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Research

Invivo Evaluation Of Anti-Diabetic Activity Of Chloroform Peel Extract Of *Mangifera Indica*

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Abstract

Diabetes mellitus is a major metabolic disorder whose prevalence is increasing daily. Medicinal plants have played an important role in the prevention and treatment of Diabetes mellitus.In ethnomedicinal practices, different parts of *Mangifera indica* are used for the treatment of diabetes. Mangifera indica extract showed presence of secondary metabolites such as tannins, xanthones, flavonoids, and terpenoids etc. These secondary metabolites are responsible for the anti-diabetic activity. In this study Mangifera indica chloroform peel extract was investigated for its promising anti-diabetic activity via an in vivo model. This experiment was conducted in a set of five with five groups of animals namely control group, toxicant group, standard group, Test I group and Test II group. To develop diabetes, Wistar rats were injected alloxan monohydrate intraperitoneally. Test I and Test II groups received a freshly prepared single dose of Mango peel chloroform extract in rice bran oil. All experimental groups received laboratory pallet feed diet and drinking water. Diabetic rats were treated for 21 days with an chloroform extract of mango peel orally daily at rates of 150 mg/kg b.w. and 200 mg/kg b.w. followed by histopathological evaluation of pancreas. It was found that Mangifera indica chloroform peel extract possessed highly significant activity ($p > 0.001$) at a concentrations of 150 mg/kg and 200 mg/ decreased the fasting blood levels in alloxan induced diabetic rats where as, standard metformin (200 mg/kg b.w.) showed significant ($p<0.001$) decrease in the fasting blood glucose levels.

Keywords: *Mangifera Indica,* Anti-Diabetic, Chloroform extract, Metformin, Alloxan monohydrate.

INTRODUCTION

Diabetes mellitus is a group of metabolic diseases characterized by chronic hyperglycaemia resulting from defects in insulin secretion, insulin action, or both. Low levels of insulin to achieve adequate response and/or insulin resistance of target tissues, mainly skeletal muscles, adipose tissue, and to a lesser extent, liver, at

the level of insulin receptors, signal transduction system, and/or effector enzymes or genes are responsible for these metabolic abnormalities. The severity of symptoms is due to the type and duration of diabetes. Some of the diabetes patients are asymptomatic especially those with type 2 diabetes during the early years of the disease, others with marked hyperglycemia and especially in children with absolute insulin deficiency may suffer from polyuria, polydipsia, polyphagia, weight loss, and blurred vision. Uncontrolled diabetes may lead to stupor, coma and if not treated death, due to ketoacidosis or rare from nonketotic hyperosmolar syndrome[1-2].

Classification of Diabetes Mellitus

Type 1 Diabetes Mellitus/ Insulin dependent diabetes mellitus (IDDM)

Type 1 diabetes mellitus (T1DM) comprises several diseases of the pancreatic ß cells which lead to an absolute insulin deficiency. This is usually considered to be the result of an autoimmune destruction of the pancreatic ß cells (type 1A). Some patients with T1DM with no evidence of ß cell autoimmunity have underlying defects in insulin secretion often from inherited defects in pancreatic ß cell glucose sensing and from other genetic or acquired diseases[3].

Type 2 Diabetes Mellitus/Non-Insulin dependent diabetes mellitus (NIDDM)

Type 2 diabetes mellitus (T2DM) is by far the more common type of diabetes and is characterized by insulin resistance resulting from defects in the action of insulin on its target tissues (muscle, liver, and fat), but complicated by varying and usually progressive failure of beta cells' insulin secretary capacity. Most patients with T2DM in the US and Europe are overweight or obese, however in India and China, most T2DM patients have a lean body mass index (BMI), albeit with increased visceral and hepatic fat.

Gestational Diabetes Mellitus

Gestational diabetes mellitus (GDM) is defined as glucose intolerance which is first recognized during pregnancy. In most women who develop GDM, the disorder has its onset in the third trimester of pregnancy. At least 6 weeks after the pregnancy ends, the woman should receive an oral glucose tolerance test and be reclassified as having diabetes, normal glucose tolerance, impaired glucose tolerance, or impaired fasting glucose. Gestational diabetes complicates about 8-9% of all pregnancies, though the rates may double in populations at high-risk for type 2 diabetes[4].

Structure and functions of the pancreas

Pancreatic ß cells secrete insulin and are found in the islets of Langerhans. These islets are specialized groups of a few hundred to a few thousand endocrine cells that are anatomically and functionally discrete from pancreatic exocrine tissue, the primary function of which is to secrete pancreatic enzymes into the duodenum. Normal subjects have about one million islets, which in total weigh only 1-2 grams and constitute less than 1% of the mass of the pancreas.

Furthermore, islets are composed of various types of cells that are interconnected as a regulatory network to regulate the disposition of nutrients and their utilization for energy use and tissue growth and repair. At least 70% are ß cells localized in the core of the islets, surrounded by α-cells that secrete glucagon, δ-cells that secrete somatostatin, and PP cells that secrete pancreatic polypeptide. All the cells communicate with each other through their extracellular spaces and through gap junctions; communication is further modulated by a rich network of sympathetic and para sympathetic innervation.

Insulin, a peptide hormone composed of 51 amino acids is synthesized, packaged and secreted in pancreatic ß cells. Insulin is synthesized as preproinsulin in the ribosomes of rough endoplasmic reticulum. The preproinsulin is then cleaved to proinsulin that is transported to the Golgi apparatus where it is packaged into secretory granules. Most of the proinsulin is cleaved into equimolar amounts of insulin and connecting (or C)-peptide in the secretory granules. Because the C-peptide sequence differs from that of insulin, and because, unlike insulin, it is not extracted by the liver, it is possible to estimate β-cell insulin secretion by measuring C-peptide, even in the presence of insulin antibodies resulting from insulin replacement therapy that impair the ability to measure insulin directly. Similarly, because Cpeptide is an index of endogenous insulin secretion, and because C-peptide is not extracted by the liver, the ratio of C-peptide: insulin should exceed 1; when it is less than 1, implying a high insulin value, exogenous insulin may have been used. This has diagnostic and forensic utility in diagnosing causes of hypoglycemia.

Glucose is a major regulator of insulin secretion .When extracellular fluid glucose concentrations rise after a meal, glucose is taken up by the ß cells via glucose transporters, GLUT2 and GLUT1. Glucose is then phosphorylated into glucose-6-phosphate by islet specific glucokinase and metabolized, thereby increasing cellular ATP concentrations. The rise in ATP raises the resting ratio of ATP:ADP, that closes ATP dependent potassium channels (K-ATP) in the β-cell membrane, resulting in accumulation of intracellular potassium, causing membrane depolarization and influx of calcium via a voltage gated calcium channel. The rise in intracellular free calcium in ß-cells promotes margination of the secretory granules, their fusion with the cell membrane, and release of cell contents which include insulin into the extracellular space. An immediately

releasable pool of insulin granules adjacent to the plasma membrane is responsible for an acute (first phase) insulin response; with ongoing stimulation, a pool of granules in the interior of the cell is mobilized and released as the "second phase" response.

Amino acids also stimulate insulin release by a similar mechanism that involves the enzyme glutamate dehydrogenase which enables metabolism and ATP production by certain amino acids. Defects in the genes regulating these processes may result in diabetes if the K-ATP channel is prevented from closing normally (activating mutations) or syndromes of hyperinsulinemichypoglycemia if the K-ATP channel is prevented from opening (inactivating mutations). These aspects are discussed in greater detail in the section on Monogenic forms of diabete[5].

Signs and symptoms of Diabetes mellitus:[6]

• Frequent fatigue
• Irritability
• Repeated infections especillay in the Genital areas
• Unexplained weight loss
✓ Urinary tract
✓ Skin
✓ Oral activity
✓ Delayed wound healing

• Dry mouth
• Burning, pain, numbness on feet
• Itching
• Reactive hypoglycaemia
• Acanthoses nigricans- the presence of velvety dark patches of the neck, arm pit, groin which is an indicator of insulin resistance
• Decreased vision
• Impotence or erectile dysfunction

Major risk factors for type 2 diabtes in Indians

• Positive family history of diabetes
• Age > 35 years
• Overweight and obesity
• Enlarged waist or upper body adiposity(>90 cm for men and >80 cm for women)
• Presence of hypertension
• Recent weight gain
• Sedentary lifestyle
• Gestational diabetes.

Complications of Diabetes Mellitus

Diabetes complications are common among patients with type 1 or type 2 diabetes but, at the same time, are responsible for significant morbidity and mortality. The chronic complications of diabetes are broadly divided into microvascular and Microvascular complications included neuropathy, nephropathy, and retinopathy, while macrovascular complications consist of cardiovascular disease, stroke, and peripheral artery disease (PAD).macrovascular, with the former having much higher prevalence than the latter.

***(A) Epidemiology and Pathogenesis of Diabetic Complications*:** The incidence rate of type 1 diabetes varies widely around the world and depends on the interaction between genetic susceptibility and certain environmental factors. Recently, it has been demonstrated that low socioeconomic status is associated with higher morbidity and mortality rates for patients with type 1 diabetes mellitus (T1DM)[7]. It is well established that obesity is a major contributory factor to insulin resistance and type 2 diabetes mellitus (T2DM)[8].

(B) Microvascular Complications: Indices of subclinical inflammation, such as higher hsCRP, are correlated with the prevalence of type 2 diabetes and metabolic syndrome[9] Meprins are metalloproteinases—expressed in kidney by proximal tubules—that have been proven to play a significant role in the development of diabetic nephropathy[10].

(C) Macrovascular complication: Peripheral artery disease is a common complication and comorbidity of diabetes. Patients with diabetic foot ulcers have coexisting PAD at a proportion of approximately 50% and may suffer from chronic ischemic pain[11].

***(D) Miscellaneous Complications*.** It has been demonstrated that patients with diabetes, who experience episodes of severe hypoglycemia, have a higher risk of cardiovascular disease[12].

(E) Treatment Option: Hyperglycemia can cause modifications in the eye lens through multiple mechanisms, and thus, patients with type 2 diabetes are at increased risk of developing cataract[13].

PLANT PROFILE

MANGIFERA INDICA

Kingdom : Plantae
Subkingdom : Tracheobionta
Superdivision : Spermatophyta
Division : Magnoliophyta
Class : Magnoliopsida
Subclass : Rosidae

Mango (Mangifera indica) is a juicy stone fruit belongs to the family of Anacardiaceae in the order of Sapindales and is grown in many parts of the world, particularly in tropical countries[14]. It is the national fruit of India and Philippines and the national tree of Bangladesh.

Over 1000 mango varieties are available worldwide. Of the available varieties, only a few are grown on commercial scales and traded. Mango is now commercially grown in more than 87 countries. Currently on an area of approximately 3.7 million has worldwide. Mango fruit conquers the second position as a tropical crop, behind only bananas in terms of production and acreage used. It has been well documented that mango fruits are an important source of micronutrients, vitamins and other phytochemicals. Moreover, mango fruits provide energy, dietary fibre, carbohydrates, proteins, fats and phenolic compounds which are vital to normal human growth, development and health[15].

Common names

The common names of Mangifera indica include:

- Hindi: Am, Ambi, Amia
- Arab: Mabaz
- Bengali: Am (Um)
- Chinese: Mi wang
- Danish: Mango, Mangofrugt, Mangotrae
- Dutch: Manga, Mangga, Manja, Mangoestanboom
- English: Mango
- Finnish: Mango, Mangopuu
- French: Mangue, Manguier
- German: Indischer Mangobaum, Mango
- Greek: Magko, Mangko
- Japanese: Anchaa, Mangoo, Mang

Order : Sapindales
Family : Anacardiaceae
Genus :Mangifera
Species : M. indica

PLANT DESCRIPTION

Tree is medium to large (10-40 m in height), evergreen with symmetrical, rounded canopy ranging from low and dense to upright and open. Bark is usually dark grey-brown to black, rather smooth, superficially cracked, peeling off in irregular, rather pieces. The tree forms a unbranched long top root (up to 6-8 m and more) plus a dense mass of superficial feeder roots. The leaves are simple alternately arranged. Leaves are variable in shapes like oval-lanceolate, lanceolate, oblong, linear-oblong, ovate, obovate-lanceolate or roundish-oblong[15].

ETHNOMEDICINAL USES

Various parts of mango are used for more than thousands of years as wide variety of ethnomedicinal use. The unripe fruits are acidic, acrid, antiscorbutic, refrigerant, digestive and carminative. They are useful in dysentery ophthalmia eruptions, and vaginopathy. The ripe fruits are refrigerant, sweet, emollient, laxative, cardiotonic, haemostatic, aphrodisiac, and tonic. In addition to fruit, leaves flowers, stone, roots and barks are having various ethnomedicinal uses.

NUTRIENT AND PHYTOCHEMICALS

Mango contains a variety of phytochemicals and nutrient. Mango peel and pulp contain other compounds such as pigment carotenoids and polyphenols, and omega-3 and omega-6 polyunsaturated fatty acids. Mango peel pigments have biological effects, including carotenoids, such as the provitamin A compound,

beta-carotene, lutein and alpha-carotene, polyphenols such as quercetin, tannins, kaempferol, gallic acid, caffeic acid

PHARMACOLOGICAL USES

Mango juice and juice extracts has anticancer activity, anti-inflammatory activity, hepatoprotective, anti-hemorrhagic, anti-tetanus, analgesic and antipyretic activity. The leaves, peel of ripen mango, stone, roots and bark are used for anti-diabetic activity. Various parts of mango and mango plant are used as antibacterial, antiviral, antifungal, anti-amoebic, cardio protective, osteoporosis prevention, bronchodilator, and laxative.

MATERIAL AND METHODS

COLLECTION OF FRUITS

The fruit *Mangifera indica* was collected from the local market dhulapally area near kompally in Hyderabad in the month of April and authenticated in Department of Botany at University College of Science, Osmania University, Hyderabad in the month of April
voucher number: OUAS-146 The fruits were washed with tap water to remove dirt and
shade dried for one week in the lab and a cracky sound was observed.The dried peels was then powdered into coarse powder using blender.

EXTRACTION

- The mango peel extract was prepared by the soxhlation process using chloroform as a solvent.
- The mango peel powder was usually placed in a thimble (made of butter paper) and then inserted into the extractor.
- The solvent chloroform was placed in the round bottom flask and boiled.
- The vapours arised from the flask were passed by the side tube into the condenser. The vapours are condensed and drips into body of the extractor as pure menstruum.
- It percolates through the drug to be extracted dissolving the soluble constituents.
- As soon as the level of menstrum in the main extractor rises above the siphon bend, the extract is drained out flowing through the siphon tube into flask.
- The cycles was repeated continuously and the desired compound was concentrated in the round bottomed flask.
- After extraction, the solvent was removed by means of evaporation, and a semisolid extract was obtained.
- The non-soluble portion of the extracted solid was remained in the thimble and usually discarded.

PHYTOCHEMICAL SCREENING[14,16]

Tannins, terpenoids, xanthones and flavonoids catechins and the unique mango xanthonoid, mangiferin are the main phytochemical constituents which are responsible for the anti-diabetic activity. Carbohydrates, proteins, Amino acids are also present which are responsible for many pharmacological activities.

Table 1:Phytochemical screening

S. No	Preliminary tests	Results
1	**CARBOHYDRATES:**To the test solution add equal volume of Benedict's reagent. Heat in boiling water bath for 5 min. Green colour was observed.	+ve
2	**PROTEINS:** To the extract, 2ml of 10% sodium hydroxide was added along with 2 drops of 10% lead acetate solution. The mixture was boiled, a black or brownish colour was observed.	+ve
3	**PHENOLIC COMPOUNDS:** To the test solution 5% ferric chloride solution was added. A deep blue-black colour was observed.	+ve
4	**TANNINS:**To the test solution iodine solution was added. A transient red colour was observed.	+ve
5	**FLAVONOIDS:** To the test solution, a small quantity of lead acetate solution was added. A yellow colour precipitate was observed.	+ve
6	**TERPINOIDS:** To the extract, 2 ml of chloroform was added along with sulphuric acid carefully. A reddish brown colouration junction of two layers was observed.	+ve

GROUPING OF ANIMALS

Our project has been approved by the Animal Ethical Committee having refernce number (1662/PO/Re/S/12/CPCSEA) and animals were purchased from the VAB BIOSCIENCES, GATKESAR(CPCSEA : 282/P0/RC BT/S/200). In the initial stage of experiment all the animals were adapted for an interval of 5-7 days to the usual laboratory environment for 24 hours with day and night cycle with optimum room temperature (24+2 ℃) and relative humidity 55-60%. For the anti- diabetic study, the wistar rats with 120-150grams were grouped into five groups. Five rats are taken in each group. Sterile metabolic cages are used to uphold the rats. The animals were provided a diet of pellets, husk and water was given. Every experiment involving animals was carried out with the approval of Animal Ethical Committee. The experiment was conducted in a set of five. Five groups of animals (five in each groups. The groups were named as control, toxicant, standard, test-1 and test-2. Single dose of Alloxan monohydrate (diabetic inducing drug) was given to the four groups i.e is toxicant, standard, test-1 and test-2.

Induction of diabetes by alloxan in wistar rats

Individually animals were choosen, weighed, and marked. To develop diabetes in fasting wistar rats weighing 120-180 mg/kg b.w., alloxan monohydrate in saline (0.9 percent NaCl) at a dose of 150 mg/kg was injected intraperitoneally (IP) into the animals. After one hour of alloxan monohydrate administration, to combat the early hypoglycemia shock, a solution of dextrose with a concentration of 5% was administered by feeding bottles for one full day. Then animals were left for about one week to increase the blood glucose levels. After the period of 72 hours, animals whose blood glucose concentrations are above 250 mg/dl were considered as diabetic and they were used for the study[17].

Method of collection of blood

Diabetes was confirmed after 4 days of alloxan injection. The blood samples were collected through the rat tail vein and retina. The serum glucose was estimated by the glucometer[18].

EXPERIMENTAL DESIGN

Total 25 rats were used in the experiment and were dived into five groups. Each group consists of 5 rats. Rats were treated with standard metformin and extract in various doses, based on their weights to show anti-diabetic activity for 21 days of continuous dosing. The standard Metformin (200 mg/kg) is diluted with vehicle (rice bran oil) is given for standard group for 21 days. The extract 150 mg/kg is diluted in vehicle and given for test 1 group for 21 days. The extract 200 mg/kg is given for test 2 groups for 21 days. After 21 days of dosing, on 22 nd day the serum glucose levels were checked with the glucometer. Those glucose values were noted and the animals were dissected[17].

Table 2: Groups of rats

Groups	Toxicant	Anti-diabetic drug
Control	Only vehicle	---------
Toxicant	Alloxan monohydrate(150mg/kg)	---------
Standard	Alloxan monohydrate(150mg/kg)	Metformin (200mg/kg)
Test 1	Alloxan monohydrate(150mg/kg)	Extract (150mg/kg)
Test 2	Alloxan monohydrate(150mg/kg)	Extract (200mg/kg)

DISSECTION

All the animals were anesthetised using chloroform. The unconcious rats are placed on the tray and pinned for dissection. After the dissection the rat pancreas was removed and placed in the formalin solution and sent to JEEVA LIFE SCIENCES (Tarnaka UPPAL, Hyderabad) for hipstopathological studies.

RESULTS AND DISCUSSION

The present study was taken to investigate the antidiabetic activity of chloroform extract of peel of Mangifera indica. Chloroform peel extract of 150 mg/kg, and 200 mg/kg andmetformin 200 mg/kg orally for 21 days, significantly lowered the blood glucose levels.

The control group mean values was found to be 87.4 ± 0.359.

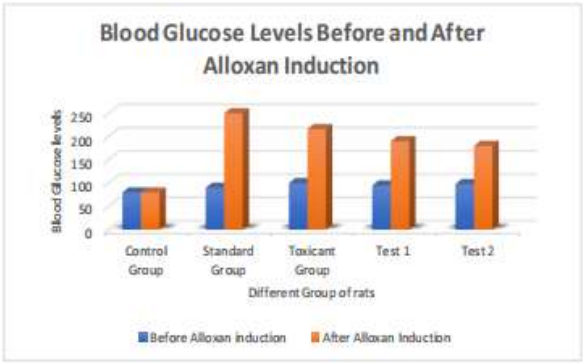
The standard group drug metformin mean value was found to be 107 ± 0.308.
The toxicant group mean value was found to be 192.2 ± 0.229.
The Test 1 group drug extract mean value was found to be 120.2 ± 0.297.
The Test 2 group drug extract mean value was found to be 124.2 ± 0.273.
With respect to student t test biostatistical analysis the results were found as to be followed:
Control v/s toxicant, Control v/s Test 1, Control v/s Test 2 the p value was found to be $p > 0.001$ and Control v/s standard was found to be significant $p < 0.001$.
According to the histopathological study reports, the following are the observations:
• For Control Group a normal physiology of islets of pancreas with beta cells was observed.
• For Toxicant Group a severe hypertrophy of islets of pancreas and hyperplasia of beta cells were observed.
• For standard group a mild hypertrophy of islets and fatty degeneration was observed.
• For Test 1 group a moderate degenerative changes and moderate necrosis of beta cells was observed.
• For Test 2 a mild periductular fibrosis was observed.

Table 3: Biostatistical Analysis

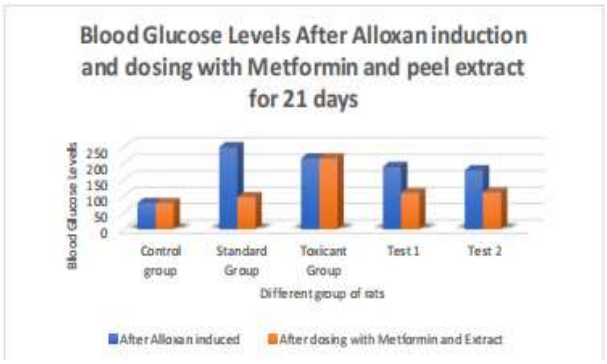
Groups	Values
Control	87.4 ± 0.359.
Standard	107 ± 0.308
Toxicant	192.2 ± 0.229.
Test 1	120.2 ± 0.297.
Test 2	124.2 ± 0.273.

All values are expressed as mean ± SEM (n=8 p > 0.001) on 21st day (Student t test).

Now a days there is increase in the incidence of diabetes mellitus and cost effective treatment is the need of the hour. Although there are several oral and parentral antidiabetic drugs available. There is a continuing effort to find secretogogues or sensitizers from synthetic or plant source for the treatment of diabetes. Plants and there bioactive constituents are used for the treatment of diabetes mellitus. There have been several reports on hypoglycemic activity of Mangifera indica. In the present study we investigated the effect of chloroform extract of Mangifera indica (150 mg/kg and 200 mg/kg) with metformin (200 mg/kg) on blood glucose level of alloxan induced diabetic rats. Following the administration of alloxan it has significantly increase the blood glucose level in the rats. The result of our study showed that chloroform extract of Mangifera indica administration orally for 21 days significantly ($p > 0.001$) decreased fasting blood level in alloxan induced diabetic rats. It was observed that standard drug Metformin showed significant ($p < 0.001$) decreases the blood glucose levels. In our phytochemical screening we have observed the presence of tannins, terpinoids, flavonoids, and xanthones which have already been reported to have antidiabetic activity as per our literature review.



Graph 1: Serum blood Glucose levels Before Administration of Alloxan and After administration of Alloxan



Graph 2: Serum blood glucose levels after administration of alloxan and dosing with standard metformin and mango peel extract for 21 days.

Histopathological study of pancreas

- Histopathological analysis of the control group revealed that the pancreas had normal structure and islets of langerhans are of significant size.
- In the group of rats that were treated with alloxan, the pancreas had severe hypertrophy of islets of pancreas and hyperplasia of the beta cells were observed.
- After the treatment with mango peel extract test 1 and test 2 groups showed moderate degenerative changes and moderate necrosis of beta cells was observed in Test 1 and mild periductular fibrosis was observed in Test 2.
- The group treated with metformin exhibited mild hypertrophy of islets and fatty degeneration was observed.

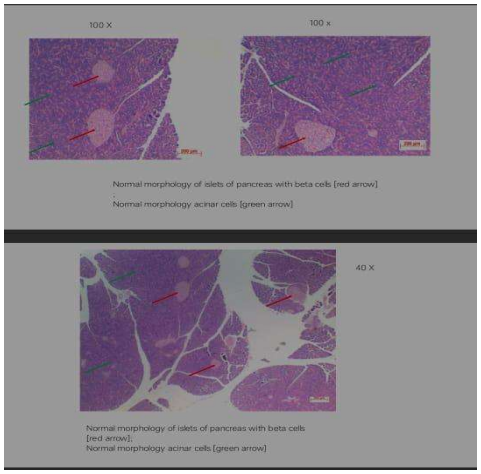


Fig 1: Control group pancreas tissue

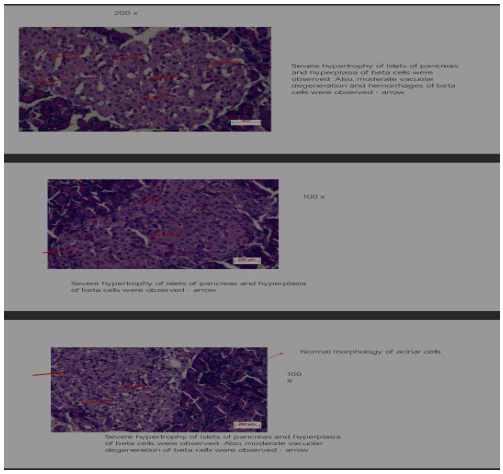


Fig 2: Toxicant group pancreas tissue

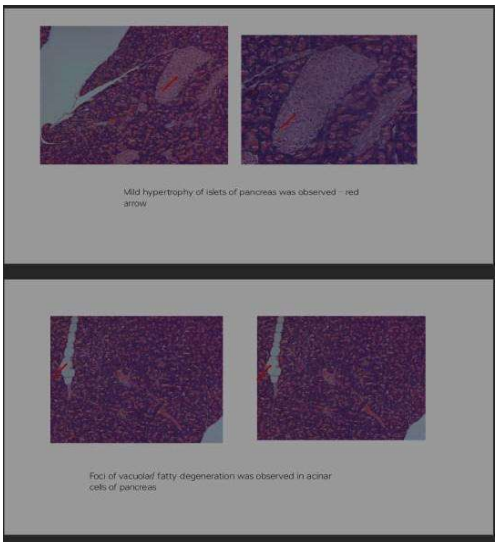


Fig 3: Standard group pancreas tissue

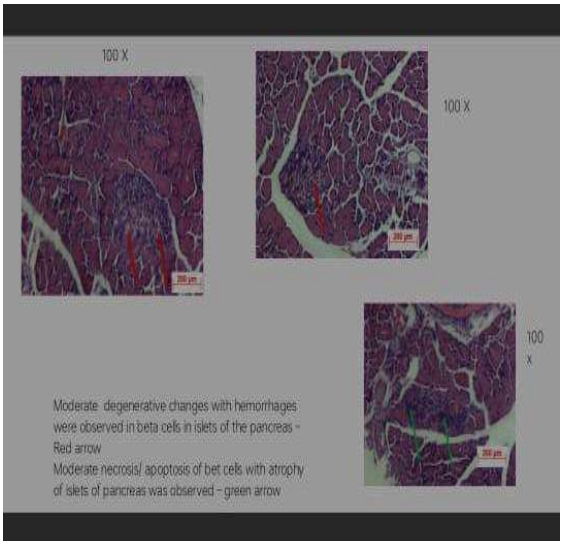


Fig 4: Test 1 group pancreas tissue

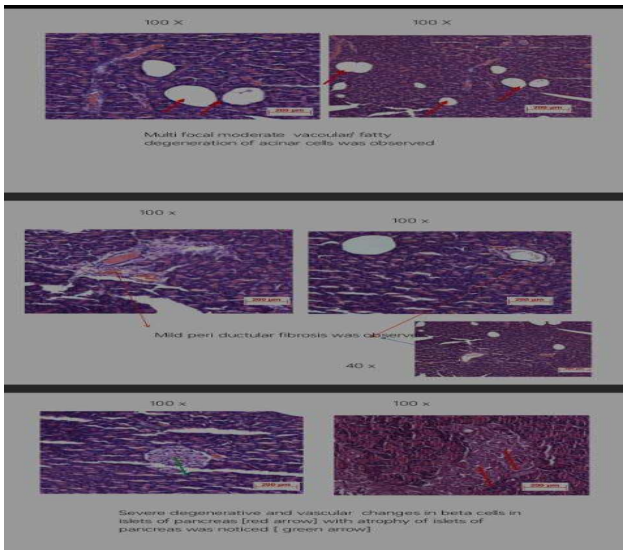


Fig 5: Test 2 group pancreas tissue

CONCLUSION

According to the findings of our research the chloroform peel extract of Mangifera indica appear to have anti-diabetic action on the diabetic rats produced by the Alloxan monohydrate comparable to the standard. The results of the study confirmed the effectiveness of chloroform peel extract of mango in the treatment of diabetes in animal models. Further research can be done through different animal models to establish anti-diabetic activity of Mangifera indica peel extract. So that it can be an good alternative medicine for the treatment of Diabetes mellitus.

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