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Studies on the antidiabetic effects of *Mangifera indica* stem-barks and leaves on nondiabetic, type 1 and 2 diabetic model rats

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Abstract

Mangifera indica Linn, locally known as mango tree has been claimed to possess antidiabetic properties by many investigators. The present study was undertaken to screen the hypoglycemic and antihyperglycemic activity of both ethanol and water extracts of leaves and stem-barks of *M. indica* in nondiabetic and diabetic model rats in different prandial state. The results showed that all of the extracts had significant antihyperglycemic effect in type 2 diabetic model rats when fed simultaneously with glucose load ($p<0.05$-0.01; $p<0.005$-0.001). Moreover, the ethanol extract of stem-barks showed significant antihyperglycemic effect when the extract was fed 30 min prior to the glucose load ($p<0.01$). Investigations were carried out to evaluate the effect of *M. indica* on glucose absorption using a rat intestinal preparation *in situ*. The ethanol extracts of stem-barks reduced glucose absorption gradually

Introduction

Diabetes mellitus is ranked seventh among the leading causes of death and third when it's fatal complications are taken into account (Trivedi et al., 2004). Traditional preparations of plant sources are widely used almost everywhere in the world to treat this disease. Therefore, plant materials are considered to be the alternative sources for finding out new leads for hypo-/antihyperglycemic agents.

Following a standardized procedure (Ali et al., 1993) antidiabetic plant materials are being screened in BIRDEM for their hypoglycemic properties. Experiment on normal, type 1 and type 2 diabetic model rats at different prandial states have been combined in this experimental approach, which screens materials for hypo-/antihyperglycemic activity as well as provide an approximate idea on the possible target tissue(s) involved. *Mangifera indica* has been reported to have hypoglycemic effect in both laboratory animals (Ojewole et al., 2005; Muruganandan et al., 2005; Perpetuo et al., 2003; Aderibigbe et al., 2001; Sharma et al., 1997) and human diabetic subjects (Mahabir et al., 1997). The purpose of this work was to evaluate the hypo- and antihyperglycemic effects of *M. indica* in normal and both type of diabetic model rats and to find out their possible mode(s) of antidiabetic action.

Material and Methods

Plant materials and preparation of test samples: M. indica Linn. leaves and stem-barks were collected from the garden of the Pritilata Hall, Jahangirnagar University, Savar, Dhaka in the month of February 2007. Newly grown, fresh, green leaves (931 g) and skin of the stem-barks (893 g) of *M. indica* were pasted by homogenizing with mortar and were suspended with water for preparing the water extract and finally 800 mL of stem-barks and leaves water extract were collected. A portion of stem-barks and leaves paste were dissolved in absolute ethanol (96% ethanol) and filtered. Suspensions were dried using a rotary vacuum evaporator (BUCHI Rota vapor R-114). These semisolid extracts were again dried with water bath at 80°C. The amount

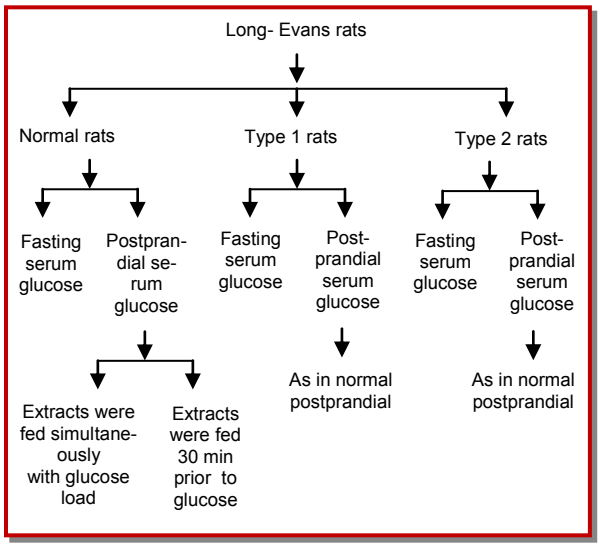
of total ethanol extract of stem-barks and leaves were found to be 30.1 g and 35.3 g. These dried extracts were kept in the Frazer and utilized for biological screening at BIRDEM.

Animals: The experiments were carried out on Long-Evans rats (180-220 g) of both sexes, bred at BIRDEM animal house and maintained at a constant room temperature of 22 ± 5°C with humidity of 50-70% and the natural 12 hours day-night cycle. Animals were fed on a standard laboratory pellet diet and water *ad labium.*

Induction of diabetes in rats: Type 1 diabetes was induced by a single intraperitoneal (*i.p.*) injection of streptozotocin (STZ, Upjohn Company, Kalamazoo, MI USA) at a dose of 65 mg/kg body weight to adult rats (3-4 months). Confirmatory fasting blood glucose test for type 1 model rats was performed after 7 days of STZ injection. Induction of type 2 diabetes was performed using a single *i.p.* injection of STZ (90 mg/kg body weight) to the 48 hours old pups as described by Bonner-Weir et al. (1981). Experiments were carried out 3 months later after performing an oral glucose tolerance test.

Biological Testing: Experiments were carried out on normal, type 1 and type 2 rats according to the following scheme.

The water extracts (leaf and stem-bark) were used at a dose of 1 mL/9 mL water/kg body weight and 96%



ethanol extracts (leaf and stem-bark) were used at a dose of 1.3 g/kg body weight/10 mL. Extracts of *M. indica* were fed to the rats by smooth metallic tube under mild-ether anesthesia (Mamun et al., 2001). The control rats were given equal volume of distilled water; positive controls were given glibenclamide (5 mg /kg) and insulin (Actrapid HM-40 IU/mL) for type 2 and type 1 model rats respectively. Blood samples from rats were drawn by amputation of the tail tip. Blood samples were collected at 0, 60, 120 min for fasting conditions, at 0, 30, 75 min for simultaneous feeding of extract with glucose and at 0, 60 and 105 min when the extract was fed 30 min before glucose load (2.5 g/kg body weight).

Effects of M. indica on intestinal glucose absorption: An intestinal perfusion technique (Swintosky and Pogonowska-Wala, 1982) was used to study the effects of *M. indica* extracts on intestinal absorption of glucose in nondiabetic and type 2 diabetic rats fasted for 36 hours and anesthetized with sodium pentobarbital (50 mg/kg). The plant extracts were added to a kreb's solution (g/L 1.02 $CaCl_2$, 7.37 NaCl, 0.20 KCl, 0.065 $NaH_2PO_4.6H_2O$, 0.6 $NaHCO_3$, pH 7.4), supplemented with glucose (54.0 g/L) and perfused at a perfusion rate of 0.5 mL/min for 30 min through the duodenum. The perfusate was collected from a catheter set at 40 cm. *M. indica* extracts were added to Kreb's solution to a final conc. of 25 mg/mL so that the amount of extract in the perfused intestine is equivalent to the dose of 1.3 g/kg. The control group was perfused only with Kreb's buffer supplemented with glucose. The results were expressed as percentage of absorbed glucose, calculated from the amount of glucose in solution before and after the perfusion.

Biochemical procedures: Serum glucose levels were estimated on the same day by glucose oxidase (GOD-POD) method using a commercial kit (Boehringer-Mannheim GmbH).

Statistical analysis: Data from the experiments were presented as mean ± Standard deviation. Statistical analysis was done by using the Statistical Package for Social Science (SPSS) software for windows version 12 (SPSS Inc., USA). Analysis of variance (ANOVA, Bonferroni Post Test) was done to see any difference between the groups. The level of significance was set at $p \leq 0.05$.

Results

Streptozotocin injection to adult rats (for simulation of type 1 diabetes) resulted in severe diabetes, which was characterized by hyperglycemia (fasting blood glucose ranging 19.8-23.2 mmol/L) on the 7th day. In type 2 diabetic model rats fasting glucose level was slightly higher (6.9-8.7 mmol/L) indicating the presence of functioning β-cells. The water extracts and ethanol extracts of *M. indica* leaves and stem-barks showed no effect in nondiabetic, type 1 and 2 diabetic model rats in the fasting state (Table I). It is seen from the Table I that glibenclamide and insulin reduced serum glucose level in the fasting condition of normal and type 1 rats respectively. Glibenclamide and insulin showed significant hypoglycemic effects both at 60 min ($p<0.02$ and $p<0.001$) and at 120 min ($p<0.001$) in normal and type1 diabetic model rats respectively.

Table II reveals that none of the extracts of *M. indica* had any significant antihyperglycemic effect in

Table I

Effect of *M. indica* of fasting blood glucose levels of diabetic model rats

Group	min 0 (mmol/ L)	min 60 (mmol/ L)	min 120 (mmol/ L)
Nondiabetic rats			
Water control (n = 6)	6.5 ± 0.7	6.3 ± 0.4	6.5 ± 0.7
Glibenclamide (n = 6)	6.7 ± 0.8	4.7 ± 0.6[a]	4.3 ± 2.2[a]
M_Indica_w_l (n = 8)	6.3 ± 0.8	6.3 ± 1.0	6.2 ± 1.1
M_Indica_eth_l (n = 7)	6.8 ± 0.8	7.0 ± 0.8	6.8 ± 0.7
M_Indica_w_b (n = 8)	6.9 ± 0.4	6.9 ± 0.9	7.0 ± 0.9
M_Indica_eth_b (n = 8)	7.0 ± 0.5	6.6 ± 0.8	7.0 ± 1.0
Type 1 diabetic model rats			
Water control (n = 6)	20.6 ± 3.0	21.2 ± 2.4	19.4 ± 3.9
Insulin (n = 6)	22.2 ± 2.2	5.4 ± 4.5[a]	4.5 ± 3.9[a]
M_Indica_w_l (n = 7)	19.8 ± 4.1	19.4 ± 4.1	18.6 ± 4.2
M_Indica_eth_l (n = 6)	21.1 ± 3.7	20.7 ± 2.6	19.8 ± 2.2
M_Indica_w_b (n = 8)	20.0 ± 3.8	21.8 ± 3.6	20.1 ± 3.5
M_Indica_eth_b (n = 9)	23.2 ± 5.3	21.0 ± 4.3	18.9 ± 3.7
Type 2 diabetic model rats			
Water control (n = 6)	8.7 ± 1.5	9.1 ± 2.6	9.0 ± 3.0
Glibenclamide (n = 6)	8.1 ± 1.3	7.3 ± 0.7	6.6 ± 0.9
M_Indica_w_l (n = 7)	8.4 ± 1.6	8.6 ± 2.0	7.6 ± 1.6
M_Indica_eth_l (n = 7)	7.6 ± 1.5	8.8 ± 3.1	9.1 ± 3.6
M_Indica_w_b (n = 7)	6.9 ± 1.2	6.4 ± 0.6	6.3 ± 0.5
M_Indica_eth_b (n = 7)	8.0 ± 1.8	9.3 ± 3.4	9.2 ± 2.9

ANOVA (Bonferroni test) was done as the test of significance. [a]p<0.01; n = number of rats

Table II

Effect of *M. indica* on blood glucose levels diabetic model rats when the extracts were fed simultaneous with glucose load

Group	min 0 (mmol/ L)	min 30 (mmol/ L)	min 75 (mmol/L)
Nondiabetic rats			
Water control (n = 6)	6.4 ± 0.9	7.8 ± 1.1	7.4 ± 0.9
Glibenclamide (n = 6)	6.4 ± 1.01	7.7 ± 0.8	5.2 ± 0.7[b]
M_Indica_w_l (n = 7)	6.1 ± 1.0	7.4 ± 0.6	6.8 ± 0.8
M_Indica_eth_l(n = 7)	6.2 ± 1.1	8.3 ± 1.4	7.6 ± 0.7
M_Indica_w_b (n = 7)	6.5 ± 1.0	8.4 ± 0.3	7.7 ± 0.7
M_Indica_eth_b (n = 7)	6.2 ± 1.0	8.0 ± 0.8	7.5 ± 0.4
Type 1 diabetic model rats			
Water control (n = 6)	24.9 ± 2.3	30.9 ± 3.3	29.2 ± 3.3
Insulin (n = 6)	23.8 ± 3.3	18.6 ± 4.2[b]	8.8 ± 3.5[b]
M_Indica_w_l (n = 6)	22.8 ± 3.5	28.7 ± 4.4	27.2 ± 2.7
M_Indica_eth_l (n = 6)	23.8 ± 3.6	28.3 ± 3.5	26.7 ± 2.9
M_Indica_w_b (n = 6)	23.8 ± 1.9	28.9 ± 1.8	25.4 ± 3.8
M_Indica_eth_b (n = 6)	22.5 ± 2.6	29.1 ± 3.8	26.6 ± 1.6
Type 2 diabetic model rats			
Water control (n = 6)	8.6 ± 0.9	15.4 ± 2.1	15.6 ± 1.8
Glibenclamide (n = 6)	7.5 ± 1.4	13.8 ± 2.5	11.7 ± 2.0
M_Indica_w_l (n = 6)	6.7 ± 1.2	9.6 ± 2.6[b]	9.8 ± 2.7[b]
M_Indica_eth_l (n = 6)	7.8 ± 1.6	10.7 ± 1.6[b]	10.9 ± 2.5[a]
M_Indica_w_b (n = 6)	8.3 ± 1.7	10.6 ± 1.6[b]	10.5 ± 1.2[b]
M_Indica_eth_b(n = 6)	8.0 ± 1.	10.3 ± 1.5[a]	11.6 ± 2.5[a]

ANOVA (Bonferroni test) was done as the test of significance. [a]p<0.05-0.01, [b]p<0.001; n = number of rat

nondiabetic and type 1 model rats when fed simultaneously with glucose load. On the contrary, all of the extracts of *M. indica* showed significant antihyperglycemic effect at 30 min (p<0.002-0.001) as well as at 75 min (p<0.05-0.001) when fed simultaneously with oral glucose load in type 2 model rats (Table II). Glibenclamide showed a significant fall in serum glucose level at 75 min (p<0.001) in normal rats. In type 1 diabetic model rats, insulin showed significant antihyperglycemic effect at both time points at 30 min and at 75 min (p<0.001).

As it is seen from Table III that none of the extracts of *M. indica* showed any significant hypoglycemic effect in nondiabetic and type 1 model rats in postprandial condition when the extracts were fed 30 min prior to glucose load. In type 2 model rats, it was evident that water and ethanol extract of leaves had no significant effect but ethanol extract of stem barks of *M. indica* had significant antihyperglycemic effect at 105 min (p<0.01) when fed prior to oral glucose load (Table III). Glibenclamide showed significant antihyperglycemic effect in normal rats at both time points that is at 60 min (p<0.001) and 105 min (p<0.01); at 105 min (p<0.01) for type 2 model rats respectively. On the other hand, insulin in type 1 diabetic model significantly lowered serum glucose levels at both time points i.e. at 60 min and at 105 min (p<0.01).

Figures 1 and 2 show the effect of ethanol extracts of stem barks and leaves of *M. indica* on upper intestinal glucose absorption in normal and type 2 diabetic rats respectively. The percent of glucose absorbed across the intestine was higher during the whole period of perfusion in normal and type 2 rats. The supplemen-

Table III

Effect of *M. indica* on blood glucose levels of diabetic model rats when the extracts were fed 30 mins before to glucose load

Group	min 0 (mmol/L)	min 60 (mmol/L)	min 105 (mmol/L)
Nondiabetic rats			
Water control (n = 6)	5.8 ± 1.1	7.7 ± 0.6	7.4 ± 1.6
Glibenclamide (n = 6)	5.3 ± 1.0	5.4 ± 0.5[b]	5.0 ± 1.0[a]
M_Indica_w_l (n = 7)	6.6 ± 0.8	7.8 ± 0.9	7.6 ± 0.8
M_Indica_eth_l (n = 7)	6.8 ± 0.7	8.2 ± 0.7	8.2 ± 0.5
M_Indica_w_b (n = 7)	6.4 ± 1.0	8.0 ± 0.5	7.7 ± 0.7
M_Indica_eth_b (n = 7)	6.5 ± 0.9	7.6 ± 0.8	7.0 ± 1.5
Type 1 diabetic model rats			
Water control (n = 6)	24.8 ± 5.3	30.1 ± 4.6	27.1 ± 4.9
Insulin (n = 6)	22.2 ± 1.9	7.0 ± 2.4[a]	5.3 ± 1.2[a]
M_Indica_w_l (n = 6)	22.1 ± 4.4	28.9 ± 3.4	25.9 ± 2.9
M_Indica_eth_l (n = 6)	22.0 ± 3.3	23.7 ± 2.2	23.3 ± 2.8
M_Indica_w_b (n = 6)	25.0 ± 2.8	30.2 ± 2.8	25.7 ± 3.7
M_Indica_eth_b (n = 6)	21.2 ± 2.6	24.6 ± 4.5	23.9 ± 5.2
Type 2 diabetic model rats			
Water control (n = 6)	8.4 ± 1.2	15.5 ± 3.8	16.7 ± 2.3
Glibenclamide (n = 6)	7.5 ± 1.6	11.8 ± 1.2	10.1 ± 1.4[a]
M_Indica_w_l(n = 7)	6.6 ± 0.5	12.9 ± 2.7	12.7 ± 2.5
M_Indica_eth_l (n = 7)	7.1 ± 1.2	11.1 ± 2.8	15.0 ± 3.2
M_Indica_w_b (n = 7)	6.7 ± 1.4	12.8 ± 3.2	15.7 ± 2.2
M_Indica_eth_b (n = 7)	7.2 ± 1.7	13.4 ± 2.8	11.3 ± 3.1[a]

Data are mean ± SD; ANOVA (Bonferroni test) was done as the test of significance. [a]p<0.01, [b]p<0.001; n = number of rats

tation of the perfusion medium either with ethanol extracts of barks or leaves of *M. indica* in normal rats did not affect the amount of absorbed glucose throughout the whole period of experiment in normal rats (Figure 1). However, in type 2 diabetic models, supplementation of the medium with ethanol extracts of stem-barks reduced glucose absorption during the whole perfusion period (13-15% reduction after 25-30 min) (Figure 2).

Discussion

Our results demonstrate that all the extracts of *M. indica* leaves and stem barks showed significant antihyperglycemic effect in type 2 diabetic model rats when the extracts were fed simultaneously with glucose. Single oral administration of a dose of 250 mg/kg body weight produces a potent and strong hypoglycemic effect in type 2 rats. The obtained results are supported by the finding of other investigators (Sharma et al., 1997; Aderibigbe et al., 2001).

Hypoglycemic activity that is found when given with a simultaneous glucose load in diabetic rats indicates that the extracts may interfere with the intestinal glucose absorption in the gut by various mechanisms (Nahar et al., 2000; Vinik and Wing, 1990; Lempcke, 1987). It may be postulated that the extracts of *M. indica* might stimulate glycogenesis in the liver, which is enhanced by feeding (Creutzfeld et al., 1979). This effect was confirmed by Perpetus et al. where they showed that blood glucose level of diabetic rats consuming mango flour for 90 days decreased 66% in comparison to control rats. It was also observed that hepatic glycogen level of those diabetic rats was 64% greater then control. The author claimed that this increase in glycogen level might have contributed to

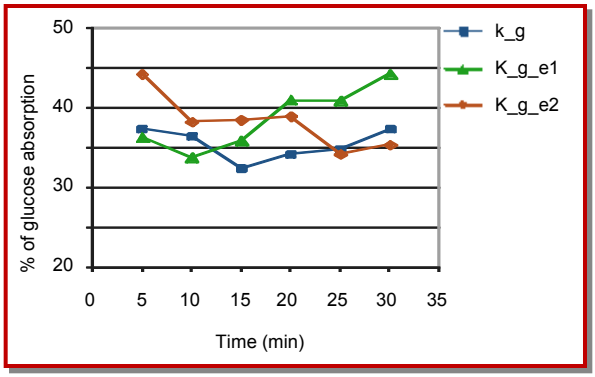


Figure 1: Effect of the *M. indica* on upper intestinal glucose absorption on normal rats

Results are presented as mean ± SD (n = 6). Rats were fasted for 36 hours and intestine was perfused with glucose solution (54 g/L) with or without ethanol extracts of *M. indica* (25 mg/mL). k_g= Krebs buffer supplemented with glucose; K_g_e1 = Ethanol extract of leaves; K_g_e2 = Ethanol extract of stem barks

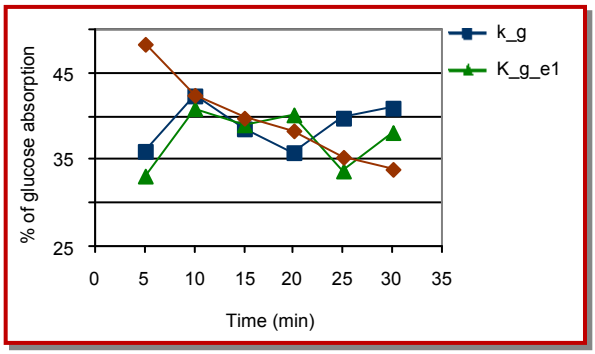


Figure 2: Effect of the *M. indica* on upper intestinal glucose absorption on type 2 diabetic rats

Results are presented as mean ± SD (n = 6). Rats were fasted for 36 hours and intestine was perfused with glucose solution (54 g/L) with or without ethanol extracts of *M. indica* (25 mg/mL). k_g = Krebs buffer supplemented with glucose; K_g_e1 = Ethanol extract of leaves; K_g_e2 = Ethanol extract of stem

the reduction of blood glucose level in these animals.

Ethanol extract of stem bark of *M. indica* was also effective in type 2 diabetic model rats when fed 30 min might be due to a systemic action, i.e. as a result of the stimulation of pancreatic β-cells and improving the insulin secretory capacity or enhancement of insulin action by the extract. This effect could not be confirmed by our study since serum insulin level after a single feeding was not determined. It has been claimed that the chronic intraperitoneal administration of mangiferin (a xanthone glucoside, isolated from the leaves of *M. indica*) at a dose of 10 and 20 mg/kg once daily for 28 days exhibited antidiabetic activity by lowering fasting plasma glucose level significantly at different time intervals in STZ diabetic rats and improved glucose tolerance. The accumulating eviden-ces suggest that both pancreatic and extra pancreatic mechanisms might be involved in its antidiabetic or antihyperglycemic action (Muruganandan et al., 2005).

One of the objectives of the present study was to investigate whether the hypoglycemic effect is related to the inhibition of glucose absorption in the gut. This was investigated in gut perfusion experiment where the ethanol extracts of stem barks showed gradual decrease in glucose absorption. Aderibigbe et al. claimed that hypoglycemic effect of the aqueous extract of leaves of *M. indica* was compatible with chlorpropamide (an oral hypoglycemic agents) and the action may be parts due to an intestinal reduction of the absorption of glucose. Therefore, the activity of the extracts of *M. indica* does not seem to be mediated by increasing insulin secretion or insulin sensitivity since it is not active in type 1 model rats.

Thus it may be concluded from the present study that the antidiabetic activity of *M. indica* is probably at least, partly due to inhibition of glucose absorption in the gut.

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