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Deepa Rajendiran

(1) Research and Development Centre, Bharathiar University, Coimbatore, Tamil Nadu, India.
(2) Department of Biochemistry, Madha Dental College and Hospital, Kundrathur, Chennai, Tamil Nadu, India

Haseena Banu Hedayathullah Khan

Department of Pathology, Dr. ALM PG IBMS, University of Madras, Taramani Campus, Chennai, Tamilnadu, India

Subbulakshmi Packirisamy

Department of Pharmacology, Meenakshi Ammal Dental College and Hospital, Maduravoyal, Chennai, Tamil Nadu, India

Dr. Krishnamoorthy Gunasekaran

Department of Biochemistry, Rajas Dental College and Hospital, Kavalkinaru Junction, Tirunelveli, Tamil Nadu, India

Correspondence

Dr. Krishnamoorthy Gunasekaran
Department of Biochemistry, Rajas Dental College and Hospital, Kavalkinaru Junction, Tirunelveli District, Tamilnadu, India

Dose dependent antidiabetic effect of *Mimosa pudica* leaves extract in type 2 diabetic rat model

Deepa Rajendiran, Haseena Banu Hedayathullah Khan, Subbulakshmi Packirisamy and Krishnamoorthy Gunasekaran

Abstract

Diabetes mellitus is a major epidemic health problem characterized by abnormal blood glucose level with alteration of carbohydrate, fat, and protein metabolism. The global prevalence of this disease is increasing day by day and is expected to rise 300 million by 2025. The side effects associated with synthetic drugs has resulted in the shifting of focus towards herbal drugs used in the traditional system of medicine. *Mimosa pudica* is one such herbal drug that has been used in the Indian system of Medicine against diabetes mellitus. The aim of the present study was to evaluate the effective dose at which the drug exhibits its potential antidiabetic effect. Male Wistar albino rats were divided into seven groups of six animals in each group. Type 2 diabetes was induced in rats by feeding them with high fat diet for two weeks followed by low dose of streptozotocin injection intraperitoneally. The diabetic rats were treated with ethanolic leaf extract of *Mimosa pudica* with four different doses of 100,200,300 and 400mg/kg/b. wt respectively and were compared with standard drug metformin (200mg/kg/b.wt) for 30 days. Increased level of glucose, glycosylated hemoglobin, lipid profile and reduced level of insulin were observed in diabetic rats. Treatment with *Mimosa pudica* leaf extract altered the level of glucose, glycosylated hemoglobin, lipid profile and insulin. The extract was found to be effective at the dosage of 300mg/kg/b. wt against high fat diet and streptozotocin induced type 2 diabetes.

Keywords: *Mimosa pudica*, STZ, Lipid profile, HbA1c

Introduction

Diabetes mellitus is a metabolic disorder characterized by increased concentration of blood glucose due to hormonal disturbances. It is one of leading disease which results in several complications. The prevalence of diabetes mellitus is increasing year by year worldwide. In India, the estimated number is expected to raise to 57.2 million by the year 2025 [1]. The increased incidence of type 2 diabetes mellitus is mainly due to the shift towards sedentary life style resulting in increased obesity among individuals. Decrease in the response of insulin target tissues towards insulin resulting in insulin resistance and compensatory hyperinsulinemia finally leading to the development of beta cell dysfunction are the major features leading to the development of type 2 diabetes mellitus. This condition results in anomalies not only in carbohydrate metabolism but also both protein and lipid metabolism are affected [2].

The agents which are most commonly used for the treatment of diabetes mellitus include synthetic drugs and these are known to be associated with severe side effects such as hypoglycemia, weight gain, drug resistance [3]. Hence, nowadays medicinal plants have invited attention for the treatment of diabetes mellitus due to low cost with fewer side effects. The phytoconstituents present in these medicinal plants or herbal formulation are known to contribute towards the hypoglycemic property of that particular plant thereby helping in the management of diabetes mellitus [4].

Mimosa pudica Linn, a traditional plant also named as sensitive or sleepy plant belongs to family of mimosaceae. In traditional medicine it is used in the treatment of alopecia, dysentery, tumor, insomnia and also against urogenital infections [5]. The phytochemical studies carried out with *Mimosa pudica* leaves have showed the presence of alkaloids, flavonoids, steroids, carbohydrates, protein, glycosides and tannin [6]. In another study, the presence of alkaloids, non-protein amino acid (mimosine), sterols, terpenoids, flavonoids C-glycosides, tannins and fatty acids have been reported [7].

Several studies carried out with the *Mimosa pudica* have reported the antioxidant [8], antihepatotoxic [9], antidiabetic [10, 11], anticonvulsant [12], antifertility [13], antifungal [14], antiviral

properties^[15] and hepatoprotective activity^[16] of the plant. In Siddha system of medicine, powdered form of both the leaves and roots of *Mimosa pudica* (Thottal Vadi Choornam) have been used for the treatment of diabetes mellitus. It has also been reported that the plant is non-toxic and safe up to the dosage of 2000 mg/kg body weight^[17]. Even though several studies have reported the antidiabetic effect of the leaves of *Mimosa pudica* at different concentrations of 100,150 and 600 mg^[18,19], most of them have tested the antidiabetic effect of the drug using alloxan induced diabetic model which is most probably known to mimic type 1 diabetes rather than type 2 diabetes mellitus. Hence, we began our study to arrive at the effect dose at which the drug exerts its antidiabetic effect using high fat diet streptozotocin induced type 2 diabetic model which is known to mimic the natural transition from insulin resistance to beta cell dysfunction in type 2 diabetes mellitus.

Material and methods

Preparation of plant extract

Mimosa pudica Linn leaves were collected from Kanchipuram district, Tamilnadu, India. The collected *Mimosa pudica* 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 soxhlation. 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.

Chemicals

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

Experimental Design

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. The animals were divided into seven groups of six animals each. Type 2 diabetes was induced by high fat diet (HFD) and low dose of streptozotocin (STZ). 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)^[20]. 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.

Experimental Groups

The animals were randomly divided into seven groups of six animals each. Group I: Normal control rats receiving olive oil

as a vehicle; Group II: HFD+STZ induced diabetic control rats; Group III, IV, V and VI HFD+STZ diabetic rats (as in group II) treated with ethanol extract of *Mimosa pudica* leaves at different doses of 100,200,300 and 400 mg/kg of body weight for 30 days. Group VII: HFD+STZ diabetic rats treated with standard drug metformin at dosage of 200 mg/kg of body weight for 30 days.

Biochemical study

Glucose was estimated by the method of Trinder (1969) using reagent kit^[21] and insulin level was assayed by Solid-phase enzyme-linked immunosorbent assay (ELISA). Glycosylated hemoglobin (HbA1c) level was estimated by the method of Rao and Pattabiraman (1990)^[22]. Total cholesterol according to the method of Parkeh and Jung (1970)^[23]. Triglyceride (TG) in plasma was determined by the method of Rice (1970)^[24] based on the method of Van Handle (1961)^[25]. HDL and atherogenic index were determined.

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 \pm SD for six animals in each group.

Results and Discussion

Type 2 diabetes mellitus has emerged as the most common and prevalent metabolic disorder in recent time. Hence, there is always an urge to screen newer drugs with lesser side effects to manage and treat the anomalies resulting from this metabolic disorder. High fat diet and streptozotocin induced model is known to mimic the natural transition from insulin resistant state to frank hyperglycemia leading to the development of type 2 diabetes mellitus and has also been known to be associated with the metabolic anomalies as well. Hence, this model was used for our study and a dose dependent study was carried out with four different dosages 100, 200, 300 and 400 mg to find out the effective dosage at which the drug can bring out its maximum potential effects. Diabetes is usually associated with characteristic loss of body weight, hyperglycemia, impaired glucose tolerance, increased glycation of hemoglobin and alterations in lipid profile. Hence all these parameters were studied to arrive at the effective dosage at which the drug can exert its potential antidiabetic effect.

The alterations in blood glucose level, insulin and HbA1c have been depicted in Table 1. The blood glucose level was raised in HFD and low dose STZ induced diabetic control rats when compared to normal control (p<0.05) rats. Hyperglycemia is one of the major clinical characteristic of diabetes mellitus associated with development of long-term complications^[26]. The capacity of beta cells to secrete insulin and control the metabolism of glucose in major insulin sensitive tissues is linked in the progression and development of type 2 diabetes mellitus^[27].

Table 1: Effect of *Mimosa pudica* leaf extract on blood glucose, insulin, hemoglobin of control and experimental animal

Group	Glucose(mg/dl)	Insulin(μ U/L)	HbA1c (mg/g Hb)
Normal control	84.37 \pm 8.14	16.83 \pm 1.64	0.46 \pm 0.03
Diabetic control (DC)	266.12 \pm 20.01 ^a	11.7 \pm 0.43 ^a	25 \pm 0.12 ^a
DC+ <i>Mimosa pudica</i> (100mg/kg b.wt)	242.42 \pm 18.34	13.82 \pm 1.32	1.12 \pm 0.08
DC+ <i>Mimosa pudica</i> (200mg/kg b.wt)	188.28 \pm 12.87	13.95 \pm 1.04	0.94 \pm 0.08
DC+ <i>Mimosa pudica</i> (300mg/kg b.wt)	114.81 \pm 8.21 ^b	15.30 \pm 1.38 ^b	0.47 \pm 0.04 ^b
DC+ <i>Mimosa pudica</i> (400mg/kg b.wt)	105.45 \pm 8.76 ^b	16.26 \pm 1.66 ^b	0.48 \pm 0.05 ^b
DC+Metformin (200mg/kg b.wt)	124 \pm 4.5 ^b	14.16 \pm 0.47 ^b	0.51 \pm 0.04 ^b

Values are expressed as mean \pm SD for 6 animals. Values are given statistically significance at $p < 0.05$. a: Control Vs. Diabetic control, DC vs. DC+*Mimosa pudica*(100mg), *Mimosa pudica* (200mg), *Mimosa pudica* (300mg), *Mimosa pudica* (400mg), metformin (200mg).

Excess glucose in blood reacts with hemoglobin to form more glycosylated hemoglobin in diabetes condition. It is one of the important parameters in the diagnosis of diabetes mellitus. Increased glycosylated hemoglobin was observed in diabetic control rats when compared to normal control rats. Similar results have been reported in earlier studies also [28]. Treatment with the drug *Mimosa pudica* effectively ameliorated the alterations in blood glucose, insulin and glycosylated hemoglobin in diabetic rats when compared to untreated rats ($p < 0.05$) in a dose dependent manner (from 100 mg/kg of body wt to 400mg/kg of body wt). Significant alteration was observed at the dosage of 300 and 400mg after the treatment period.

The decreased level of glycosylated hemoglobin is due to alteration of level of insulin and glucose after the *Mimosa pudica* treatment. The antidiabetic effect of the plant is mainly due to the presence of phenolic and flavonoid compounds present in the plant *Mimosa pudica*. These compounds are reason for the antioxidant's property of *Mimosa pudica*,

which favor to increase the absorption of glucose and body's sensitivity to insulin [29]. It has been reported that during diabetes mellitus condition a variety of derangement occur in metabolic process so that it leads to hyperlipidemia [30].

Hypertriglyceridemia and hypercholesterolemia are common lipid abnormalities reported in diabetic condition [31]. The increased concentration of cholesterol, triglycerides and decreased HDL level was observed in the present study. The raised level of triglycerides is important marker for insulin resistance. Zheng *et al.* have been reported the similar result in the previous study [32]. Atherogenic index, a strong predictor of atherosclerosis and coronary heart diseases [33], is also increased in diabetes rats when compared to normal control rats. Both atherosclerosis and coronary heart diseases are secondary complication associated with diabetes mellitus. Table 2 represents the level of cholesterol, triglycerides, HDL and atherogenic index. The treatment with *Mimosa pudica* leaf extract and metformin significantly altered ($p < 0.05$) the level of cholesterol, triglycerides and HDL in treated rats. The significant reduction of cholesterol and triglycerides was observed at dosage of 300 and 400 mg of *Mimosa pudica* leaf extract treatment whereas the HDL concentration significantly increased at same dosage.

Table 2: Effect of *Mimosa pudica* leaf extract on cholesterol, triglyceride, HDL and atherogenic index of control and experimental animal

Group	Cholesterol(mg/dl)	Triglycerides(mg/dl)	HDL (mg/dl)	Atherogenic index
Normal control	68.12 \pm 5.53	80.45 \pm 6.37	22.52 \pm 2.08	2.02 \pm 0.13
Diabetic control (DC)	145.45 \pm 10.55 ^a	162.68 \pm 10.18 ^a	10.66 \pm 0.71 ^a	12.64 \pm 1.25 ^a
DC+ <i>Mimosa pudica</i> (100mg/kg b.wt)	138.50 \pm 9.61	155.26 \pm 13.25	10.95 \pm 0.90	11.65 \pm 0.96
DC+ <i>Mimosa pudica</i> (200mg/kg b.wt)	112.32 \pm 10.04	132.34 \pm 9.03	12.62 \pm 1.24	7.90 \pm 0.58
DC+ <i>Mimosa pudica</i> (300mg/kg b.wt)	82.72 \pm 6.21 ^b	98.12 \pm 8.78 ^b	19.32 \pm 1.43 ^b	3.28 \pm 0.30 ^b
DC+ <i>Mimosa pudica</i> (400mg/kg b.wt)	80.26 \pm 4.92 ^b	94.54 \pm 7.01 ^b	19.74 \pm 1.76 ^b	3.07 \pm 0.24 ^b
DC+Metformin (200mg/kg b.wt)	79.62 \pm 7.02 ^b	91.82 \pm 8.59 ^b	19.86 \pm 1.42 ^b	3.01 \pm 0.27 ^b

Values are expressed as mean \pm SD for 6 animals. Values are given statistically significance at $p < 0.05$. a: Control Vs. Diabetic control, DC vs. DC+ *Mimosa pudica*(100mg), *Mimosa pudica*(200mg), *Mimosa pudica*(300mg), *Mimosa pudica*(400mg), metformin(200mg).

The results of the above study reveal that the potential anti-diabetic effect of *Mimosa pudica* was found to be at 300 mg/kg b.wt. as evidenced by (i) a significant decrease and increase in the levels of blood glucose and insulin respectively, (iii) improved glucose tolerance, (iv) improvement in glycemic control as indicated by decrease in HbA1c levels and (v) a significant decrease in the levels of serum lipid profile.

Conclusion

Preliminary studies involving basic parameters to diagnosis diabetes was taken into account to arrive at the effective dose of the drug. The results of the present finding indicates that the ethanolic extract of the leaves of *Mimosa pudica* has antidiabetic effect and the drug is known to exhibit its

maximum potential effect at the dosage of 300mg/kg/b.wt against high fat diet and streptozotocin induced type 2 diabetes mellitus. The phytochemical constituents present in *Mimosa pudica* extract might have contributed to the hypoglycemic and hypolipidemic activity of the drug as evidenced from the improvement in the levels of glucose, insulin and serum lipids. Further biochemical and molecular studies are in progress to elucidate the molecular mechanism behind the effect of the drug.

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