjects used are selectively destroyed leading to a total lack or deprived insulin production, hence chronic hyperglycaemia (Atangwho et al., 2010). The glucose analogue streptozotocin (STZ) is widely used experimentally to induce *diabetes mellitus*. During STZ-induced diabetes, various nerves, organs and tissues may be affected. Vascular dysfunctions have been described in the eye, heart and kidney (Vinik et al., 2000) with altered responses to various vasodilator or vasoconstrictor agents during the diabetic state.

Antidiabetic medicinal plants are in general known to exert their beneficial effect (s) on diabetes via various modes and mechanisms depending on the phytochemicals and bioactive agents endowed in such plants or a collection of plants. Many different studies with various plant extracts have shown evidence that the destroyed β cells can be regenerated and in most cases, the partly non destroyed cells are protected from further degeneration by the activity of the extract (Kim et al., 2009). Several drugs such as biguanides and sulfonylureas are presently available to reduce hyperglycemia in *diabetes mellitus* (Nirmala et al., 2009). These drugs have side effects and thus search for a new class of compounds is essential to overcome

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these problems (Kamaeswara Rao et al., 2001). Many herbs have been shown to have hypoglycemic action in animals and humans (Singh et al., 2001).

Aloe barbadensis vera has been used in herbal medicine in many cultures. Aloes are members of the *Liliaceae* family and it is cactus-like plants, with green, dagger-shaped leaves that are fleshy, spiny and filled with a clear viscous gel (Rehman et al., 2011). There are some compounds that were evaluated for anti-hyperglycemic effect of *A. vera* and isolated from the gel, on the basis of spectroscopic data, these compounds were identified as lophenol, 24-methyl-lophenol, 24-ethyl-lophenol, cycloartanol, and 24-methylene-cycloartanol. These five phytosterols were evaluated for their anti-hyperglycemic effects in type II diabetic in mice (Tanaka et al., 2006).

Clinical evaluations have revealed that the pharmacologically active ingredients are concentrated in both the gel and rind of *A. Vera* leaves. *A. Vera* has many effects such as wound healing (De Azevedo et al., 2001) anti-inflammatory (Davis et al., 1991) antiseptic (Capasso et al., 1998) and has got antitumor activities (Saito, 1993). The present work was undertaken to study the antidiabetic effect of *A. vera* extract and its effect on the pancreas, liver, kidney, and small intestine on healthy and diabetic mice models.

Materials and Methods

Animal's model

In this study 48 male Swiss albino mice (8 weeks, 20-25 g) were caged randomly into four groups. Two weeks in cages was provided for adaptation. In this period, all animals were fed standard pellet and water.

Group I: Control (non-diabetic) group and did not receive extract. GroupII: Normal mice were daily injected with *A. Vera* (300 mg/kg) intraperitoneally administration for a week. Goup III: Diabetic control group, were injected single dose streptozotocin (200mg/kg) for induce diabetes by intraperitoneal administration. Group IV: Diabetic mice were injected single dose of streptozotocin (200mg/kg, IP administration) to induce diabetes and after that they were daily treated with *A. vera* extract (300 mg/kg, IP administration) for a week.

Preparation of plant extracts

The leaves were washed first by water and dried at room temperature (about 28°C) in dark then grinded to powder using an electrical blender. The powdered leaves (100 g) were extracted with 600 ml aqueous ethanol (70%). The extracts were then kept for 24h at 4°C and then filtered through a Whatman No. 4 filter paper the solution concentrated in a rotary evaporator at 40°C. The residue obtained was lyophilized in a freeze-dryer and the resulting powdered material was stored at 80°C until tested (Malekinejad et al., 2010).

Induction of diabetes

The mice were fasted for 16 h prior and then received STZ 200 mg/kg body weight by intraperitoneally administration (Noor et al., 2008). After 3 days of administration, the blood glucose levels were increased more than 250 mg/dl that showed induction of diabetes. Blood glucose levels were measured initially after induction of diabetes and at the end of experimental period. Blood samples were collected from tail vena and glucose level was detected on days 0, 1st and 8th using the glucose oxidase enzymatic test kit (Medisense glucometer).

Histopathology

The mice sacrificed by thiopentone sodium (40 mg/kg BW, IP) and the liver, kidney, pancreas, small intestine were removed and samples were taken. The samples were fixed in 10% formalin saline for 1 week at room temperature. The 5-6µ sections were made using paraffin embedded sections and stained with hematoxylin-eosin for histological examination under a light microscope. The extent of β cells damage was further estimated by specific staining for functional β cells with aldehyde fuschin (Noorafshan et al., 2012) and some sections of liver were also stained with periodic acid-Schiff (PAS) for visualization of the polysaccharide material.

Statistical analyses

Statistical analysis was performed by one way analysis of variance (ANOVA) followed by Tukey-Kramer multiple range tests. All values were expressed as mean with their Standard Deviation (SD). P values < 0.05 were considered as significant.

Results

Table 1 indicates that the *A. vera* exhibited antidiabetic property in streptozotocin-induced diabetic mice as evident from changes in blood glucose level. There was an increased level of blood glucose in STZ-induced animals (diabetic control) which was drastically reduced by supplementing with *A. vera*. The amount of blood glucose level in non-diabetic group which received

Table 1: Effect of *Aloe vera* extracts on blood glucose level of diabetic group and non-diabetic mice

Groups	Group I (Non-diabetic control)	Group II (Non-diabetic + Aloe vera)	Group III (Diabetic control)	Group IV (Diabetic + Aloe vera)
Blood Glucose (mg/L)	110.7 ± 11.5^{A}	85.2 ± 13.6^{A}	285.5 ± 22.7^{B}	208.4 ± 17.5^{B}

Values bearing different superscript differ significantly (P<0.05)

A. vera was found to be decreased when compared with non-diabetic control group.

Our finding showed that after induced diabetes, the blood glucose was 285.5±22.7 mg/dl which subsequently dropped down to 208.4±17.5 mg/dl after a week treatment of *A. vera.* Meaningful difference was observed between the diabetic group under *A. vera* treatment and the group without the treatment of plant extract. The amount of blood glucose reduction was 23% in non-diabetic group while in diabetic group, it was recorded 27%. Streptozotocin (200 mg/kg) induced diabetic mellitus in mice and blood glucose reached to 285.5±22.7 mg/dl. Administration of *A. vera* (300 mg/kg) reduced blood glucose level significantly ($P<0.05$).

Histopathological findings

In the pancreas of group I, the histology of pancreatic islet cells was normal and in group II many round and elongated islets were evenly distributed throughout the cytoplasm, with their nucleus lightly stained than the surrounding acinar cells. In group III, the islets were damaged, the number of panceratic islets, size of pancreatic islets and the number of β cells were significantly decreased. (Fig. 1a). In group IV, islets were comparable to normal mice. The number and the diameters of islets were significantly increased compared to diabetic group III (Fig. 1b).

In group III the histologic sections of liver showed irregular areas and distribution in liver structure. Focal areas of lymphocytes infiltration and necrosis were observed (Fig. 2a). The hepatocytes were swollen with margination of chromatin in nuclei. PAS reaction showed marked increase of glycogen content in hepatocytes. In the hepatocytes of group IV, these degenerative changes were partly reduced and the architecture of the hepatic lobule that appears more or less like control group (Fig. 2b). Glycogen content of hepatocytes was similar to the control group.

The kidney sections of animals in group III revealed marked distortion of cyto-architecture of the renal cortical structures, with degenerative changes. There were vacuolations appearing in the renal tubules (Fig. 3a). The renal corpuscles were enlarged and the Bowman's spaces were sparsely distributed as compared to the control group (Fig. 3b). In the group IV kidney structures were similar to the control group.

In group III, the histologic sections of small intestine showed fibrinous enteritis and excess destruction of epithelium with infiltration of inflammatory cells in mucosal layer (Fig. 4a). No significant pathological changes were observed in group IV (Fig. 4b).

Discussion

The present study was undertaken to evaluate the hypoglycemic effect of *A. vera* extract in STZ-induced diabetic mice. The first study on human model for the hypoglycaemic effect of *Aloe* species was made by Agarwal (1985) who reported that *A. vera* leaves in the diet of diabetic patients twice daily for 5 years induced marked decrease in blood sugar as well as serum total cholesterol and triglyceride levels. Subsequently, Ghannam et al. (1986) using the dried sap of the plant, revealed that *A. vera* lowered the blood sugar level of alloxan-diabetic mice. Later, Ajabnoor (1990) reported that the blood glucose level of the rats which received *A. vera* tended to bring the blood glucose levels of diabetic rats to the normal level (Rehman et al., 2011). The effects of processed *A. vera* gel (PAG) on the course of established diet-induced non-insulin-dependent *diabetes mellitus* (NIDDM) reduced circulating blood glucose concentrations to a normal level in mice. The antidiabetic effects of PAG were also confirmed by intraperitoneal glucose tolerance testing. PAG appeared to lower blood glucose levels by decreasing insulin resistance (Kim et al., 2009). Such finding agrees with the present study, which indicates that *A. vera a*dministration to mice leads to an increase of pancreatic β cells activity. Diabetes can be induced in animals by injection of STZ, a glucose analogue, 2-deoxy-2-3-methyl-3-nitrosuuredio-D-gluco-pyranose, which is stable at pH 4.5 and degrades rapidly in alkaline solution, forming diazomethane, an alkylating agent. STZ synthesized by *Streptomycetes achromogenes* and induced experimental diabetes is a valuable model for induction of type I diabetes (Szkudelski, 2001). STZ is directed to the pancreatic β cells by its deoxyglucose moiety and be taken up via glucose transporters 2 (GLUT2) that are expressed on the β cells. The nitrosurea moiety on the chemical structure of STZ decomposes within β cells, forming carbonium ions (CH3+) that are highly reactive, effecting DNA alkylation and eventual fragmentation (Elsner et al., 2000). Therefore, STZ causes nitric oxide level to rise within the β cells, which contribute to further DNA damage, cell destruction, and restriction of mitochondrial ATP generation. A dose of 200 mg/kg of STZ gave rise to a pronounced diabetic state (mean blood glucose level above 250 mg/dl). Imbalance between energy intake and expenditure results in a change in body weight. STZ induced diabetic mice showed decreased level of body weights. In our study, intraperitoneal injection of *A. vera* extract (300 mg/kg body wt) daily to diabetic mice (200 mg/kg STZ) reduced the FPG levels by 27%. The results indicate that the *A. vera* extract was effective in lowering hyperglycaemia in STZ-induced mice. These findings are correlated with the work of Eman et al. (2003) and Ayse et al. (2004) who observed a significant reduction in blood glucose level in mice and rats respectively. Mohapatra et al. (2013) reported that administration of *A. vera* aqueous extract at dose rate of 150 and 300 mg/kg for a period of 21 days did not influence the mean fasting plasma glucose level in normal rats. The antidiabetic

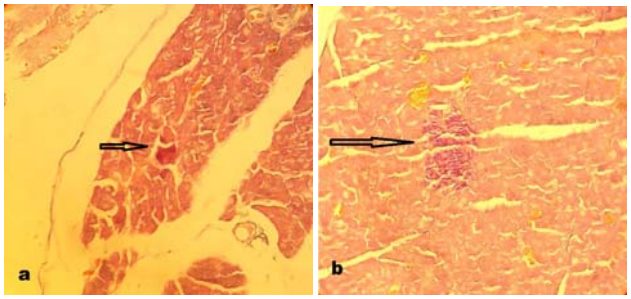

Fig. 1: A photomicrograph of pancreas sections. (Aldehyde Fuschin x 100). (a) Diabetic mice, showing atrophied islet and decrease of β cell, (b) diabetic mice treated with *A. vera* showing improvement of islets and diameters of islets were significantly increased (Aldehyde Fuschin X 100).

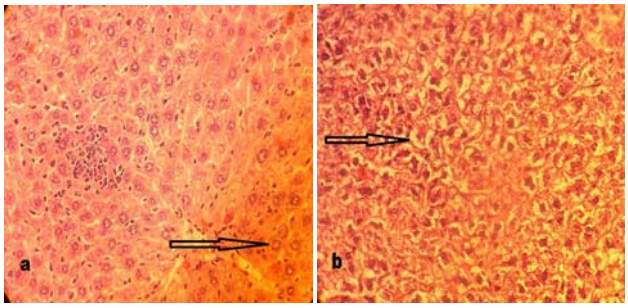

Fig. 2: A photomicrograph of sections of liver (H & E 100 X). (a) Diabetic mice, showing focal infiltration of lymphocytes and cell swelling with margination of chromatin in nuclei, (b) Diabetic mice treated with *A. vera* showing the degenerative changes were partly reduced and the architecture of the hepatic lobule that appears more or less like control group.

activity of the *A. vera* may be possible through various mechanisms such as stimulation of glucose uptake by peripheral tissue, inhibition of endogenous glucose uptake by peripheral tissue, or activation of gluconeogenesis in liver and muscles (Leiro et al., 2003). Blumenhal et al. (1998) reported that *A. vera* contained high calcium level. Abu Amra (1994) stated that calcium stimulates the β cells of Langerhans that lead to an increase in insulin and liver glycogen levels. The behaviour of normal mice treated with *A. vera* (group-II) appeared normal. They were healthy and no mortality was observed indicating that there was no toxic effect of *A. vera* injection. The histological sections of the pancreas, liver, kidney and small intestine tissues were observed to know the effect of *A. vera* treated in non-diabetic and diabetic mice. This was done to observe any protective or harmful effect of *A. vera* extract on non-diabetic and diabetic mice. In pancreatic sections of diabetic mice (group III), the number, the size of pancreatic islets and number of β cells were decreased. In *A. vera* treated diabetic mice, there were more islets and they were comparable to normal

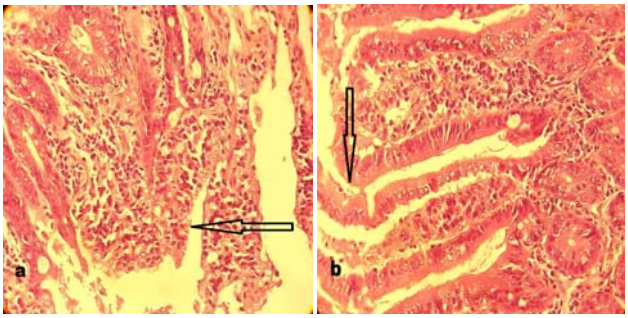

Fig. 3: A photomicrograph of sections of the intestine (H & E 100 X). (H & E X 400). (a) Diabetic mice showing infiltration of lymphocytes in mucosal layer and necrosis of the vili. (b) No significant pathological changes were observed in treated group.

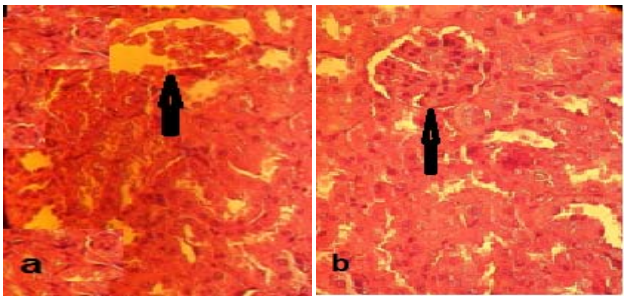

Fig. 4: A photomicrograph of sections of the kidney. (H & E 100 X). (a) Diabetic mice showing glomerular swelling and necrosis in tubular epithelial cells, (b) diabetic mice treated with *A. vera* showing kidney structures similar to the control group.

mice islets, although there were individual differences. The relative distribution of pancreatic islet cells was similar to control mice which may be correlated with the increase in insulin production, suggesting that β cells are probably functioning at higher capacity. Our histological findings are in agreement with the degenerative structural changes reported in pancreas tissues (Sefi et al., 2011). In the untreated hyperglycemic rats, the pancreatic islets were diminished in sizes (Sefi et al., 2011) and islets appeared to be reduced in cellular density (Ukwenya et al., 2012). In group III, the histologic sections of liver showed many large cytoplasmic granules, glycogen granules, hyperaemia in the sinusoids, focal necrosis of hepatocytes, swollen hepatocytes with lucent cytoplasm and the enlarged hepatocyte nuclei. These changes were reduced in *A. vera*-treated mice of group IV. This may be due to beneficial and protective effect of *A. vera* extract on liver tissues of diabetic mice (Zafar et al., 2009). Can et al. (2005) observed an increase in degeneration in central veins to portal veins, excess vacuolization, granular appearance in the cytoplasm, dilations in the sinusoids and moderate hyperaemia. Noor et al. (2008) also reported that pancreas and liver sections of diabetic rats fed with *A. vera* were found to be normal when

compared with diabetic control rats. In our study, there were hydropic degeneration in renal tubules, glomerulus hypertrophy and increased cellularity, congested glomerular capillaries in the kidney of diabetic mice group which is similar to control mice after treating with *A. vera*. Excess proliferation of epithelium was noticed in the small intestine of diabetic mice (group III), which was reduced after treatment of *A. vera.*

The result of the present study showed that *A. vera* brings back the blood glucose to normal levels in diabetes-induced mice. Histologically, *Aloe vera* showed protective effect on the organ.

References

Abu-Amra, S. 1994. Influence of Venom extracted factors separated from shakes on serum insulin, serum glucose, liver glycogen and skeletal muscle pyruvate levels of rats. J. *Egypt. Ger. Soc. Zoo1*, 15: 205-214.

Agarwal, O.P. 1985. Prevention of atheromatous heart disease. *Angiology,* 36: 485-492.

Ajabnoor, M. 1990. Effect of aloes on blood glucose levels in normal and alloxan diabetic mice. *Journal of Ethnopharmacology*, 28: 215-220.

Atangwho, I.J., Ebong, P.E., Egbung, G.E., Akpaso, M.I. and Asuquo, E.E. 2010. Histological Effect of combined extracts of *Vernonia Amygdalina* and *Azadirachta Indica*on normal and diabetic rats: the pancreas and liver. *Research Journal o f Agriculture & Biological Sciences*, 6: 514-521.

Ayse, C.A.N., Ozsoy, N., Bolkent, S., Rada, B.P., Yanardag, R. and Okyar, A. 2004. Effect of Aloe vera Leaf Gel and Pulp Extracts on the Liver in Type-II Diabetic Rat Models. *Biol. Pharm. Bull*, 27: 694-698.

Blumenhal, M., Busse, N.R. and Golddberg, A. 1998. The complete commission E. monograph therapeutic guide to herbal medicine. Boson M.A. Integrative Medicines Communications. Pp:80-81.

Can, B., Ulusu, N.N., Kilinc, K., Acan, N.L., Saran, Y. and Turan, B. 2005. Selenium Treatment Protects Diabetes-Induced Biochemical and Ultra structural Alterations in Liver Tissue. *Biological Trace Element Research*, 105: 135-150.

Capasso, F., Borrelli, F. and Capasso, R. 1998. Aloe and its therapeutic use. *Phytotherapy Research*, 12:4-127.

Davis, R.H., Parker, W.L., Samson, R.T. and Murdoch, D.P. 1991. The isolation of an active inhibitory system from an extract of Aloe vera. *J. Am. Podi. Med. Assoc*, 81: 258-261.

De Azevedo, E., Pribitkin, M.D. and Boger, M.D.G. 2001. Herbaltherapy: What every facial plastic surgeon must know. *Arch. Facial last. Surg*, 3: 127-132.

De Fronzo, R.A., Bonadonna, R.C. and Ferrannini, E. Pathogenesis of NIDDM, International Text book of *Diabetes mellitus*, 2nded. 1997. Chichester, John Wiley, pp: 635-712.

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

Eman, G.E.H., Hasan, M.H.A., Mustafa, A.M. and Al-Kamel, A. 2003. Effect of Aloe vera extract on some physiological parameters in diabetic albino rats. *Egyp. J. Hosp. Med*, 12: 53-61.

Ghannam, N., Kingston, M., Al-Meshaal, I.A., Tariq, M., Parman, N.S. and Woodhouse, N. 1986. The antidiabetic activity of aloes: preliminary clinical and experimental observations. *Hormone Research*, 24: 288-294.

Kamaeswara Rao, B., Giri, R., Kesavulu, M.M. and Apparao, C. 2001. Effect of oral administration of bark of *Pterocarpus santalinus* L.on blood glucose level in experimental animals. *Journal of Ethnopharmacology*, 74: 69-74.

Kim, K., Kim, H., Kwon, J., Lee, S., Kong, H., Im, S.A., Lee, Y.H., Lee, Y.R., Oh, S.T., Jo, T.H., Park, Y.I., Lee, C.K. and Kim, K. 2009. Hypoglycemic and hypolipidemic effects of processed *Aloe vera* gel in a mouse model of non-insulin-dependent *diabetes mellitus*. *Phytomedicine*, 16: 856-863.

Leiro, J.M., Alvarez, E., Arranz, J.A., Siso, I.G. and Orallo, F. 2003. In vitro effects of mangiferin on superoxide concentrations and expression of the inducible nitric oxide synthase, tumor necrosis factor and transforming growth factor genes. *Bioch Pharmacol*, 65: 1361-1371.

Malekinejad, H., Alizadeh, A., Cheraghi, H., Meshkini, S. and Dardmeh, F. 2010. The Protective Effect of Liquorice Plant Extract on CCl4-Induced Hepatotoxicity in Common Carp *(Cyprinus carpio*). *Veterinary Research Forum*, 1: 158-164.

Mohapatra, s., Rath, B., Maharana, C.S., Pradhan, S. and Tripathy, S. 2013. Hypoglycemic, hypolipidemic properties of *aloe vera* in streptozotocin induced diabetic rats. *Int J Biol Med Res*. 4: 2783-2787.

Nirmala, A., Saroja, S., Vasanthi, H.R. and Lalitha, G. 2009. Hypoglycemic effect of *Basella rubra* in streptozotocin-induced diabetic albino rats. *J. Pharmacognosy Phytother*, 1: 025-030.

Noor, A., Gunasekaran, S., Manickam, A.S. and Vijayalakshmi, M.A. 2008. Antidiabetic activity of Aloe *vera* and histology of organs in streptozotocin-induced diabetic rats. *Curr.Sci,* 94: 1070-1076.

Noorafshan, A., Hoseini, L., Karbalay-Doust, S. and Nadimi, E. 2012. A Simple Stereological Method for Estimating the Number and the Volume of the Pancreatic Beta Cells. *Journal of the Pancreas*, 13: 427-432.

Ogbonnia, S.O., Odimegwu, J.I. and Enwuru, V.N. 2008. Evaluation of hypoglycaemic and hypolipidaemi effects of aqueous ethanolic extracts of *Treculia africana* Decne and *Bryophyllum pinnatum* Lam.

and their mixture on streptozotocin (STZ)-induced diabetic rats. *Afr J Biotech*, 7: 2935-2939.

Rehman, S.U., Jafri, S.A., Hassan, S., Ahmed, I. and Naim, M. 2011. Study on Antidiabetic Effect of *Aloe vera* Extract on Alloxan Induced Diabetic Rats. *Libyan Agric. Res. Cen. J. Intl*, 2: 29-32.

Saito, H. 1993. Purification of active substances of aloe arborescens Miller and their biological and pharmacological activity. *Pytother Res*, 7: 14-19.

Sefi, M., Fetoui, H., Lachkar, N., Tahraoui, A., Lyoussi, B., Boudawara, T. and Zeghal, N. 2011. Centaurium erythrea (Gentianaceae) leaf extract alleviates streptozotocin-induced oxidative stress and beta cell damage in rat pancreas. *Journal of Ethnopharmacology*, 135: 243-250.

Singh, S.N., Vats, P., Suri, S., Shyam, R., Kumria, M.M.L., Ranganathan, S. and Sridharan, K. 2001. Effect of an antidiabetic extract of *Catharanthus roseus*on enzymic activities in streptozotocin induced diabetic rats, *J. Ethnopharmacol*, 76: 269-277.

Szkudelski, T. 2001.The mechanism of alloxan and Streptozotocin action in beta cells of rat pancreas. *PhysiolRes*, 50: 536-546.

Takeshi, K., Shoichi, N., Yasunori, K. and Yasuhiko, I. 2002. Report of the committee on the classification and diagnostic criteria of *diabetes mellitus*. *Diabetes Res Clin Pract*, 55: 65-85.

Tanaka, M., Misawa, E., Ito, Y., Habara, N., Nomaguchi, K., Yamada, M., Toida, T., Hayasawa, H., Takase, M., Inagaki, M. and Higuchi, R. 2006. Identification of Five Phytosterols from Aloe Vera Gel as Anti-diabetic Compounds. *Biol Pharm Bull*, 29: 1418-1422.

Ukwenya, V.O., Ashaolu, J.O., Adeyemi, A.O., Akinola, O.A. and Caxton-Martins, E.A. 2012. Antihyperglycemic activities of methanolic leaf extract of *Anacardium occidentale* (Linn.) on the pancreas of streptozotocin-induced diabetic rats. *J. Cell Anim. Biol*, 6; 169-174.

Vinik, A.I., Park, T.S., Stansberry, K.B. and Pittenger, G.L. 2000. Diabetic neuropathies. *Diabetologia*, 43: 957-973.

Zafar, M., Naqvi, S.N., Ahmad, M. and Kaimkhani, Z.A. 2009. Altered liver morphology and enzymes in streptozotocin induced diabetic rats. *Int. J. Morphol*, 27: 719-725.