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Research Article

Antidiabetic and Antilipidemic Effect of *Aloe barbadensis* Gel Extract in Alloxan Induced Diabetic Mice

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Authors' Contributions
SSIB designed and executed the experimental work. NJ supervised the project. MKAK helped in tissue sectioning, study and data analysis. MZ and SJ helped in literature review, results and discussion.

Keywords
Alloxan monohydrate, Antidiabetic, Antihypercholestermic, *Aloe barbadensis*, Mice

Abstract | *Aloe barbadensis* is known for its antidiabetic and antihyperlipidemic activity, this study was aimed to check efficacy and toxic limits of different doses of gel extract in diabetic induced albino mice. Male albino mice, weighing (25±5g) were divided into three groups; Group 1: normal (non diabetic nontreated), Group 2: diabetic non treated (DNT), Group 3: diabetic treated (DT) mice. Group 3 was treated with three doses of *A. barbadensis* (200 mg/kg, 300 mg/kg and 400 mg/kg) per day for 14 days were assigned as DT1, DT2 and DT3 respectively. *Aloe vera* given orally produced significantly decline in the serum biochemical parameters viz. total cholesterol, triacylglycerols and glucose in Group 3 in comparison to Group 1 ($p<0.05$). An overall statistically significant decline in serum values of studied parameters was noted compared to the corresponding control values. High dose (400mg/kg) was effective in reducing blood sugar random and fasting blood glucose level (58.00±6.35 and 66.00±2.5 mg/dl) respectively. High dose was effective in reducing bilirubin (0.67±0.15), SGPT (35.67±2.03), SGOT (127.67±4.67) and alkaline phosphatase (86.33±1.86) compared to their corresponding control group values. *A. barbadensis* (400mg/kg) reduced cholesterol (78.00±2.08), triglycerides (83.67±3.28), HDL cholesterol (49.33.67±2.33) and LDL cholesterol (61.67±3.84). Pancreatic and hepatic sections from diabetic induced group 2 mice showed vacuolization and inflammation of cells whereas, group 3 showed improvements with normal islets with surrounding acini and lobular structure of hepatocytes.

Novelty Statement | This study reports that *Aloe vera* which is commonly grown in houses has very strong antidiabetic and antihyperlipidemic properties.

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Introduction

Diabetes mellitus is among major cause of worldwide deaths (Zheng *et al.*, 2018). Diabetes falls in cluster of metabolically oriented diseases with hyperglycemia because of defective insulin production or action. Chronic situation of hyperglycemia can lead to dysfunction and damage of vital body organs mainly liver, kidney and heart (Pavithra *et al.*, 2018). Reactive oxygen species (ROS) are produced as a result of diabetes causing destruction of body tissues including pancreatic beta cells (Newsholm *et al.*, 2019). There are evidences specifying magnified free radicals production that become necessary contributory factor of diabetes based complications. Several hypotheses have been put forth to explain the genesis of free radicals in

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diabetes (Tiwari and Rao, 2002). High levels of glucose and lipids are 2 main features of diabetes due to which person experience different complications like coronary heart problem, atherosclerosis, nephropathy due to diabetes (Seshasai *et al.*, 2011). Various chemicals are used for the treatment of diabetes since long (Hasan and Mohieldein, 2016), however chemicals used for the treatment of diabetes are more costly and have side effects (Buse *et al.*, 2009; Curtis *et al.*, 2018).

Side effects free diabetic management is still a challenging for medical system which has led to increased natural products demand for antidiabetic and with zero side effects (Mentreddy, 2007). Most of the plants and herbal product has hypoglycemic action (Modak *et al.*, 2007). These effects against diseases are due to the bioactive components present in plant extract (Pierre *et al.*, 2012). *Aloe barbadensis* is one of these antidiabetic plants (Malik *et al.*, 2021). *Aloe vera* is known as "secret plant" from old Egypt and Turkey. *Aloe barbadensis* contains many photochemical vitamins and nutrients found in foods (Maenthalsong *et al.*, 2007). Leaf extract of *Aloe vera* had showed hypoglycemic activity on diabetes (John, 2017). Fresh *Aloe vera* pulp contains almost 96% of water, polysaccharides, D-glucose, tannins, steroid, plant hormones, enzymes, many minerals and vitamins (Samulsson, 2004). Considerable amount of (Zn and Cr) present in its gel makes it antioxidant (Mohamed, 2011; John, 2017). There is no reported toxic effect of *Aloe vera* on liver and other organs (Luka *et al.*, 2012). *Aloe vera* is acting biologically in healing of wounds, antifungal, antidiabetic, anti inflammation, anticancer, immunomodulator and gastroprotective properties (Kumar *et al.*, 2019).

Statement of hypothesis

Alloxan monohydrate is reputed as diabetic agent initiating diabetes and acute phase response linked with hyperlipidemia and hyperglycemia. *Aloe barbadensis* is part of ethno medication but how it can be a potentially efficient agent to treat change in blood chemistry due to diabetes at various recommended oral doses.

Materials and Methods

Sampling site, sampling collection and identification of plant material

Aloe barbadensis plant was taken during December from GC University lawn at Lawrence road Lahore, Pakistan. *Aloe barbadensis* was identified by Botany Department, Government College University Lahore and given identification number as G.C.Herb.Bot\2285.

Animals and experimental design

Adult Swiss male albino mice weighing (25g±5g) were reared for experiment in the animal house zoology department GCU Lahore Pakistan. Mice were caged separately provided with constant environment in stainless steel boxes, temperature (26°C±4°C), humidity (55%-60%), and light cycle was 12/12 hr. During the experimental time period of 6 weeks water and food were given (*ad libitum*).

Animal's diet

Oval shaped pelleted diet from Pico Lab® Laboratory Rodent diet was used. Containing carbohydrates 70%, protein 18 %, fat 4.9%, fiber 3.2% and other allied components like ash minerals and vitamins. All the groups were fed on the same feed.

Preparation of aloe gel extract

Plant of 3 years old *Aloe barbadensis* was rinsed and weighed to obtain pulp of leaf (gel + pulp), which was further homogenized with a same amount of saline phosphate buffer (pH=7.0, 0.1 M). This pulp was then filtered with muslin cloth after overnight storage at 4°C. Filtrate which was obtained was stored at 20°C in one milliliter aliquots for further use. This fresh *Aloe barbadensis* pulp yield was almost 35% v/w in terms of starting fresh leaf extract.

Induction of diabetes

Mice were made diabetic by one dose of intraperitoneal (IP) alloxan injection. Mice were starved overnight for with one dose of Alloxan Monohydrate (200 mg/kg b.w.) for induction of diabetes, freshly prepared in sterilized water intraperitoneally. Control animals were given only water. Mice were provided with 10% sucrose water. It was necessary to avoid sudden hypoglycemia after injection (Bukhari *et al.*, 2015).

Experimental design

Mice were categorized in three groups. Whole experiment was performed as per ethical parameters after obtaining approval from institutional ethical committee with ref # G.C.ETH.COM\314. All mice were treated as per institutional guidelines by German Convention for Protection of Animals and NIH (Clarke and Cynthia, 2013; Sheikh *et al.*, 2007). The experimental groups illustrated as follow:

Group 1: Control (C): Six mice with no diabetes induction and without treatment served as negative control, these healthy mice were fed on pelleted diet.

Group 2: Diabetic Non Treated (DNT): Nine diabetic animals were kept without any plant extract treatment for fourteen days which served as positive control fed on pelleted diet.

Group 3: Diabetic Treated Groups (DT1), (DT2) and (DT3) (*Aloe barbadensis* given after diabetes induction): All the twenty-seven animals (Diabetic) were gavaged *Aloe barbadensis* through oral route for 2 weeks (14 days). Diabetic treated (DT1) as low dose group: with 200 mg/kg (Luka *et al.*, 2013), diabetic treated (DT2) as medium dose group: with 300mg/kg (Bukhari *et al.*, 2015) and diabetic treated (DT3) as high dose group: with 400mg/kg

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(Barmak *et al*., 2013). *Aloe barbadensis* extract was gavaged to mice with syringe attached with needle (butterfly) orally one time in a day for fourteen days.

Blood collection

Animals were anesthetized by terminal anesthesia using 0.1ml ketamine (Clarke and Cynthia, 2013) with injection water in ratio of 1:2 injected intraperitoneally before blood collection through puncture of heart. Diabetes was confirmed using Glucosure plus glucometer from Apex Bio (Taiwan). Mice with fasting Blood Glucose Levels >150mg/dl were taken as diabetics were inducted for next experimental study. One ml blood was taken directly from the heart, using 5cc disposable syringe and collected in EDTA tubes.

Collection of tissues for histology

Mice sacrificed using terminal anesthesia with ketamine and normal saline water in 1:2 ratio was given 0.1 milliliter intraperitoneally before tissue collection.

Histology of various organs

After dissection liver, kidney and pancreas from every mouse was cut into very small pieces and preserved into 10% solution of formalin. Fixation is required to prevent autolysis and to avoid microbial activity. Dehydration was carried out by passing tissues via ascending ethanol grades following clearing with xylene, infiltration and embedding with wax.

Biochemical assays

Fasting blood glucose and blood glucose level

All the readings of fasting blood glucose and random blood glucose were taken with glucometer (Apex Bio, Taiwan). It contains biosensor technology. Blood from punctured mice tail was placed on the sensor point of the strip to take reading. Blood sugar less than 120 mg/dl was taken as normal as and more than 150 mg/dl were considered diabetic.

Serum separation

The blood was allowed to clot by leaving it without any disturbance for 1-2 hours at 37°C. When clot was formed sample was put into refrigerator overnight at 4°C. The serum was separated from the blood in the form of straw colored supernatant. The supernatant was removed by pipette and transferred to tube. Sample was centrifuged (Mikro 22 Hettich, Germany) at 5000 rpm for 15 minutes. After centrifugation serum was pipetted out and stored in sterile tubes and labeled and frozen for further process.

Liver function test and lipid profile

Serum Bilirubin was determined by using Crescent Diagnostic Kit method. For blood chemistry analysis, several serological parameters were studied; (i) Centrifuge; Mikro-22, Hettich Zentrifugen, Germany; (ii) Spectrophotometer; FP 901 Chemistry analyzer, Finland Crescent Diagnostic Kit; (iii) Dia Sys Diagnostic Systems GmBH. Alte Strabe 9-65558 Holzheim Deutschland. SGOT (AST) was determined by the rate of NADH utilization. SGPT (ALT) was determined by kinetic determination of alanine aminotransferase. Alkaline Phosphatase was determined by AP calorimetric method. Total cholesterol (TC) was determined in serum according to the enzymatic colorimetric method described by Richmond (1973). Triacylglycerols were determined in serum according to the enzymatic colorimetric method described by Fassati and Prencipe (1982). HDL Cholesterol was determined by enzymatic reaction.

Microscopic analyses

All histological findings were performed using computer based image analysis for organ damage assessment. Briefly, microscopic photographs were taken by a IRMECO-GmbH model 1M-910, 21493 Schwarzenbek/ Germany latterly used Scope Tek® (scope photo 3.0) to display on computer.

Statistical analysis

The data was presented as Mean±S.E.M. One Way Analysis of variance (ANOVA) was used for determining difference among groups ($p<0.05$). After calculating statistical significance by ANOVA, inter group comparison was checked by applying Tukey's Multiple Comparison Test as Post Hoc.

Results

Results in Table 1 and Figure 1 showed alloxan effect to rise in serum glucose level significantly (318.00±4.73) in DNT (Group 2) compared with the C (Group 1) ($P< 0.05$). High dose of *Aloe barbadensis* was effective in reducing blood sugar level and fasting blood sugar level to (58.00±6.35) and (66.00±2.5) respectively in group DT3($P< 0.05$).

Diabetes induction by alloxan injection caused a significant increase in bilirubin and liver enzymes level. As shown in Table 2 and Figure 2 serum bilirubin levels were twice as high in DNT (1.23±0.12) than in C (0.53±0.03). Moreover, there was a significant rise in liver enzymes ratio in DNT in comparison to C. After *Aloe barbadensis* gel extract treatment these levels were close to that in the control group. High dose of the *Aloe barbadensis* reduced the level of bilirubin (0.67±0.15), SGPT (35.67±2.03), SGOT (127.67±4.67) and alkaline phosphatase to 86.33±1.86.

Increase in serum glucose level in diabetic group was accompanied by a significant increase in serum cholesterol and triacylglycerols in comparison control ($P< 0.05$). *Aloe barbadensis* gel extract after 14 days caused decrease in these elevated values in DT3. Oral intake of

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Aloe barbadensis extract reduced serum cholesterol levels and triglycerides levels to be near the normal levels. High dose of *Aloe barbadensis* reduced cholesterol (78.00±2.08), triglycerides (83.67±3.38), HDL cholesterol (49.33±2.33) and LDL cholesterol to 61.67±3.84 in group DT3 (Table 3).

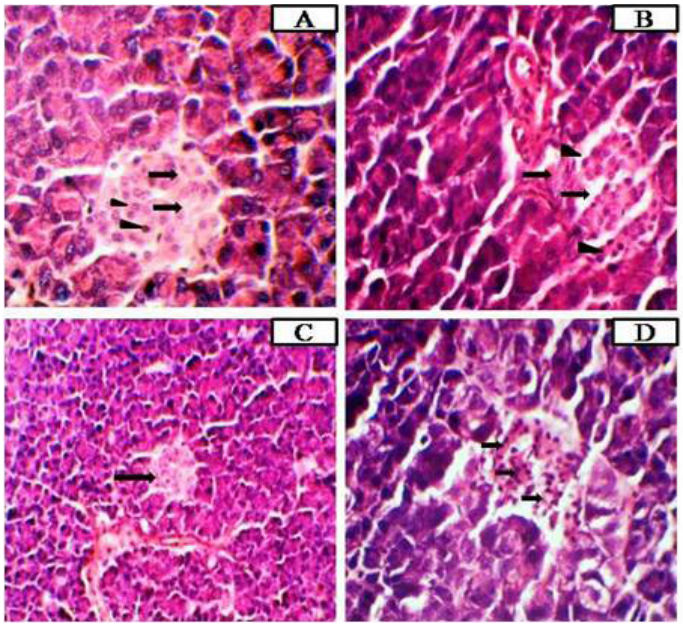

Figure 1: Hematoxylin-eosin (H and E X100 and 400) staining of Pancreas sections of diabetic 1(B), high dose 1(C) and medium dose of *A. barbadensis* 1(D) treated mice after 14 days treatment compared with control 1(A). Arrows indicating cell vacuolations. Entries Key: Mean values ± Standard error of mean. Asterisks show significant differences compared to control mice: *, p<0.05; **, p<0.01; ***, p<0.001.

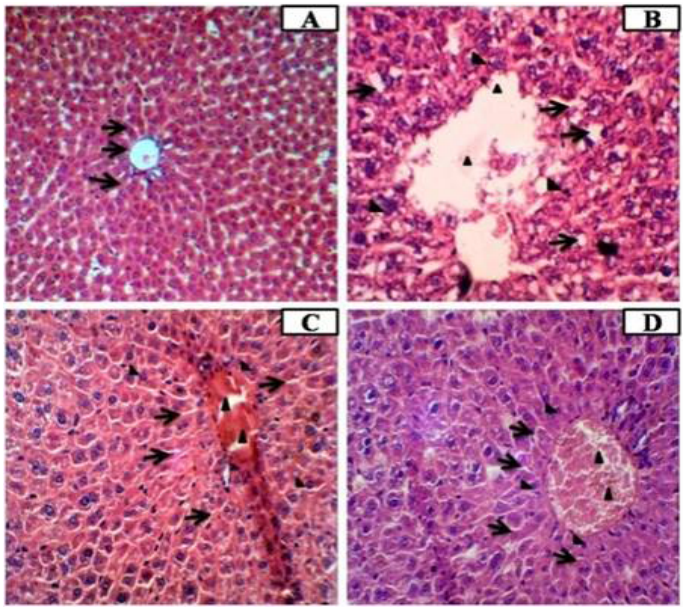

Figure 2: Hematoxylin-eosin staining (H and E X 100 and 400) of liver sections of diabetic 2(B), high dose 1(C) and medium dose of A. barbadensis 1(D) treated mice, 14 days treated compared with control 2(A). Arrows indicating cell vacuolations.

Pancreas

Pancreatic section from C group showed an islet of Langerhans that appeared as slightly stained area in between darkly stained exocrine part. Cells of islets were crowded and separated by blood capillaries. Islet was closely related to pancreatic acini with no detectable space (Figure 1A).

Effect of diabetes induction by alloxan on pancreas of diabetic mice

Pancreatic section from diabetic showed distorted islet of Langerhans with decreased cellular density, increased inters cellular space as well as wide separation between islets of Langerhans. There was found congestion and destruction of cells. Blood capillaries were also ruptured (Figure 1B).

Effect of Aloe barbadensis *s on pancreas of diabetic mice*

Pancreatic section from treated group with medium dose of *Aloe barbadensis* (DT1) showed islet of Langerhans with decreased cellular density, increased inter cellular space as well as wide separation between Islets of langerhans and the pancreatic acini with the presence of many apoptotic cells whereas, pancreatic section from treated group with high dose of *Aloe barbadensis* (DT3) showed islet with surrounding acini. An islet of Langerhans formed of crowded cells with no wide spaces between them. Most of the cells were seen to be normal (Figure 1C).

Liver

Liver section from control group was without pathological abnormality. Sections showed normal cellular construction. Normal arrangement of the hepatocytes was apparent without lesions. It was composed of lobules and hepatocytes which were arranged in the form of hepatic cords which extended radiantly from the central veins (Figure 2A).

Effect of diabetes induction by alloxan on liver of diabetic mice

Liver sections showed vacuolations with the damage of hepatocytes disturbed with enlarged sinusoidal spaces and marked extravasations of leukocyte. Focal necrosis of hepatocytes with congestion and inflammation of cells were observed (Figure 2B).

Effect of Aloe barbadensis *on liver of diabetic mice*

Liver section from treated group with medium dose of *Aloe barbadensis* (DT2) showed enlarged sinusoidal spaces and vacuolations. Focal necrosis of hepatocytes, a lot of congestion, and inflammation of cells were observed (Figure 2C). Liver section from treated group with high dose of *Aloe barbadensis* (DT3) showed normal arrangement of the hepatocytes. It was composed of lobules and hepatocytes which were arranged in the form of hepatic cords which extended radiantly from the central veins (Figure 2D).

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Table 1: Blood sugar and fasting blood glucose levels in different experimental groups.

Parameter	Mice group				
	C	DNT	DT1	DT2	DT3
Blood sugar level (mg/dl)	64.33±2.40	318.00±4.73*	126.33±3.53**	101.00±1.15**	58.00±6.35***
Fasting blood glucose level (mg/dl)	64.33±2.40	312.33±5.93*	54.33±3.8**	60.33±0.88**	66.00±2.5***

Entries Key: parameter size ± Standard error of mean. Asterisks show significant differences compared to control mice. *, p<0.05; **, p<0.01; ***, p<0.001.

Table 2: Levels of Liver enzymes and Bilirubin in different experimental groups after 14 days treatment with *Aloe barbadensis*.

Parameter	Mice group				
	C	DNT	DT1	DT2	DT3
Bilirubin (mg/dl)	0.53±0.03	1.23±0.12*	0.93±0.03**	0.90±0.00**	0.67±0.15***
SGPT(ALT) (U/L)	27.00±1.15	363.67±7.36*	104.33±1.45**	62.67±1.45**	35.67±2.03***
SGOT(AST)U/L	126.33±4.33	336.33±5.93*	192.33±7.17**	118.67±1.45**	127.67±4.67***
Alkaline phosphatase(U/L)	91.67±1.20	238.33±7.26*	99.00±4.58**	84.33±2.19**	86.33±1.86***

Entries Key: parameter size ± Standard error of mean. Asterisks show significant differences compared to control mice. *, p<0.05; **, p<0.01; ***, p<0.001.

Table 3: Levels of Lipid profile in different experimental groups after 14 days treatment with *Aloe barbadensis*.

Parameter	Mice group				
	C	DNT	DT1	DT2	DT3
Cholesterol (mg/dl)	71.33±5.49	201.67±1.76*	93.33±2.40**	63.67±1.45**	78.00±2.08***
Triglycerides(mg/dl)	82.67±4.98	253.33±6.49*	115.33±4.84**	58.67±3.38**	83.67±3.28***
HDL Cholesterol (mg/dl)	52.33±1.45	25.33±2.60*	45.67±2.40**	46.00±2.08**	49.33±2.33***
LDL Cholesterol (mg/dl)	61.00±4.62	194.00±3.79*	70.00±4.73**	71.00±5.20**	61.67±3.84***

Entries Key: parameter size ± Standard error of mean. Asterisks show significant differences compared to control mice. *, p<0.05; **, p<0.01; ***, p<0.001.

Discussion

Oral intake of *Aloe barbadensis* pulp extract reversed glucose level whereas, no significant decline in glucose level in serum of normal mice. These results suggest hypoglycemic activity of *Aloe barbadensis* gel was evident in diabetic mice but not in normal mice. These findings were in accordance with the study of Gwarzo *et al*. (2010) about I.P (intraperitoneal) injection of alloxan induced diabetes mellitus. Hypoglycemic role of *Aloe barbadensis* extract was established by our experiment has also been demonstrated by other workers Akinmoladun and Akinloye (2004), they also found a significant decrease in the fasting blood glucose in alloxan induced albino rat after oral administration of *Aloe barbadensis* for thirty days.

The results of Rajasekaran *et al*. (2004) and Noor *et al*. (2008) depicted that *Aloe barbadensis* extract was useful for decreasing blood glucose of diabetic rats of streptozotocin induced. The previous study of Abuelgasim *et al*. (2008) confirmed that antidiabetic action of *Aloe barbadensis* gel extract was produced in hyperglycemic rats only but no effects in normoglycemic rats which are comparable to current study. Whereas, results of Akinmoladun and Akinloye (2004) reported that *Aloe barbadensis* extract prevent hyperglycemia in alloxan treated rabbits. Mohamed *et al*. (2009) reported the *Aloe barbadensis* gel caused significant development in diabetic rats in comparison to control (non diabetic). This can also explain the antioxidative effect of *Aloe barbadensis* in diabetic rats is because of blood glucose reduction, which can avoid surplus free radicals formation via different biochemical pathways.

The results of Rajasekaran *et al*. (2006) supported the findings of current study about oral intake of *Aloe barbadensis* for twenty-one days thus resulting in significantly decrease in blood cholesterol and triacylglycerols. Kim *et al*. (2009) also confirmed about the use of *Aloe barbadensis* for eight weeks produced a significant decline in serum triacylglycerols. The present results indicated that induction of diabetes by alloxan produced a significant decrease in total antioxidant capacity. Previously studies by Jackson *et al*. (2007) also found the levels of antioxidant capability diminished in diabetic rats (alloxan induced) rats compared to normal control. They explained the declined action of antioxidant capability in diabetes can be due to the secretion of ROS like super oxides (O_2), hydrogen peroxides (H_2O_2) and hydroxyl radical (OH). The results of the current study were similar with that

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reported by Rajasekaran *et al.* (2005) who showed that induction of diabetes mellitus by alloxan in animals was associated with oxidative stress and oral administration of *Aloe barbadensis* extract have antioxidative effect. Our results were in accordance with those reported by Nwnajo (2006) who confirmed that oral intake of *Aloe barbadensis* extract reduce lipid peroxidation in tissues of diabetic rats. Hypoglycemic role of *Aloe barbadensis* may be because of presence of trace elements i.e. Cr, Zn and Mn which may be involved in insulin action being hypoglycemic. Also, the glucose lowering effect could be explained by the antioxidant activity of *Aloe barbadensis* because it attenuated oxidative damage in the serum of alloxan induced diabetic mice.

Histology of diabetic pancreas of mice showed the distorted islets of Langerhans associated significantly with the decrease of the insulin production. Many experimental studies (Kanther *et al.*, 2004; Slavin *et al.*, 2010; Akapaso *et al.*, 2011; Haligur *et al.*, 2012; Shaker and Sourour, 2013; Gomathi *et al.*, 2013; Alimohammadi *et al.*, 2013) have reported the pancreatic damage in diabetes. Moreover, *Aloe barbadensis* (400mg/kg) treatment prevented the islet destruction and preserved the islet architecture where most of the islet cells returned to their normal structure. A study conducted by Shaker and Sourour (2013) depicted that the use of 300 mg/kg of pomegranate seeds for 4 weeks prevented islet destruction. Current study suggested that and *Aloe barbadensis* treatment has protective effect against pancreatic islets structural damage and have potentially efficient to increase the insulin section from surviving β-cells in the experimental model of the diabetic mice which might be the repair of the endocrine pancreas. Liver histology also demonstrated the distortion of hepatocytes in diabetes induced mice. However, treatment with *Aloe barbadensis* prevented the destruction and preserved the basic structure. Motshakeri *et al.* (2014) also reported that 300 mg/kg of *Sagassum polycystum* showed significantly reduced degenerative effect.

Conclusions and Recommendations

In conclusion *Aloe barbadensis* proved as effective antihyperglycemic and antihyperlipidemic agents with recommended dose of 400 mg/kg. Moreover, histological examination of pancreas, liver and kidney depicted the prevention of structural damage to maintain their function. Cholesterol and triglycerides levels were also maintained at normal in diabetic mice.

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Conflict of interest

The authors have declared no conflict of interest.

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