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Antidiabetic activity of extracts of *Kandelia rheedii* in streptozotocin-induced diabetes model

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Abstract
Streptozotocin is a naturally occurring nitrosourea, widely used to induce insulin-dependent diabetes mellitus in experimental animals because of its toxic effects on islet beta cells. This study was untertaken to investigate the effect of methanolic extract of barks of *Kandelia Rheedii* W. & A. (KRM) and aqueous extract of *Kandelia Rheedii* W. & A. Barks (KRA) against streptozotocin induced diabetes. Hyperglycaemia was induced by administering a single dose of streptozotocin (50 mg/kg b.w) following evaluation of antidiabetic activity of extracts of *kandelia rheedii* and its traditional formulation. Biochemical parameters were determined and pancreatic tissues from various groups were processed for histological examination. Significant ($p < 0.05$) reduction in glucose and lipids was observed. Significant difference in biochemical parameters was observed when compared to control group. Histopathological data showed improvement in hepatocyte and pancreatic β-cells islets architecture. Further studies to standardise the extract and evaluation of safety profile in long-term toxicity studies are recommended for safe and effective antidiabetic nutraceuticals development.

Keywords: diabetes mellitus, antidiabetic, mangrove plants, *Kandelia rheedii*, streptozotocin

Introduction
Diabetes mellitus, one of the major public health problems worldwide, is a metabolic disorder of multiple etiologies distinguished by a failure of glucose homeostasis with disturbances of carbohydrate, fat and protein metabolism as a result of defects in insulin secretion and/or insulin action [1, 2]. According to World Health Organization (WHO) projections, the prevalence of diabetes is likely to increase by 35%. Currently there are over 150 million diabetics worldwide and this is likely to increase to 300 million or more by the year 2025. Statistical projection about India suggests that the number of diabetics will rise from 15 million in 1995 to 57 million in the year 2025, the highest number of diabetics in the world [3]. Reasons for this rise include increase in sedentary lifestyle, consumption of energy rich diet, obesity, higher life span etc. Other regions with greater number of diabetics are Asia and Africa, where there could be a two-three fold rise in diabetes mellitus cases [4]. Evaluation of plant products to treat diabetes mellitus is of growing interest as they contain many bioactive substances with therapeutic potential. In recent years several authors evaluated and identifi ed the antidiabetic potential of traditionally used Indian medicinal plants using experimental animals. Previous studies confi rmed the effi cacy of several medicinal plants in diabetes mellitus. Although a large number of medicinal plants have been already tested for their antidiabetic effects, these effects remain to be investigated in several other Indian medicinal plants [5].
Mangrove plants are widely used by the community as traditional medicine.
This mangrove plant is efficacious to cure some of the diseases such as hepatitis, diuretic, leprosy, antimalarial, diarrhea, asthma, diabetes, fever, swelling, rheumatism, skin diseases, smallpox, antitumor, antiviral, leukemia, anticancer, treat throat mumps, and beriberi [6, 8]. Several types of mangrove plants that are as antidiabetic drugs such as; *Acanthus illicifolius*, *Avicennia ebracteatus*, *Bruguiera conjugate*, *Bruguiera cylindrical*, *Bruguiera rumphii*, *Bruguiera sexangula*, *Dalbergia ecastophyllum*, *Excoecaria agallocha*, *Hertiera macrophylia*, *Kandelia candel*, *Kandelia rheedii*, *Rhizophora conjugata*, *Rhizophora gymnorrhiza*, *Rhizophora mangle*, *Rhizophora racemosa*, *Rhizophora stylosa*, *Salicornia brachiata*, *Sonneratia alba*, *Sonneratia ovata*, and *Xylocarpus granatum*, and *Xylocarpus moluccensis* [9, 10]. Part of the mangrove plant tissue used as an antidiabetic drug is part of the root tissue, stem wood, bark, leaves, twigs, flowers, and fruit. Chemical content suspected to be antidiabetic in some types of mangrove plants are alkaloid compounds, steroids, triterpenes, phenolic compounds, flavonoids, stilbene, carotenoids, triterpenes, anthocyanins, anthocyanidins, inositol, saponins, long chain alcohols, tannins, amino acids, benzoquinone, coumarin, quinine, chalcone, lipid compounds, phorbol ester, rotenone, polyphenols, benzofuran, limonoid, sulfur alkaloids, procyanidin, gibberellin, and xiloccensins [7, 10].
The literature screened in the process of the work indicates that the bark of *Kandelia rheedii* contain classes of chemical constituents which have shown antidiabetic activity. Pharmacological investigations of the selected plant may yield useful information and material for better management for preventing diabetes. Therefore the present study was untertaken to investigate the effect of methanolic extract of barks of *Kandelia Rheedii* W. & A. (KRM) and aqueous extract of *Kandelia Rheedii* W. & A. Barks (KRA) against streptozotocin induced diabetes.

Materials and methods
Chemicals, reagents and plant materials
Glibenclamide was obtained from Sigma Lab Pvt Ltd and streptozotocin extrapure was obtained from Sisco research Lab Pvt Ltd. All solvents used were of analytical reagent purity grade. The barks of *Kandelia Rheedii* W. & A. were

collected in the month of March from the coastal region of Bhadrak situated near Cuttak (Odhisa). These were identified and authenticated by Dr. S. N. Dwivedi (HOD) and voucher specimens were deposited in the herbarium of the Department of Botany, Janata PG College, A.P.S. University, Rewa (M.P.). The barks were washed, shade dried, pulverized into moderately coarse powder and stored in airtight container for further use.

Extraction

The barks were washed, shade dried and pulverized into moderately coarse powder using hand grinder. Powdered barks were weighed and packed in soxhlet apparatus. The powdered bark was defatted with petroleum ether (40°- 60° C) for about 09 hrs & complete defatting was ensured by placing a drop from the thimble on a filter paper which did not exhibited any oily spot. The defatted material was removed from the soxhlet apparatus and air dried to remove last traces of petroleum ether. The defatted material was subjected to extraction by methanol as solvent. The extracts were collected in a tarred conical flask. The solvent was removed by distillation. Last traces of solvent being removed under vacuum. The extract obtained with each solvent was weighed to a constant weight and percentage w/w basis was calculated. The obtained crude extract was stored in dark glass bottles for further processing.

Traditional formulation of *Kandelia rheedii* (TFKR)

It was prepared by maceration using *Kandelia rheedii* bark (50mg), dried ginger (50mg) and rose water (qs to make 100 ml). The bark mixed with dried ginger or long peper & rose water, is said to be cure for diabeties [11].

Animals

Albino rats of either sex weighing 150-200g were purchased from the local breeder and were kept at animal housing facility of Faculty of Pharmaceutical Sciences, VNS group of institutions, Bhopal with free access to routine feed and water *ad libitum*. The housing environment was set at standard environmental conditions i.e., temperature set at 22 ± 2 °C with alternative dark and light cycle of 12 hours. All the *in vivo* experiments were carried out with the prior of Institutional Animal Ethical Committee.

Streptozotocin (STZ) induced diabetes (15 days study)

In this study, methanolic extract of barks of *Kandelia Rheedii* W. & A. (KRM) and aqueous extract of *Kandelia Rheedii* W. & A. barks (KRA) were evaluated for antidiabetic activity against streptozotocin induced diabetes mellitus in rats. Rats were divided into 8 groups consisting of six rats each. The rats were acclimatized for a period of 7 days before starting the experiment. After an overnight fasting, hyperglycaemia was induced by administering a single dose of streptozotocin (50 mg/kg b.w) [12] to all rats excepting group I which served as normal control. Streptozotocin was freshly dissolved in 0.1 M citrate buffer (pH=4.5) and injected intraperitioneally within 15 min of dissolution in a vehicle volume of 0.4 mL with 1 mL of tuberculin syringe fitted with 24 gauge needle. Diabetes was confirmed by the determination of fasting glucose concentration on the third day post administration of streptozotocin. During this period, the animals were given free access to water. After 3rd day of STZ administration, fasting blood glucose levels of rats were checked by glucostrips. The animals having blood glucose levels > 250 mg/dl were separated and selected for further studies and then re-grouping of these hyperglycemic rats was done as per the following protocol, for studying the anti-diabetic activity of different extracts. Rats were given the following treatment in this study.

Group I Normal Control (2% of gum acacia).
Group II Diabetic Control. Received STZ (50 mg/kg b.w single dose i.p)
Group III STZ + Glibenclamide (3 mg/kg,)
Group IV STZ + + TFKR (10 ml/kg b.w)
Group I STZ + KRM (50 mg/kg b.w)
Group VI STZ + KRM (100mg/kg b.w)
Group VII STZ+ KRA (50 mg/kg b.w)
Group VIII STZ+ KRA (100 mg/kg b.w)

The treatment was started from the same day except normal control and diabetic control groups for a period of 15 days orally. During this period, animals in all groups had free access to standard diet and water. Blood glucose levels were estimated on 1st, 4th, 9th and 15th day of the treatment. Besides this during this study the body weight of the rats were recorded on 1st, 4th, 9th and 15th day of the treatment. On day 16th, blood samples were collected from overnight fasted rats by cardiac puncture. The animals were anaethesized by mild ether anaesthesia before cardiac puncture. Blood was collected and allowed to stand for one hour; serum was separated by centrifuging and evaluated for different biochemical parameters. The animals were killed and pancreas was taken out for histopathological studies.

The pancreas was removed, and the tissues were washed in ice-cold normal saline immediately after sacrificing the animal. The tissues were fixed in 10% formal saline for 24 h to avoid decomposition. Afterward, the tissues were cleaned and embedded in paraffin wax (melting point 58–60 ◦C). Sectioning of the paraffin-embedded pancreas (at 7 µm) was performed using a semi-automated microtome. Then, a hot plate was used to mount the tissue sections on a glass slide. The tissue sections were subjected to deparaffinization and dehydration using xylene and alcohol, respectively. Finally, the tissue sections were stained using hematoxylin and eosin stain and were examined.

Statistical analysis

The data obtained from the different studies and the biochemical estimations is expressed as Mean ± SEM for each group. After this, the statistical analysis was carried out using one way analysis of variance (ANOVA) followed by Students t-test. Values $p > 0.05$ were considered Non-Significant; $p < 0.05$ as significant, $p<0.01$ as highly significant and $p<0.001$ as very highly significant respectively.

Results and Discussion

There was very highly significant rise ($p<0.001$) in serum glucose levels in rats in the diabetic group (Group II) (207.50±2.97 mg/dl) as compared to normal control (Group I) (77.62±4.95 mg/dl). Traditional formulation of *Kandelia Rheedii* W. & A. barks (TFKR) at the dose levels of 10 ml/kg b.w showed a significant decrease in the serum glucose levels (136.65±2.37mg/dl). Methanolic extract of barks of *Kandelia Rheedii* W. & A. (KRM) at the dose levels of 100 and 200 mg/kg b.w showed a significant decrease in the serum glucose levels. A dose of 100 mg/kg administered to rats of Group V showed a highly significant

decrease (p<0.01) of (181.75±4.03mg/dl) and a dose of 200 mg/kg administered to rats of Group VI showed a significant level (p<0.01) of (166.99±3.29mg/dl).
Aqueous extract of *Kandelia Rheedii* W. & A. barks (KRA)at the dose levels of 100 and 200 mg/kg b.w showed a very highly significant decrease in serum glucose levels in a dose dependent manner, as compared to the group II that had received only STZ. A dose of 100 mg/kg b.w administered to rats of Group VII showed a significant level (p<0.01) of (152.06±4.35 mg/dl) and a dose of 200 mg/kg b.w administered to rats of Group VIII showed a very highly significant level (p<0.001) of (145.96±1.94mg/dl).

Table 1: Effect of traditional formulation of *Kandelia Rheedii* W. & A. barks (TFKR), methanolic extract of barks of *Kandelia Rheedii* W. & A. (KRM) and aqueous extract of *Kandelia Rheedii* W. & A. barks (KRA) on Serum Glucose Levels (mg/dl) against Streptozotocin (STZ) induced diabetes mellitus in rats (15 day study)

S. No.	Group-I	Group-II	Group –III	Group-IV	Group-V	Group –VI	Group-VII	Group-VIII
Rats	Normal control (0.2ml of 2% Gum acacia)	Diabetic control (STZ)	STZ + Std Anti diabetic Drug Glibenclamide (3mg/kg.)	STZ + TFKR (10ml/kg b.w)	STZ + KRM (100mg /kg)	STZ + KRM (200mg / kg)	STZ + KRA (100mg /kg)	STZ + KRA (200mg /kg)
1	62.34	201.24	125.32	140.34	169.36	175.56	160.31	140.23
2	92.23	220.31	190.51	145.16	184.64	165.06	153.14	143.12
3	90.63	210.32	110.05	138.41	169.14	175.05	164.63	154.31
4	68.42	205.36	100.42	135.21	187.56	155.45	138.23	145.32
5	80.05	207.32	130.72	130.42	190.12	160.62	140.32	147.45
6	72.05	200.45	120.34	130.41	189.71	170.23	155.73	145.34
Mean	77.62	207.5***	129.56***	136.65***	181.75***	166.99**	152.06**	145.96***
SD	12.14	7.28	31.77	5.81	9.87	8.07	10.67	4.76
SEM	4.95	2.97	12.97	2.37	4.03	3.29	4.35	1.94
P Value		p < 0.001	p < 0.001	p < 0.001	p < 0.01	p < 0.01	p < 0.01	p < 0.001
Statistically Compared Groups		II Vs I	III Vs II	IV Vs II	V Vs II	VI Vs II	VII Vs II	VIII Vs II

STZ Dissolved in 0.1M citrate buffer at a. dose of 50mg/kg b..w and injected i.p. single dose Diabetes confirmed on third day post administration of streptozotocin. Standard drug Glibenclamide & extracts were administered orally for 15 days, in a single dose daily after confirmation of hyperglycaemia.
n = 6 (Number of animals in each group)
Group II is compared with Group I and all other groups are compared with group II
*** p < 0.001 Very highly significant; ** p< 0.01; Highly significant;

As compared to group I (88.22 ±2.01 mg/dl) the levels in the group II rats which had received only STZ, there was very highly significant increase (p<0.001) in the total cholesterol levels (195.18±3.54 mg/dl). Traditional formulation of *Kandelia Rheedii* W. & A. barks (TFKR) at the dose levels of 10 ml/kg b.w showed a significant decrease in the total cholesterol levels (180.56±1.56 mg/dl).When methanolic extract of barks of *Kandelia Rheedii* W. & A. (KRM) (100 mg/kg b.w) was administered to rats of Group V, it showed a significant decrease (p<0.05) (182.54±1.97mg/dl) and dose of 200 mg/kg b.w administered to rats of Group VI showed a highly significant decrease (p<0.001) in the total cholesterol levels (132.92±4.63mg/dl).
Aqueous extract of *Kandelia Rheedii* W. & A. barks (KRA) at the dose levels of 100 and 200 mg/kg b.w showed a very highly significant decrease in total cholesterol levels in a dose dependent manner, as compared to the group II that had received only STZ. A dose of 100 mg/kg b.w administered to rats of Group VII showed a highly significant level (p<0.01) of (171.09±1.2mg/dl) and a dose of 200 mg/kg administered to rats of Group VIII showed a significant level (p<0.01) of (161.46±2.66mg/dl).

Table 2: Effect of traditional formulation of *Kandelia Rheedii* W. & A. barks (TFKR), methanolic extract of barks of *Kandelia Rheedii* W. & A. (KRM) and aqueous extract of *Kandelia Rheedii* W. & A. barks (KRA) on Serum Cholesterol Levels (mg/dl) against Streptozotocin (STZ) induced diabetes mellitus in rats.

S.No.	Group-I	Group-II	Group –III	Group-IV	Group-V	Group –VI	Group-VII	Group-VIII
Rats	Normal Control (0.2ml of 2% Gum acacia)	Diabetic control (STZ)	STZ + Std Anti diabetic drug Glibenclamide (3mg/kg.)	STZ + TFKR (10 ml/kg b.w)	STZ + KRM (100mg /kg)	STZ + KRM (200mg / kg)	STZ + KRA (100mg /kg)	STZ + KRA (200mg /kg)
1	92.06	190.31	215.98	180.53	183.87	132.32	173.65	165.96
2	81.65	187.42	187.54	174.08	176.34	147.65	168.43	169.54
3	82.73	192.43	224.67	180.41	184.32	124.32	174.32	153.34
4	90.23	190.05	190.65	183.56	179.56	145.53	169.67	164.32
5	89.12	210.34	1656.56	179.62	190.42	127.67	173.07	154.19
6	93.56	200.53	180.67	185.21	180.74	120.05	167.43	161.45
Mean	88.22	195.18***	193.34	180.56*	182.54**	132.92***	171.09**	161.46**
SD	4.92	8.67	13.94	3.56	4.84	11.34	2.94	6.51
SEM	2.01	3.54	5.69	1.56	1.97	4.63	1.2	2.66
P Value		p < 0.001	p >0.05	p < 0.05	p < 0.01	p < 0.001	p < 0.01	p < 0.01
Statistically Compared Groups		II Vs I	III Vs II	IV Vs II	V Vs II	VI Vs II	VII Vs II	VIII Vs II

STZ Dissolved in 0.1M citrate buffer at a. dose of 50mg/kg b..w and injected i.p. single dose Diabetes confirmed on third day post administration of streptozotocin. Standard drug Glibenclamide extracts were administered orally for 15 days, in a single dose daily after confirmation of hyperglycaemia.
n = 6 (Number of animals in each group)
Group II is compared with Group I and all other groups are compared with group II
*** p < 0..001 Very highly significant; ** P< 0.01; Highly significant; *p< 0.05 significant

The rats of group I showed a level of (76.71±3.45 mg/dl), while the rats of group II which received only STZ showed a very highly significant level (p<0.001) of (193.01±4.84 mg/dl). Traditional formulation of *Kandelia Rheedii* W. & A. barks (TFKR) at the dose levels of 10 ml/kg b.w showed a significant decrease in the serum triglycerides levels (162.44±4.44mg/dl).The rats of the groups receiving methanolic extract of barks of *Kandelia Rheedii* W. & A. (KRM) showed a dose dependent reduction in serum triglycerides indicating significant reduction in lipid profile. A dose of 100 mg/kg b.w administered to rats of Group V revealed a significant level (p<0.01) of (152.34±3.6mg/dl) and a dose of 200 mg/kg b.w administered to rats of Group VI showed a very highly significant level (p<0.001) of (124.95± 5.68mg/dl). The dose of 100 and 200 mg/kg b.w of aqueous extract of *Kandelia Rheedii* W. & A. barks (KRA) when administered to rats showed significant decrease when compared to the levels of diabetic control rats of Group II rats. A dose of 100 mg/kg b.w administered to rats of Group VII showed a highly significant level (p<0.01) of (159.90±5.68 mg/dl) while a dose of 200 mg/kg b.w administered to rats of Group VIII showed a very highly significant level (p<0.001) of (134.69±3.3mg/dl).

Table 3: Effect of traditional formulation of *Kandelia Rheedii* W. & A. barks (TFKR), methanolic extract of barks of *Kandelia Rheedii* W. & A. (KRM) and aqueous extract of *Kandelia Rheedii* W. & A. barks (KRA) on Serum Triglycerides Levels (mg/dl) against Streptozotocin (STZ) induced diabetes mellitus in rats.

S.No.	Group-I	Group-II	Group –III	Group-IV	Group-V	Group –VI	Group-VII	Group-VIII
Rats	Normal control (0.2ml of 2% Gum acacia)	Diabetic control (STZ)	STZ + Std Anti diabetic Drug Glibenclamide (3mg/kg.)	STZ + TFKR (10 ml/kg b.w)	STZ + KRM (100mg /kg)	STZ + KRM (200mg / kg)	STZ + KRA (100mg /kg)	STZ + KRA (200mg /kg)
1	84.05	190.67	213.89	163.53	153.96	120.37	165.07	132.64
2	78.56	184.32	175.53	157.06	160.23	134.21	154.96	142.07
3	66.32	195.96	214.56	180.64	156.63	141.56	174.45	125.34
4	80.53	200.45	190.56	147.32	159.56	110.63	157.34	126.63
5	66.04	176.63	150.64	164.34	137.74	112.85	162.62	136.13
6	84.73	210.07	176.59	161.76	145.95	130.08	140.06	145.38
Mean	76.71	193.01***	186.96	162.44**	152.34**	124.95***	159.90**	134.69***
SD	8.46	11.86	10.57	10.9	8.82	12.33	1.27	8.09
SEM	3.45	4.84	4.31	4.44	3.6	5.68	5.68	3.3
P Value		p < 0.001	p >0.05	p < 0.01	p < 0.01	p < 0.001	p < 0.01	p < 0.001
Statistically Compared Groups		II Vs I	III Vs II	IV Vs II	V Vs II	VI Vs II	VII Vs II	VIII Vs II

STZ Dissolved in 0.1M citrate buffer at a. dose of 50mg/kg b.w and injected i.p. single dose Diabetes confirmed on third day post administration of streptozotocin. Standard drug Glibenclamide extracts were administered orally for 15 days, in a single dose daily after confirmation of hyperglycaemia.
n = 6 (Number of animals in each group)
Group II is compared with Group I and all other groups are compared with group II
*** p < 0.001 Very highly significant; ** p< 0.01; Highly significant; p>0.05 Non significant

There was very highly significant decrease (p<0.001) in serum HDL cholesterol levels in rats in the diabetic group (Group II) (18.88±2.62 mg/dl) as compared to normal control (Group I) (33.07±2.15 mg/dl). Traditional formulation of *Kandelia Rheedii* W. & A. barks (TFKR) at the dose levels of 10 ml/kg b.w showed a non significant decrease in the serum HDL cholesterol levels (25.91±4.64mg/dl). Methanolic extract of barks of *Kandelia Rheedii* W. & A. (KRM) at the dose levels of 100 and 200 mg/kg b.w showed a significant level of serum HDL cholesterol levels. A dose of 100 mg/kg administered to rats of Group V showed a significant level (p < 0.01) of (29.59±2.86mg/dl) while a dose of 200 mg/kg given to rats of Group VI showed significant level (p<0.05) of (22.65± 0.77 mg/dl).

Aqueous extract of *Kandelia Rheedii* W. & A. barks (KRA) at the dose levels of 100 and 200 mg/kg b.w showed significant increase in serum HDL cholesterol levels in a dose dependent manner, as compared to the group II that had received only STZ. A dose of 100mg/kg b.w administered to rats of Group VII showed a significant level (p<0.05) of (26.11± 3.73mg/dl) and a dose of 200 mg/kg b.w administered to rats of Group VIII showed significant level (p<0.01) of (26.48±1.86mg/dl).

Table 4: Effect of traditional formulation of *Kandelia Rheedii* W. & A. barks (TFKR), methanolic extract of barks of *Kandelia Rheedii* W. & A. (KRM) and aqueous extract of *Kandelia Rheedii* W. & A. barks (KRA) on HDL Cholesterol Levels (mg/dl) against Streptozotocin (STZ) induced diabetes mellitus in rats.

S.No.	Group-I	Group-II	Group –III	Group-IV	Group-V	Group –VI	Group-VII	Group-VIII
Rats	Normal control (0.2ml of 2% Gum acacia)	Diabetic control (STZ)	STZ + Std Anti diabetic drug Glibenclamide (3mg/kg.)	STZ + TFKR (10 ml/kg b.w)	STZ + KRM (100mg /kg)	STZ + KRM (200mg / kg)	STZ + KRA (100mg /kg)	STZ + KRA (200mg /kg)
1	33.97	16.41	18.97	26.08	26.32	25.07	23.86	27.45
2	30.45	14.07	19.76	45.34	21.34	20.45	35.06	31.75
3	29.64	12.46	20.45	31.64	32.04	23.74	32.45	24.78
4	26.34	21.08	19.74	21.34	38.52	20.67	21.43	22.31
5	37.73	30.34	21.98	16.53	23.28	23.95	32.78	21.06
6	40.34	18.96	17.64	14.56	36.07	22.07	11.05	31.56
Mean	33.07	18.88***	19.75	25.91	29.59**	22.65*	26.11*	26.48**

SD	5.27	6.42	4.79	11.38	7.01	1.88	9.14	4.56
SEM	2.15	2.62	1.95	4.64	2.86	0.77	3.73	1.86
P Value		p < 0.001	p >0.05	p < 0.01	p < 0.01	p < 0.05	p < 0.05	p < 0.01
Statistically Compared Groups		II Vs I	III Vs II	IV Vs II	V Vs II	VI Vs II	VII Vs II	VIII Vs II

STZ Dissolved in 0.1M citrate buffer at a. dose of 50mg/kg b.w and injected i.p. single dose Diabetes confirmed on third day post administration of streptozotocin. Standard drug Glibenclamide extracts were administered orally for 15 days, in a single dose daily after confirmation of hyperglycaemia.

n = 6 (Number of animals in each group)

Group II is compared with Group I and all other groups are compared with Group

*** p < 0.001 Very highly significant; ** P< 0.01; Highly significant; *p<0.05 significant; p>0.05 Non significant

As compared to group I (42.51±2.35 mg/dl) the levels in the group II rats which had received only STZ there was very highly significant increase (p<0.001) in the serum LDL cholesterol levels (87.02±3.07 mg/dl). Traditional formulation of *Kandelia Rheedii* W. & A. barks (TFKR) at the dose levels of 10 ml/kg b.w showed a non significant decrease in the serum LDL cholesterol levels (82.36±3.91 mg/dl). When methanolic extract of barks of *Kandelia Rheedii* W. & A. (KRM) (100 mg/kg b.w) was administered to rats of Group V it showed a non significant decrease (p>0.05) (72.26±2.67 mg/dl) while a dose of 200 mg/kg b.w administered to rats of Group VI showed a significant decrease (p<0.05) in the serum LDL cholesterol levels (63.21±3.62 mg/dl).

Aqueous extract of *Kandelia Rheedii* W. & A. barks (KRA) at the dose levels of 100 and 200 mg/kg b.w showed a decrease in serum LDL cholesterol levels in a dose dependent manner, as compared to the group II that had received only STZ. A dose of 100 mg/kg b.w administered to rats of Group VII showed a non significant level (p>0.05) of (92.56±2.52 mg/dl) while a dose of 200 mg/kg administered to rats of Group VIII showed a significant level (p<0.05) of (74.04±3.76mg/dl).

Table 5: Effect of traditional formulation of *Kandelia Rheedii* W. & A. barks (TFKR), methanolic extract of barks of *Kandelia Rheedii* W. & A. (KRM) and aqueous extract of *Kandelia Rheedii* W. & A. barks (KRA) on LDL Cholesterol Levels (mg/dl) against Streptozotocin (STZ) induced diabetes mellitus in rats.

S.No.	Group-I	Group-II	Group –III	Group-IV	Group-V	Group –VI	Group-VII	Group-VIII
Rats	Normal control (0.2ml of 2% Gum acacia)	Diabetic control (STZ)	STZ + Std Anti diabetic drug Glibenclamide (3mg/kg.)	STZ + TFKR (10 ml/kg b.w)	STZ + KRM (100mg /kg)	STZ + KRM (200mg / kg)	STZ + KRA (100mg /kg)	STZ + KRA (200mg /kg)
1	43.07	9.56	89.07	89.74	70.75	65.73	98.65	76.42
2	36.43	86.54	90.45	83.72	75.83	67.62	95.32	69.63
3	42.67	74.42	76.12	79.64	63.23	48.82	84.73	78.62
4	38.73	90.56	94.45	86.06	67.52	73.05	90.07	64.86
5	41.03	83.67	87.96	90.45	81.74	56.45	99.54	89.03
6	53.12	96.42	79.56	65.56	74.52	67.62	87.05	65.72
Mean	42.51	87.02	86.26	82.36	72.26	63.21*	92.56	74.04*
SD	5.76	7.53	7.41	9.58	6.54	8.88	6.18	9.21
SEM	2.35	3.07	3.02	3.91	2.67	3.62	2.52	3.76
P Value		p < 0.001	p >0.05	p >0.05	p >0.05	p < 0.05	p >0.05	p < 0.05
Statistically Compared Groups		II Vs I	III Vs II	IV Vs II	V Vs II	VI Vs II	VII Vs II	VIII Vs II

STZ Dissolved in 0.1M citrate buffer at a. dose of 50mg/kg b..w and injected i.p. single dose Diabetes confirmed on third day post administration of streptozotocin. Standard drug Glibenclamide extracts were administered orally for 15 days, in a single dose daily after confirmation of hyperglycaemia.n = 6 (Number of animals in each group)

Group II is compared with Group I and all other groups are compared with group II

***p<0.001 Very highly significant; ** P< 0.01; Highly significant; *p<0.05 significant; p>0.05 Non significant

The rats of group I showed a level of (0.55±0.05 mg/dl), while the rats of group II which received only STZ showed a highly significant level (p<0.001) of (3.11±0.23 mg/dl). Traditional formulation of *Kandelia Rheedii* W. & A. barks (TFKR) at the dose levels of 10 ml/kg b.w showed a significant decrease (p<0.01) in the serum bilirubin levels (0.75± 0.11 mg/d).The rats of the groups receiving methanolic extract of barks of *Kandelia Rheedii* W. & A. (KRM) showed a dose dependent reduction in serum bilirubin levels. A dose of 100 mg/kg b.w administered to rats of Group V showed a significant level (p<0.05) of (2.83±0.11 mg/dl) while a dose of 200mg/kg b.w administered to rats of Group VI showed a highly significant reduction (p<0.05) of (1.65±0.12 mg/dl).

The doses of 100 and 200 mg/kg b.w of aqueous extract of *Kandelia Rheedii* W. & A. barks (KRA) when administered to rats showed an extremely significant decrease when compared to the levels of diabetic control rats of Group II. A dose of 100 mg/kg b.w administered to rats of Group VII showed a significant level (p<0.05) of (1.61±0.17 mg/dl) while a dose of 200 mg/kg b.w administered to rats of Group VIII showed a significant value (p<0.01) of (1.55±0.10 mg/dl).

Table 6: Effect of traditional formulation of *Kandelia Rheedii* W. & A. barks (TFKR), methanolic extract of barks of *Kandelia Rheedii* W. & A. (KRM) and aqueous extract of *Kandelia Rheedii* W. & A. barks (KRA) on Serum Bilirubin Levels (mg/dl) against streptozotocin (STZ) induced diabetes mellitus in rats.

S.No.	Group-I	Group-II	Group –III	Group-IV	Group-V	Group –VI	Group-VII	Group-VIII
Rats	Normal Control (0.2ml of 2% Gum acacia)	Diabeti control (STZ)	STZ + Std Anti diabetic drug Glibenclamide (3mg/kg.)	STZ + TFKR (10 ml/kg b.w)	STZ + KRM (100mg /kg)	STZ + KRM (200mg / kg)	STZ +KRA (100mg /kg)	STZ + KRA (200mg /kg)
1	0.37	3.85	2.42	0.56	2.84	1.34	2.03	1.21
2	0.72	3.21	3.01	0.76	2.67	1.74	1.61	1.54
3	0.52	2.95	2.45	1.12	3.17	2.18	1.45	1.94
4	0.48	3.67	1.98	0.95	2.78	1.56	0.97	1.45
5	0.57	2.56	2.43	0.32	3.12	1.45	2.15	1.78
6	0.64	2.45	2.97	0.83	2.45	1.67	1.45	1.43
Mean	0.55	3.11***	2.54	0.75**	2.83*	1.65*	1.61*	1.55**
SD	0.12	0.57	0.38	0.28	0.27	0.29	0.43	0.26
SEM	0.05	0.23	0.15	0.11	0.11	0.12	0.17	0.1
P Value		p < 0.001	p >0.05	p <0.01	p < 0.05	p < 0.05	p < 0.05	p < 0.01
Statistically Compared Groups		II Vs I	III Vs II	IV Vs II	V Vs II	VI Vs II	VII Vs II	VIII Vs II

STZ Dissolved in 0.1M citrate buffer at a. dose of 50mg/kg b..w and injected i.p. single dose Diabetes confirmed on third day post administration of streptozotocin. Standard drug Glibenclamide extracts were administered orally for 15 days, in a single dose daily after confirmation of hyperglycaemia.

. n = 6 (Number of animals in each group)

Group II is compared with Group I and all other groups are compared with group II

*** p < 0.001 Very highly significant; ** P< 0.01; Highly significant; *p<0.05 significant; p>0.05 Non significant

There was a highly significant rise (p<0.01) in serum SGOT levels in rats in the diabetic group, Group II (32.12±4.23 IU/L)) as compared to normal control (Group I) (21.61±1.31 IU/L). Traditional formulation of *Kandelia Rheedii* W. & A. barks (TFKR) at the dose levels of 10 ml/kg b.w showed a significant decrease (p<0.01) in the serum SGOT levels (17.95±2.27 IU/L). Methanolic extract of barks of *Kandelia Rheedii* W. & A. (KRM) at the dose levels of 100 and 200 mg/kg b.w showed a significant decrease in the serum SGOT levels. A dose of 100mg/kg administered to rats of Group V showed a non-significant decrease (p>0.05) of (28.39±1.26 IU/L) and a dose of 200 mg/kg administered to rats of Group VI showed a significant decrease of (21.90±1.51 IU/L) (p<0.05).

Aqueous extract of *Kandelia Rheedii* W. & A. barks (KRA) at the dose levels of 100 and 200 mg/kg b.w showed a significant decrease in serum SGOT levels in a dose dependent manner, as compared to the group II that had received only STZ. A dose of 100 mg/kg b.w administered to rats of Group VII showed a non-significant level (p>0.05) of (25.98±1.85 IU/L), a dose of 200 mg/kg b.w administered to rats of Group VIII showed a significant level (p<0.05).of (18.17±1.02 IU/L).

Table 7: Effect of traditional formulation of *Kandelia Rheedii* W. & A. barks (TFKR), methanolic extract of barks of *Kandelia Rheedii* W. & A. (KRM) and aqueous extract of *Kandelia Rheedii* W. & A. barks (KRA) on SGOT (IU/L) against Streptozotocin (STZ) induced diabetes mellitus in rats.

S.No.	Group-I	Group-II	Group –III	Group-IV	Group-V	Group –VI	Group-VII	Group-VIII
Rats	Normal control (0.2ml of 2% Gum acacia)	Diabetic control (STZ)	STZ + Std Anti diabetic drug Glibenclamide (3mg/kg.)	STZ + TFKR (10 ml/kg b.w)	STZ + KRM (100mg /kg)	STZ + KRM (200mg / kg)	STZ + KRA (100mg /kg)	STZ + KRA (200mg /kg)
1	17.63	34.14	32.45	14.05	29.05	20.81	21.45	14.95
2	22.32	32.09	32.67	15.03	26.45	27.07	27.45	17.56
3	21.72	41.53	31.89	12.64	23.43	21.46	24.62	19.07
4	27.21	38.73	28.67	27.96	30.56	19.06	32.86	21.45
5	21.04	41.23	34.98	19.43	32.13	17.47	28.57	20.13
6	19.75	21.53	29.98	18.63	28.75	25.56	20.96	15.91
Mean	21.61	32.12**	31.77	17.95*	28.39	21.9*	25.98	18.17*
SD	3.2	10.36	3.58	5.56	3.08	3.72	4.55	2.5
SEM	1.31	4.23	1.46	2.27	1.26	1.51	1.85	1.02
P Value		p < 0.01	p >0.05	p < 0.05	p > 0.05	p < 0.05	p > 0.05	p <0.05
Statistically Compared groups		II Vs I	III Vs II	IV Vs II	V Vs II	VI Vs II	VII Vs II	VIII Vs II

STZ Dissolved in 0.1M citrate buffer at a. dose of 50mg/kg b..w and injected i.p. single dose Diabetes confirmed on third day post administration of streptozotocin. Standard drug Glibenclamide extracts were administered orally for 15 days, in a single dose daily after confirmation of hyperglycaemia.

n = 6 (Number of animals in each group)

Group II is compared with Group I and all other groups are compared with group II

** P< 0.01; Highly significant; *p<0.05 significant; p>0.05 Non significant

As compared to group I (26.06 ±1.78 IU/L) the levels in the group II rats which had received only STZ, there was highly significant increase (p<0.01) in the serum SGPT levels (40.72±2.28 IU/L). Traditional formulation of *Kandelia Rheedii* W. & A. barks (TFKR) at the dose levels of 10 ml/kg b.w showed a non-significant level (p > 0.05) in the serum SGPT levels (29.69±2.27 IU/L). When methanolic extract of barks of *Kandelia Rheedii* W. & A. (KRM) (100 mg/kg b.w) administered to rats of Group V it showed a non-significant decrease (p>0.05) of (28.13±1.02 IU/L) while a dose of 200 mg/kg b.w administered to rats of Group VI showed a non-significant decrease in the serum SGPT levels (26.06±1.63 IU/L) (p > 0.05).

Aqueous extract of *Kandelia Rheedii* W. & A. barks (KRA) at the dose levels of 100 and 200 mg/kg b.w showed a significant decrease in serum SGPT levels, as compared to the group II that had received only STZ. A dose of 100 mg/kg b.w administered to rats of Group VII showed a significant level (p<0.01) of (23.45±0.99 IU/L) and a dose of 200 mg/kg administered to rats of Group VIII showed a highly significant level (p<0.01) of (18.92±0.73 IU/L).

Table 8: Effect of traditional formulation of *Kandelia Rheedii* W. & A. barks (TFKR), methanolic extract of barks of *Kandelia Rheedii* W. & A. (KRM) and aqueous extract of *Kandelia Rheedii* W. & A. barks (KRA) on SGPT (IU/L) against Streptozotocin (STZ) induced diabetes mellitus in rats.

S. No.	Group-I	Group-II	Group –III	Group-IV	Group-V	Group –VI	Group-VII	Group-VIII
Rats	Normal control (0.2ml of 2% Gum acacia)	Diabetic control (STZ)	STZ + Std Anti diabetic drug Glibenclamide (3mg/kg.)	STZ + TFKR (10 ml/kg b.w)	STZ + KRM (100mg /kg)	STZ + KRM (200mg / kg)	STZ + KRA (100mg /kg)	STZ + KRA (200mg /kg)
1	20.43	48.45	39.78	23.74	29.46	30.14	21.61	16.74
2	26.39	45.56	34.67	27.75	23.43	25.45	21.62	19.03
3	28.06	41.82	40.34	38.65	29.56	27.62	20.73	21.57
4	32.56	38.43	32.54	24.52	30.52	18.63	25.57	18.02
5	27.03	36.05	39.51	31.48	27.95	28.46	24.67	20.46
6	21.49	34.04	41.98	32.04	27.86	25.07	26.53	17.75
Mean	26.06	40.72	38.13	29.69	28.13	26.06	23.45*	18.92**
SD	4.38	5.58	4.48	5.56	2.51	4.01	2.43	1.8
SEM	1.78	2.28	1.97	2.27	1.02	1.63	0.99	0.73
P Value		p < 0.01	p >0.05	p > 0.05	p > 0.05	p > 0.05	p <0.01	p <0.01
Statistically Compared groups		II Vs I	III Vs II	IV Vs II	V Vs II	VI Vs II	VII Vs II	VIII Vs II

STZ Dissolved in 0.1M citrate buffer at a. dose of 50mg/kg b.w and injected i.p. single dose Diabetes confirmed on third day post administration of streptozotocin. Standard drug Glibenclamide extracts were administered orally for 15 days, in a single dose daily after confirmation of hyperglycaemia.

n = 6 (Number of animals in each group) significant

Group II is compared with Group I and all other groups are compared with group II

** P< 0.01; Highly significant; *p< 0.05 significant; p> 0.05 Non significant

The rats of group I showed a level of (7.13±0.31 g/dl) while the rats of group II which received only STZ showed a significant decrease (p<0.05) of (4.79±0.33 g/dl). Traditional formulation of *Kandelia Rheedii* W. & A. barks (TFKR) at the dose levels of 10 ml/kg b.w showed a non-significant level (p > 0.05) in the serum total proteins levels (5.99±0.17 g/dl).The rats of the groups receiving methanolic extract of barks of *Kandelia Rheedii* W. & A. (KRM) showed a non-significant increase in serum total proteins. A dose of 100 mg/kg b.w administered to rats of Group V showed a non-significant level (p>0.05) of (4.67±0.27 g/dl) and a dose of 200 mg/kg b.w administered to rats of Group VI showed a non-significant level (p>0.05) of (4.92±0.18 g/dl).

The doses of 100 and 200 mg/kg b.w of aqueous extract of *Kandelia Rheedii* W. & A. barks (KRA) when administered to rats showed a non-significant increase when compared to the levels of diabetic control rats of Group II rats. A dose of 100 mg/kg b.w administered to rats

of Group VII showed a non-significant level (p>0.05) of (5.41±0.26 g/dl) while a dose of 200 mg/kg b.w administered to rats of Group VIII showed a non-significant level (p>0.05) of (5.93±0.31 g/dl).

There was significant decrease in serum albumin levels in rats in the diabetic group (Group II) (1.16±0.19 g/dl) (p<0.05) as compared to normal control (Group I) (2.65±0.09 g/dl). Traditional formulation of *Kandelia Rheedii* W. & A. barks (TFKR) at the dose levels of 10 ml/kg b.w showed a non-significant level (p > 0.05) in the serum albumin levels (2.08±0.21 g/dl). Methanolic extract of barks of *Kandelia Rheedii* W. & A. (KRM) at the dose levels of 100 and 200 mg/kg b.w showed a non-significant level in the serum albumin levels. A dose of 100 mg/kg administered to rats of Group V showed a non-significant level (p>0.05) of (1.34±0.07 g/dl) while a dose of 200 mg/kg administered to rats of Group VI showed a non-significant level (p>0.05) of (1.40±0.10 g/dl).

Aqueous extract of *Kandelia Rheedii* W. & A. barks (KRA) at the dose levels of 100 and 200 mg/kg b.w showed a non-significant increase in serum albumin levels, as compared to the group II that had received only STZ. A dose of 100 mg/kg b.w administered to rats of Group VII showed a non-significant level of (p>0.05) (1.46±0.18 g/dl), a dose of 200 mg/kg administered to rats of Group VIII b.w showed a non-significant level (p>0.05) of (1.68±0.03 g/dl).

As compared to group I (78.20±4.60 U/L), the levels in the group II rats which had received only STZ, there was highly significant increase in the serum alkaline phosphatase levels (92.88±2.58 U/L) (p<0.01). Traditional formulation of *Kandelia Rheedii* W. & A. barks (TFKR) at the dose levels of 10 ml/kg b.w showed a non-significant level (p > 0.05) in the serum alkaline phosphatase levels (86.92±1.59 U/L). When methanolic extract of barks of *Kandelia Rheedii* W. & A. (KRM) (100 mg/kg b.w) was administered to rats of

Group V it showed a non-significant levels ($p>0.05$) of (92.34±3.09 U/L) but dose of 200 mg/kg b.w administered to rats of Group VI showed a non-significant levels ($p>0.05$) in the serum alkaline phosphatase levels (92.28±2.06 U/L).
Aqueous extract of *Kandelia Rheedii* W. & A. barks (KRA) at the dose levels of 100 and 200 mg/kg b.w showed a non-significant levels of serum alkaline phosphatase levels, as compared to the group II that had received only STZ. A dose of 100 mg/kg b.w administered to rats of Group VII showed a non-significant level ($p>0.05$) of (91.53±1.68 U/L) and a dose of 200 mg/kg administered to rats of Group VIII showed a non-significant level ($p>0.05$) of (91.31±3.84 U/L)
The rats of group I showed an average weight of (267.23±13.09 g) while the rats of group II which received only STZ showed a very highly significant decrease of (158.80±7.51 g) ($p<0.001$) in average body weight. Traditional formulation of *Kandelia Rheedii* W. & A. barks (TFKR) at the dose levels of 10 ml/kg b.w showed a significant increase ($p < 0.01$) in average body weight (245.50±4.28 g). The rats of the groups receiving methanolic extract of barks of *Kandelia Rheedii* W. & A. (KRM) showed a dose dependent increase in average body weight. A dose of 100 mg/kg b.w administered to rats of Group V showed a significant level ($p<0.05$) of (220.45±6.27 g) and a dose of 200 mg/kg b.w administered to rats of Group VI showed a significant level ($p<0.05$) of (222.12 ±13.83 g).
The doses of 100 and 200 mg/kg b.w of aqueous extract of *Kandelia Rheedii* W. & A. barks (KRA) when administered to rats showed an extremely significant increase when compared to the levels of diabetic control rats of Group II. A dose of 100 mg/kg b.w administered to rats of Group VII showed a significant average body weight ($p<0.05$) of (238.78±10.12g) while a dose of 100 mg/kg b.w administered to rats of Group VIII showed a significant average body weight ($p<0.01$) of (240.57±7.68 g).

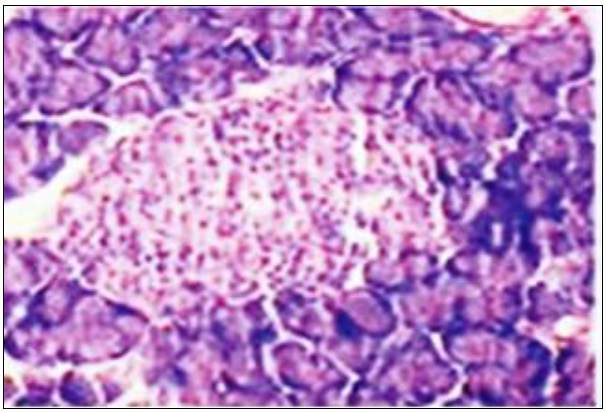

Fig 1: Normal control (presence of normal pancreatic islet cells)

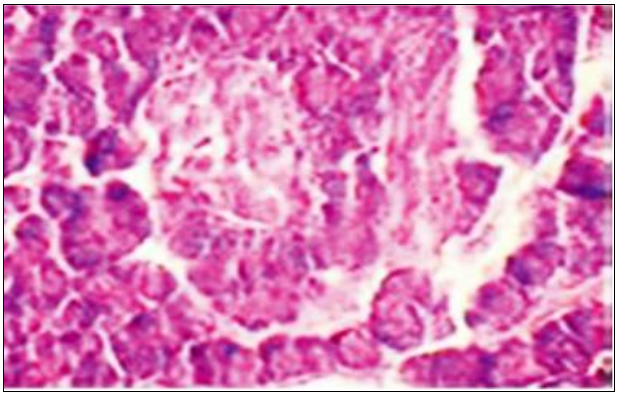

Fig 2: Diabetic control (expansion and dilated islet cells)

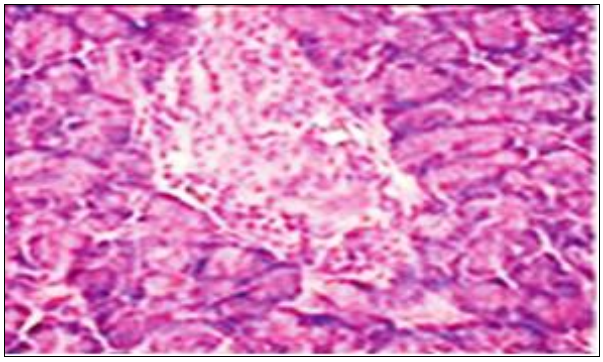

Fig 3: Mild expansion and absence of dilations

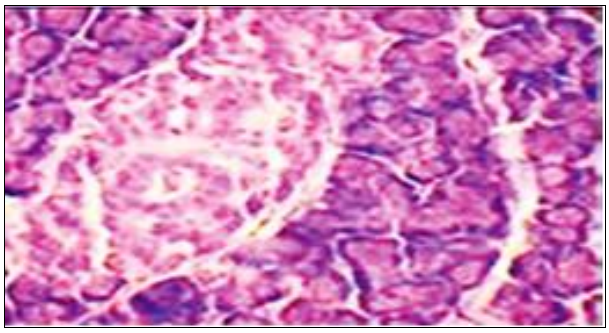

Fig 4: Moderate expansion of pancreatic islets, showing prominent hyper plastic islet

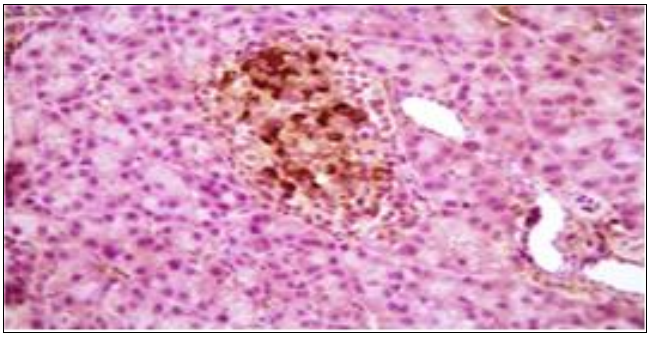

Fig 5: Showing no pathological changes

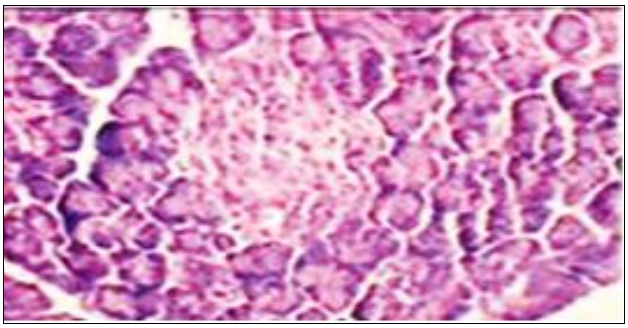

Fig 6: Absence of dilation and prominent hyperplastic of islets

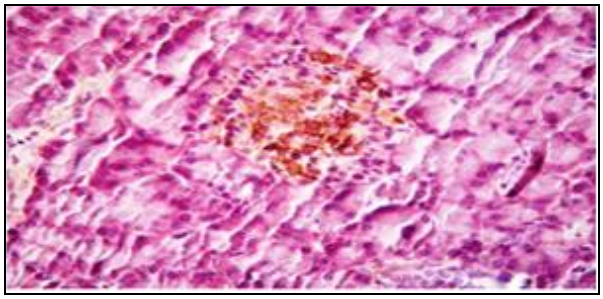

Fig 7: Showing no or less pathological changes

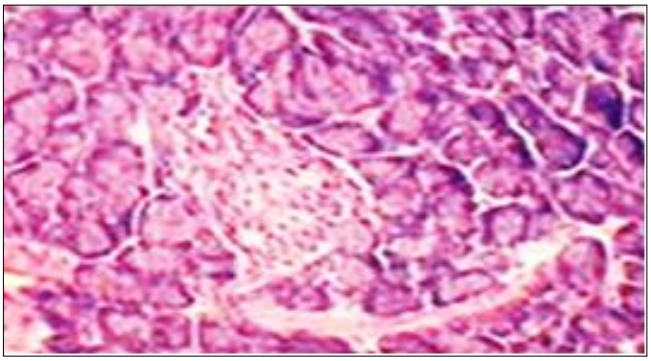

Fig 8: Absence of dilation and prominent hyperplastic of islets

Kandelia rheedii (locally known as Guria or Rasunia) is a wellknown herbal cure to tuberculosis. Several small molecules, for example Skyrin, Fusaric acid and Emodin, from the plants have been reported up till now. Skyrin, a fungal bisanthroquinone, exhibits functional glucagon antagonism by uncoupling the glucagon receptor from adenylate cyclase activation in rat liver membranes Fusaric acid is a picolinic acid derivative. It is typically isolated from various Fusarium species, and has been proposed for a various therapeutic applications. Fusaric acid is an important antibacterial agent and can also be used to kill cancer cells. It thus can be used as a biocontrol agent. Emodin is a purgative resin, 6-methyl-1,3,8-trihydroxyanthraquinone. Emodin is being studied as a potential agent that could reduce the impact of type2 diabetes [13].

Streptozotocin is well known for its selective pancreatic islet β-cells cytotoxicity and has been extensively used to induce diabetes mellitus in animals. It interferes with cellular metabolic oxidative mechanisms [14]. Compared to the other existing models of diabetes in rats, the streptozotocin rat model is considered to be better for elucidation of the mechanisms related to renal, hepatic and pancreatic functions in type 2 diabetes [15].

Intraperitoneal administration of streptozotocin effectively induced diabetes in normal rats, as observed by hyperglycemia, when compared with normal rats.. In this study significant hyperglycemia was achieved within 48 hours after streptozotocin (50mg/kg body wt. i.p.) injection. Streptozotocin induced diabetic rats with more than levels above 200mg/dL of blood glucose were considered to be diabetic and used for the study. In this study it was observe that the oral administration of the extract (200mg/kg body wt) could reverse the above mentioned diabetic effect, possibly due to an insulin-like effect of the extract on peripheral tissues, either by promoting glucose uptake and metabolism, or by inhibiting hepatic gluconeogenesis. The mechanism of action may be by stimulation of the pancreatic β-cells and the enzymes that regulate glycolysis. However, the hypoglycemic effect due to either rise in insulin production by stimulating the pancreatic β-cells or by enhancing the peripheral cellular glucose uptake cannot be ruled out.

Conclusion

The present data indicated that the extracts of *Kandelia rheedii* and its traditional formulation significantly decreased serum glucose in diabetic rats as compared with control diabetic rats. The mechanism of hypoglycemic action probably involves direct or indirect stimulation of insulin secretion. In conclusion, extracts of *Kandelia rheedii* and its traditional formulation could be considered an excellent candidate for future studies on diabetes mellitus. In addition, further comprehensive pharmacological investigations, including experimental chronic studies, should be carried out.

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