CLINICAL INVESTIGATION OF HYPOGLYCEMIC EFFECT OF UNRIPE FRUIT ON *MOMORDICA CHARANTIA* IN TYPE-2 (NIDDM) DIABETES MELLITUS

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ABSTRACT
The present study was designed to investigate clinically the hypoglycemic effect of unripe fruit of *Momordica charantia* 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 divided doses) and high (1.5 g/kg/d in two divided doses) doses of powdered part, aqueous extract and alcoholic extract of unripe fruit of *Momordica charantia* for 14 days. 15th day blood and urine samples for glucose were taken. Based on results obtained it was found that *Momordica charantia* has significant hypoglycemic activity and can be given to type-2 diabetic patients with no previous medication alone or in combination to patients taking oral hypoglycemic agents with inadequate control of blood glucose both in low or high doses depending upon their plasma glucose concentration.

INTRODUCTION
The bitter gourd is a common vegetable cultivated extensively in tropical areas including Mica, Asia, Caribbean, South America and Subcontinent. Being a relatively common food item, the bitter gourd was traditionally used for a dazzling array of conditions by people in tropical regions. Numerous infections, cancer and diabetes are among the most common conditions it was reported to improve (Duke, 1985).

The leaves and fruit have both been used occasionally to make tea and beer or to season soups in the western world. The berries also produces wax, which can be used to made candles. Juice of fresh leaves is valuable in piles. A paste of the roots can also be applied over piles with beneficial result. Bitter gourd with lime-juice is highly beneficial in treatment of disorders like boils, scabies ringworm and other fungal diseases. Bitter gourd roots’ paste in combination with equal part of honey taken regularly is beneficial for asthma, bronchitis, pharyngitis, rhinitis etc. Fresh juice of leaves (2 teaspoonful) mixed with equal quantity of white onion juice and lime-juice is effective in diarrhoea (Raman and Lau 1996).

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 (WHO study group on diabetes mellitus, 1985, Geneva technical report series 727) without any
detectable/visible complications (WHO, 1985).
2. Type 2 diabetic patients taking oral hypoglycemic 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.
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 water before coming for testing (Bahajiri et al., 2000). Patients already taking oral hypoglycemic 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**
*Momordica charantia* unripe fruits were obtained from the local area. Dr. Mir Ajab Khan department of biological sciences Quaid-i-Azam University Islamabad identified the fruits of selected plant. The unripe fruits 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°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 hypoglycemic agents (with history of inadequate control) were given dry powdered unripe fruits of *Momordica charantia* 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 *Momordica charantia* unripe fruits 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 *Momordica charantia* fruits 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 (1.5 g/kg/d in two divided doses) of the plant.

Six healthy subjects were kept as control. Three subjects received low dose and three subjects received high dose of powdered, aqueous and alcoholic extracts of unripe fruits of *Momordica charantia* as described above. All the patients and control subjects were monitored for any adverse reaction of the extract. Plasma assay of glucose was done by kit method and urinary glucose was estimated by strip method (Burtis *et al*., 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 *Momordica charantia* (4 patients, 80%). Mild headache initially was complained by some patients belonging to all groups. The basis of headache was psychological. Symptoms of mild hypoglycemia e.g., feeling of hunger, apprehension, sweating, yawning were reported by only two patients (40%) taking chlorpropamide and glyburide respectively with high dose of *Momordica charantia* but these symptoms disappeared on adjusting the diets of these patients accordingly.

**DISCUSSION**

Diabetes mellitus has been defined as a syndrome of abnormal carbohydrate metabolism, resulting in hyperglycemia with acute metabolic complications and chronic vascular, neurogenic and orthopedic complications affecting many organs of the body.

There was a significant decrease in mean concentration of plasma glucose two weeks after administration of both low (0.5 gm/kg) and high (1.5 gm/kg) dose of powdered part, aqueous extract and alcoholic extract of fruits of *Momordica charantia* in type-2 diabetic patients. There was a marked fall in mean value of plasma glucose with high dose of fruit of *Momordica charantia* as compared to that of low dose. The mean value of plasma glucose was in the normal controlled range of diabetes mellitus (although at upper limit of normal with low dose). Glycosuria disappeared two weeks after administration of both low and high dose of fruit of *Momordica charantia*.

*These results were correlated with the following studies:*

In one study the treatment of streptozocin diabetic rats with *Momordica charantia* fruit extract over a period of 10 weeks returned high blood glucose levels to normal (Ahmed *et al*., 2001). In other study, in the streptozocin diabetic rats, *Momordica charantia* improved the oral glucose tolerance causing significant reduction in plasma glucose to 26% at 3.5 hour. *Momordica charantia* extract (500 mg/kg) caused a 4-5 fold increase in the rate of glycogen synthesis from 4-14 C-glucose in the
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Lininger et al. (1998) have recommended that a small bitter gourd (*Momordica charantia*) can be eaten as food or up to 50 ml of fresh juice can be drunk per day or 5 ml bid or tid per day for lowering the blood glucose levels. Rahman and Zaman, (1989), in their review article have reported the anti-diabetic effect of *Momordica charantia* (fruit). The activity of BF (bitter fruit/bitter gourd) juice was tested on STZ treated RIN (Rat insulinoma) cells and isolated islets in vitro. It was found that feeding with BF juice caused reduction in STZ-induced hyperglycaemia in mice. It also reduced the STZ-induced apoptosis in RIN cells indicating the mode of protection of BF juice on RIN cells, islets and pancreatic beta-cells (Sitawad et al., 2000).

Investigations were carried out to evaluate the effect of *Momordica charantia* on the liver of normally fed rats (Sarkar et al., 1996).

<p>| Table showing effects of dry powdered part, aqueous extract and alcoholic extract of Unripe fruit of <em>Momordica charantia</em> 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+10+6) |</p>
<table>
<thead>
<tr>
<th>Blood glucose (mg/dl)</th>
<th>Urinary Glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before Administration</td>
<td>After Administration</td>
</tr>
<tr>
<td><strong>Dry Powdered Part</strong></td>
<td></td>
</tr>
<tr>
<td>No previous medication</td>
<td></td>
</tr>
<tr>
<td>Low dose</td>
<td>209 ± 14.31</td>
</tr>
<tr>
<td>High dose</td>
<td>207.5 ± 17.46</td>
</tr>
<tr>
<td>Taking oral hypoglycemics</td>
<td></td>
</tr>
<tr>
<td>Low dose</td>
<td>157 ± 11.83</td>
</tr>
<tr>
<td>High dose</td>
<td>163.6 ± 10.35</td>
</tr>
<tr>
<td><strong>Control</strong></td>
<td></td>
</tr>
<tr>
<td>Low dose</td>
<td>70</td>
</tr>
<tr>
<td>High dose</td>
<td>75</td>
</tr>
<tr>
<td><strong>Aqueous Extract</strong></td>
<td></td>
</tr>
<tr>
<td>No previous medication</td>
<td></td>
</tr>
<tr>
<td>Low dose</td>
<td>198.6 ± 10.59</td>
</tr>
<tr>
<td>High dose</td>
<td>206.2 ± 13.34</td>
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<tr>
<td>Taking oral hypoglycemics</td>
<td></td>
</tr>
<tr>
<td>Low dose</td>
<td>156 ± 10.48</td>
</tr>
<tr>
<td>High dose</td>
<td>159.2 ± 12.89</td>
</tr>
<tr>
<td><strong>Control</strong></td>
<td></td>
</tr>
<tr>
<td>Low dose</td>
<td>80</td>
</tr>
<tr>
<td>High dose</td>
<td>95</td>
</tr>
<tr>
<td><strong>Alcoholic Extract</strong></td>
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<tr>
<td>No previous medication</td>
<td></td>
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<tr>
<td>Low dose</td>
<td>206 ± 9.48</td>
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<tr>
<td>High dose</td>
<td>207.8 ± 11.18</td>
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<tr>
<td>Taking oral hypoglycemics</td>
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<tr>
<td>Low dose</td>
<td>153.2 ± 8.48</td>
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<tr>
<td>High dose</td>
<td>161.8 12.69</td>
</tr>
<tr>
<td><strong>Control</strong></td>
<td></td>
</tr>
<tr>
<td>Low dose</td>
<td>66</td>
</tr>
<tr>
<td>High dose</td>
<td>70</td>
</tr>
</tbody>
</table>

Low dose: 0.5 g/kg in two divided doses  
High dose: 1.5 g/kg in two divided doses  
*Significant  
NS: Non significant
glucose tolerance of maturity onset diabetic patients. The fruit juice of *Momordica charantia* was found to significantly improve the glucose tolerance of 73% of the patients investigated while 27% failed to respond. In another study the juice or tablets from the powder of the fruits of *Momordica charantia* showed significant blood glucose lowering effect on patients and the infusion of the drug and crude crystalline substance showed same effect (Khan, 2000).

**Mechanism of Action**

In a study the long term administration (10 weeks, orally) of *Momordica charantia* fruit extract to normal and streptozocin (STZ) induced type-1 diabetic rats, returned the blood glucose and lipid profile levels to normal (Ahmed et al., 2001). The *Momordica charantia* is said to contain a insulin like hypoglycemic principle, plant insulin, which is highly beneficial in lowering the blood sugar levels (Bakhru, 2000). *Momordica charantia* fruit include a mixture of steroidal saponins as charantin, insulin like peptides and alkaloids (Lininger et al., 1998). All of the above mentioned studies indicate that the antidiabetic effect of *Momordica charantia* is due to:

- Increased utilization of glucose in the liver.
- Insulin like activity.
- Inhibit glucose absorption.
- Acts as insulin secretagogue.

Steroidal glycosides, insulinomimetic lectins and alkaloids are responsible for hypoglycemic and anti-hyperglycaemic effect of *Momordica charantia* (Raman and Lau, 1996).

**CONCLUSION**

*Momordica charantia* has significant hypoglycemic activity and can be given to type-2 diabetic patients with no previous medication alone or in combination to patients.
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taking oral hypoglycemic agents with inadequate control of blood glucose both in low or high doses depending upon their plasma glucose concentration.

REFERENCES


