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EVALUATION OF ANTIDIABETIC ACTIVITY OF AN IMPORTANT MEDICINAL PLANT *ALOE CIM-SHEETAL* LEAF EXTRACT ON STREPTOZOTOCIN INDUCED DIABETIC RATS

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Abstract: Diabetes mellitus belongs to the group of metabolic diseases characterized by hyperglycemia and defective protein metabolism. This study was undertaken to study the antidiabetic effect of the methanol extract of *Aloe CIM- Sheetal* (CAL 14) on streptozotocin induced diabetic rats. Diabetes was induced experimentally in fasted SD rats (170-180gm) by intra-peritoneal injection of STZ at a dose of 55 mg/kg b.w. and leaf extract of Aloe: control rats received (0.4 ml of 0.1 M of cold citrate buffer). Diabetic rats treated with Glibenclamide (0.60mg /kg) decreased blood glucose level from 298.66 ± 2.16 mg/dl to 192.00 ± 4.14 mg/dl (58.94%). Diabetic rats treated with Aloe 300 mg/kg showed decreased blood glucose levels from 299.16 ± 1.94mg / kg to 190.00 ± 7.61 mg/kg (52.86 %) at the end of 21st day indicating that blood glucose levels was significantly ($P \leq 0.05$) decreased compared to diabetic control groups. The sub-acute toxicity study of methanol leaf extract of Aloe does not produce any significant toxicity symptoms in body weights and histological changes were observed in pancreas, liver and kidney. These data suggest that *Aloe CIM- Sheetal* leaf extract have ameliorative hypoglycemic effect and could be a useful source of an antidiabetic agent.

Key words: *Aloe CIM-Sheetal,* fasting blood glucose, Diabetes mellitus, Streptozotocin, herbal medicine.

INTRODUCTION

The Egyptians called Aloe "The plant of immortality" and the gel has been evaluated for a number of biological activities and used worldwide in drug and cosmetic industry, commonly called *Aloe vera* (Syn. of *Aloe barbadenciss* Mill belongs to Family Liliaceae). Aloe species are propagated worldwide and recognized by their leaf structure, inflorescences and rosettes of succulent leaves [1]. Medicinal plants have been used virtually in all cultures since past times as supply of drugs. It has been calculable that concerning about 80-85% of population both in developed and developing countries rely on traditional medicine for their primary health care needs and it is assumed that a major part of traditional therapy involves the use of plant extracts or their active principles [2]. Due to lack of organized health care systems in developing countries like Ethiopia, South Africa, and Asia, people with chronic diseases like diabetes are among the worst suffers in their communities till date and majority of the people still have limited access or no access to modern medicines in those remote areas. Instead they use traditional medicines for a range of diabetic complications. Earlier studies reported that *Aloe vera* plant has potential health benefits and leaf contain antioxidant, anticancer, gastric ulceration, cardiac stimulatory and immunomodulatory activity [3] wound healing, anti- inflammatory and antiviral effects and the potency of leaf gel in reducing chemically induced toxicity was reported [4]. Aloe juice has been shown to lower cholesterol and triglycerides while demonstrating antidiabetic activity [5].

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Diabetes mellitus is one of the most common metabolic diseases of human beings. Type II diabetes is a more common kind of diabetes found in 90% of the diabetic population [6]. Mortality and morbidity increases in diabetes because of associated chronic complications such as nephropathy and atherosclerosis characterized by hypoglycemia and biochemical changes by glucose and lipid metabolism [7]. WHO classification also recognized malnutrition-related diabetes mellitus and gestational diabetes. The three main types of diabetes are Type I, Type II diabetes and Gestational diabetes. Type I diabetes mellitus is characterized by loss of insulin-producing β cells of the islets of Langerhans in the pancreas leading to insulin deficiency. Type II diabetes mellitus is characterized by loss of hypoglycemic agent and producing β cells of the islets of Langerhans within the exocrine gland resulting in deficiency of insulin and the defective responsiveness of body tissues to hypoglycemic agent is believed to involve the hypoglycemic agent receptor. In the early stage of Type II diabetes, the predominant abnormality is reduced agent (insulin) sensitivity. At this stage, hyperglycemia is reversed by a variety of measures and medications that improve hypoglycemic sensitivity or reduce glucose production by the liver.

Streptozotocin (STZ) is widely used to induce experimental diabetes in animals. The mechanism of their action in β cells of the pancreas has been intensively investigated. The cytotoxic action of this diabetogenic agent is mediated by reactive oxygen

species; however, the source of its generation is different in the case of other diabetogenic agents [8, 9] STZ enters the β cell via a glucose transporter (GLUT2) and causes alkylation of Deoxyribonucleic acid (DNA). DNA damage induces activation of poly ADP-ribosylation, a process that's a lot of vital for the diabetogenicity of STZ than DNA injury itself. Poly ADP-ribosylation ends up in depletion of cellular nicotinamide adenine dinucleotide (NAD) + and adenosine triphosphate (ATP). Increased ATP dephosphorylation after STZ treatment provides a substrate for xanthine oxidase resulting to the formation of superoxide radicals. Consequently, peroxide and chemical group radicals are also generated. Furthermore, STZ liberates toxic amounts of nitric oxide that inhibits aconitase activity and participates in DNA damage. As a result of the STZ action, β cells endure the destruction by necrosis. Diabetes mellitus is a chronic disease which is difficult to cure. However, in this study we have chosen a miracle *Aloe CIM-Sheetal*, an important medicinal plant inspired us to investigate its antidiabetic activity and histopathology of organs in streptozotocin evoked as diabetic rats.

Therefore, the objective of the present study was conducted to know the antidiabetic effect of leaf extract of *Aloe CIM-Sheetal* and to evaluate its protective role in pancreas; liver and kidney in STZ induced diabetes in SD rats as animal models. World Health Organization (WHO) has recommended that the evaluation of medicinal plants treatment for diabetes were more effective, non- toxic and less or no side effects considered for oral therapy [10].

MATERIAL AND METHODS

Chemicals

The analytical graded chemicals were used for all the experiments. Streptozotocin (sigma chemicals), Glibenclamide (local market) were used in the experimental protocol. Streptozotocin was purchased from Sigma chemicals Hyderabad, India and was dissolved in 0.1 M citrate buffer (pH = 4.5) at the dose of 55mg/kg body weight. This was injected intraperitoneally within 15 min of dissolution in an exceedingly vehicle volume of 0.4 mL with 1 mL of liquid syringe fitted with twenty four gauge needle and normal control group was given citrate buffer 0.4 mL only.

Glibenclamide.

It is an oral antidiabetic preparation with an efficient hypoglycemic action. Daonil (glibenclamide) manufactured by Aventis Pharma Ltd. Goa, India was collected from local market and preserved at room temperature.

Collection of plant material

Aloe CIM - Sheetal (CAL 14) was obtained and authenticated from Central Institute of Medicinal and Aromatic Plants (CIMAP) Boduppal, Hyderabad, India vide voucher no: CIMAP / 63 / 6222 dated 20.07.2011.The plants used in this study were predominantly grown about two years of age and maintained at the research farm of Indian Immunologicals Ltd, Hyderabad, India. Aloe leaves were shade dried and ground into coarse powder.

Preparation of extract

500g of powdered leaf of *Aloe CIM-Sheetal* was extracted continuously using soxhlet apparatus with methanol successively for about 48 hours at 30°C. The extracts were focused under reduced pressure using rotary vacuum flash evaporator to get a constant volume.

Animals

Healthy male SD (Sprague Dawley) rats weighing about 150 - 200 g, procured from National Institute of Nutrition (NIN) Hyderabad, India were used in the present investigation. The animals were grouped and housed in polyacrylic cages and maintained under standard laboratory conditions with dark and light cycle (12:12 hour) and temperature 22±0.5°C. They were fed *ad libitum* everyday with standard chow dry pellet diet procured from NIN and were given free access to water[11]. Animals represented as fasting were deprived of food for at least 18 h but were allowed free access to drinking water. All the rats were given a period of acclimatization for 7 days before starting the experiment and protocol has been approved by the institutional animal ethics committee and by the animal regulatory body of the Indian Government (Registration No. **380/01/a**/ CPCSEA).

Toxicity Studies

The toxicity profile of the methanol extract of *Aloe CIM- Shetal* doesn't produce significant toxicity and mortality effect in rats during acute and sub-acute treatments. The experimental study was evaluated by the World Health Organization (WHO) guideline and the Organization of Economic Co-operation and Development (OECD) guide line for chemical testing[12,13].

Acute toxicity

In this study rats were divided into four groups. The treated groups were given *Aloe CIM - Sheetal* methanol extract orally in single dose of 10, 20, 30 g/kg body weight while the control group received only water. The animals were monitored for 14 days for apparent signs of toxicity. Oral administration of *Aloe CIM-Sheetal* extracts, including aqueous and methanol extract did not show visible signs of toxicity and

mortality in SD rats at the highest dose of 30 g/kg body weight. There was no evidence for differences in physiological and behavioral responses between the normal control group and methanol extract treated groups and also found that no differences in the consumption of feed and water which implied that *Aloe CIM-Sheetal* is not toxic.

Sub-acute toxicity

SD rats were divided into 6 groups and the treated group was orally given the extract at a dose of 1 (dose 1), 5 (dose 2), 10 (dose 3), 15 (dose 4) and 20 (dose 5) g/kg body weight for 42 days and the control group received the same volume of water. All the rats were observed for apparent signs of toxicity during the experimental period.

Experimental design

Rats were divided into seven groups as follows. Group I: Consisted of six rats which served as normal control (non - streptozotocin) and were given only citrate buffer (0.4 ml pH 4.5) daily. Group II: Consisted of six STZ induced diabetic rats and served as diabetic control (STZ-induced@ 55 mg/ Kg body weight) and were given citrate buffer (0.4 ml pH 4.5) daily. Group III: Consisted of six STZ induced diabetic rats and were treated orally with 100 mg/ kg body weight methanolic extract of *Aloe CIM-Sheetal* (ALE) once a day for 21 days. Group IV: Consisted of six STZ induced diabetic rats and were treated orally with a dose of 200 mg/ kg body weight of methanolic extract of *Aloe CIM-Sheetal* leaf extract (ALE) once a day daily for 21 days, Group V: Consisted of six STZ induced diabetic rats which were treated orally with 300 mg / kg body weight of methanolic extract of *Aloe CIM-Sheetal* leaf extract (ALE) once a day daily for 21 days. Group VI: Consisted of six STZ induced diabetic rats which were given Glibenclamide (GBC) daily for 21 days, once a day at the dose of 0.60.mg/kg body weight. Group V11: Consisted of six STZ induced diabetic rats which were treated orally with a dose of 500 mg/kg body weight of methanolic extract of *Aloe CIM-Sheetal* leaf extract (ALE) once a day daily for 21 days.

Collection and processing of blood for estimation of blood sugar levels

After 21 days of herbal treatment the experiment was terminated and observations were made. Body weight was taken before and after the experiment, with the help of one pan balance and blood glucose levels were estimated on 0 day, 7th, 14th and 21st day of experiment with the help of glucometer using strip method and blood was collected from tip of the tail (Fig.1). Diabetes was confirmed by the determination of fasting glucose concentration levels on the third day of post administration of streptozotocin [14].

Statistical analysis

Statistically, the values were evaluated with the analysis of variance (one way ANOVA) to determine the significance of difference within the experimental groups. P-values of 0.05 or less were taken as significant.

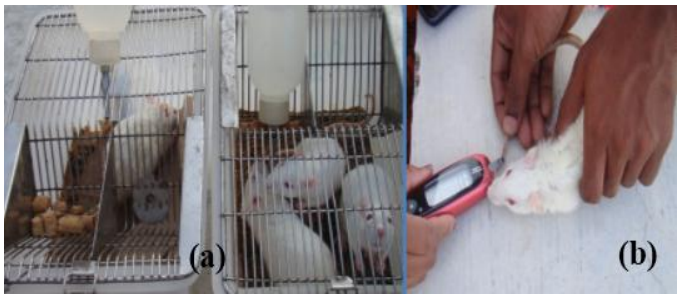


Fig1: (a) Rats in the cages fed with NIN provided standard dry pellet diet. (b) Blood glucose levels testing with *One-touch* glucometer from tail.

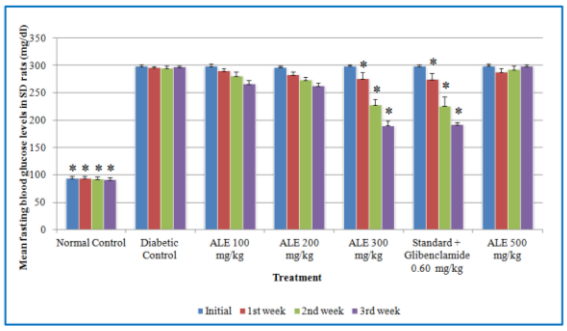
RESULTS AND DISCUSSION

In the present study, the methanol extract of *Aloe CIM- Sheetal* produced a significant decrease in the blood glucose level at a dose of 300mg/kg and 200 mg/kg in diabetic rats. The animals which are treated with 300 mg/kg of aloe leaf extract showed a significant decrease in the blood glucose levels when compared to the 100, 200 and 500 mg/kg. Streptozotocin (STZ) selectively destroys the pancreatic insulin β cells, leaving less active cell resulting in a diabetic state. STZ action in β cells is accompanied by characteristic alterations in blood insulin and glucose concentrations. STZ induced hyperglycemia has been described as a useful experimental model to study the activity of hypoglycemic agents [15]. The changes in blood glucose and insulin concentrations reflect abnormalities in β cell function. STZ impairs glucose oxidation [16] and reduced insulin biosynthesis and secretion [17]. It was observed that STZ at first abolished the β cell response to glucose and the temporary return of responsiveness then appears which is followed by its permanent loss and cells are damaged [18]. The fact that some herbal preparations enhance the beta cell regeneration and peripheral glucose utilization in Alloxan and STZ induced diabetic rats' supports the above assumption. The results revealed that, the body weight was significantly diminished by the treatment with the extracts (300 mg/kg) after 21 days (Table I). It was observed that there was a significant effect of *Aloe CIM-Sheetal* (300 mg/kg) on plasma glucose level of STZ treated SD rats. Diabetic rats treated with Glibenclamide (0.60mg /kg) decreased blood glucose level from 298.66 ± 2.16 mg/dl to 192.00 ± 4.14 mg/dl (58.94%). Diabetic rats treated with methanolic extract of *Aloe CIM- Sheetal* 300 mg/kg showed decreased blood glucose levels from 299.16 ±

1.94mg/kg to 190.00 ± 7.61 mg/kg (52.86 %) at the end of 21st day of treatment indicating that blood glucose levels was significantly ($P \leq 0.05$) decreased compared to diabetic control groups (Fig.2). Further, a similar trend like that of the 7th day was observed on 14thday $P<0.05$ and 21st day $P<0.05$ also.

It was observed that the healthy control group rats showed a stable body weight in comparison to diabetic rats which showed reduction in body weight. The acute and sub- acute toxicity studies of *Aloe CIM-Sheetal* shows that the maximum dose of 20g/kg body weight of rats. The rats were orally given a multiple dose of the methanol extract from the leaf of *Aloe CIM - Sheetal* at 5, 10, 15 and 20 g/kg and neither signs of toxicity nor death of rats were observed during the 14 days of the acute toxicity study and body weights were recorded as shown in (Table III) and significant difference was noticed as compared to control group. The sub- acute toxicity study of methanol extract of *Aloe CIM - Shetal* with the same above doses did not reveal any toxicity symptoms in body weights. The experimental animal body weights and control rats were increased throughout the duration of oral feeding (Fig. 3).

Figure 2: Graph representing the effect of *Aloe CIM-Sheetal* extract on blood glucose in Oral glucose tolerance test.



Error bars indicate standard deviation. Significance of differences was analysed by one-way ANOVA and Newman-Kuel's multiple comparisons test and is indicated by one asterisk ($p \leq 0.05$).

Mean (± SD) of blood glucose after 21 days treatment in treated, diabetic and control rats. Represents significant difference between diabetic rats and control or treated groups ($p<0.05$), n=6

Error bars indicate standard deviation. Significance of difference was analyzed by one-way ANOVA and Newman-Kuel's multiple comparisons test and is indicated by one asterisk ($p \leq 0.05$).

Table I: Antidiabetic study for various groups of SD Rats using *Aloe CIM-Sheetal*

Group	Treatment	Mean Fasting blood glucose level (mg/dl)			
		Basal value	1st week	2nd week	3rd week
Group I	Normal Control	93.66 ± 3.5^{c}	93.33 ± 4.08^{f}	91.83 ± 3.97^{e}	91.33± 4.08^{d}
Group II	Diabetic Control	299.00±1.78^{a}	296.16 ± 1.6^{a}	295.33± 3.72^{a}	297.16± 1.47^{a}
Group III	ALE 100mg/kg	298.83±3.31^{a}	290.50±3.27^{b}	280.66±6.77^{b}	266.33±5.68^{b}
Group IV	ALE 200mg/kg	296.83±2.22^{b}	282.83±5.52^{d}	273.50± 5.30^{c}	262.83 ± 4.44^{b}
Group V	ALE300 mg/kg	299.16±1.94^{a}	276.16±10.18^{e}	227.50± 9.52^{d}	190.00 ± 7.61^{c}
Group VI	Standard + Glibenclamide 0.60mg/kg	298.66±2.16^{a}	274.50±11.04^{e}	226.00±16.02^{d}	192.00 ± 4.14^{c}
Group VII	ALE 500mg/kg	299.16±2.92^{a}	288.16±5.49^{c}	293.00±5.72^{a}	298.50 ± 2.16^{a}

Values are rendered as Mean ± SD (n=6) ($p<0.05$)
Statistically significant compared with group - I (Normal control) and diabetic rats treated with Glibenclamide.
Statistically significant decrease compared with diabetic control (group11) and diabetic rats fed with *Aloe CIM-Sheetal* (Group V, IV, III and VII): $p<0.001$
Day 0, correspondence to the start of *Aloe CIM-Sheetal* feeding with confirmation of diabetes in diabetic- induced rats.

Table II: Phytochemical constituents of different extracts of *Aloe CIM- Sheetal* leaves

TESTS	ALE-EA	Gel Extract -EA	ALE - MET	ALE -AC	ALE -CH	ALE- H_2O
Glycosides	+	-	+	+	-	+
Alkaloids	+	-	-	-	-	-
Flavonoids	+	+	+	-	-	-
Anthraquinones	+	+	+	-	-	-
Carbohydrates	-	+	+	+	+	+
Saponins	+	-	+	-	+	-
Sterols	-	+	-	-	-	-
Terpenoids	+	-	-	-	-	-
Steroids	-	-	-	-	+	-
Phenolics	+	-	+	-	-	+
Acid compounds	+	-	-	-	-	-
Tanins	+	+	+	-	+	+
Resins	+	-	-	-	-	-
Reducing sugars	-	+	+	-	+	-
Phlobatanins	-	-	+	-	+	-

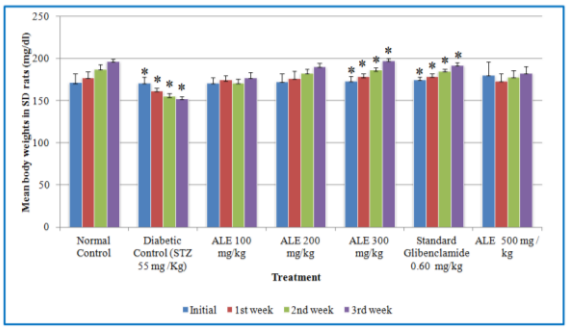
+ present, - absent, ALE-EA: *Aloe CIM - Sheetal* leaf extract with Ethyl acetate, Gel extract with Ethyl acetate, MET: Methanol, AC: Acetone, CH: Chloroform and H_2O: Water

Table III: Effect of *Aloe CIM- Sheetal* leaf extracts on body weights in control and experimental group rats.

Group	Treatment	Initial	1st week	2nd week	3rd week
Gr I	Normal control	171.50 ±10.33^{d}	177.33 ± 6.77^{a}	187.5 ± 5.46^{a}	196.83 ± 2.48^{a}
Gr II	Diabetic control (STZ 55 mg /Kg)	170.83 ± 7.22^{d}	161.50 ± 3.45^{c}	155.16 ± 3.06^{e}	152.33 ± 2.42^{e}
Gr III	ALE 100 mg/kg	171.33± 5.75^{d}	174.66 ± 5.20^{ab}	171.16 ± 4.79^{d}	177.33 ± 5.98^{d}
Gr IV	ALE 200 mg/kg	172.83 ± 9.04^{c}	176.33 ± 9.02^{a}	182.66 ± 4.92^{b}	190.33 ± 3.83^{b}
Gr V	ALE 300 mg/kg	173.33 ± 5.24^{c}	178.50 ± 3.56^{a}	186.16 ± 2.92^{a}	197.50 ± 2.07^{a}
Gr VI	Standard + Glibenclamide 0.60 mg/kg	175.16 ± 2.92^{b}	178.66 ± 3.01^{a}	184.83 ± 2.63^{ab}	192.33 ± 2.65^{ab}
Gr VII	ALE 500 mg / kg	180.33 ± 15.66^{a}	173.16 ± 8.70^{b}	177.83 ± 7.96^{c}	182.83 ± 7.65^{c}

Values are shown as means ± SD. Means followed by the same letter in a column are not significantly different ($p \leq 0.05$) by Newman-Kuel's multiple comparisons test.

Figure 3: Effect of methanol extracts *Aloe CIM- Sheetal* on the relative on body weights. Values are rendered as mean ± SD.



Error bars indicate standard deviation. Significance of differences was analysed by one-way ANOVA and Newman-Kuel's multiple comparisons test and is indicated by one asterisk ($p \leq 0.05$).

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Histopathology

At the end of 21st day, all the rats were euthanized by pentobarbitone sodium (60 mg/kg) and sacrificed by cervical dislocation. The pancreas, liver and kidney were dissected out, washed immediately in ice-cold saline. These organs were fixed overnight in 10% neutral buffered saline and sent to Department of pathology, NIN. In the department these organs were sliced, processed and histology sections were done on paraffin embedded blocks and 5 Micron thick sections were stained with hemotoxylin and eosin stains and were mounted with DPX. The H &E slides were then visualized under routine light microscope.

Liver

In Diabetic rats fed with *Aloe CIM-Sheetal* no significant changes in liver. The changes in liver were shown in Fig.4

Kidneys

Histological sections from kidneys of diabetes induced rats (Positive control) showed increased PAS (Periodic Schiff) positive mesangial matrix in the glomeruli with dilated tubules. Histological sections from the kidneys of the experimental animals showed lesser changes consisting of mild decrease in PAS positive mesangial matrix which was however less than the positive control thus indicating improvement in histology with the extract. The results were shown in Fig.5.

Pancreas

In the pancreatic sections of diabetic rats fed with *Aloe CIM-Sheetal*, the islets were decreased in number with increased vacuolation. Sections from the positive control and animals fed with *Aloe CIM Sheetal* leaf extract 100 mg/kg body weight in the number of islets along with vacuolation. Sections from the rest of the experimental animals however showed similar positive changes of improvement consisting of increase in the islet cell number with decrease in the vacuolation. The results were shown in Fig. 6.

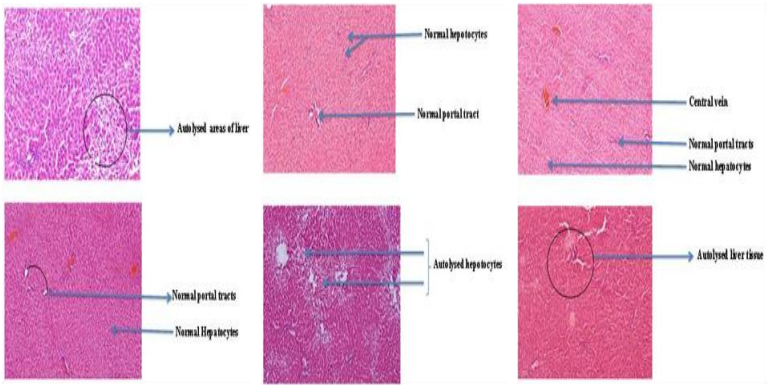

Figure 4: Histopathological results of various groups of SD-Rats of liver. (a) Gr III- Liver (Diabetic + Plant extract treated with 100 mg/kg conc.) H&E Stained section shows areas of autolysis, H&E 10X (b) Gr I–Liver Normal Control, H&E Stained section from control shows normal liver histology with normal portal tracts& hepatocytes,H&E,10X; (c) Gr VI-Liver (Diabetic + standard drug Glibenclamide 0.60 mg/kg) Section Shows normal hepatocytes, Portal tracts & Central vein, H&E,10X; (d) Gr V- Liver (Diabetic +Plant extract treated with 300 mg/kg) Section shows normal portal tracts & hepatocytes H&E,10X; (e) Gr-II Liver (Diabetic Control, STZ induced and untreated) H&E Stained section, shows few autolysed hepatocytes in addition to normal hepatocytes & portal tracts H&E, 10X; (f) Gr VII- Liver (Diabetic + Plant extract treated with 500 mg/kg) Section shows focal autolysed areas H&E,10X.

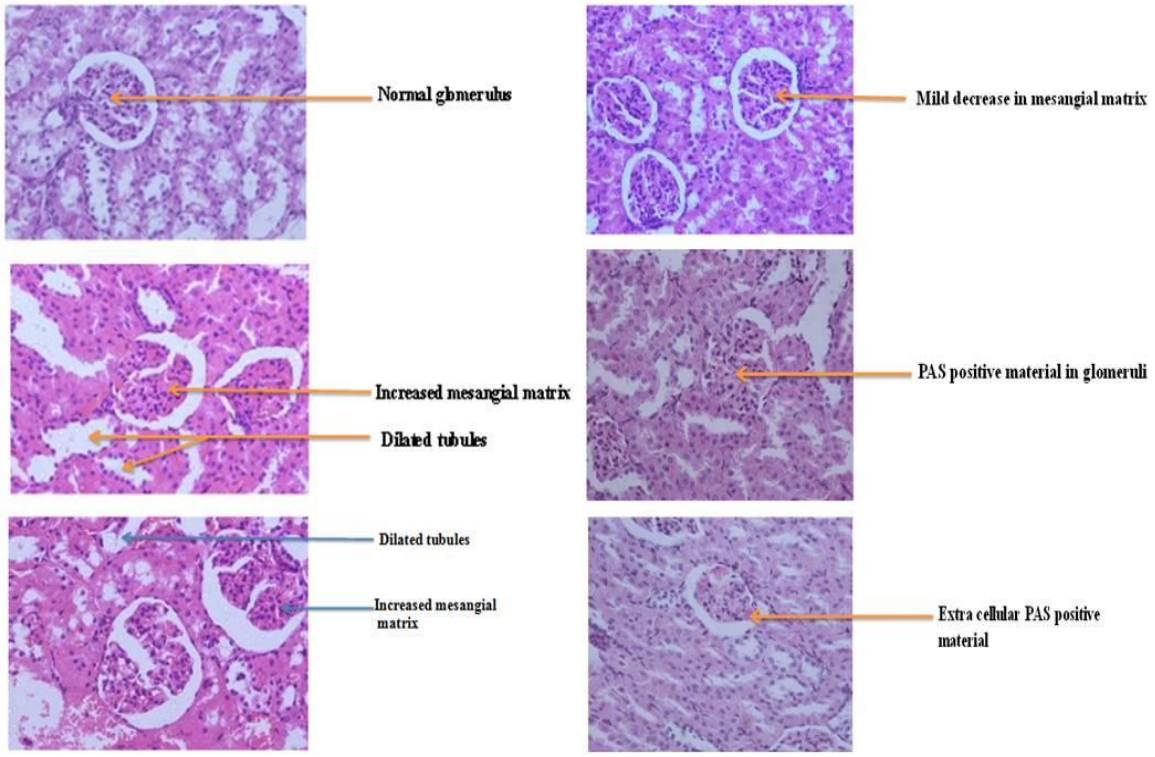

Figure 5: (a) Gr 1- Kidney normal control, PAS stained section shows normal renal glomeruli and normal tubules with no deposits PAS, 40X: (b) Gr II - Kidney (Diabetic Control STZ induced and untreated), PAS stained section shows glomeruli with increase in mesangial matrix which is PAS positive and normal tubules PAS 40X: (c) Gr VII - kidney (Diabetic + *Aloe CIM- Sheetal* leaf extract treated with 500mg / kg conc.) PAS stained section showed dilated tubules around glomeruli with increased mesangial matrix PAS 40X. (d) Gr V - Kidney (Diabetic + *Aloe CIM- Sheetal* leaf extract treated with 300 mg / kg conc.) PAS stained section shows increased mesangial matrix in glomeruli with normal surrounding tubules, PAS 40X :(e) Gr VI- Kidney (Diabetic + standard drug treated with Glibenclamide 0.60 mg/kg conc.) PAS stained section shows PAS^{+}ve material indicating mildly increased mesangial matrix in the glomeruli PAS 40X: (f) Gr III - Kidney (Diabetic + *Aloe CIM Sheetal* leaf extract treated 100 mg / kg with conc.) PAS stained section shows mesangial matrix which is mildly increased and is PAS^{+}ve, PAS 40X:

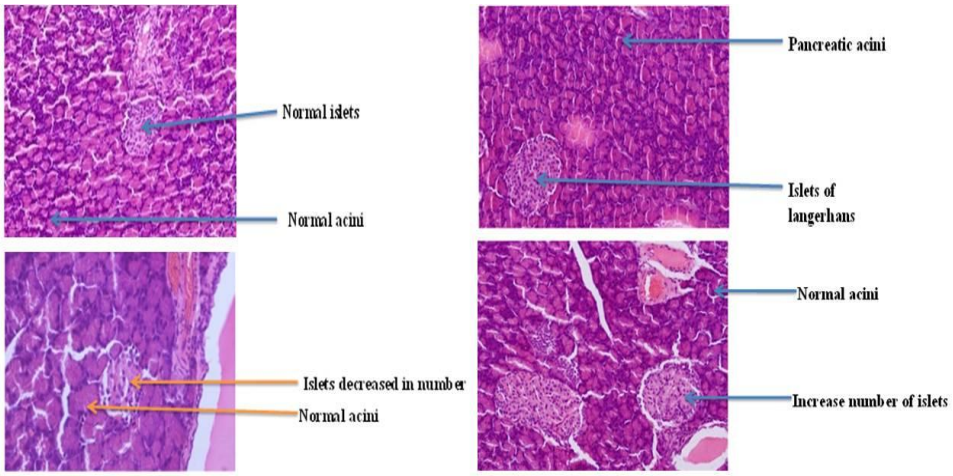

Fig.6: (a) Gr1-Pancreas Normal Control, H&E stained section shows normal sized islets of langerhans surrounded by normal pancreatic acini H&E, 20X: (b) Gr II- Pancreas (Diabetic Control STZ induced and untreated), H&E stained section shows decrease in size & number of pancreatic islets normal surrounding acini, H&E, 40X: (c) Gr IV- Pancreas (Diabetic +Plant extract treated with 200mg/kg conc.) H&E stained section shows islets with moderate increase in number and normal acini H&E, 40X: (d) Gr V- Pancreas (Diabetic +Plant extract treated with 300mg / kg conc.) H&E stained section shows increase number of islets in normal acini H&E, 20 X.

The present study has demonstrated for the first time the antidiabetic properties of *Aloe CIM-Sheetal* which caused significant decrease in the blood glucose levels in diabetic rats treated with *Aloe CIM–Sheetal* leaf extract. This may be by stimulation of the residual mechanism of pancreas may be increasing due to peripheral utilization of glucose [19]. STZ was found to generate reactive oxygen species, which also contribute to DNA fragmentation and evoke other deleterious changes in the cells [20].It is well known that oxygen free radicals are involved in diabetogenic action of alloxan and plants containing flavonoids, triterpenoids and isoflavanoids have been shown to be effective in diabetes due to their antioxidants property[21]. This study suggests that the antidiabetic activity of *Aloe CIM -Sheetal* may be due to free radical scavenging activity which enhances the β cell regeneration against STZ induced free radicals. The literature reports reveal that flavonoids and tannins present in some plant extracts are responsible for antidiabetic activity. In the present investigation we have observed the antidiabetic potential of *Aloe CIM-Sheetal* leaf extract (ALE) may be due to presence of similar phytoconstitutes which was evident by preliminary phytochemical screening studies (Table II.) The different extracts of *Aloe CIM- Sheetal* revealed that the methanol extract was rich in saponins, chloroform extracts was rich in saponins, steroids and tannins : alkaloids, carbohydrates, and glycosides were found to be the present in acetone, methanol and aqueous extracts and methanol extracts were also found to possesses tannins and phenolic compounds.

The results of blood glucose level and body weight indicate that ALE can be useful in reducing the effects of STZ induced diabetes. One of the major complications of type II diabetes is weight loss. It arises because of impairment in insulin action in conversion of glucose to glycogen and catabolism of fats, inhibition of lipolysis because of its unavailability due to destruction in β cells [22]. Due to this there will be a decrease in the body weight of the animals and thereby death. Treatment with methanol extract has substantially prevented the body weight loss. Daily treatment of animals with extract for three weeks led to a dose dependent fall in blood glucose levels. Maximum effect was seen in animals which are treated with 300 mg/kg of ALE.

Our current study aimed to evaluate the antidiabetic potency of *Aloe CIM- Sheetal* leaf extract in Streptozotocin (STZ) induced diabetic rats and its effect was compared with glibenclamide. 42 adult male SD (Sprague Dawley) rats were used in the experiment for studying the antidiabetic activity and histopathology evaluation was also done. In this study, we address the beneficial effects of *Aloe CIM-Sheetal* (CAL-14), which is a variety of *Aloe barbadensis* Mill has been promoted by Central Institute of Medicinal and Aromatic Plants (CIMAP), Lucknow, India to emphasize the role of active compounds using streptozotocin induced diabetic rats to prove its antidiabetic activity. We have used methanolic extract to study the pharmacological activity. *Aloe CIM- Sheetal* methanolic extract in different concentrations (100, 200, 300 and 500 mg/kg b.w.) was given to rats which were divided into seven groups, by oral administration for 21 days. It was observed that the fasting plasma glucose levels were reduced in experimental animals when compared to normals / controls and the body weights also increased. From our studies, the methanol leaf extract of *Ale CIM-Sheetal* has significant anti-diabetic activity and histopathological changes are shown in pancreas, kidney and liver. The glucose lowering activity were observed in the diabetic animals because of stimulation of the β cells of the pancreatic islets and body weights of diabetic treated with *Aloe CIM- Sheetal* group were significantly recovered when compared to the diabetic control and diabetic treated with glibenclamide groups. Subsequently, at the same time the blood glucose levels were decreased because of the stimulation of the β cells of the pancreatic islets naturally in diabetic group followed by increased oxidative levels and no tissue damage were observed by the activity of *Aloe CIM-Sheetal* in STZ treated animals. It has been observed that only 300 mg/ kg body weight of *Aloe CIM- Sheetal* leaf extract has a protective effect compared STZ treated and glibenclamide treated groups and assumed that *Aloe CIM-Sheetal* is a potential antidiabetic candidate in streptozotocin-induced diabetic model by reducing oxidative damage and modulating antioxidant enzymes. Acute and sub-acute toxicity of *Aloe CIM- Sheetal* in SD rats indicated that the methanol extract at the dose of 1, 5, 10, 15, 20 g/kg body weight does not produce significant dose related biochemical and histopathology parameters in internal organs. It may be hence concluded that the methanolic extract of *Aloe CIM-Sheetal* does not produce significant toxicity and mortality impact, in SD rats during acute and sub-acute treatment in rats. Hence the extract can be used for pharmaceutical industry.

Further pharmacological and biochemical investigations will clearly elucidate the mechanism of action and will be helpful in projecting this plant as a therapeutic target in cancer research. It can be stated that the crude extract of the leaves of *Aloe CIM-Sheetal* has a potential anti diabetic activity in herbal treatment because there was no case showing acute hypoglycemic conditions during the administration of *Aloe CIM- Sheetal* leave extract or its antidiabetic compounds, and no adverse effect symptoms were observed from the viewpoints of pathological findings. Thus *Aloe CIM- Sheetal* leaf extract could be useful to prevent Type II diabetes mellitus. This extract may be similar to compounds like acemannan for the treatment of anticancer and further, isolation and establishment of exact mechanism of action of specific compound from *Aloe CIM-Sheetal* has to be carried out in future.

CONCLUSION

The result of this experimental animal study indicated that the methanol extract of *Aloe CIM- Sheetal* has antidiabetic activity in diabetic SD rats' animal models. Based on the reports and their potential effectiveness against diabetes, it is assumed that the methanol extract of *Aloe CIM-Sheetal* leaves possess antidiabetic properties in Streptozotocin (STZ) induced diabetic rats. It also shows the presence of biological active compounds in the extract of leaves i.e. flavonoids, tannins and anthroquinones which could be responsible for the antidiabetic effect and histological changes were also observed in STZ induced diabetic rats. Therefore authenticated genotypes have a major role to play in the management of diabetes which needs further exploration for the necessary development of drug and pharmaceuticals from natural resources.

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