RESEARCH ARTICLE

A Comparative Study on the Anti-Diabetic Activity of *Ficus racemosa* Linn. Leaves (Moraceae) and *Diospyros melanoxylon* Roxb. Leaves (Ebenaceae)

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ABSTRACT

Diabetes mellitus, the most common long-term metabolic disease, is characterized by abnormalities in either insulin action or secretion, or both. A serious public health issue is the substantial morbidity and death of late-diabetic complications. The World Health Organisation (WHO) states that the lack of ability of current modern therapies to control all pathological aspects of diabetes mellitus, their high cost, and their limited availability for many rural populations in developing countries make alternative strategies urgently needed. Measured as a metabolic regulator of insulin activity was glucose. Diabetic individuals are known to have impaired glucose homeostasis and elevated plasma glucose. The current study found that when *Diospyros melanoxylon* leaves (DML) and *Ficus racemose* leaves (FRL) extracts were given to diabetic rats, the levels of GlyHb and plasma glucose were recovered, and insulin, C-peptide, and Hb parameters were elevated. Diabetic rats also had reduced levels of insulin, C-peptide, and Hb when compared to normal control rats. An important observation of antidiabetic efficacy was made for the DML and FRL extracts. On the last day, diabetic control was significantly different from both normal control and other drug-treated groups (DRL and FRL). The groups' differences on the first day were significant at the 0.05 level. The current investigation showed that the direct destruction of ß-cells by streptozotocin caused diabetes. The diabetic pancreas with streptozotocin ultra-structure revealed significantly fewer islets langerhans and deficient islets. There was pancreatic islet regeneration in the diabetic rats. The ability of DML and FRL variety extract to regenerate pancreatic cells through the exocrine cells of the pancreas may shed light on the beneficial effects of these agents on insulin production.

Keywords: *Ficus racemose* leaves, *Diospyros melanoxylon* leaves, Diabetes mellitus, STZ

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INTRODUCTION

The most prevalent long-term metabolic illness, diabetes mellitus is defined by deficiencies in either insulin secretion, insulin action, or both. The enormous morbidity and mortality of late-diabetic complications is a main public health issue. The World Health Organisation (WHO) states that the lack of ability of current modern therapies to control all pathological aspects of diabetes mellitus, their high cost, and their limited availability for many rural populations in developing countries make alternative strategies urgently needed. Thus, research is being done in many labs worldwide in an effort to find a medication that is inexpensive, has greater potential, and has no negative side effects. Concerns regarding prescription pricing and safety have led to an increase in interest in natural substances in recent years. The main function of insulin's physiological role is to promote the fusion among proteins, fats, carbohydrates, and genetic acids. Insulin regulates gluconeogenesis, the creation of glycogen in the liver, and inhibits glycogenolysis, and stimulates transfer of glucose via eight adipocyte and muscle cell membranes in relation to carbohydrate metabolism.[1] In the end, these procedures result in lower blood glucose levels. Insulin enhances protein synthesis, prevents proteolysis, and facilitates the passage of amino acids across membranes in relation to protein metabolism. Insulin stimulates adipose triglyceride production and the incorporation of fatty acids from circulating triglycerides; lipolysis is prevented. Insulin promotes the production of ATP, DNA, and RNA, which helps in the synthesis of nucleic acids.[2] A reduction in insulin sensitivity or secretion, which leads to dysregulation of protein, lipid, carbohydrate, and nucleic acid synthesis, is the hallmark of diabetes.[3] Among various plant secondary metabolites, phenolic compounds have a vital role in health prophylaxis along with their ubiquitous nature in vascular plants which make them best subject for studying bioactive phytoconstituents. Phenolic compounds demonstrate various bioactivities including antioxidant, autoimmune treatment, prevents atherogenesis, inflammation reducer, antibacterial, anti-diabetic, circulatory system, hepatoprotective and widening of blood vessels due to their antioxidant action, phenolic compounds are linked to health

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Table 1: Impact of DML and FRL on animal body weight in experimental as well as control rats

Body Weight	Group-I (mean ± S.D.)	Group-II (mean ± S.D.)	Group-III (mean ± S.D.)	Group-IV (mean ± S.D.)	Group-V (mean ± S.D.)
Initial day (gm)	186.66 ± 2.88	185.00 ± 5.00	186.66 ± 2.88	183.33 ± 5.77	188.33 ± 5.77
Final day (gm)	221.66 ± 2.88	148.33 ± 7.63	198.33 ± 2.88	185.00 ± 5.00	215.00 ± 5.00

Table 2: Impact of DML and FRL on animal organ weight in experimental as well as control rats

Organ Weight	Group-I (mean ± S.D.)	Group-II (mean ± S.D.)	Group-III (mean ± S.D.)	Group-IV (mean ± S.D.)	Group-V (mean ± S.D.)
Liver (gm)	6.50 ± 0.06	8.51 ± 0.51	6.89 ± 0.02	7.86 ± 0.12	6.51 ± 0.09
Kidney (gm)	1.30 ± 0.05	1.75 ± 0.01	1.48 ± 0.02	1.65 ± 0.01	1.31 ± 0.01
Pancreas (gm)	0.84 ± 0.01	1.12 ± 0.06	0.95 ± 0.04	1.04 ± 0.02	0.85 ± 0.01

Table 3: Impact of FRL and DML on C-peptide, glucose, Hb, GlyHb, and plasma insulin

Biomarker	Group-I (mean ± S.D.)	Group-II (mean ± S.D.)	Group-III (mean ± S.D.)	Group-IV (mean ± S.D.)	Group-V (mean ± S.D.)
Glucose (mg/dL)	83.53 ± 3.50	253.88 ± 8.77	115.28 ± 4.59	158.59 ± 5.89	87.83 ± 3.94
Hb (gm/dL)	14.41 ± 0.14	8.65 ± 0.27	12.60 ± 0.15	10.82 ± 0.24	14.17 ± 0.15
GlyHb (%Hb)	6.51 ± 0.13	13.70 ± 0.14	7.56 ± 0.39	9.33 ± 0.12	6.55 ± 0.14
Insulin (µU/ml)	15.44 ± 1.10	5.27 ± 0.14	13.62 ± 0.11	9.81 ± 0.14	15.31 ± 0.28
C-peptide (µU/ml)	256.51 ± 12.11	129.95 ± 11.50	210.13 ± 11.79	185.87 ± 8.72	248.07 ± 17.09

benefits and are abundant in veggies, grains, fruit, bark, roots, flowers, seeds, tea, and wine. The primary food sources of phenolic compounds for humans are fruits and beverages among these vegetables anymore. The capacity of phenolic compounds to eliminate free radicals, donate ions or atoms of hydrogen, or attach metal cations is the mechanism that gives them their antioxidant action.[4,5]

METHODS

Collection of Plant material

In August, fully developed *Diospyros melanoxylon* Roxb. plants are obtained from Rajasthan, Bundi district, India; in July, fully grown *Ficus racemosa* Linn. plants are collected from Rajasthan, Jaipur district, India. The director of the Chambal Agricultural Research and Training Centre in Kota, Rajasthan, recognized and verified the plant.

Preparation of leaf extracts

Standard procedure and analytical grade solvents were used for the extraction. 40 g of powdered plant parts (leaves) was preliminary extracted with chloroform and n-hexane, respectively by soxhlet apparatus separately and further with the same procedure extracted with hydroalcoholic solvent at temperature between 50-65ºC.

Induction of diabetes in rat

In order to produce diabetic mellitus, adult male wistar albino rats weighing 120–150g were given just one intraperitoneal shot containing 65 mg/kg body weight after fasting for the whole night. Fresh STZ was dissolved in 0.01M pH 4.5 citrate buffer. The injection capacity was designed to hold 65 mg/ml when administered as 0.1 ml/100 g of body weight.[6,7] Blood glucose levels were measured five days later, and hyperglycaemic (>210 mg/dL) animals were gathered for the study.[8]

Experimental design

Following their acclimation in the lab, the rats were split into 5 batches, each having of six individuals, at random. There were thirty male Wistar albino rats (n = 6) split up into five groups.

Group I: Functioned as the typical non-diabetic control group (saline). The remaining groups (II–V) received the above-mentioned STZ injection, which caused diabetes.

After 5 days of STZ treated animals grouped into following:

Group II: functioned as the STZ-only diabetes control.

Group III: Given 200 mg/kg b.w. (per.os.) of *Ficus racemosa* Linn. every day for fifteen days

Group IV: Given 200 mg/kg b.w. (per os.) of *Diospyros melanoxylon* Roxb. every day for fifteen days

Group V: Received for fifteen days, oral glibenclamide 0.5 milligrammes per kilogramme one day as the reference medication.[9] The rats' body weights were recorded both at the start of the trial and after 15 days. In the morning, body weights were taken simultaneously.

Collection of samples

The experimental animals were given a 12-hour fast with no water restrictions, and their orbital vein plexus was used to take blood samples from rats that had been anaesthetised with diethyl ether. After one portion of the blood was poured into EDTA tubes, the haematological indices were examined. The serum was then extracted for the biochemical parameters. Additionally, The pancreas, kidney, and liver were extracted right away, washed with icy salt water, uniformised in a pH 7.4 buffer solution having 0.25 M sucrose in it and 0.1 M Tris-HCl, 3000 rpm rotated for ten minutes, and the remainder was utilised to detect several oxidative stress biomarkers.

Biochemical Parameters and Histopathology

Pancreas, kidney, and liver tissues were promptly removed from each experimental group for histological analysis and preserved in formaldehyde 10% buffered. Light microscopes were used to examine every segment. The blood was collected and serum was separated for the determination of biochemical parameters such as glucose, plasma insulin level, glycogen, glycosylated hemoglobin, haemoglobin, liver function test (SGOT, SGPT, total protein, albumin, globulin, alkaline phosphatase, serum creatinine), lipid profile test (total cholesterol, triglycerides,

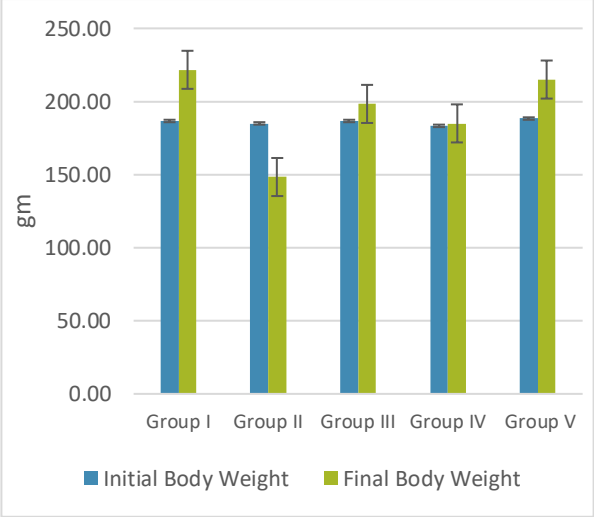

Figure 1: Impact of DML and FRL on animal body weight in experimental as well as control rats

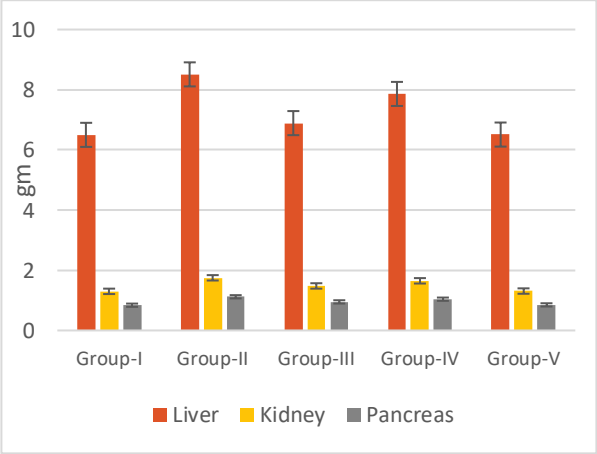

Figure 2: Impact of DML and FRL on animal organ weight in experimental as well as control rats

HDL, LDL, VLDL, phospholipids), urea, uric acid, C-Peptide. Various oxidative stress biomarkers are assayed such as malondialdehyde (MDA), superoxide dismutase (SOD), catalase (CAT), glutathione (GSH), GPx, ascorbic acid, α-tocopherol. Several enzymes were also estimated that are involved in gluconeogenesis (glucose-6-phosphate dehydrogenase, glucose-6-phosphatase, fructose-1,6-bisphosphatase, glucokinase).

Statistical Analysis

Using the latest version of SPSS 24 for statistical analysis of one-way ANOVA, after the fact, and DMRT assessment. The homogeneous subgroups, whose means are within the row and are denoted by distinct letters, are of statistical significance ($P<0.05$) in contrast to the other cohorts. All the values are represented in mean ± standard deviation (S.D.).

RESULTS AND DISCUSSION

Impact of DML and FRL on the weight of the body and organs in experimental as well as control rats

The streptozotocin-treated diabetic animals' body weight was observed to have significantly dropped while increased organs weight were observed in diabetic rats. On supplementation of *Diospyros melanoxylon* and *Ficus racemosa* restored the body and organs weight. Both of them has significant activity was observed and nearest to the standard Glibenclamide (Table 1 and Table 2).

Group-I: Normal control; Group-II: Control of diabetes (STZ alone); Group-III: *Ficus racemosa* Linn. powder drug, Group-IV: *Diospyros melanoxylon* Roxb. powder drug, Group-V: STZ + Glibenclamide (Std. Drug). Group II (Diabetic control) was significant compared with other drug treated groups (DML and FRL) and normal control for final day. Initial day was between the groups were significant level 0.05. (Figure 1 and Figure 2). One of the most widely utilised drugs to cause hyperglycemia in rats is streptozotocin. Through alkylation of DNA, this toxin kills the cells in the pancreas, reducing the production of insulin and the creation of DNA.[10] When rats are given STZ at doses greater than 40 mg/kg, their cells in the pancreas are destroyed and continuous hyperglycemia develops, a condition similar to hyperglycemia in humans.[11] The current investigation revealed that giving rats STZ at a dose of 65 mg/kg could raise glucose levels in the blood on the third day of the trial. This could be because STZ destroys pancreatic islets and kills β-cells. When a person has diabetes mellitus, for instance, their body uses proteins as an energy source instead of glucose since they are incapable to use it. This leads to a decrease in protein storage & reduces body weight.[12] Furthermore, it is commonly recognised that diabetes mellitus results in an inability to use glucose for vitality, which increases the use of animal protein and reduces its storage. This changes the weight of the body and its organs, including the liver, kidney, and pancreas, mostly through the depletion of body proteins. The presence of diabetes has been linked to both weight loss and dehydration. Food consumption was found to be higher and body weight to be lower in diabetic rats. This shows that the patient is polyphagic and has lost weight as a result of excessive tissue protein breakdown.[13] When compared with animals with diabetes, it was discovered that the various dosages of hydro-ethanolic extract from DML and FRL-treated animals significantly increased the weight of their bodies and organs. The total body mass and organ weight of those with diabetes were restored with treatment with DML and FRL extracts. The DML and FRL extracts showed signs of anti-diabetic action. This might be because the diabetic rats' hypoglycemia state was better managed. The current result is consistent with the research.[14,15] The pancreas is the main organ responsible for detecting the body's nutritional and energy needs through blood glucose concentrations. When blood glucose levels rise, insulin is secreted.[16] The levels of glucose in the blood rise as a result of streptozotocin's selective death of pancreatic islet cells. Micro and macrovascular consequences of diabetes mellitus are linked to hyperglycemia, the predominant clinical manifestation of the disease. A major contributing factor to hyperglycemia in diabetes mellitus is the liver's overproduction of glucose via excessive glycogenolysis and glyconeogenesis.[17] After treating both experimental and control rats with the hydro-ethanolic extract of DML and FRL for fifteen days, plasma glucose levels were measured.

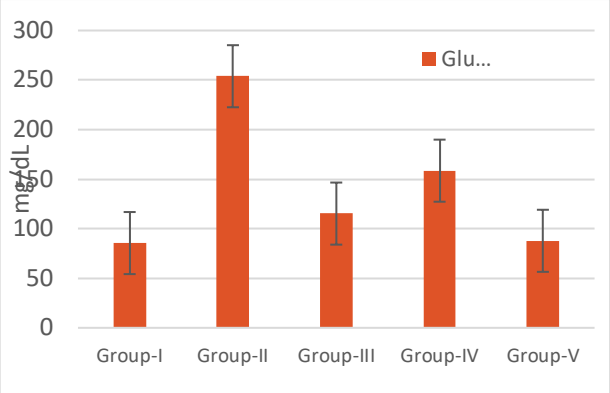

Figure 3: Effect of DML and FRL on Glucose levels in experimental and control rats

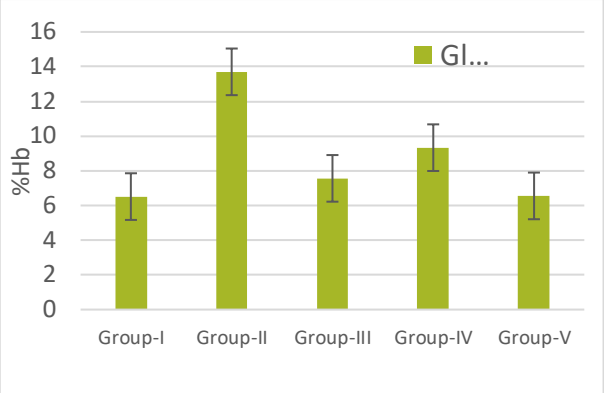

Figure 4: Impact of DML and FRL on GlyHb in experiment and control rats

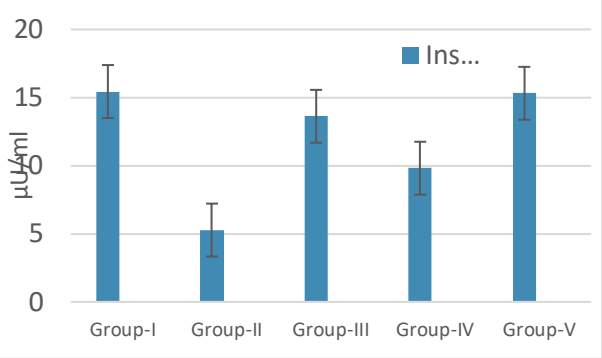

Figure 5: Impact of DML and FRL on the hormone insulin

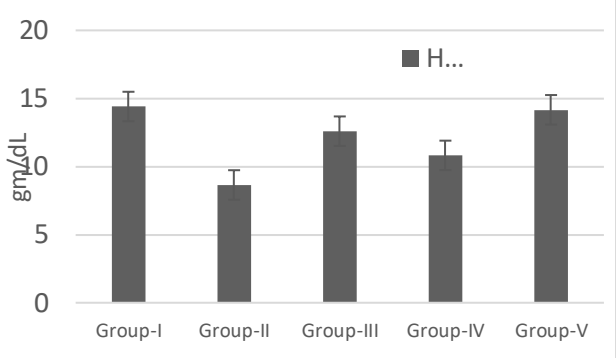

Figure 6: Impact of DML and FRL on the Hb

When diabetic rats were administered DML, FRL, and Glibenclamide, the animals blood glucose levels decreased. There was evidence of antidiabetic action in the DML and FRL extracts. One theory for the mechanism is that beta cells are stimulated, and then insulin is released, activating the insulin receptors. The body needs insulin, the most powerful anabolic hormone, for proper tissue development and growth as well as the preservation of glucose equilibrium throughout its lifespan.[18] There is a rise in hepatic glucose synthesis, a decrease in peripheral glucose uptake, and a decrease in the liver's breakdown of glucose to glycogen in diabetics with insulin insufficiency, resistant to insulin, or hyperglucagonemia.[19] The amount of the glycogen in diabetic rats liver muscle is reduced. Glycogen synthase activity may have diminished as a result of this. A significant drop in the amount of liver glycogen is linked to diabetes mellitus. Diabetes caused by streptozotocin was associated with a decrease in hepatic glycogen, which may have happened as a result of low insulin levels lowering the availability of the enzyme glycogen synthase's active form. On the other hand, the liver glycogen contents of diabetic rats treated with DML and FRL significantly increased. In the liver of diabetic rats, glycogen synthase activity was reduced and glycogen phosphorylase activity was elevated. Insulin reduces blood glucose levels by promoting muscle and adipose tissue's uptake and metabolism of glucose while blocking the liver's ability to produce glucose. According to reports, an additional pancreatic effect akin to

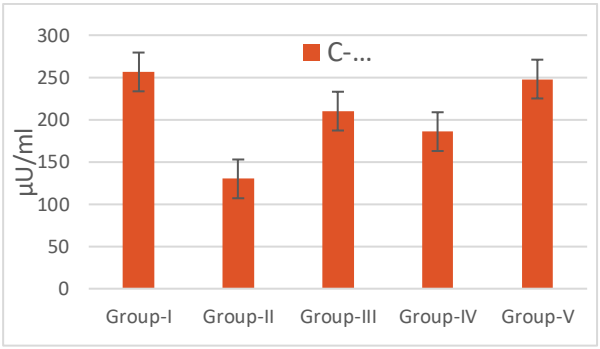

Figure 7: Impact of DML and FRL on C-peptide in experiment as well as control rats

insulin may be the cause of the increase in glucose uptake. Given that the diabetic treatment animals' glycogen levels significantly decreased in the current study's assessment of glycogen, this could be due to feedback control of the glycogen synthetase system, which impairs the liver's normal ability to synthesis glycogen. Compared to rats treated with DML and FRL, diabetic rats had a considerable drop in their glycogen levels. The content of glycogen was significantly increased as a consequence. Insulin is stimulated and secreted by beta cells. The hepatic muscle of rats with diabetes has a higher concentration of glycogen. It might be because DML and FRL activated the glycogen synthase system. For glycogen synthase and glycogen phosphorylase, it is reciprocal in nature. Glycogen

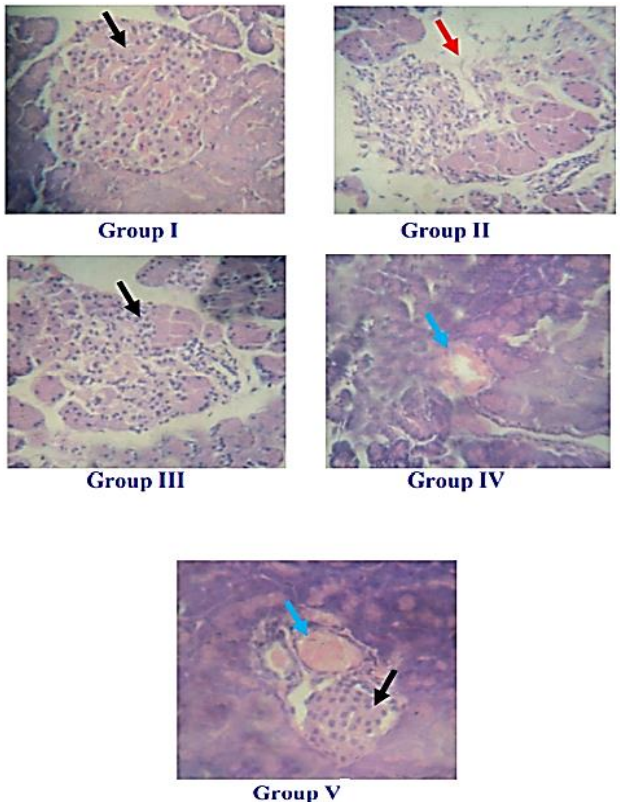

Figure 8: Pancreas histology in experiment and normal rats (40x10 resolution; H&E stain)

phosphorylase activity was increased while glycogen synthase activity was decreased in the livers of diabetic rats. Glycogen synthase activity is increased while glycogen phosphorylase activity is decreased, DML and FRL reversed the liver's glycogen. The main soluble form of glucose found inside cells is called glycogen, and the amount of this substance in different tissues—particularly skeletal muscle—reflects the activity of the insulin hormone, which stimulates the production of glycogen synthase and inhibits the enzyme glycogen phosphorylase to promote the deposition of glycogen. A lack of insulin causes an animal to experience a number of metabolic changes, including elevated blood sugar, elevated cholesterol, and elevated transaminase and alkaline phosphatase levels. The altered parameters were restored when diabetic rats were supplemented with DML and FRL types. Further confirmed in the histopathological studies of pancreas. These results confirm the antidiabetic activity of DML and FRL. DML and FRL extract shows the potential activity to maintain the glucose homeostasis. It is hypothesised that these secondary metabolites, which differ in their claimed antidiabetic potential, account for the variations in these extracts' actions. Numerous phenolic substances including flavonoids have been shown to have antidiabetic properties.

Effect of DML and FRL on glucose homeostasis in control and experimental rats

Measured as a insulin's metabolic regulator activity was glucose. Diabetics are known to have impaired glucose homeostasis and elevated levels of plasma glucose. In the current investigation, Rats with diabetes displayed greater levels of plasma glucose, GlyHb, and Hb and lower levels of insulin, C-peptide, and Hb in comparison to normal control rats. When DML and FRL extracts were given to diabetic rats, the levels of GlyHb and plasma glucose were recovered, and insulin, C-peptide, and Hb parameters were elevated. Among the DML and FRL extracts, antidiabetic activity was significantly observed. Further confirmed in the histopathological studies of pancreas (Figure 8). This result suggested that DML and FRL have glucose regulating activity. Table 3 and Figure 3–7 represents the effect of DML and FRL on Glucose, Hb, GlyHb, C-peptide and plasma insulin under control and experimental rats. Using the latest version of SPSS 24 for statistical analysis of one-way ANOVA, after the fact, and DMRT assessment. The homogeneous subgroups, whose means are within the row and are denoted by distinct letters, are of statistical significance ($P<0.05$) when compared to the other groups Group-I: Normal control; Group-II: Diabetic control (STZ only); Group-III: *Ficus racemosa* Linn. Powder drug, Group-IV: *Diospyros melanoxylon* Roxb. Powder drug, Group-V: STZ + Glibenclamide (Std. Drug). Group II (Diabetic control) was significant compared with other drug treated groups (DML and FRL) and normal control for final day. Initial day was between the groups were significant level 0.05. Group I included a microscopy photograph of a normal rat's pancreatic islet, demonstrating the duct that runs through the pancreas and normal islet of Langerhans; The duct of the pancreas and islet Langerhans of the STZ-induced rat were shown to be degenerating in Group II's microscopy photograph of the pancreatic islets; Group III to V showed a microscopy photograph of the pancreatic islets in a rat injected with a sample and a strain of STZ, demonstrating the regrowth of the duct that runs through the pancreas and islet Langerhans. (Red arrow indicates degeneration of islet Langerhans while blue arrow indicates regeneration of pancreatic duct and black arrow normal of islet Langerhans). Both normal and experimental rats were used to study the histological alterations in the pancreas. The current investigation demonstrated that the direct destruction of ß-cells by streptozotocin caused diabetes. The diabetic pancreas with streptozotocin the internal structure revealed significantly fewer islets langerhans and depleted islets. There was pancreatic islet regrowth in the diabetic rats. The ability of DML and FRL variety extract to regenerate pancreatic cells through the exocrine cells of the pancreas may shed light on the beneficial effects of these agents on insulin production. Its promise as an antidiabetic is further demonstrated by the function DML and FRL extract play in restoring the condition of diabetes at the level of the cells in addition to metabolic normalisation.

CONCLUSION

DML and FRL extract to STZ rats showed the restoration of body and organ weight, glucose, insulin and glycogen content. These results showed that DML and FRL extract possess antidiabetic effect. Overall, the experimental studies concluded that *Diospyros melanoxylon* Roxb. leaves and *Ficus racemosa* Linn leaves extracts has potential anti-diabetic activity.

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