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CLINICAL INVESTIGATION OF HYPOGLYCEMIC EFFECT OF LEAVES OF *MANGIFERA INIDCA* IN TYPE-2 (NIDDM) DIABETES MELL1TUS

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ABSTRACT:

The present study was designed to investigate clinically the hypoglycemic effect of leaves of *Mangifera indica* in Type-2 diabetes mellitus. After assaying fasting plasma and urinary glucose, 10 patients of type-2 diabetes mellitus with no previous medication, 10 patients of type-2 diabetes mellitus taking oral hypoglycemic agents with history of inadequate control and six control subjects were given low (0.5 g/kg/d in two divide doses) and high (1 g/kg/d in two divided doses) doses of powdered part, aqueous extract and alcoholic extract of leaves of *Mangifera indica* for 14 days. On 15th day blood and urine samples for glucose were taken. Based on results obtained it was found that *Mangifera indica* has significant hypoglycemic activity in high dose and can be successfully combined with oral hypoglycemic agents in type-2 diabetic patients whose diabetes is not controlled by these agents.

INTRODUCTION

Mangifera indica is a large evergreen tree belonging to the family Anacardiaceae. It is commonly known as mango and its fruits are eaten all over the world. Its different parts have been used for treatment of various diseases. Unripe green mangoes cut into pieces and dried in the sun are believed to be valuable in the treatment of scurvy. Ripe mangoes are rich in Vitamin A and are used in the treatment of night blindness.

The fresh leaves of *Mangifera indica* have been used in Asian traditional medicine to treat diabetes mellitus (Bakhru, 2000).

MATERIALS AND METHODS

The present study was carried out in the laboratories of Hamdard Institute of Pharmaceutical Sciences, Islamabad and Army Medical College, Rawalpindi. The following criteria was used to include or exclude the patients in the study.

Inclusion Criteria

1. Type 2 diabetic patients with fasting plasma glucose level equal to or greater than 140 mg/dl of blood (WHO study group on diabetes mellitus, 1985, Geneva technical report series 727) (WHO 1985) with out any detectable I visible complications.
2. Type 2 diabetic patients taking oral hypoglycaemic agents with history of inadequate control of blood glucose with these agents.
3. Normal healthy subjects with no family history of diabetes mellitus.
4. The patients and control subjects were of either sex (male or female) between the ages of 35-60 years.

Exclusion Criteria

1. Pregnant or nursing patients.
2. Smokers

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3. Patients with GIT, hepatic, cardiovascular, renal or endocrine disorder (other than diabetes mellitus) which can interfere with the absorption, metabolism and excretion of the study plant.
4. Patients with any complication of diabetes mellitus.
5. Patients suffering from type 1 (IDDM) diabetes mellitus.

Subjects

The selected subjects (patients and controls) were medically examined and given code numbers and were asked to present themselves on a specified date for sample collection. They were requested to come with fasting (no food before 12 hours) and to void their morning urine and to drink 250ml glass of water before coming for testing (Bahajiri *et al*., 2000). Patients already taking oral hypoglycaemic agents were requested to take their usual medicine and food after sampling.

Blood Sample

Blood samples (3-5 ml) were drawn from each patient and control subject by venepuncture through plastic disposable syringes. The blood samples were collected in clean oven dried glass bottles which were previously rinsed with 1% sodium fluoride, 3% potassium oxalate solution to prevent coagulation and glycolysis. The plasma was separated after centrifugation. Any sample showing haemolysis was discarded. After separation of plasma, it was transferred to clean, previously acid rinsed, washed and oven dried glass bottles with plastic caps. The plasma glucose estimation was done immediately on the same day by kit method (Trinder, 1969).

Plant

Mangifera indica leaves were obtained from the local area. Dr. Mir Ajab Khan department of biological sciences Quaid-i-Azam University Islamabad identified the leaves of selected plant. The leaves were shade dried, pulverized by a mechanical grinder and passed through 40-mesh sieve. Filtrate from powdered samples of leaves soaked overnight in 95% ethanol and distilled water, were used as alcoholic and aqueous extract respectively for studied plant (Ahmed *et al*., 1995).

Aqueous Extract

After grinding in an electric grinder, the powder was soaked in equal amount of water and stirred intermittently and then left overnight. The macerated pulp was then filtered through a coarse sieve and the filtrate was dried at reduced temperature. This dry mass served as aqueous extract of plant for experimentation (Vats *et al*., 2002).

Alcoholic Extract

Alcoholic extract was prepared by powdering 1 kg plant material in an electric grinder. The powder was then mixed with 500 ml of alcohol and kept at room temperature for 36 hours. The slurry was stirred intermittently for 2 hours and left overnight. The mixture was then filtered and the filtrate was freed from solvent under partial vacuum (71 mmHg) at 35-45^{o}C to yield pulp. A few drops of silicon emulsion were added near the end of distillation to avoid frothing. The final residue collected was a thick paste. This was dried at reduced temperature. This dried mass served as alcoholic extract for experimentation (Vats *et al*., 2002).

General Plan of Study

The fasting blood and urine samples from patients and control subjects were assayed for respective glucose levels. 10 patients of type 2 diabetes mellitus with no previous medication and 10 type-2 diabetic patients taking oral hypoglycaemic agents (with history of inadequate control) were given dry powdered leaves of *Mangifera indica* for fourteen days. On 15th day blood and urine samples of glucose were taken.

After an interval of one-week fasting blood and urine samples were again taken from these patients.

These patients were given aqueous extract of *Mangifera indica* leaves for 14 days. On 15th day blood and urinary samples of glucose were taken.

After an interval of one-week fasting blood and urine samples for the monitoring of glucose level were again taken from these patients.

These patients were given alcoholic extract of the *Mangifera indica* leaves for 14 days. On 15th day blood and urinary samples of glucose were taken.

Out of the ten patients five received low dose (0.5 g/kg/d in two divided doses) and five received high dose (1 g/kg/d in two divided doses) of the plant.

Six healthy subjects were kept as control. Three received subjects low dose and three subjects received high dose of powdered, aqueous and alcoholic extracts of leaves of *Mangifera indica* as described above.

All the patients and control subjects were monitored for any adverse reaction of the plant. Plasma assay of glucose was done by kit method and urinary glucose was estimated by strip method (Burtis and Ashwood, 1998). The data was statistically evaluated (Glazer, 2001).

RESULTS

The results are summarized in the following table and graph.

Untoward Effects

GIT upsets e.g., nausea, abdominal discomfort (with high dose), vomiting was reported on administration of first high dose of *Mangifera indica* (2 patients, 40%) Diarrhoea was reported with high dose (3 patients, 60%) but was mild in nature and disappeared after few days without any treatment. Mild headache initially was complained by some patients belonging to all the groups. The basis of headache was psychological.

DISCUSSION

Diabetes mellitus has been defined as a syndrome of abnormal carbohydrate metabolism, resulting in hyperglycaemia with acute metabolic complications and chronic vascular, neurogenic and orthopedic complications affecting many organs of the body (Jamil *et al*., 2001).

There was a significant decrease in mean concentration of plasma glucose two weeks after administration of high (1 g/kg/d) dose of powdered part, aqueous extract and alcoholic extract of leaves of *Mangifera indica*. The fall in mean concentration of plasma glucose was more marked in patients taking oral hypoglycaemic agents with history of inadequate control. With addition of high dose of *Mangifera indica* their plasma glucose fell within the normal controlled range of diabetes mellitus. Glycosuria disappeared two weeks after administration of both low and high dose of Mangifera indica. These results are in accordance with the following two studies carried out in animals:The effect of aqueous extract of leaves of *Mangifera indica* on blood glucose level was assessed in normoglycaemic, glucose-induced hyperglycaemic and streptozocin (STZ) induced diabetic rats. The aqueous extract given orally (1 gm/kg) did not alter the blood glucose levels in either normoglycaemic or STZ induced diabetic rats. In glucose-induced hyperglycaemia, however, anti-diabetic activity was seen when the extract and glucose were administered simultaneously and also when the extract was given to the rats 60 min before the glucose. The results of this study indicate that the aqueous extract of leaves of *Mangifera indica* possess hypoglycaemic activity (Aderibigbe *et al*., 1999).

In another study, the alcoholic extract of the leaves of *Mangifera indica* was administered in doses of 50, 100,150, and 200 mg/kg body weight to normal and alloxan diabetic rabbits. The blood glucose levels were estimated before and 2, 4, 6 and 8 hours after the administration of the extract. The extract exerted a significant hypoglycaemic effect in normal rabbits but had no significant effect in alloxan treated diabetic rabbits (Wadood *et al*., 2000).

Table

Table showing effects of dry powdered part, aqueous extract and alcoholic extract of leaves of *Mangifera indica* on blood and urinary glucose in type-2 diabetic patients with no previous medication, taking oral hypoglycemic agents with history of inadequate control and control subjects before and two weeks after administration The values are given as Mean ± SD (n=10+l0+6) Blood glucose (mg/dl)

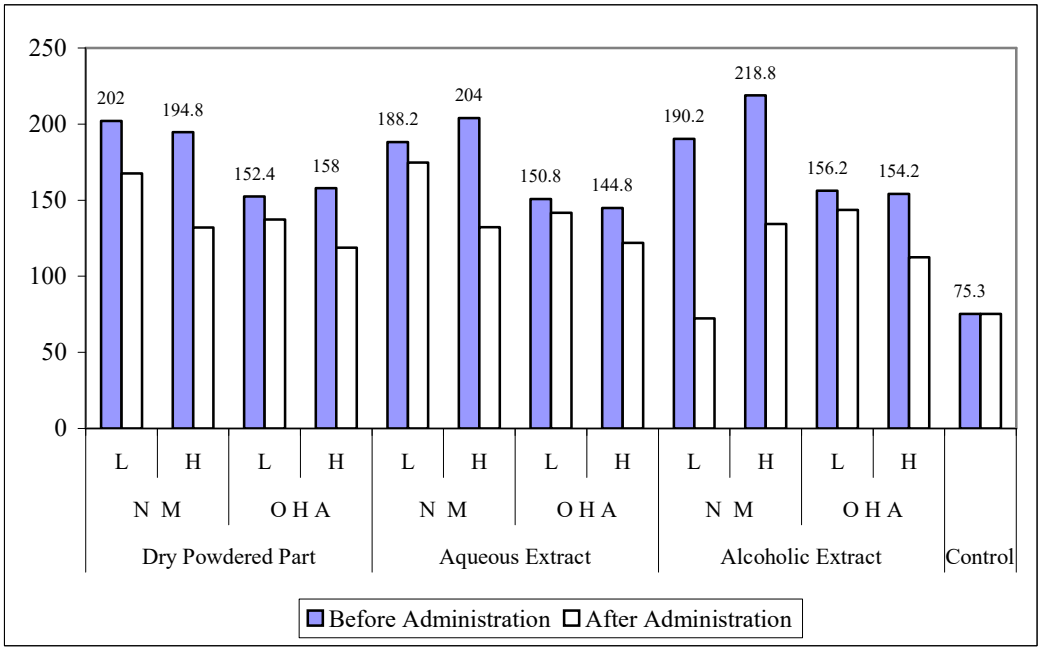
	Blood glucose (mg/dl)		Urinary Glucose	
	Before Administration	After Administration	Before Administration	After Administration
Dry Powdered Part				
No previous medication				
Low dose	188.4 ± 7.43	168.2 ± 8.43*	Glycosuria	No. Glycosuria
High dose	201.2 ± 7.04	130.6 ± 6.73*	Glycosuria	No. Glycosuria
Taking oral hypoglycemics				
Low dose	155.2 ± 8.69	132.4 ± 3.64*	No. Glycosuria	No. Glycosuria
High dose	162 ± 13.83	117.4± 9.91*	No. Glycosuria	No. Glycosuria
Control				
Low dose	79	74^{NS}	No. Glycosuria	No. Glycosuria
High dose	64	71^{NS}	No. Glycosuria	No. Glycosuria
Aqueous Extract				
No previous medication				
Low dose	190.2± 7.08	170.8± 6.30*	Glycosuria	No. Glycosuria
High dose	200.8± 11.03	128.4± 8.35*	Glycosuria	No. Glycosuria
Taking oral hypoglyceinics				
Low dose	155.2 ± 8.92	139.4± 2.40*	No. Glycosuria	No. Glycosuria
High dose	151.6± 11.80	123 ± 10.39*	No. Glycosuria	No. Glycosuria
Control				
Low dose	73	69^{NS}	No. Glycosuria	No. Glycosuria
High dose	79	82^{NS}	No. Glycosuria	No. Glycosuria
Alcoholic Extract				
No previous medication				
Low dose	196.8 ± 9.23	168.6± 955*	Glycosuria	No. Glycosuria
High dose	193.2± 13.02	131.6± 7.16*	Glycosuria	No. Glycosuria
Taking oral hypoglycemics				
Low dose	160.2± 10.20	148 ± 5.38*	No. Glycosuria	No. Glycosuria
High dose	160.8± 13.40	127.6± 7.50*	No. Glycosuria	No. Glycosuria
Control				
Low dose	83	74^{NS}	No. Glycosuria	No. Glycosuria
High dose	81	66^{NS}	No. Glycosuria	No. Glycosuna

Low dose: 0.5g /kg in two divided doses, High dose: 1gm/kg in two divided doses, *Significant, NS Non significant

Mechanism of Action

In a study the alcoholic extract of the leaves of *Mangifera indica* did not show any significant effect on blood glucose levels of alloxan treated rabbits. For comparison the effect of the standard hypoglycaemic drug tolbutamide (500 mg/kg) was observed on the blood glucose levels of normal and alloxan treated diabetic rabbits. Tolbutamide produced significant hypoglycaemic effect in normal rabbits but not in alloxan treated rabbits.

In view of the similarity between the effects of tolbutamide and *Mangifera indica* it may be likely that the hypoglycaemic effect of *Mangifera indica* is due to release of insulin from the pancreatic beta cells. Thus increasing glycogen deposition in the liver, causing a



Comparison of effect on blood glucose in type-2 diabetic patients and control subjects before and two weeks after administration of dry powder part aqueous and alcoholic extract of M*angifera indica.*

L=LOW DOSE H=HIGH DOSE HM Patients taking No Medication OHA Patients taking ORAL HYPOGLYCAEMIC AGENTS

reduction of glycogen levels in blood and having an extra pancreatic effect to possibly increase the number of insulin receptors (Wadood *et al*., 2000 and John and Katzung, 1995). In another study, the orally given aqueous extract of leaves of *Mangifera indica* to normoglycaemic, glucose induced hyperglycaemic and streptozocin (STZ) induced diabetic rats did not alter the blood glucose levels in either normoglycaemic or STZ-induced diabetic rats. In glucose-induced hyperglycaemia, however, the anti-diabetic activity was seen when the extract and glucose were administered simultaneously and also when the extract was given to the rats 60 min before the glucose. The hypoglycaemic effect of the aqueous extract was compared with that of an oral dose of chlorporpamide (200 mg/kg) (Aderibigbe *et al*., 1999). Thus hypoglycaemic activity of leaves of *Mangifera indica* may be due to:

Increase release of insulin from pancreatic beta cells.

Intestinal reduction of absorption of glucose.

CONCLUSION

Mangifera indica leaves (powdered part, aqueous or alcoholic extract) can be combined in high dose with oral hypoglycaemic agents to bring the blood glucose at normal levels in patients whose diabetes is not controlled with these agents or in those patients in whom these agents produce adverse effects on dose increments.

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