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Potential Antidiabetic Effect of *Mimosa pudica* Leaves Extract in High Fat Diet and Low Dose Streptozotocin-Induced Type 2 Diabetic Rats

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Abstract
Mimosa pudica (Mp) is a traditional plant, which (leaves, roots and whole plant of Mp) are used for the treatment of diabetes mellitus (DM). In siddha medicine, Mp Chooranam is prepared and used for the treatment of type 2 DM. The present study was designed to evaluate the antidiabetic effect of Mp leaves extract on key enzymes of carbohydrate metabolic enzyme activities in control and streptozotocin (STZ) induced diabetic rats. Diabetes was induced by feeding high fat diet (HFD) for 2 weeks followed by intraperitoneal injection of streptozotocin (35 mg/kg bwt). Seven days after STZ injection, diabetic rats were supplemented with ethanolic Mp leaves extract (300 mg/kg bwt) daily for 30 days. The effect of ethanolic Mp leaves extract on blood glucose, plasma insulin, glycosylated hemoglobin, glucose metabolizing enzymes of Type 2 diabetic rats were studied. The ethanol extract of Mp leaves showed significant effect of antihyperglycemic activity by altering carbohydrate metabolizing enzymes activity and insulin secretion.

Keywords: antidiabetic effect, *mimosa pudica*, streptozotocin, diabetes mellitus, carbohydrates

1. Introduction
Diabetes mellitus (DM) is the most significant chronic metabolic disease characterized by increased level of blood glucose and it leads to serious damage to heart, blood vessels, eyes, kidneys and nerves. It is a major health problem in the world. World Health Organization (WHO) has reported about diabetes in 2016, where the global report showed that the number of people with diabetes has increased from 108 million in 1980 to 422 million in 2014[1].The prevalence of diabetes mellitus has increased from 4.7% to 8.5% globally [1]. The people with diabetes mellitus in India was 61.3 million in 2011 and is expected to reach 101.2 million by 2030 [2].

Type 2 DM is a major metabolic disorder that results from defect in both insulin secretion and action [3]. It is mainly due to insulin resistance which causes insulin mediated metabolic deregulation and insulin signaling pathway [4]. The major factor which is responsible for insulin resistance is obesity, which is generally caused by western style high fat diet and physical inactivity [5].

STZ is a glucosamine nitrasourea compound, structurally resembling 2-deoxy-D-Glucose, which enters into beta cell through GLUT 2 transporter and causes DNA alkylation inside the cell leading to beta cell destruction [6]. STZ induces both type 1 and type 2 DM in animal model. High dose of STZ strongly impair insulin secretion which mimic type 1 diabetes mellitus while low dose of STZ slightly impair insulin secretion, which resembles the clinical features of type 2 diabetes. Hence in the present study, a high fat diet and a low dose of STZ has been used for the induction of type 2 diabetes mellitus.

Recently plant based therapies were focused for the treatment of DM because of low cost, less toxicity with fewer side effects. Hence there is a lot of scope for alternative therapy, considering the side effects associated with conventional drugs [7]. Several plant extracts have been studied for the treatment of DM including WHO expert committee recommended plant based therapies to treat various types of diseases [8]. Moreover nowadays herbal drugs or plant extract of several species are widely used for the treatment of DM due to the presence of biologically active compounds. Some of the plants which possess antidiabetic activity include *Clitoria ternatea* [9], *Swertia corymbosa* [10], *Toddalia asiatica* [11], *Salacia chinensis* [12] and *Mimosa pudica Linn* [13].

Mimosa pudica Linn is an annual or perennial herb belonging to the family of mimosaceae, commonly found in moist waste ground, lawns, and open plantation and weedy thickets, which grow throughout India. The leaves are small leaflet on stalk and on touch, fold together. The stems are branched, with bristly hairs [14]. Mp commonly known as sensitive plant or ‘‘touch me not plant’’ in English, ‘‘thottalsenungi’ in Tamil,

ajalikalika in Sanskrit, lajawanti in hindi, lajjabate in bangali, hadergitte in kannada and attapatti in telugu. It is traditionally used for the treatment of many diseases [15].

Mp is a well-known medicinal plant, all the parts of this plant have reported medicinal property. Phytochemical studies have revealed the presence of more active constituents, which include alkaloids, glycosides, carbohydrate, steroids, flavonoids, phenols, resin, triterpene and c-glycoflavines[16- 18]. It has been reported that it possesses anticonvulsant, antimalarial, anti-bacterial, anti-ulcer and antidiabetic activity. The medicinal plant which contains flavonoids, triterpeniods, phenolics, coumarins, and quercetin has been reported of their antidiabetic property [19]. Vishwanathan *et al.* (2013) have reported that Mp is nontoxic up to 2,000 mg/kg body weight [20].

Based on available literature, antidiabetic activity of various parts of Mp has been studied previously. But the antidiabetic activity of ethanol extract of Mp leaves was available only in few studies. Sutar *et al*. (2009) compared the antidiabetic activity of ethanol and petroleum ether leaf extract of Mp with standard metformin in alloxan induced diabetic rats. Petrolium ether extract didn't show any changes when compared with both standard metformin and ethanol leaf extract of Mp. In that study, ethanol extract significantly decreases the blood glucose level in alloxan induced diabetic rats. However, there is a lack of detailed study of its effectiveness in the previous studies. We aimed to evaluate the antidiabetic effect of Mp in type 2 diabetic rat model, hence in the present study the antidiabetic effect of ethanol extract of Mp leaves were investigated in HFD and low-dose of STZ-induced type 2 diabetic rats.

2. Materials and Methods

2.1 Chemicals

Streptozotocin was purchased from Sigma chemicals, St. Louis, MO, USA. All other reagents used in the present study were of analytical grade.

2.2 Animals

Healthy male Albino rats of Wistar strain were used in this study. The animals were housed in large spacious cages, bedded with husk, and were given food with water *ad libitum*. The animal room was well ventilated with a 12-h light/dark cycle throughout the experimental period. Animals were maintained as per the National Guidelines and Protocols approved by the Institutional Animal Ethical Committee. (IAEC No.SU/CLAR/RD/001/2016).

2.3 Preparation of plant extract

Mimosa pudica Linn leaves were collected from Kanchipuram district, Tamilnadu, India. The plant was authenticated by Dr.P.Jayaraman, Director of plant anatomy research institute, Tambaram, Chennai, Tamilnadu, India. The Mp leaves were dried at room temperature, powdered and stored at 5°C until needed. A 100 g of the powder was defatted with 500 ml of petroleum ether (60–80°C) overnight, and it was then extracted with 500 ml of 95% ethanol by soxhalation. Ethanol was evaporated in a rotary evaporator at 40–50°C under reduced pressure. The yield of the plant extract was 3.8% w/w.

2.4 Induction of Diabetes

Type 2 diabetes was induced by high fat diet and low dose of streptozotocin. The normal control rats were fed with normal pellet diet and experimental group were fed with a high fat diet for 2 weeks. After two weeks of high fat diet, the animals were fasted overnight and injected with low dose of streptozotocin (35 mg/kg body weight in 0.1 M citrate buffer pH 4.5)[21]. The animal had free access to food and water after the injection. Both diabetic induced rats and normal rats continued on their diet for the duration of the study. After 12 hrs fast, glucose level was measured in all experimental rats. Rats having 250 mg/dl of fasting blood sugar were considered as diabetic and used for the experiment.

2.5 Experimental Groups

The rats are divided into five groups of six animals each. Group I: Normal control rats receiving olive oil as a vehicle; Group II: HFD+STZ diabetic control rats; Group III: HFD+STZ diabetic rats treated with ethanol extract of Mp leaves 300mg/kg of bwt for 30 days; Group IV: HFD+STZ diabetic rats treated with standard drug metformin 200 mg/kg of bwt for 30 days; Group V: Control rats were treated with ethanol extract of Mp leaves 300 mg/kg of bwt for 30 days.

After 30 days of treatment, the animals were fasted overnight, anesthetized and sacrificed by cervical decapitation. The blood was collected with and without anticoagulant for plasma and serum separation, respectively. Body weights of all the animals were recorded prior to the treatment and sacrifice.

2.6 Estimation of plasma Glucose

Glucose was estimated by the method of Trinder (1969) using reagent kit [22]. Glucose is oxidized in the presence of enzyme glucose oxidase to produce D-Gluconic acid and H_2O_2. H_2O_2 in the presence of enzyme peroxidase oxidizes phenol which combines with 4-aminoantipyrine to produce coloured quinoneimine dye. The intensity of the colour developed is proportional to the glucose concentration in the sample.

2.7 Oral Glucose Tolerance Test (OGTT)

Oral Glucose Tolerance Test was performed according to the method of Du Vigneaud and Karr (1925) [23]. The animal was fasted overnight, the fasting blood sample was taken from control and experimental rats at 0 minutes. Glucose solution (2g/kg of body wt.) was administered orally to all groups of animals. Blood sample was drawn at 60 and 120 minutes time intervals after glucose load. The blood sample was used for determination of glucose. OGTT curves were drawn by plotting blood glucose level against time.

2.8 Insulin

Plasma insulin level was assayed by Solid-phase enzyme-linked immunosorbent assay (ELISA).

2.9 Glycosylated Hemoglobin

Glycosylated hemoglobin (HbA1c) level was estimated according to the method of Nayak and Pattabiraman (1981) [24].

2.10 Preparation of Tissue Homogenate

The liver tissue was dissected out, washed in ice-cold saline,

and weighed. Tissue was minced and homogenized (10%, w/v) with 0.1 M Tris–HCl buffer (pH 7.4) and centrifuged (3000 × g for 10 min). The resulting supernatant was used for enzyme assays.

2.11 Estimation of key enzyme of Carbohydrates metabolism

Hepatic Hexokinase activity was assayed by method of Brandstrup *et al.* (1957) [25]. Phosphofructokinase activity was estimated by the method of Gancedo and Gancedo (1971) [26]. Pyruvate kinase activity was estimated by the method of Pogson and Denton (1967) [27]. Fructose-1, 6-bisphosphatase activity was measured by the method of Gancedo and Gancedo (1971). Glucose-6-phosphatase was assayed according to the method of Gancedo and Gancedo (1971), Glucose 6 phosphate dehydrogenase (G6PDH) activity was assayed by the method of Beutler (1983) [28]. Glycogen Phosphorylase activity was determined by the method of Shull *et al.* (1956) [29]. Glycogen content was estimated by the method of Morales *et al.* (1973) [30].

2.12 Statistical Analysis

The data were statistically evaluated with SPSS 21.0 software. Hypothesis testing methods included one way analysis of variance (ANOVA) followed by least significant difference (LSD) test. p-value of less than 0.05 was considered to indicate statistical significance. All the results were expressed as the mean ± SD for six animals in each group.

3. Results

3.1 Effect of ethanol extract of Mimosa pudica leaves on body Weight, blood glucose, insulin and glycosylated hemoglobin level in HFD and low dose of STZ induced- Type 2 diabetic rats

The body weight, blood glucose, insulin and glycosylated hemoglobin level in the control and experimental group of rats are shown in Figure 1. The level of glucose and HbA_{1C} was significantly increased and insulin level, body weight were decreased in diabetic rats when compared to normal rats ($p<0.05$). The treatment with ethanol extract of Mp leaves and metformin significantly altered the level of blood glucose, HbA_{1C}, insulin and body weight of animal compared to diabetic rats.

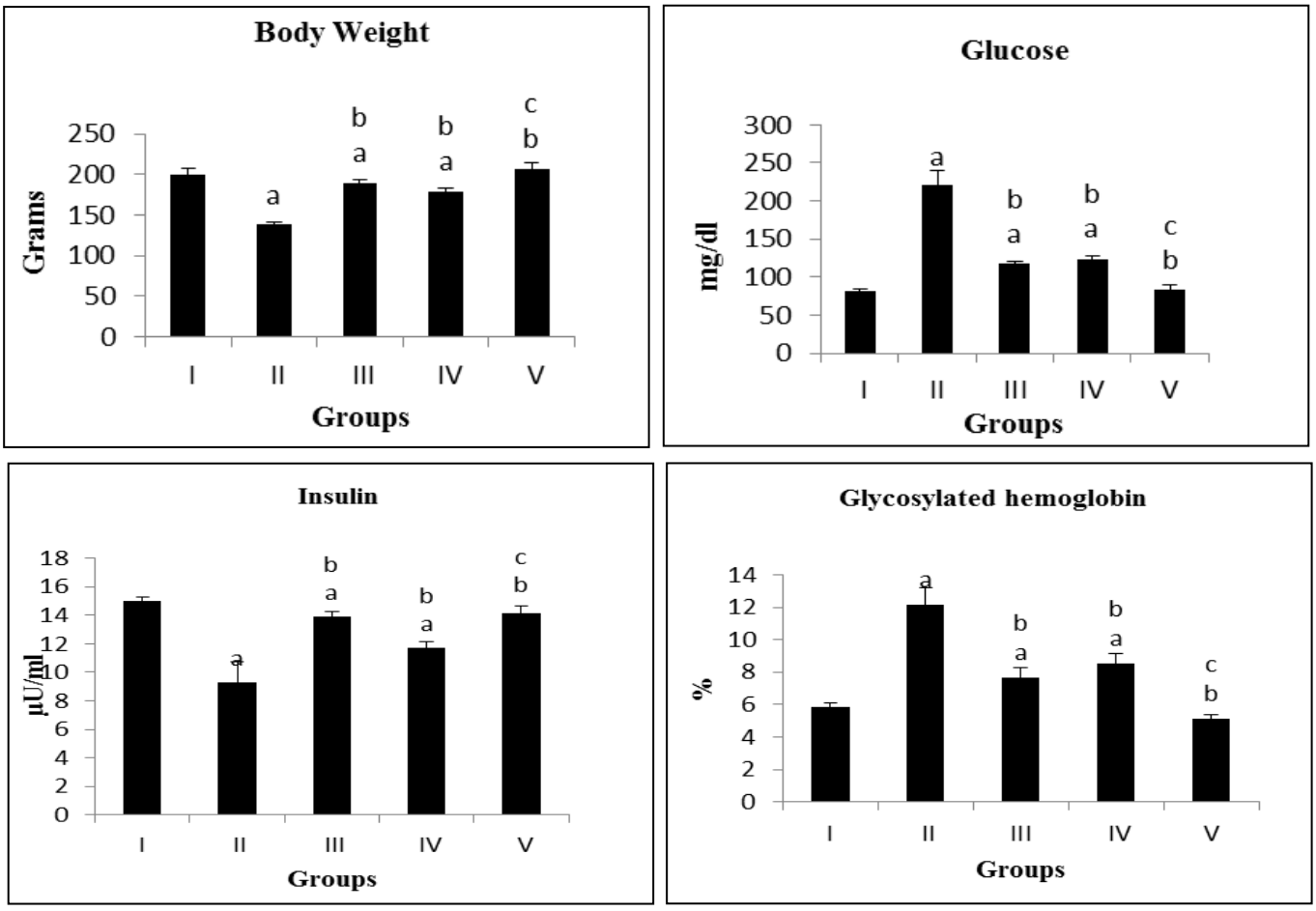

Fig 1: Effect of Mimosa pudica extract on body weight, blood glucose, insulin and glycosylated hemoglobin level in HFD and low dose of STZ induced- type 2 diabetic rats. Group I: Control, Group II: HFD+STZ-Induced diabetic rats, Group III: Diabetes +*Mimosa Pudica*, Group IV: Diabetes+ Metformin, Group V: *Mimosa Pudica* Alone .Each bar represents mean ±SEM for 6 animals. a: Control Vs Diabetic control, b: DC Vs. DC+Mp and DC+Metformin. c: Mimosa pudica Vs Other groups.

3.2 Effect of ethanol extract of Mimosa pudica leaves on OGTT in HFD and low dose of STZ induced-Type 2 diabetic rats

Figure 2 shows the result of oral glucose tolerance test of control and experimental rats. After the oral dose of glucose, the glucose level reached the fasting level at 2 hrs in normal control rats, whereas in diabetic control rats the glucose level remained high even after 2 hours. Treatment with ethanol extract of Mp leaves and metformin improved glucose tolerance which is indicated by reduction in peak blood glucose level at 1 and 2 hrs in diabetic rats during OGTT.

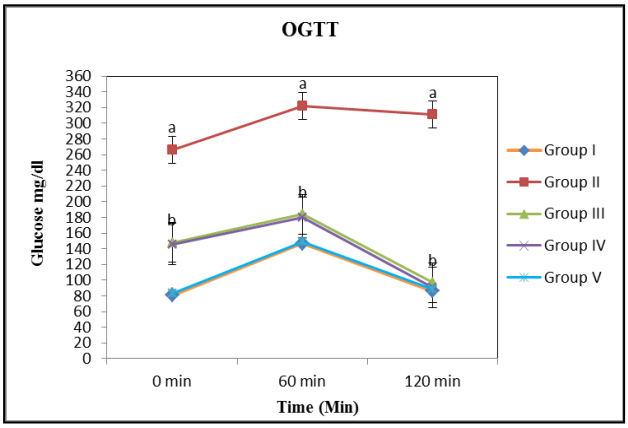

Fig 2: Effect of Mimosa pudica extracts on OGTT in HFD and low dose of STZ Induced- Type 2 diabetic rats. Group I: Control, Group II: HFD+STZ-Induced diabetic rats, Group III: Diabetes +*Mimosa Pudica*, Group IV: Diabetes+ Metformin, Group V: *Mimosa Pudica* Alone. Values are given as mean ±SEM for 6 animals. a: Control Vs Diabetic control, b: DC Vs. DC+Mp and DC+Metformin.

3.3 Effect of ethanol extracts of Mimosa pudica leaves on glycolytic enzymes in HFD and low dose of STZ induced-Type 2 diabetic rats

Figure 3 shows the changes in the activities of glycolytic enzymes in liver of control and experimental rats. The activity of hexokinase, phosphofructokinase and pyruvate kinase were significantly decreased ($p<0.05$) in diabetic rats when compared to normal control rats. However, upon treatment with ethanol extract of Mp leaves and metformin to diabetic rats reversed the activity of these enzymes to near normal level.

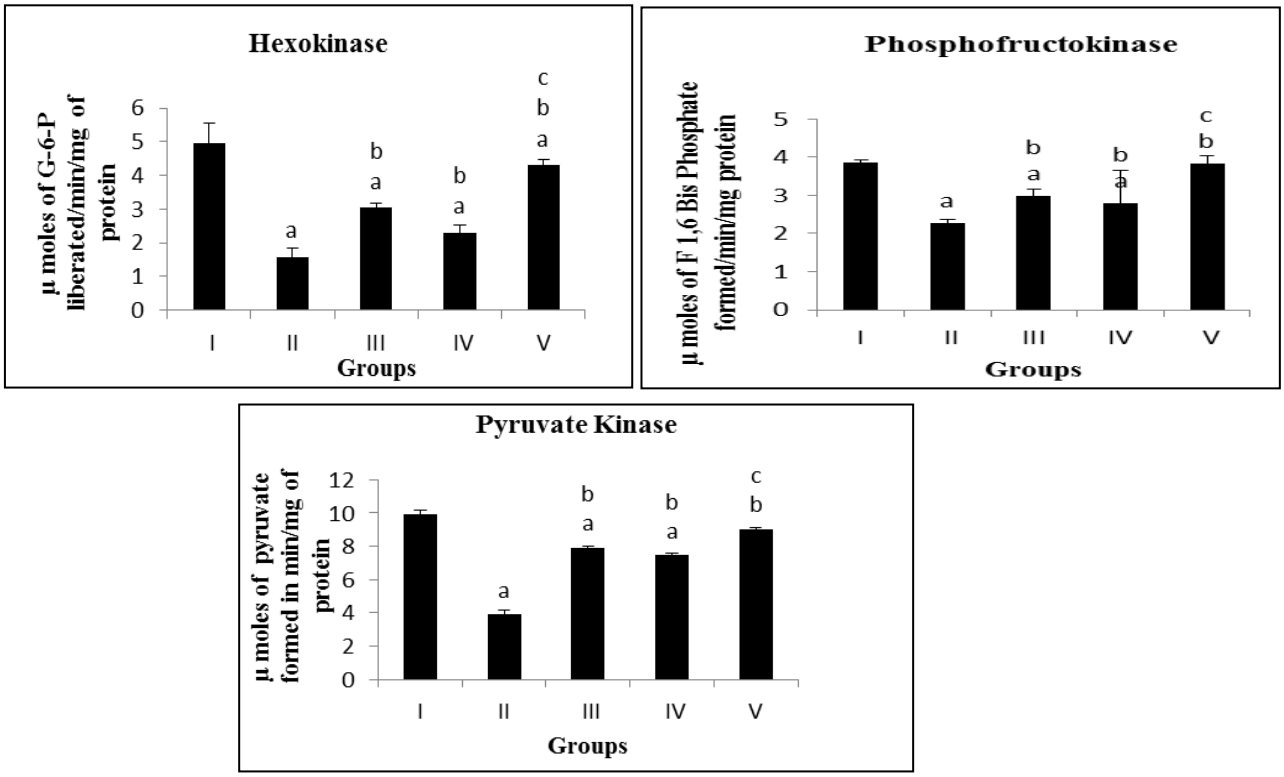

Fig 3: Effect of ethanol extracts of Mimosa pudica leaves on glycolytic enzymes in HFD and low dose of STZ induced- Type 2 diabetic rats. Each bar represents mean ± SEM for 6 animals. a: Control Vs Diabetic control, b: Diabetic Control Vs Diabetic + Mp and Diabetic + Metformin. c: Mimosa pudica Vs Other groups. a, b and c denotes Statistical significance at *$p<0.05$.

3.4 Effect of ethanol extract of Mimosa pudica leaves on Glucose-6-Phosphatase, Fructose 1,6-bisphosphatase and Glucose-6-Phosphate Dehydrogenase in HFD and low dose of STZ induced-Type 2 diabetic rats

The activities of enzymes Glucose-6-phosphatase and Fructose 1,6–bisphosphatase was shown in Figure 4. These enzyme activities were significantly increased in diabetic rats when compared to normal control rats. Oral administration of ethanol extract of Mp leaves as well as metformin recovered the activities of these enzymes in diabetic rats closer to the levels in control rats.

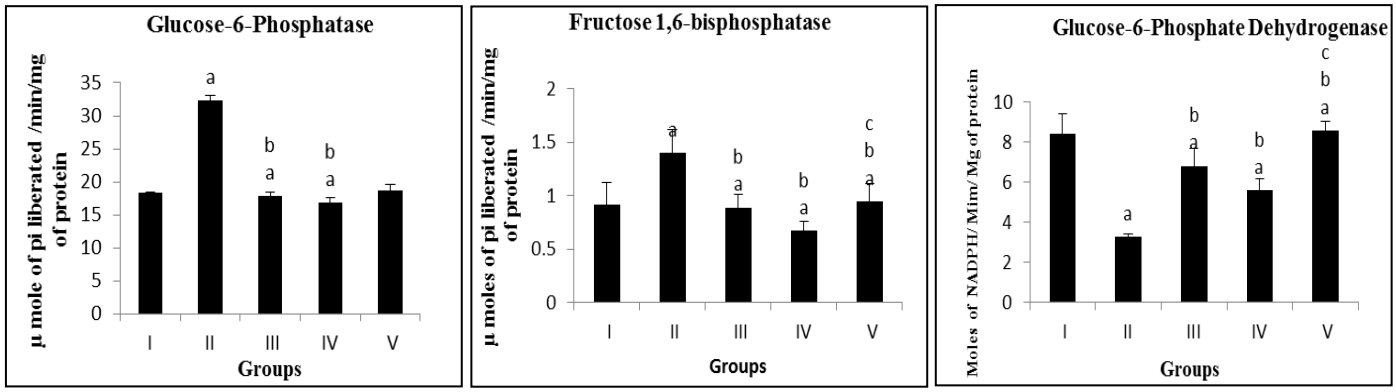

Fig 4: Effect of ethanol extract of Mimosa pudica leaves on Glucose-6-Phosphatase, Fructose 1, 6-bisphosphatase and Glucose-6-Phosphate Dehydrogenase in HFD and low dose of STZ Induced- Type 2 diabetic rats. Each bar represents mean ± SEM for 6 animals. a: Control Vs Diabetic control, b: Diabetic Control Vs Diabetic + Mp and Diabetic + Metformin. c: Mimosa pudica Vs Other groups. a ,b and c denotes Statistical significance at *$p<0.05$.

3.5 Effect of ethanol extract of Mimosa pudica leaves on Glycogen content and Glycogen phosphorylase in HFD and low dose of STZ induced-Type 2 diabetic rats

Figure 5 represents the effect of Mp leaves extract treatment on the level of glycogen and the activities of glycogen phosphorylase in liver of control and experimental groups of rats. A significant decrease in the glycogen content and a concomitant increase in the activity of glycogen phosphorylase were noted in the liver of diabetic rats. The treatment with Mp leaves extract and metformin to diabetic groups of rats reinstated the level of glycogen and glycogen phosphorylase to near normal level when compared to control group of rats.

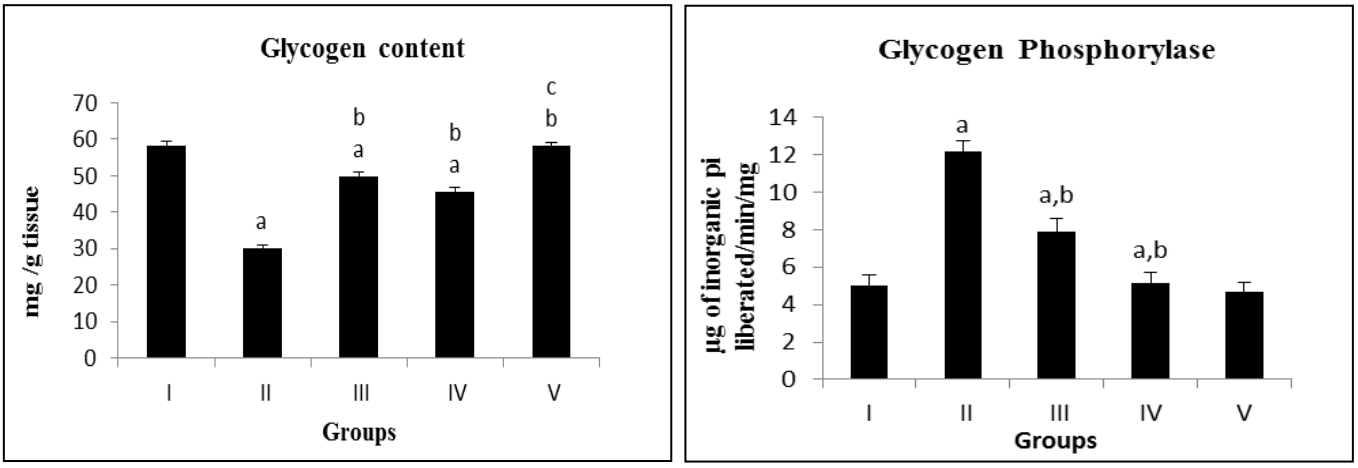

Fig 5: Effect of ethanol extract of Mimosa pudica leaves on Glycogen content and Glycogen phosphorylase in HFD and low dose of STZ induced- Type 2 diabetic rats. Each bar represents mean ± SEM for 6 animals. a: Control Vs Diabetic control, b: Diabetic Control Vs Diabetic + Mp and Diabetic + Metformin. c: Mimosa pudica Vs Other groups. a, b and c denotes Statistical significance at *$p<0.05$.

4. Discussion

Diabetes mellitus induced by high fat diet and low dose of STZ in experimental animal is considered a good model for preliminary screening of hypoglycemic agents. Type 2 DM is characterized by hyperglycemia and dyslipidemia which mainly affects carbohydrate and lipid metabolism [31, 32]. The present study was designed to evaluate the effect of ethanol extract of Mp leaves in HFD and STZ induced diabetic rats in comparison with standard drug metformin.

The result of this study showed the alteration in fasting glucose, insulin, body weight of animal in STZ induced diabetic rats. STZ destroy the beta cells of pancreas that result in increased glucose concentration and decreased insulin level and the body weight of the diabetic animal. The body weight was decreased in diabetic animal because due to the deficiency of insulin, the fat and protein are catabolized.

Hence the protein content is decreased in muscular tissue by proteolysis while the structural proteins are a major contributor for body weight [33, 34], Treatment with ethanol extract of Mp leaves and metformin significantly increased the body weight of diabetic rat which is due to improvement in glucose homeostasis, which in turn promotes body weight gain. Preceding experimental studies have suggested that the plant which has antioxidant property is found to control blood glucose level and complications in animal model [35]. Hence the antioxidant present in the drug might have contributed to this effect.

The measurement of HbA_{1C} is the most reliable parameter which is used for diagnosis and management of diabetes [36]. The HbA_{1C} was found to be increased in patient with diabetes, since in diabetic condition the hemoglobin was glycosylated non-enzymatically to form more glycosylated hemoglobin. This is due to persistent hyperglycemia and low level of total hemoglobin. A significant increase was observed in the levels of HbA_{1c} in diabetic rats when compared to control rats. Administration of Mp leaves extract to type 2 diabetic rats reduced the glycosylation of hemoglobin. While the decrease in blood glucose level might also have contributed to decreased level of glycosylated hemoglobin. It is proved by OGTT and fasting blood glucose in drug treated rats.

Liver is a major organ responsible for the production of glucose either from gluconeogenesis or from glycogen via glycogenolysis. The elevated endogenous glucose level is a common abnormality associated with diabetes mellitus. Insulin is a hormone that regulates the metabolism by modulating the uptake and utilization of glucose in target organs by controlling the activities of metabolic enzymes. In the present study, a significant decrease in the activities of glycolytic enzymes hexokinase, phosphofructokinase and pyruvate kinase were observed in diabetic rats. Hexokinase is a key enzyme of glucose catabolism which is involved in the phosphorylation of glucose to form glucose-6-phosphate. It is also one of the regulating enzymes of glycolysis. The decreased level of insulin in STZ induced diabetic rat leads to impairment of hexokinase activity [37]. However the treatment with Mp leaves extract to diabetic rats showed a notable increase of glycolytic enzymes.

Glucose-6-phosphatase is one of key enzyme of gluconeogenesis, which is involved in dephosphorylation of Glucose-6-phosphate to glucose, as the final step in gluconeogenesis and glycogenolysis. Fructose1,6-bis phosphatase is another enzyme that catalyzes dephosphorylation of fructose1, 6-bisphosphate to fructose-6-phosphate. Both of these enzymes were elevated in experimental animal model of diabetes, which is mainly due to insulin resistance. During diabetic condition the gluconeogenic enzymes are activated or increased so it leads to the production of more glucose in liver [38]. Hence in normal conditions, insulin suppresses the activity of these enzymes. Oral administration of ethanol extract of Mp leaves showed a significant effect on these enzymes in high fat fed STZ-induced diabetic rats. Hence it reduces the production of glucose by altering the enzyme activities.

Glucose-6-phosphate dehydrogenase enzyme catalyzes the rate limiting step of HMP shunt, as a result of which ribose-5-phosphate and NADPH are produced. The activity of G6PDH enzyme also found to be decreased in diabetic rats. The decrease of this enzyme may be due to reduced insulin secretion and action, however in normal rats insulin increases the enzyme activity of rat liver cell while high glucose concentration inhibits it [39]. Diabetic rats treated with Mp leaves extract significantly increased liver glucose-6-phosphate dehydrogenase activity, via enhanced secretion of insulin. The present study shows the similar effect as previous literature.

Glucose is stored as glycogen in intracellular region, and serves as a tissue reserve for the body's glucose needs. Insulin favors the formation of glycogen from glucose via stimulation of enzyme glycogen synthase, as a rate limiting enzyme which dispose glucose by catalyzing the transfer of glucose from UDPG to glycogen in animal cell. At the same time insulin inhibits the enzyme glycogen phosphorylase, which is a key enzyme of glycogenolysis. During diabetic condition the glycogen level, glycogen synthase activity and responsiveness to insulin signaling are diminished, and glycogen phosphorylase activity is increased [40]. Same result was observed in the present study. Treatment with ethanol extract of Mp leaves to diabetic rats regulated the activity of glycogen metabolizing enzymes by stimulating the remnant beta cell to secrete more insulin, thereby normalized the altered glycogen content.

5. Conclusion

The ethanol extract of Mp leaves has a potential to restore the activities of key enzymes involved in glucose and glycogen metabolism. The extract possesses antidiabetic effect through an increased production of insulin, which enhances glycolytic enzymes and decline gluconeogenic enzymes. Through these favorable effects, ethanol extract of Mp leaves contributes to glucose homeostasis in treated rats. Therefore ethanol extract of *Mimosa pudica* leaves has antidiabetic effect and can be utilized as an adjunct in the treatment of diabetes mellitus. However further investigation needed to explore molecular mechanism of antidiabetic effect of *Mimosa pudica* leaves in diabetes.

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