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AN INVESTIGATIONAL ON THE TYPE I ANTI-DIABETIC ACTIVITY OF THE METHANOLIC EXTRACT OF *MORINGA OLEIFERA* IN STREPTOZOTOCIN INDUCED RAT MODEL

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ABSTRACT

Moringa oleifera is a plant with excessive nutritional and medicinal value. The objective of the present study was an investigational on the Type I anti-diabetic activity over the methanolic extract on *Moringa oleifera* in Streptozotocin induced rat model. Extracted *Moringa oleifera* was in subjected to evaluate the toxicity, biochemical, hematological and gross pathological evaluation. Type I Diabetes has been induced in Wistar rats via STZ 65mg/kg/b.w. I.P. During the experiment, Rat's body weight and blood glucose level have been monitored. At the end of study, animals have been sacrificed and biochemical parameters like Lipid profile, C-Peptide, HbA1c, Serum insulin, pancreatic insulin, and histology over pancreas had been performed. *Moringa oleifera* used to be additionally screened for pro-inflammatory cytokines viz., IL-1β, IL-6 and TNF-a have been observed by ELISA. Furthermore, Antioxidant Enzymes kind of SOD, CAT, LPO and GSH have been performed. Key findings: The *Moringa oleifera* was proven to safe in animal study. And it has been reported to significant an impact on in vivo to manage the diabetic markers like weight gain, blood glucose, lipid profile, C-Peptide, HbA1c, release of insulin secretion, and pancreatic insulin. Diabetic rats tested diminished of beta cell density and disruption of normal architecture. But treated groups were observed to restoration the mass of beta cells. Mediator of inflammatory cytokines as elevated in STZ group then used to be inhibited by test chemicals. Elevated oxidative enzymes also have been seen to limit upon the treatment with Moringa *oleifera*. All this findings and phytoconstituents existing into the extract ought to keep the viable chemicals involved in the prevention of diabetes.

Keywords: *Moringa oleifera,* STZ, Toxicity, Diabetes, Cytokines

Introduction

Diabetes is a common health burden and eventually causes an insufficient of beta cells. Approximately $100 billion each year is associated to the health care. DM that influences millions globally and such is predicted will reach to 552 million ends over 2030.[1] Diabetes Mellitus is a cluster of metabolic disorder typified by means of hyperglycemia, may be inherited or obtained defect in the pancreas within terms of release of insulin, and ineffective utilization of glucose due to insulin insensitiveness of peripheral tissues as skeletal muscle. It is estimated that, there have been numerous mechanisms for destruction of β-cell, which includes inflammatory markers certain namely cytokines, circulatory FFA, & hyperglycemia.[2]

All kinds of diabetes can be manageable, the insulin for Type I and accessible in seeing that 1921, and Type II diabetes execute additionally managed with the help of anti-hyperglycemic drugs. If both Types I & II continue to be for a longer duration, it's very hard to cure, solely choice is in imitation of superintend all through the life. Pharmacological and non-pharmacological remedy of DM is essential here, as much properly as adjustment over emphasis fulfilled life, then perfect nutrients therapy and normal physical workout are the key element for minimize the progression on diabetes.

Plants are normally among the popular treatment sources. Since a number of testing groups scan natural extracts because of strong modern drug marketers for infectious diseases upon the vast variety on chemical compounds inside natural items.[3] Herbal plants an extract and isolated compounds or their derivatives, offer infinite probabilities in conformity with discovery of novel molecules. Use of herbal herbs appears to stand an historical record of human friendly with the nature. Natural herbs known in imitation of keep old for traditional medicine, as that contain enormous extent on molecules that can be good for infectious ailments as properly as like chronic illness. There were many herbal plants hold maintain the appreciation as like treatments over diabetes mellitus. However, not many keep enticed scientific and clinical scrutiny so the WHO has endorsed remedy of diabetes including herbal plants; that requires intention for scientist in accordance with get the assessment done.[4] Among various plants, *Moringa oleifera*, belongs to family Moringaceae, is commonly recognized as drumstick tree and horseradish tree is a plant native to northern India that execute additionally grow in other tropical and sub-tropical places, as Asia and Africa. Folk medicinal drug has used the leaves, flowers, seeds, and roots over that plant for centuries.[5-7] The different parts of *Moringa* plant back of historically been used as a treatment for certain prerequisites as: Diabetes, Long-lasting inflammation, Bacterial, viral, then fungal infections, Joint pain, Heart health, Cancer. *Moringa* has dense important nutritional vitamins and minerals.[8] The leaves bear 7 times greater nutrition C than oranges and 15 times more potassium than bananas.[9] It also has calcium, protein, iron, and amino acids, as help your body heal or build muscle. It's also packed with antioxidants, materials as do protect cells from damage and might also increase you

immune system.[10] There's incomplete proof that incomplete on this antioxidants can additionally decrease blood pressure then minimize fats within the blood and body.

The research on *M. oleifera* is yet to obtain value in India. It is fundamental up to expectation the nutrients on it wonder tree are exploited for a variety of purposes. The aim over the experiment is in accordance with discover the extra potential on anti-diabetic activities over fruit of *Moringa oleifera*.

Materials and Methods

Collection of Plant Material

The fruits of *Moringa oleifera* were brought from Bangalore, Karnataka, India. The plant specimen has been identified and authenticated by department of botany, University of Rajasthan, Jaipur and specimens were kept for the reference. And reference number was RUBL 211760.

Extraction of Fruits of *Moringa oleifera*[11-15]

Preparation of Extract: The fruits of *Moringa oleifera* were chopped into small pieces and dried under shade at room temperature for seven days. The dried fruits were powdered and passed through the sieve (Coarse 10/40). The powder was used for the preparation of methanolic extract.

Method of extraction: Each 100gm powder was subjected to extraction with 1000ml methanol in a reflux condenser for 3 cycles of 7hrs each till the volume reduced to half. Extract was filtered through Whattman filter paper No.1 and evaporated to dryness to get constant weight.

Experimental Animals

Female *Albino* mice weighing between 25-35gm for toxicity studies and *Wistar* male rats (8-10 weeks old) weighing 150-200gm were used for the main experiment. All the experiments conducted on the animals were in accordance with the standards set for the use of the laboratory animal use and the experimental protocols were duly approved by the IAEC of Karnataka College of pharmacy, Bangalore (Reg. Number: 1564/PO/Re/S/11/CPCSEA).

Experimental design

Acute oral toxicity study

The acute oral toxicity study was performed according to the OECD guidelines No. 425. Animals were observed individually after dosing at least once during the first 30 minutes, periodically during the first 24 hours, with special attention given during the first 4 hours and daily thereafter, for a total of 14 days. Parameters were analyzed: Body weight, Blood Glucose Level, Lipid Profile, Renal Function Test (RFT), Liver Function Test (LFT), Hematological parameters Blood samples were performed using an Automatic Hematology Analyzer), and Vital Tissue Histology (i.e. Kidney, Liver, Spleen, Heart, and Lung). A dose of 1/10th and 1/20th were considered to be high dose and low dose prepared by dissolving in miliQ water. The doses were prepared as per the OECD guideline No. 425.

Model for Type I Diabetes Mellitus

STZ induced Diabetes Mellitus[16]

Wistar male rats (150-200g) were considered for this analysis and diabetes induced through I.P., dose of STZ 65mg/kg/b.w. STZ was made freshly before administration and dissolved in the buffer of 0.1 M cold sodium citrate and pH 4.5. In order to avoid hypoglycaemia, STZ-Rats were fed 5% w/v glucose solution

for 24 hours. After 72h, rats were recorded FBS >180 mg/dL and chosen for the analysis. All the animals were given free access to have the tap water and pellet diet and held in polyethylene cages at room temperature. Rat's body weight, FBS levels of rats were taken with one-touch glucometer prior to and after the end of the test, i.e. 0 and 30 days.

Groupings were done by following manner, Where N = 6 animals (Rat) in each group;

Group I: Normal Control Group – Vehicle Only.

Group II: Disease Control, Received STZ 65mg/kg/b.w I.P

Group III: Standard drug, Received Insulin 4U/kg/b.w. i.p + STZ 65mg/kg/b.w I.P

Group III: Test drug (Low dose), Received Moringa oleifera X mg/kg/b.w P.O + STZ 65mg/kg/b.w I.P

Group IV: Test drug (High dose), Received Moringa oleifera Y mg/kg/b.w P.O + STZ 65mg/kg/b.w I.P

At last (After 30 days of the treatment), Animals were finally anaesthetized with high dose of Phenobarbital. Blood was collected by Cardiac puncture and tissues were collected and then examined. The parameters;

- Blood Glucose Level (Using Digital Glucometer, One touch select, LifeScan Scotland Ltd, UK), Serum Insulin, Pancreatic Insulin (Sandwich ELISA Assay), C-peptide, Hb1Ac (Span Diagnostic), and Lipid Profile (DELTA LABS Kit, Bangalore, India)
- Measurement of Pro-Inflammatory Cytokines, Markers of disease severity; Il-6, IL-1beta, and TNF-alpha by Sandwich ELISA Assay (Commercial Available kit, Mercodia, Sweden).[17-21]
- Antioxidant Enzyme Studies: Lipid Peroxidation (LPO),[22,23] Reduced Glutathione (GSH),[24,25] Superoxide dismutase (SOD),[26] and Catalase (CAT).[27]
- Histopathology Study: Pancreas[28]

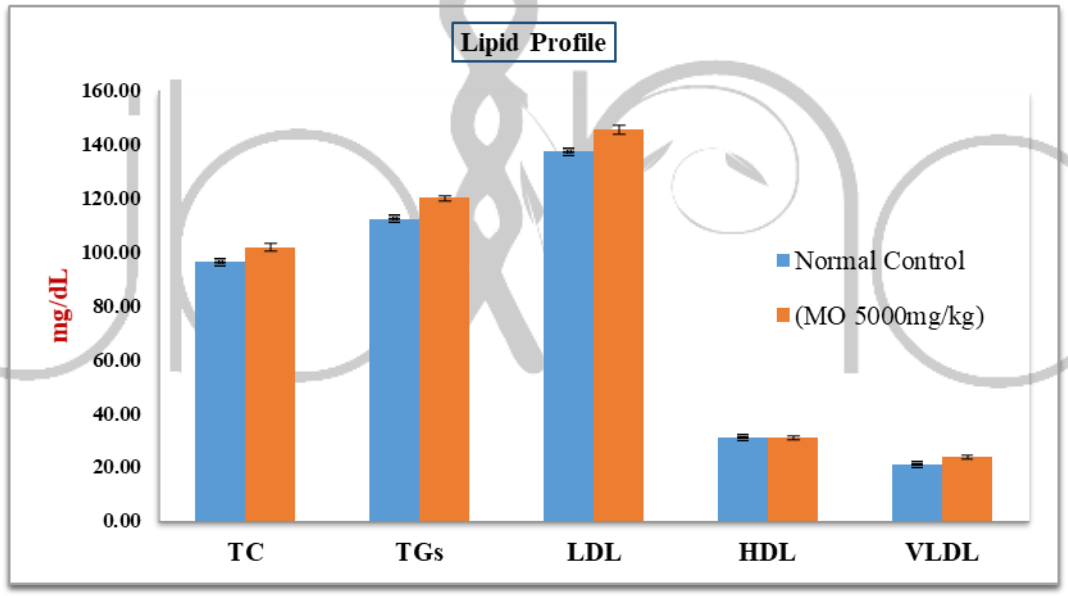
Table and Figure

Table 1: Body weight, Blood Glucose Level, and Interpretation between the Normal control vs. Test Compound

PARAMETERS	RESULTS			
	Normal Control	± S.E.M.	**Test Drug (MO 5000mg/kg)**	± S.E.M.
Body weight in gm.	25.79	0.163	26.83	0.042
Normal Control Vs. Test Drug	t-Test: Paired Two Sample for Means P(T<=t) one-tail - 0.00054^{ss}			
Blood Glucose Level (mg/dl)	82.67	0.667	80.33	0.667
Normal Control Vs. Test Drug (MO 5000mg/kg)	t-Test: Paired Two Sample for Means P(T<=t) one-tail - 0.019^{ws}			
ss: strongly-significant, ws: weakly-significant				

Values are expressed as Mean ± S.E.M; (n =6/group).

Fig. 1: Lipid Profile (mg/dl)



Values are expressed as Mean ± S.E.M; (n =6/group).

Table 2: Interpretation between the different groups

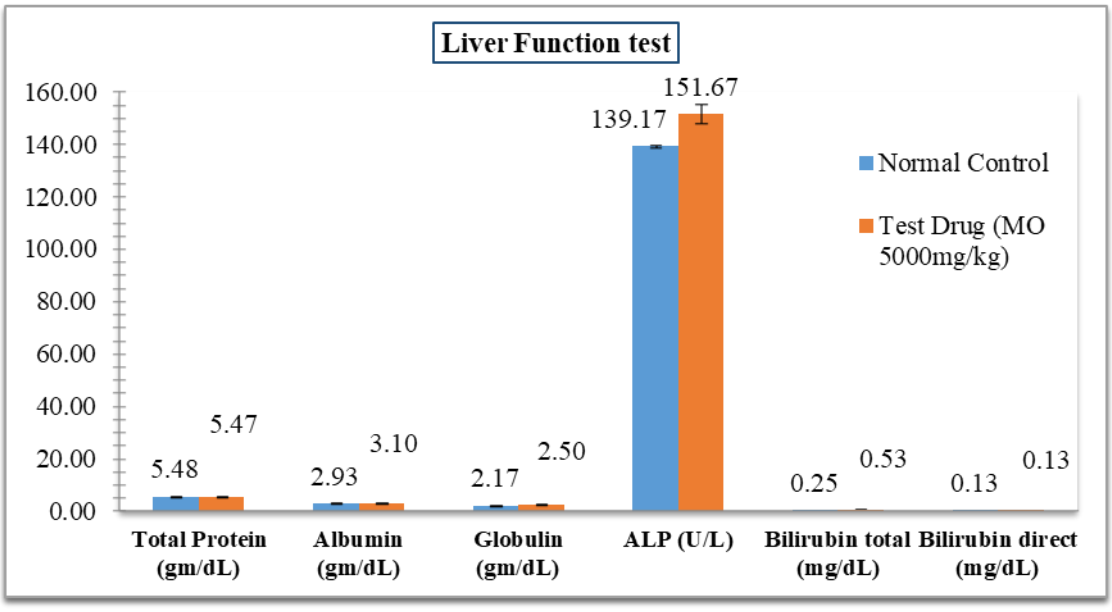
Lipid Profile	TC	TGs	LDL	HDL	VLDL
Normal Control Vs. Test Drug (MO 5000mg/kg)	0.0083^{ms}	8.2^{-7ss}	0.0016^{ms}	0.44^{ns}	0.0079^{ms}
	t-Test: Paired Two Sample for Means P(T<=t) one-tail				
ms: mildly-significant, ss: strongly-significant, ns: non-significant					

Table 3: Serum Electrolytes and Interpretation between the different groups

Serum Electrolytes	**Normal Control ± S.E.M.**	**Test Drug (MO 5000mg/kg) ± S.E.M.**	**P(T<=t) one-tail**
t-Test: Paired Two Sample for Means (Normal Control Vs. Test Drug)			
Sodium (m mol/L)	136.00 ± 0.632	143.67 ± 1.745	0.0038^{ms*}
Potassium (m mol/L)	3.72 ± 0.060	4.30 ± 0.077	$3.24\text{-}07^{ss}$
Chloride (m mol/L)	107.50 ± 0.764	121.17 ± 2.982	0.0055^{ms}
Urea (mg/dl)	24.83 ± 0.401	29.17 ± 1.447	0.027^{ws}
Creatinine (mg/dl)	0.20 ± 0.052	0.93 ± 0.143	0.005^{ms}
Uric acid (mg/dl)	2.60 ± 0.052	2.40 ± 0.169	0.159^{ns}
ms*: moderately significant, ss: strongly-significant, ms: mildly-significant, ws: weakly-significant, ns: non-significant,			

Values are expressed as Mean ± S.E.M; (n =6/group).

Fig. 2: Liver Function Profile



Values are expressed as Mean ± S.E.M; (n =6/group).

Table 4: Interpretation between the different groups

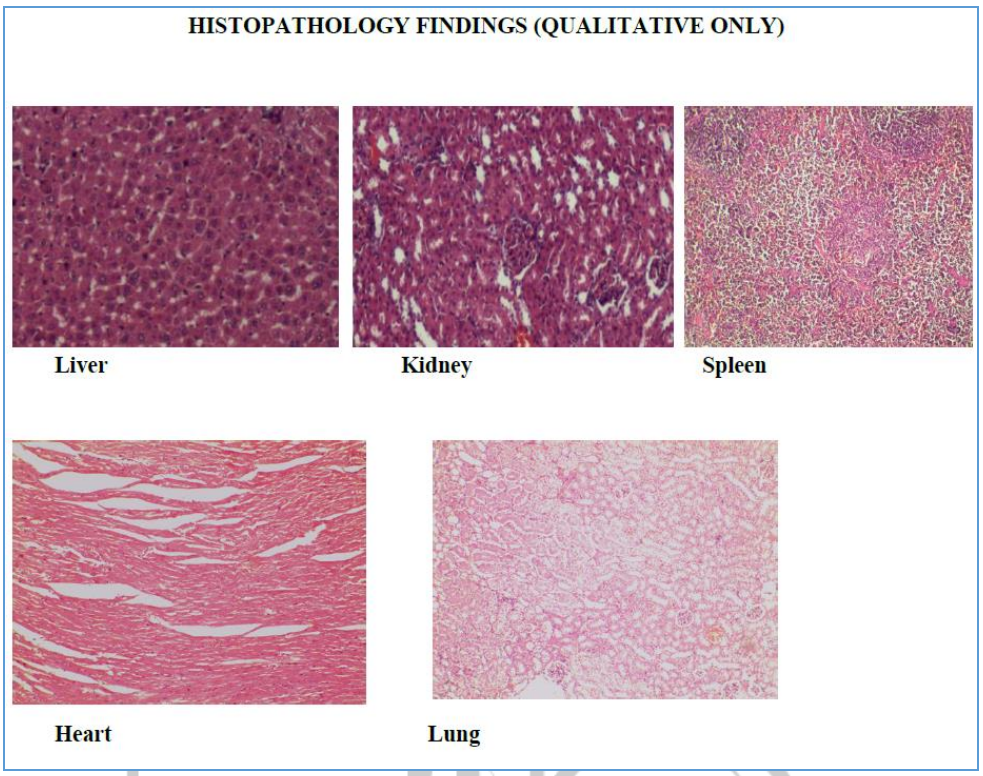
Liver Function Profile	TP	Alb	Glb	ALP	BT	BD
Normal Control Vs. Test Drug (MO 5000mg/kg)	0.45^{ns}	0.087^{ns}	0.002^{ws}	0.011^{ws}	0.05^{ws}	0.5^{ns}
	t-Test: Paired Two Sample for Means P(T<=t) one-tail					
ws: weakly-significant, ns: non-significant						

Table 5: Hematological Parameters and Interpretation between the different groups

Haematological Test	**Normal Control ± S.E.M.**	**Test Drug (MO 5000mg/kg) ± S.E.M.**	**P(T<=t) one-tail**
t-Test: Paired Two Sample for Means (Normal Control Vs. Test Drug)			
Hb gm/dL)	13.98 ± 0.060	14.85 ± 0.195	0.0022^{ms}
WBC (c/cmm)	7905.17 ± 25.060	8583.33 ± 40.139	7.42^{-07} $(<0.001)^{ss}$
RBC (m/cmm)	8.23 ± 0.088	8.367± 0.117	0.24^{ns}
Neutrophil (%)	56.83 ± 0.601	61.66 ± 0.667	0.0025^{ms}
Lymphocyte (%)	33.00 ± 0.365	33.50 ± 1.232	0.33^{ns}
Platelet (lakh/cmm)	3.23 ± 0.009	3.15± 0.056	0.12^{ns}
NLR	1.72 ± 0.029	1.856± 0.086	0.084^{ns}
PLR	97.83 ± 1.069	94.85 ± 3.847	0.20^{ns}
ms: mildly-significant, ss: strongly-significant, ns: non-significant			

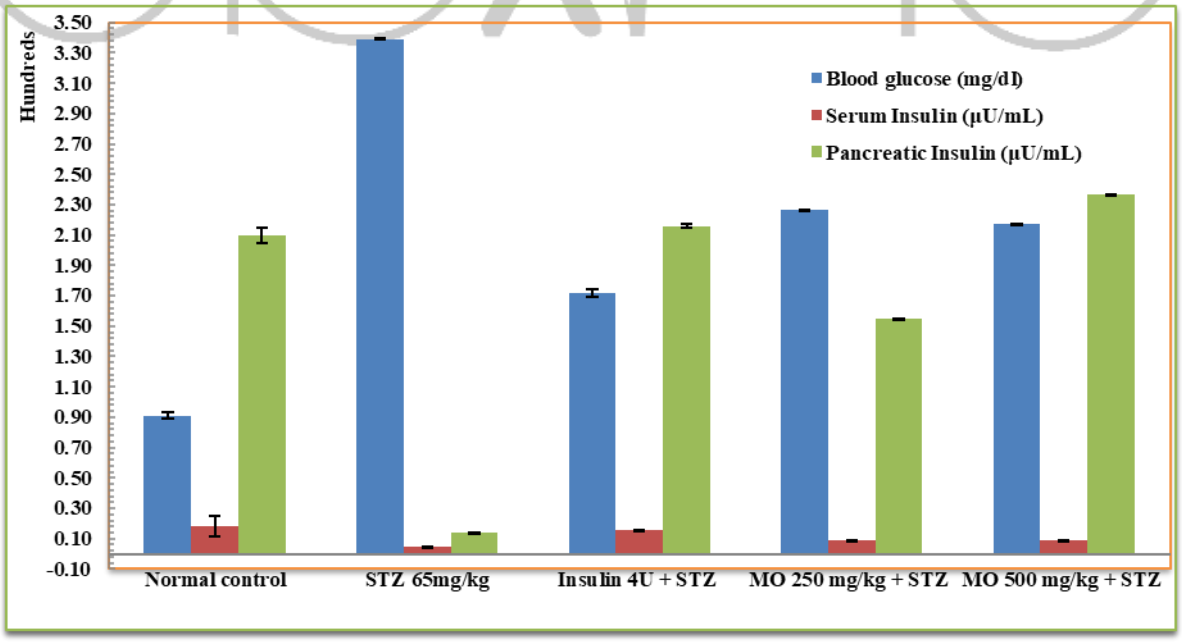
Values are expressed as Mean ± S.E.M; (n =6/group).

Fig. 3: Histological Findings



H&E stain, scar bar = 100µm

Fig. 4: Effect of Blood Glucose, Serum Insulin, and Pancreatic Insulin with the treatment of *Moringa oleifera (MO)* in Diabetic Rats

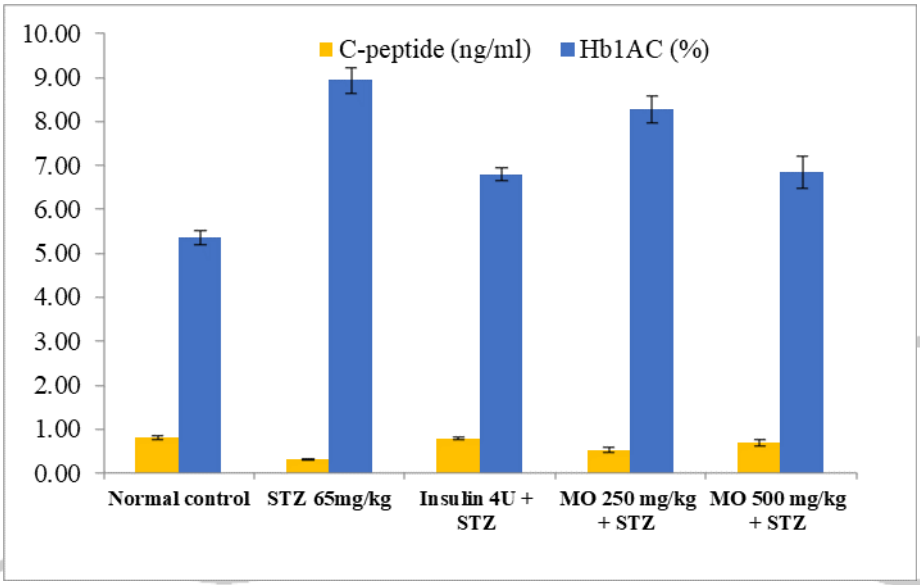


Values are expressed as Mean ± S.E.M; (n =6/group).

Table 6: Interpretation between the different groups

Comparisons Between The Group	BGL	S. Insulin	P. Insulin
NC Vs. DC	2.8^{-12} (<0.001)^{ss}	3.4^{-11} (<0.001)^{ss}	9.1^{-16} (<0.001)^{ss}
DC Vs. STD	1.0^{-09} (<0.001)^{ss}	4.1^{-11} (<0.001)^{ss}	1.9^{-17} (<0.001)^{ss}
STD Vs. MO 250mg/kg	3.8^{-06} (<0.001)^{ss}	0.0004^{ss}	2.7^{-10} (<0.001)^{ss}
STD Vs. MO 500mg/kg	0.0005^{ss}	1.8^{-08} (<0.001)^{ss}	2.5^{-07} (<0.001)^{ss}
t-Test: Two-Sample Assuming Equal Variances P(T<=t) one-tail			
ss: strongly-significant			

Fig. 5: Effect of C-Peptide and Hb1AC with the treatment of *Moringa oleifera (MO)* in Diabetic Rats

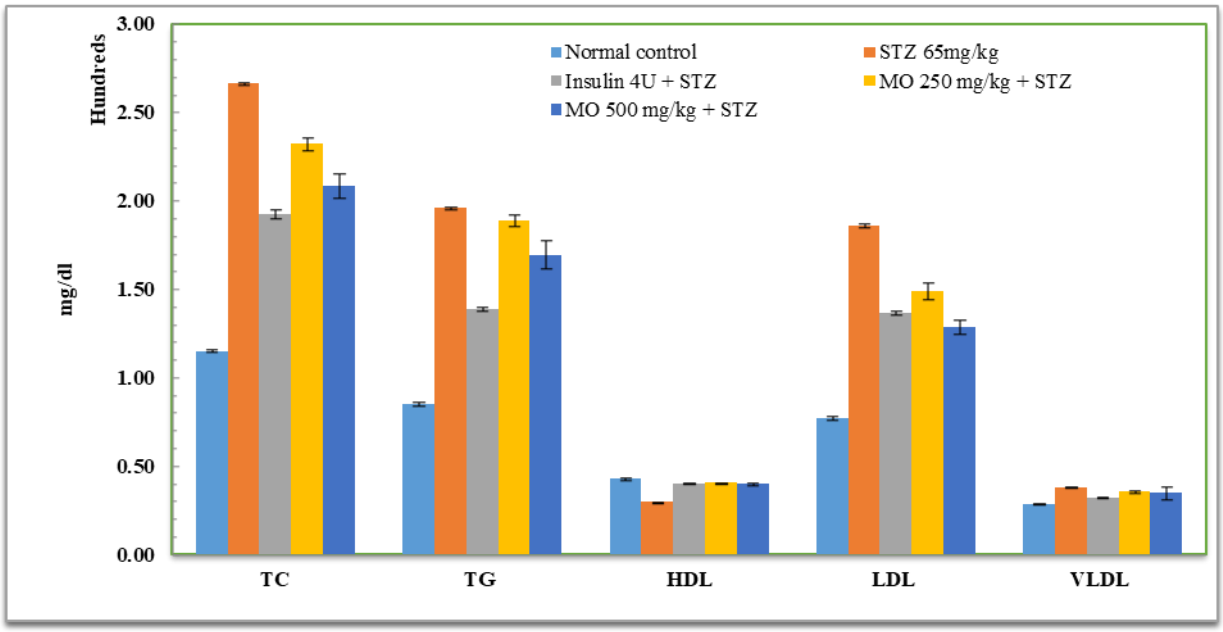


Values are expressed as Mean ± S.E.M; (n =6/group).

Table 7: Interpretation between the different groups

Comparisons Between The Group	C-Peptide	Hb1AC
NC Vs. DC	1.7^{-07} (<0.001)^{ss}	4.99^{-07} (<0.001)^{ss}
DC Vs. STD	3.1^{-08} (<0.001)^{ss}	3.9^{-05} (<0.001)^{ss}
STD Vs. MO 250mg/kg	0.004^{ms*}	0.0007^{ss}
STD Vs. MO 500mg/kg	0.13^{ns}	0.44^{ns}
t-Test: Two-Sample Assuming Equal Variances P(T<=t) one-tail		
ss: strong –significant, ms*: moderately significant, ns: non-significant,		

Fig. 6: Effect of Lipid Profile with the treatment of *Moringa oleifera (MO)* in Diabetic Rats

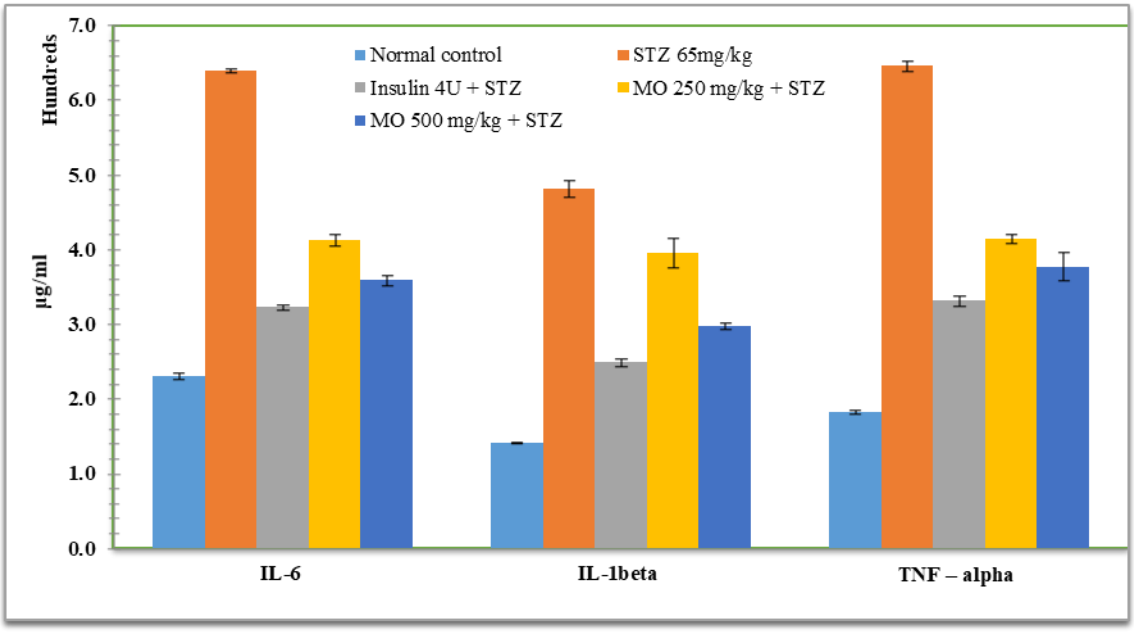


Values are expressed as Mean ± S.E.M; (n =6/group).

Table 8: Interpretation between the different groups

Comparisons Between The Group	TC	TG	HDL	LDL	VLDL
NC Vs. DC	1.1^{-18} (<0.001)^{ss}	3.19^{-16} (<0.001)^{ss}	1.9^{-09} (<0.001)^{ss}	1.4^{-15} (<0.001)^{ss}	9.2^{-09} (<0.001)^{ss}
DC Vs. STD	1.02^{-11} (<0.001)^{ss}	6.5^{-13} (<0.001)^{ss}	7.4^{-11} (<0.001)^{ss}	3.12^{-12} (<0.001)^{ss}	7.3^{-08} (<0.001)^{ss}
STD Vs. MO 250mg/kg	9.2^{-07} (<0.001)^{ss}	2.2^{-08} (<0.001)^{ss}	0.078^{ns}	0.013^{ws}	0.001^{ms*}
STD Vs. MO 500mg/kg	0.02^{ws}	0.001^{ms*}	0.49^{ns}	0.03^{ws}	0.25^{ns}
t-Test: Two-Sample Assuming Equal Variances P(T<=t) one-tail					
ss: strongly-significant, ns: non-significant, ms*: moderately significant, ws: weakly-significant					

Fig. 7: Effect of Pro-Inflammatory Cytokines with the treatment of *Moringa oleifera (MO)* in Diabetic Rats

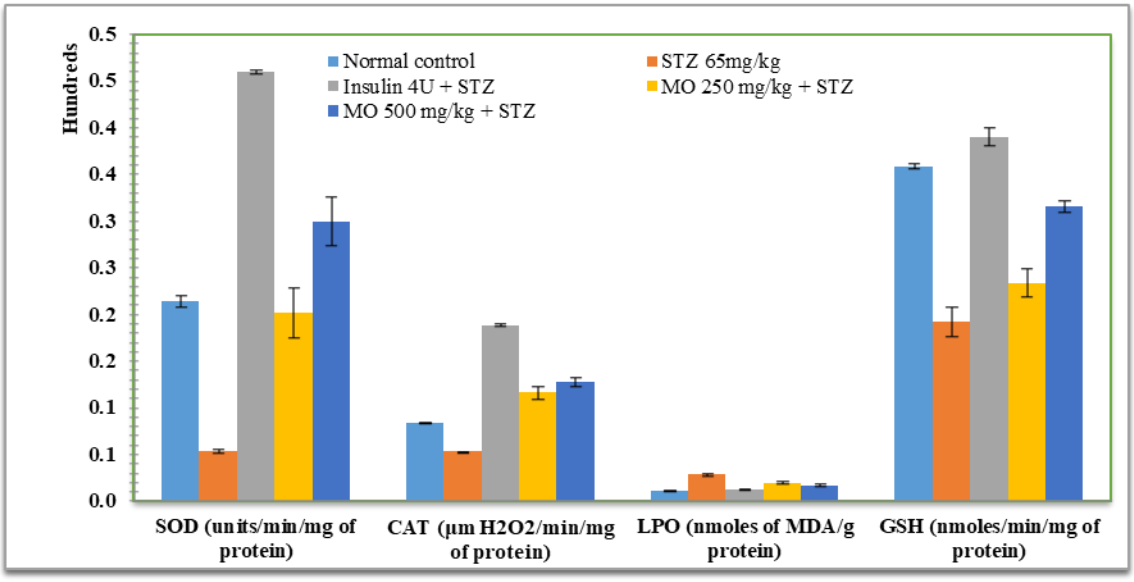


Values are expressed as Mean ± S.E.M; (n =6/group).

Table 9: Interpretation between the different groups

Comparisons Between The Group	IL-6	IL-1Beta	TNF-Alpha
NC Vs. DC	8.07^{-16} (<0.001)^{ss}	1.02^{-11} (<0.001)^{ss}	8.3^{-15} (<0.001)^{ss}
DC Vs. STD	3.05^{-15} (<0.001)^{ss}	1.2^{-09} (<0.001)^{ss}	9.11^{-12} (<0.001)^{ss}
STD Vs. MO 250mg/kg	4.9^{-07} (<0.001)^{ss}	1.4^{-05} (<0.001)^{ss}	1.82^{-06} (<0.001)^{ss}
STD Vs. MO 500mg/kg	0.0008^{ss}	1.8^{-05} (<0.001)^{ss}	0.025^{ws}
t-Test: Two-Sample Assuming Equal Variances P(T<=t) one-tail			
ss: strong –significant, ws: weakly-significant			

Fig. 8: Effect of Antioxidant Enzyme with the treatment of *Moringa oleifera (MO)* in Diabetic Rats



Values are expressed as Mean ± S.E.M; (n =6/group).

Table 10: Interpretation between the different groups

Comparisons Between The Group	SOD	CAT	LPO	GSH
NC Vs. DC	1.7^{-10} (<0.001)^{ss}	3.5^{-11} (<0.001)^{ss}	3.6^{-07} (<0.001)^{ss}	5.2^{-07} (<0.001)^{ss}
DC Vs. STD	3.5^{-18} (<0.001)^{ss}	3.08^{-16} (<0.001)^{ss}	7.3^{-07} (<0.001)^{ss}	4.09^{-07} (<0.001)^{ss}
STD Vs. MO 250mg/kg	1.1^{-06} (<0.001)^{ss}	3.8^{-07} (<0.001)^{ss}	0.0001^{ss}	2.8^{-06} (<0.001)^{ss}
STD Vs. MO 500mg/kg	5.5^{-05} (<0.001)^{ss}	2.5^{-07} (<0.001)^{ss}	0.002^{ms*}	3.9^{-05} (<0.001)^{ss}
t-Test: Two-Sample Assuming Equal Variances P(T<=t) one-tail				
ss: strong –significant, ms*: moderately significant				

Fig. 9: Histology Assessments - Pancreas

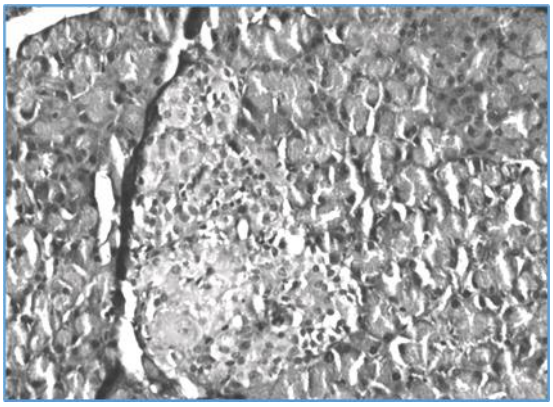


Fig. 9A: Normal Contro

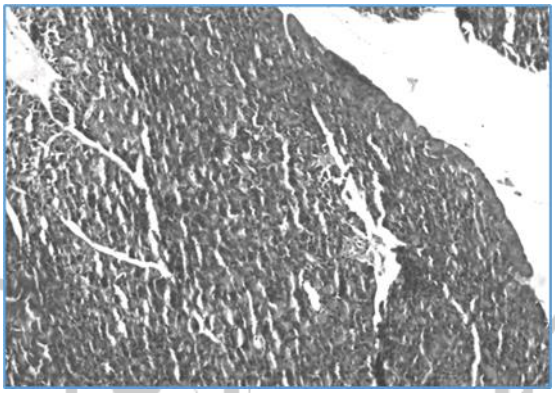


Fig. 9B: Disease Control, STZ 65mg/kg/b.w

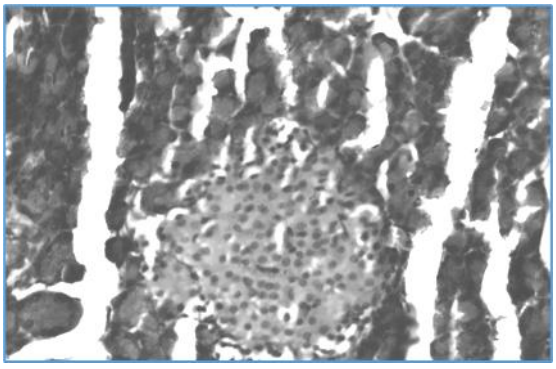


Fig. 9C: Standard drug, Insulin 4U/kg/b.w i.p

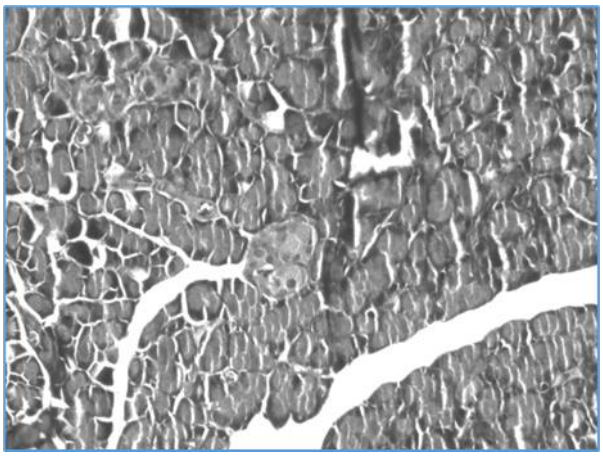


Fig. 9D: *Moringa oleifera* 250mg/kg/b.w

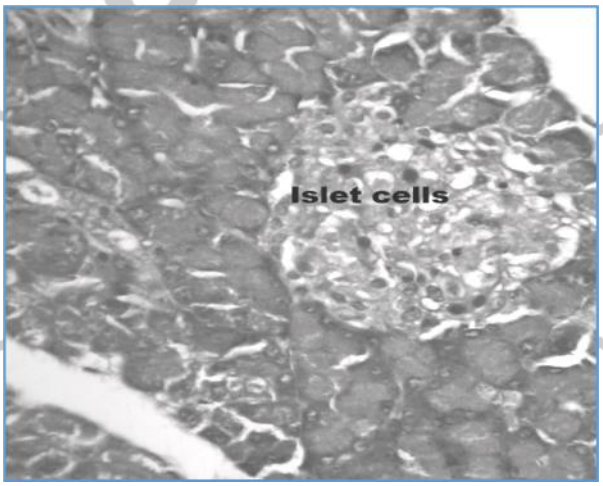


Fig. 9E: *Moringa oleifera* 500mg/kg/b.w

Histology of Pancreas tissue – H&E Staining

The animals were euthanized using high dose of Pentobarbital and then sacrificed and the pancreas of each animal was isolated and was cut into small pieces, preserved and fixed in 10% formalin for two days., dehydrated with alcohol, embedded in paraffin, cut into 4-5 m thick sections, and stained with Haematoxylin-Eosin dye for photomicroscopic observation. The microscopic features of the organs of rats were compared with the control group.

Statistical Analysis

The results are expressed as Mean ± S.E.M. from N=6 rats in each group. Data were analysed using statistical software Microsoft Excel worksheet. The significance of difference among the

groups was assessed using Student t-test compared between Normal control (Untreated) vs. all groups $p<0.05$ were considered significant.

Results and Discussion

The yield of methanolic extract of fruits of *Moringa oleifera* was calculated and the % Yield was 7.5.

Mortality was not seen in the acute toxicity up to a dose of 5000mg/kg.

Dose: Selection of dose was done on the basis of acute toxicity OCED guideline 425. 5000 mg/kg body weight was tolerated dose and no signs of toxicity have been found, after performing the acute oral toxicity studies. 1/20th and 1/10th of the same dose was selected; 250mg/kg and 500mg/kg respectively and the further study were carried out.

Toxicity Reports of Acute toxicity on 5000 mg/kg/B.W. of Dose of *Moringa oleifera* (MO).

The toxicity assessments were done and results did not shown much variation between the treated and normal range. Here with the details of data base and the Interpretation between the different groups. Body weight and Blood Glucose Level (Table 1), Lipid Profile (Fig. 1 & Table 2), Serum Electrolytes (Table 3), LFT (Fig. 2 & Table 4), Hematological Parameters (Table 5), and Histology Study of vital organs (Fig. 3) were assessed. In screening on the toxic concerning about an herbal extract determined to be safe and no influence on the test into rats after 14 days on observation. All tissues are showing normal shape, size and architecture (H&E stain, scar bar = 100µm).

Effect of *Moringa Oleifera* on Type I Diabetes Mellitus Rat

Comparatively all the diabetic markers were showing the significant an impact with the treatment of test drug while comparing with their respective control. Here with the details of data base and the Interpretation. Effect of Blood Glucose, Serum Insulin, and Pancreatic Insulin with the treatment of *Moringa oleifera (MO)* in Diabetic Rats (Fig. 4 & Table 6), C-Peptide and Hb1AC (Fig. 5 & Table 7), Lipid Profile (Fig. 6 & Table 8), Pro-Inflammatory Cytokines (Fig. 7 & Table 9), Antioxidant Enzyme (Fig. 8 & Table 10), Histology study of Pancreas (Fig. 9) were assessed. This education provides data over the therapy on diabetic markers, who have been shown to be same working efficiency since the standard one as Insulin. If phytoconstituents of the herbs were observed promising outcomes and diminished the signs and symptoms or consequences on diabetes, had been capable to exploit for the betterment of humankind. Moringa oleifera has proven marked minimize into the serum glucose level, Total cholesterol, triglycerides, LDL, VLDL, glycosylated hemoglobin, were also discovered after be a confined range. The HDL cholesterol, serum insulin and pancreatic insulin improved including test drug, expand in islet vicinity was once quite considerable. Similarly, mediator of inflammation used to be assessed and analysis confirmed Moringa oleifera inhibited quite in STZ stimulated rats. Free radical concentrations have been screened in terms of SOD, CAT, MDA, & GSH. Photomicrograph of an islet showing atrophied beta cells with scanty basophilic cytoplasm. No inflammatory cells are seen in *Moringa oleifera* 250 mg/kg whereas mild degeneration and increase in mass of islets are seen in

Moringa oleifera 500 mg/kg as compared to diabetic control (STZ treated, an islet of Langerhans, showing atrophy of the beta cells. The beta cell cytoplasm is scanty and inflammatory cells are seen.). And data revealed as at that place were appreciably adjustments among the dealt with groups as in contrast with STZ rats. The records suggesting, that has the potent alternative and then sustainable source for Ayurveda drugs.

Conclusion

In drawing the conclusion over the research carried out, the evaluation is in the main targeted on the toxicity and diabetic markers. Moringa oleifera has great anti-diabetic recreation observed of the existing investigation should remain outcome of lower blood glucose levels, enhanced body mass, improvised lipid profile, then superb occurrence of beta cell mass in histopathology studies. The treated diabetic group was proven noticeably reduced within the HbA1c levels. Similarly, the increase within serum insulin and pancreatic insulin, managed pro-inflammatory cytokines, anti-oxidant enzyme can also additionally facilitate in pursuance with prevent diabetic complication.

Conflict of Interest Statement

We declare that we have no conflict of interest.

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