Antihyperglycemic and Antihyperlipidemic Potential of Aloe Vera Against Streptozotocin-Induced Diabetic Rats

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ABSTRACT

Aloe vera has commonly used for treatment and prevention varieties of diseases through over the world. Diabetes mellitus (DM) is an inability to regulate blood glucose levels. Alternative and complementary medicines have been used widely in these years for chronic diseases either for curing or limit its progression. This study aims to clarify the curative role of Aloe vera (*Liliaceae*) leaves gel (ALG) on experimentally induced diabetes in rats. Four groups of male albino rats (120 ±10 g) (8 each): control, DM rats, ALG supplemented group and DM rats treated with ALG. Diabetes was induced by a single streptozotocin (STZ) intraperitoneally (i.p.) injection (65 mg/kg b.wt) and the treatment with ALG was done by a daily oral dose (500 mg/ kg b. wt.), for 4 weeks starting from ALG supplementation. Diabetic rats showed significantly hyperlipidemic, elevated lipid peroxide and glucose levels, and significantly decrease liver glycogen content compared with control group. Ingestion ALG to DM rats had a potent hypoglycemic and antioxidant effects, and significantly improve lipids profile parameters compared with DM group. It is concluded that ALG could be valuable in diabetes treatment and the antioxidant action observed in the current study may be one of the underlying mechanism for Aloe's hypoglycemic actions. Therefore, the present study recommended the use of ALG as a supplement in some beverage for diabetic and hypercholesterolemic patients.

Key Words: Aloe vera, diabetes, rats, antihyperglycemic, antioxidant.

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INTRODUCTION

Diabetes is a chronic disease and has become a public health concern, it is one of the most prevalent diseases worldwide with an increasing incidence [1]. It causes substantial morbidity, mortality and long-term complications [2]. Plants are considered as pharmacological a
ctivities and have been used in natural products with therapeutic properties around the world [3]. Natural products derived from medicinal plants have an important role as pharmaceuticals used in conventional medicine [4].

Aloe vera plant widely utilized as medical interest for many years due to their therapeutic value, it has anti-inflammatory, antioxidant, anti-diabetic, anti-infective, antimicrobial and immune-boosting properties [5]. Aloe genus consists of more than 500 species throughout the world, it is known as Aloe vera, "true aloe" or a desert plant [6]. Aloe vera gel consisting of a great variety of components, it contains many minerals, vitamins, enzymes, proteins, polysaccharides and biological stimulators [7]. It

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showed superior antioxidative action and suppresses free radical-induced oxidative damage [8]. A randomized controlled trial was found that there is a significant effect of A.vera on glucose and lipids in diabetic subjects, it regulates glucose level and reverts the levels of lipid profile [9]. The objective of this study is to assay the influence of ALG treatment on biological, metabolic and antioxidant disorders on experimentally induced DM rats.

MATERIALS AND METHODS

Plant samples preparation

Aloe vera leaves (Family Liliaceae) were obtained from Horticultural Research Institute, Agricultural Research Center, Egypt. Fresh leaves were washed to remove substantially all surface dirt. Each leaf was cut at both ends, by scratching with a stainless steel spoon and gel was separated, then homogenized by a Moulinex blender. The extracted was filtered, then lyophilized and stored at 4° C [10].

Chemicals and kits

Streptozotocin (STZ) and all chemicals and kits used with highest laboratory purity purchased from Sigma-Aldrich Co. (St. Louis, MO, USA).

Induction of diabetes

Male rats (n=32) were kept under identical laboratory conditions, ordinary diet [11] and water ad-libitum were provided. After a week as adaptation period, they were divided to four groups as follows: Control; rats received a single intraperitoneally (i.p.) injection with 0.2 ml of 0.05 M citrate buffer pH=4.5; diabetic (DM); rats injected i.p. with 65 mg/kg b.wt. STZ dissolved in 0.2 ml of 0.05 M citrate buffer pH=4.5, they received orally 5% sucrose solution for 48 h [12,13]; ALG, rats received the same injection as in control group, after 72 h rats supplemented daily with an oral dose of ALG (500 mg/kg b.wt) [14]; and DM rats treated with ALG. Blood samples were obtained after 72 h from an orbital plexus vein of each rat to confirm diabetes induction. After 4 weeks animals were fasted overnight, with free access to drinking water, rats were sacrificed under ether anesthesia. Blood samples were collected and serum was obtained, then stored at -20 ºC.

Biochemical analysis

Serum samples were used for the determination of malondialdehyde (MDA) [15], glucose [16], total cholesterol (TC) [17], high-density lipoprotein cholesterol (HDL-C) [18], triacylglycerols (TG) [19], and low-density lipoprotein cholesterol (LDL-C) [20]. Determination of liver glycogen was performed [21].

Statistical analysis

Results are presented as mean ± SE., data analysis was done by one-way ANOVA, LSD to detect differences between groups. SPSS version 22 was used for these calculations.

RESULTS

Biological effect of ALG

Table (1) showed the effect of ALG supplementation on BWG, FI and FER in DM rats. There were significant ($p<0.001$) decrease in BWG (- 83.28 % as percent change from control group), while no significant difference between ALG and the control group was found. Treatment of DM with ALG induced an apparent increase in BWG, there was significant difference ($p < 0.01$) between DM treated with ALG and DM rats. Regarding the FI and FER, DM rats showed an increase in FI with percentage 10.42 % as percent change from the control group, meanwhile, the FER showed a significant decrease ($p<0.01$) compared with control group. Treatment of DM rats with ALG showed noticeable improvement in FER as compared with DM group, there was a significant difference between DM and DM+ALG groups.

Table (1): Effect of ALG supplementation on body weight gain (BWG), food intake (FI) and food efficiency ratio (FFR) in experimental rats

Experimental groups	Control	DM	ALG	DM + ALG
BWG (g)	53.56± 2.7	8.42±0.98 [a ***]	48.75 ± 4.1	35.61 ±2.82 [b ***]
FI (g/day/group)	75.5 ± 4.8	83.37± 4.77	81.01± 2.45	72.03 ± 3.59
FFR	0.14± 0.01	0.02±0.01 [a **]	0.13 ± 0.01	0.11 ± 0.02 [b*]

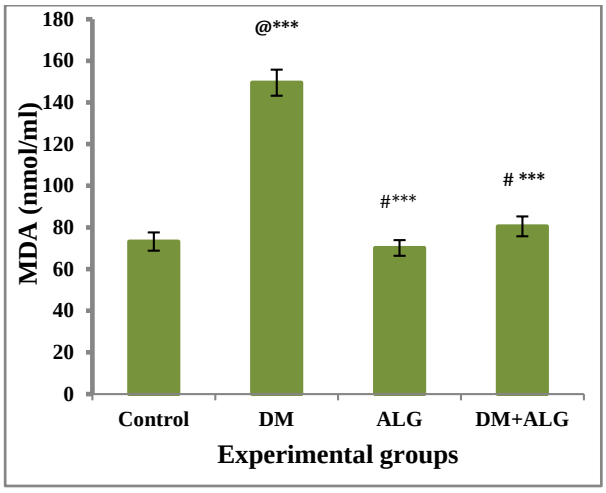
Each value represents mean of 8 rats ± SE.
[a] Significant difference from control group.
[b] Significant difference between DM and DM+ALG. * p< 0.05, * p<0.01 & *** p< 0.01.

Antioxidant effect of ALG

Serum MDA concentration of different groups is presented in Figure (1). DM rats revealed significant increased ($p<0.001$) in MDA. The results of rats receiving ALG showed slightly decrease in MDA compared with control group. Treatment of DM rats with ALG significantly decrease ($p<0.001$) MDA concentration compared to DM group, at the same time there was no significant difference as compared with control and ALG groups.

Effect of ALG on glucose and liver glycogen

The glucose level in DM rats showed significantly ($p<0.001$) increased accompanied by significant ($p<0.001$) decreased in liver glycogen level comparing with control, with percent change 116.79 and -25.74 %, respectively from control values. Treatment of DM rats with ALG markedly overcame the rise in glucose and drop in liver glycogen levels, there was a significant difference ($p<0.001$) between DM and DM+ALG groups, at the same time their values were significant ($p< 0.05$) compared with the control values Figures (2&3).



Figure(1): Effect of ALG supplementation on lipid peroxidation (MDA) in rats

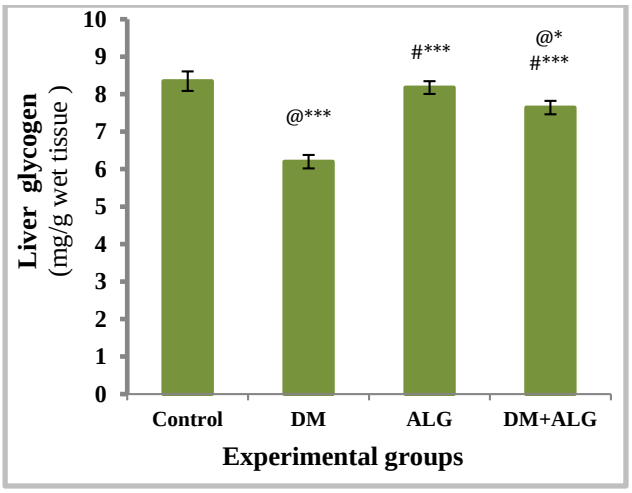


Figure (3): Effect of ALG on liver glycogen content in experimental rats

Each value represents mean of 8 rats ± SE. @ Significant difference from control group. # Significant difference between DM and DM+ALG. (* p< 0.05, ** p<0.01 & ** p< 0.001).

Each value represents mean of 8 rats ± SE. @ Significant difference from control group. # Significant difference between DM and DM+ALG. (* p< 0.05, ** p<0.01 & ** p< 0.001).

Hypolipidemic effect of ALG

Results of lipids profile parameters in different groups tabulated in Table (2). DM rats showed significant increased (p<0.001) in TC, TG & LDL-C with significant decreased (p<0.001) in HDL-C as compared with control group, the percent change recorded for TC, TG, HDL-C & LDL-C were 86.37, 79.52, - 41.99 & 79.58 %, respectively when compared with control values. There were no significant changes in lipid parameters in rats administrated ALG. DM+ALG revealed a significant enhancement in lipid profile compared with DM group, while, the changes were non-significant when compared with control values.

Table (2): Effect of ALG on lipid profile parameters in experimental rats

Experimental groups	Control	DM	ALG	DM + ALG
TC (mg/dl)	90.38±2.42	168.44 ±4.83 ^{a***}	88.80±1.57 ^{b***}	97.76 ±6.14 ^{b***}
TG (mg/dl)	79.12 ±2.22	142.04 ± 6.28 ^{a***}	81.59 ± 2.69 ^{b***}	89.43 ± 4.13 ^{b***}
HDL-C (mg/dl)	47.24 ± 1.68	27.40 ±1.41 ^{a***}	48.54 ± 2.23 ^{b***}	44.49 ± 2.92 ^{b***}
LDL-C (mg/dl)	15.82± 0.87	28.41 ± 2.89 ^{a***}	16.32 ± 0.60 ^{b***}	17.89 ± 0.93 ^{b***}

Each value represents mean of 8 rats ± SE.
[a] Significant difference from control group.
[b] Significant difference between DM and DM+ALG. * p< 0.05, * p<0.01 & *** p< 0.01.

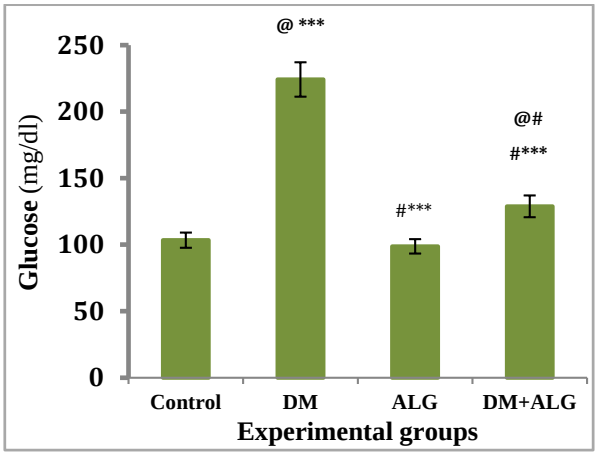


Figure (2): Effect of ALG on glucose concentration in rats

Each value represents mean of 8 rats ± SE. @ Significant difference from control group. # Significant difference between DM and DM+ALG. (* p< 0.05, ** p<0.01 & ** p< 0.001).

DISCUSSION

Diabetes, an endocrine disorder, has serious affecting damage on vital organs as liver, heart, and kidney. Oxidative stress has a major role in the development of DM complications [22]. Recently diabetes treatment focus not only on insulin secretion but also on antioxidant protection of the β-cell, thus may facilitate β-cells repair, which undergoing damage by hyperglycemia induced-oxidative stress [23]. Aloe vera is belongs to Liliaceae family. It contains many phytochemicals, polysaccharides (mucilage), vitamins, nutrients and antioxidants [24]. However, the present study investigated the possible protection action of ALG supplementation against some biological, lipid

peroxides and biochemical parameters changes induced in diabetic rats.

Diabetes rats revealed significant decreased in the BWG and increased in FI, meanwhile FER was significant decreased compared with non-diabetic control rats. The reduction in BWG in DM may be associated with reduce in energy intake, which may be attributed to inability to use carbohydrates including lipolysis, glycogenolysis and acidosis [25]. Moreover, insulin stimulates muscle and adipose tissue to uptake glucose that significantly induce a weight loss. The increase in FI may be explained by Chen and Dawing [26] they attributed these effect in diabetic rats to polyphagia and polydipsia.

Ingestion ALG to rats revealed no significant effect on biological evaluation compared with control rats, this confirmed its safe use. Our results explained by Herlihy et al. [27] who reported that long-term ingestion of Aloe vera had no any effect of rat growth and organs/ body weight ratio, and elicited the same growth that seen in control.

In the obtained results treatment of DM rats with ALG showed enhancement in BWG and FER, there was a significant difference between DM and DM+ALG groups. Robert et al. [28] found that diabetic mice underwent body weight decrease compared with the increase in normal mice, while in A. vera treated diabetic rats the decrease was slightly insignificant as compared with control, the significant weight loss demonstrated by diabetic animals, most probably indicative of decreased insulin-dependent anabolic pathways. Takaku et al. [29] found that Aloe vera constituents may contain some growth factors and/or a component with insulin-like effect, which inhibit epinephrine-induced lipolysis and decreased body weight. Sivagnanam et al. [30] attributed the beneficial effect of Aloe vera to cytoprotective and regulating properties of the Aloe leaves gel.

In present results, DM group revealed a significant increase in MDA level compared with control. Meanwhile, ingestion of ALG to DM rats reduce this oxidative stress and tended to normalize the level of MDA, there was a significant difference as compared with non-treated DM group. One of the major route pathophysiological condition during DM is oxidative stress. Continual hyperglycemia increase free radicals generation in tissues from glucose auto-oxidation and protein glycosylation, thus implicated in diabetic complications. Increased free fatty acids levels positively correlated to insulin resistance and cell function deterioration thus concomitant hyperglycemia and increase ROS [31, 32, 33].

Antioxidants protect cells and tissues against oxygen free radicals damage. Studies have focused on the antioxidant effect of Aloe vera [34,35], this effect of ALG explained by the constituents of Aloe vera, which have biological activities, these substances have a potent antioxidative activity and inhibit production of oxygen radicals [36, 37]. Aloe vera fresh leaf extract caused a decrease in malondialdehyde formation, thus protecting against pro-oxidants which cause cellular and membrane damage [38].

The current study elicited marked a significant increase in serum glucose level with a significant decrease in liver glycogen content in DM rats compared with control group. Treatment of DM rats with ALG ameliorated these effect, their values revealed significant difference comparing with DM non-treated rats. This result was in accordance with Abd El Razek [39], this may be attributed to insulin deficiency, hyper-gluconeogenesis and/or hyper-glycogenolysis [40]. The obtained results of ALG ingestion was in accordance with Herlihy et al. [41] who found that feeding Aloe did not alter the plasma glucose and insulin levels in healthy rats, even after long-term of ingestion. Furthermore Okyar et al.[42] found that A. vera exhibited hypoglycemic activity on diabetic rats type I and II, this hypoglycemia may be attributed to increasing in calcium level, which in turn stimulates β-cells and increase insulin secretion, enhanced rate of glycogenesis and increase liver glycogen level. Moreover, this effect of ALG may be attributed to increasing in the glucose tolerance or to the active ingredients in ALG which can stimulate and help in the recovery of β-cells [43-44].

In the current study, DM rats showed significant hyperlipidemic compared with control rats, while in DM+ALG group significant improvement in lipid parameters was found compared with DM. From a common complication of DM is hypercholesterolemia due to impaired activity of lipoprotein lipase. Badawy and Hegazi [45] found that significantly higher values of total lipids of diabetic compared with non-diabetic control, which fed the same diets, this effect may be due to the rapid release of fatty acids into the blood circulation, which often results in a hyperlipidemia. The therapeutic effect of ALG in DM rats was in accordance with Rajasekaran et al. [46] who found a marked reduction in plasma lipids after oral administration of aloe vera gel. The effect of ALG may be attributed to the glycoprotein, the main constituent of ALG, which has a radical scavenging activity and inhibits thromboxane formation [37].

CONCLUSION

the present results indicated that ingestion of ALG has a potent hypoglycemic and hypolipidemic effects in diabetics, this could be explained possibly by its antioxidant activity of its active constituents.

REFERENCES

[1] Wu,X., Ma,C., Han,L., Nawaz,M., Gao,F., Zhang,X., Yu,P., Zhao,C., Li,L., Zhou, A., Wang, J., Moore,J.E., Millar, B.C. and Xu,J., 2010. Molecular characterization of the faecal microbiota in patients with type II diabetes. Curr Microbiol, 61(1),pp.69-78.

[2] Thurston,G.D., Burnett,R.T., Turner,M.C., Shi,Y., Krewski,D., Lall,R., Ito,K., Jerrett,M., Gapstur,S.M., Diver,W.R. and Pope,C.A., 2016. Ischemic heart disease mortality and long-term exposure to source-

related components of US fine particle air pollution. Environmental Health Perspectives, 124(6), pp.785-94.

[3] Dutra,R.C., Campos,M.M., Santos,A.R. and Calixto,J.B.,2016. Medicinal plants in Brazil: pharmacological studies, drug discovery, challenges and perspectives. Pharmacol Res,112, pp. 4-29.

[4] Fox,L.T. Mazumder,A., Dwivedi,A., Gerber,M., du Plessis,J. and Hamman,J.H., 2017. In vitro wound healing and cytotoxic activity of the gel and whole-leaf materials from selected aloe species. J Ethnopharmacol, 22(200),pp.1-7.

[5] Pradeep,A.R., Garg,V., Raju,A., Singh,P., 2016. Adjunctive local delivery of Aloe vera gel in patients with type 2 diabetes and chronic periodontitis: A randomized, controlled clinical trial. J Periodontol, 87(3), pp.268-74.

[6] Radha,M.H. and Nampoothiri, P.L., 2015. Evaluation of biological properties and clinical effectiveness of Aloe vera: A systematic review. J of traditional and complementary Med, 5(1), pp. 21-6.

[7] Pandey,A. and Shweta,S., 2016. Aloe vera: a systematic review of its industrial and ethno-medicinal efficacy. Int J of Pharmaceutical Res and Allied Sci, 5(1), pp. 21-33

[8] Mojahed,L.S., Saeb,M., Mohammad,M.M. and Nazifi,S.,2016. Long period starvation in rat: the effect of Aloe vera gel extract on oxidative stress status. Int Archives of Med, 9(252), pp.1-9.

[9] Alinejad-Mofrad,S., Foadoddini,M., Saadatjoo,S.A. and Majid Shayesteh,M., 2016. Improvement of glucose and lipid profile status with Aloe Vera in pre-diabetic subjects: a randomized controlled-trial. J of Diabetes and Metabolic Disord, 14(22), pp.1-7.

[10] Hamman,J.H., 2008. Composition and applications of Aloe vera leaf gel. Molecules, 13 (8),pp.1599-616.

[11] Reeves,P.G., Nielsen,F.H. and Fahey,G.C.,1993. AIN-93 Purified diets for laboratory rodents: final report of the American Institute of Nutrition Ad Hoc writing committee on the reformulation of the AIN-76.A rodent diet. J Nutr,123 (1), pp.1939-51.

[12] Lutz,W. and Pardridge,M., 1993. Insulin therapy normalizes glucose transporter mRNA but not immunereactive transporter protein in streptozotocin diabetic rat. Metabolism, 42 (8): 939-44.

[13] Peschke,E., Ebelt,H., Bromme,H.J. and Peschke,D., 2000. Classical and new diabetogens: Comparison of their effects on isolated rat pancreatic islets in vitro. Cell Mol Life Sci, 57(1),pp. 158-64.

[14] Rajasekaran,S.,Sivagnanam,K.,Narayanan,V. and Subramanian,S., 2001. Hypoglycemic and hypolipidemic effects of Aloe vera on experimental rabbits. Biomedicine, 21(4), pp.40-5.

[15] Yoshioka,T.,Kawada,K.,ShimadA,T. and Mori,M.,1979. Lipid peroxidation in maternal and cord blood and protective mechanism against activated oxygen toxicity in the blood. Am J Obstet Gynecol, 135, pp. 372-6.

[16] Trinder,P., 1969. Determination of blood glucose using 4-amino phenazone as oxygen acceptor. J Clin Pathol, 22(2), pp. 246.

[17] Richmond,W.,1973. Preparation and properties of a cholesterol oxidase from Nocardia sp. and its application to the enzymatic assay of total cholesterol in serum. Clin Chem, 19(12), pp.1350-6.

[18] Lopes-Virella,M.F.,Stone,S., Ellis,S. and Collwell,J.A., 1977. Cholesterol determination in high-density lipoproteins separated by three different methods. Clin Chem, 23(5), pp. 882-6.

[19] Fassati,P. and Prencipe,L., 1982. Serum triglycerides determined colorimetrically with an enzyme that produces hydrogen peroxide. Clin Chem, 28(10), pp. 2077-80.

[20] Friedwald,W.T., Levy,R.I. and Fredriclsor,D.S., 1972. Estimation of the concentration of low density lipoprotein cholesterol in plasma without use of the preparative ultracentrifuge. Clin Chem, 18(6), pp.499-502.

[21] Hassid,W.T. and Abraham,S., 1957. Determination of glycogen and starch. " In method in enzymology" p: 43. Academic press, New York.

[22] Giacco,F. and Brownlee,M.Z., 2010. Oxidative stress and diabetic complications. Circulation Res, 29(107), pp.1058-70.

[23] Robertson,R.P., 2010. Antioxidant drugs for treating beta-cell oxidative stress in type 2 diabetes: glucose-centric versus insulin-centric therapy. Discov Med, 9(45), pp.132-7.

[24] Maenthalsong,R., Chalyakunapruk,N. and Niruntrapon.S.,2007. The efficiency of Aloe vera for burns and wound healing, a systematic review. Burns, 33, pp.713-8.

[25] Lamont,B.J., Waters,M.F. and Sofianos,A.,2016. A low-carbohydrate high-fat diet increases weight gain and does not improve glucose tolerance, insulin secretion or β-cell mass in NZO mice. Nutr diabetes 6,pp. e194.

[26] Chen,V. and Dawing,E.S., 1991. Amelioration of hyperlipidemia by low fat diets in diabetic rats. Life Sci, 49, pp. 857-64.

[27] Herlihy,J.T., Bertrand,H.A., Kim,J.D., Ikeno,Y. and Yu,B.P., 1998. Effects of Aloe vera ingestion in the rat I: Growth, food and fluid intake and serum chemistry. Phytotherapy Res, 12 (3):pp.183-8.

[28] Robert, H.D., Mark,G.L. and Joseph,M.R., 1998. Aloe vera: A natural approach for treating wounds, edema and pain in diabetes. J of Am Podiatric Med Association, 78(2), pp. 60-8.

[29] Takaku,T., Kameda,K., Matsuura,Y., Sekiya,K. and Okuda,N., 1990. Studies on insulin-like substances in Korean red ginseng. Planta Medica, 56 (1),pp.27-30.

[30] Sivagnanam,K., Rajasekaran,S., Narayanan,V. and Subramanian,S., 2003. Biochemical evaluation of the ulcer curative effect of Aloe vera on experimental rats. J of Natural Remedies, 3(2), pp. 161-5.

[31] Asbun,J.1. and Villarreal,F.J., 2006. The pathogenesis of myocardial fibrosis in the setting of diabetic cardiomyopathy. J Am Coll Cardiol, 47(4), pp. 693-700.

[32] Poitout,V. and Robertson, R.P., 2002. Minireview: Secondary beta-cell failure in type 2 diabetes--a convergence of glucotoxicity and lipotoxicity. Endocrinology, 143(2), pp.339-42.

[33] McGarry,J.D., 2002. Banting lecture 2001: Dysregulation of fatty acid metabolism in the etiology of type 2 diabetes. Diabetes, 51(1), pp.7-18.

[34] Haritha,K., Ramesh,B. and Saralakumari,D., 2014. Effect of Aloe vera gel on antioxidant enzymes in streptozotocin-induced cataractogenesis in male and female Wistar rats. J Acute Med, 4(1), pp. 38-44.

[35] Nahar,T., Uddin,B., Hossain,S., Sikder,A.M. and Ahmed,S., 2013. Aloe vera gel protects liver from oxidative stress-induced damage in experimental rat model. J Comp Integrative Med, 10(1), pp.47-53.

[36] Lee,K.Y., Weintrub,S. and Yu,B.P., 2000. Isolation and identification of a phenolic antioxidant from Aloe Barbafensis. Free Rad Biol Med, 28, pp. 261-5.

[37] Yagi,A., Kabash,A., Mizuno,K., Moustafa,S.M., Khalifa,T.I. and Tsuji,H., 2003. Radical scavenging glycoprotein inhibiting cyclooxygenase-2 and thromoboxane A2 syntheses from Aloe vera gel. Planta Med, 69(3), pp.269-71.

[38] Singh,R.P., Dhanalakshmi,S. and Rao,A.R., 2003. Chemomodulatory action of Aloe vera on the profiles of enzymes associated with carcinogen metabolism and antioxidant status regulation in mice. Phytomedicine, 7(3), pp. 209-19.

[39] Abd El Razek,F.H., 2004. Biochemical and biological changes in diabetic female rats after affected by feeding lupine (Termis) and locust bean pod (carob pod). Bull Nat Nutr Inst Cairo Egypt, 24, pp.93-120.

[40] Defronzo,R.A. and Simonson,D.C.,1992. Glucose toxicity. In: Advances in endocrinology and metabolism, vol 3rd Lours, M.O. Mosby, pp. 1-53.

[41] Herlihy,J.T., Kim,J.D., Kalu,D.N., Nelson,J.F., Ward,W.F., Ikeno,Y. and Yu,B.P., 1998. Effects of Aloe vera ingestion in the rat II: Hormonal and metabolic characteristics. Phytotherapy Res, 12: 355-60.

[42] Okyar,A., Can,A., Akey,N., Baktir,G. and Sutlupinar,N., 2001. Effect of Aloe vera leaves on blood glucose level in type I and type II diabetic rat models. Phytotherapy Res,15, pp. 157-61.

[43] Blumenthal,M., Busse,W.R. and Goldberg,A., 1998. Therapeutic guide to herbal medicines. Boston, M.A.: Integrative medicines Communications, pp. 80-1.

[44] Zhang,L. and Tizard,I.R., 1996. Activation of a mouse macrophage cell line by acemannan: the major carbohydrate fraction from Aloe vera gel. Immunopharmacology, 35(2), pp. 119-28.

[45] Badawy,I.H. and Hegazi,S.M., 2004. Effect of natural and synthetic sweeteners on serum lipids and glucose of alloxan diabetic rats. Egyptian J of Nutr, XIX (1), pp.131-50.

[46] Rajasekaran, S., Ravi, K., Sivagnanam, K. and Subramanian, S., 2006. Beneficial effects of aloe vera leaf gel extract on lipid profile status in rats with streptozotocin diabetes. Clin Exp Pharmacol Physiol, 33(3), pp.232-7.