Preliminary clinical trials of karela, *Momordica charantia*, on non-insulin-dependent diabetes mellitus patients

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Background
Traditional methods of treatment for diabetes was recommended by WHO in 1985. On *in-vivo* trials in animal models, one of the authors revealed the potentiality of karela in the treatment of diabetes.

Aim
The aim of the study was to evaluate the effects of *Momordica charantia* as a hypoglycemic in type 2 diabetic patients. Formulated tablets from *M. charantia* (karela) juice of the unripe fruits were used.

Materials and methods
Juice from immature fruits was filtrated through specific membranes to separate active polypeptide mimic insulin. The powder obtained after spray drying was formulated as a 20 mg tablet of polypeptide. Eighteen of 60 patients continued the treatment. All patients had type 2 diabetes. They were followed up for 1–8 weeks and examined clinically and investigated for different parameters.

Results
As this trial is a case analysis, the result of each case was presented and the overall trial results were discussed.

Conclusion
M. charantia can be used as an effective oral adjunct hypoglycemic, with no reportable clinical side effects. The treatment must be continued for 4 weeks.

Keywords:
hypoglycemic, karela tablets, type 2 diabetes

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Introduction

The earliest recorded treatment for diabetes mellitus involved the use of plants. The papyrus Ebres of 1550 BC recommended a high fiber diet of wheat grains and okra. A multitude of herbs, spices, and other plant materials have been described for the treatment of diabetes worldwide (Baily and Day; 1988) [1]. Since the availability of insulin, folklore medicines for diabetes have almost disappeared in occidental societies, although they continue to be the cornerstone of therapy in underdeveloped countries.

Renewed attention to alternative medicines and natural therapies has stimulated a new wave of research interest in traditional practices, and the WHO expert committee on diabetes has listed it as one of its recommendations that traditional methods of treatment for diabetes should be further investigated [2].

Baily and Day 1989 demonstrated that more than 400 traditional plant treatments for diabetes mellitus have been recorded, but only a small number of them have received scientific and medical evaluation to assess their efficacy. A hypoglycemic action from some treatments has been confirmed in animal models and non-insulin-dependent diabetic patients. Various hypoglycemic compounds have been identified.

Baily *et al*. [3] stated that botanical substitute for insulin seems unlikely, but traditional treatment methods may provide valuable clues for the development of new oral hypoglycemic agent and simple dietary adjuncts.

Momordica charantia (MC), bitter melon, karela, balsam pear, the plant involved in this investigation, is a remedy used mainly in West Africa and exerts a mild hypoglycemic effect in healthy rabbits [4]. In India and China, the herb has been crushed and dried to form tablets [5,6].

Consumption of 50 ml of aqueous extract of karela with a 50 g of oral glucose challenge reduced glucose concentrations of non-insulin-dependent diabetes mellitus by 20% within 1 h [7]. Many studies conducted on MC using animal models [7–10] proved that oral consumption of karela does not enhance insulin release, although an aqueous extract has been shown to stimulate insulin release from normal isolated islets *in vitro*. It has also been reported that acute administration of karela juice with glucose

load resulted in a significant improvement in glucose tolerance without increasing insulin levels in blood. In a study carried out in nine Asian non-insulin-dependent diabetes mellitus patients living in the UK, a significant reduction in glycosylated hemoglobin was recorded, indicating an improved control of blood glucose levels after 8–11 weeks [7].

It was reported that treatment of diabetic patients with powdered fruit for 3–7 weeks led to a mean fall of 25% (range 11–48%) in postprandial (PP) glucose levels. There was a marked fall in both blood and urine sugar after 7 weeks in a group treated with an aqueous extract of the fruit. Glycosylated hemoglobin showed significant reduction by the end of the trial [11].

Karela juice shows certain insulin mimetic effects such as increased glucose uptake into muscle, stimulation of lipogenesis, and inhibition of lipolysis on tissue preparation *in vitro* [12].

Therefore, the aim of this study was to clinically evaluate the hypoglycemic effect of the tablet formulated from a polypeptide of karela fruits.

Materials and methods

Plant

Immature fruits of karela were squeezed to a juice form. The juice obtained was filtered after centrifugation. The filtrate was again filtered through membranes of regenerated cellulose with a molecular weight cutoff of 30 000 and 10 000 kg Da successively. The obtained juice was evaporated under reduced pressure (40°C) to a syrupy-like matter. The syrup obtained was spray dried after mixing with multidextrene in a special ratio. The powder obtained was analyzed to estimate the polypeptide in it. This powder was formulated as a tablet having a polypeptide of 20 mg.

Patients

Eighteen patients could be followed up from the Internal Medicine Clinic of the Medical Service Unit of the NRC. All patients had type 2 diabetes. They were examined clinically and investigated for fasting blood sugar (FBS), 2 h PP blood sugar, glycosylated hemoglobin, liver function tests, kidney function tests, complete blood count, and lipogram (total cholesterol, triglycerides, and high density and low density lipoprotein cholesterol). No previous treatment was withdrawn.

No weaning period from treatment was necessitated. They were followed up weekly for 1–8 weeks (mostly 4 weeks).

FBS and 2 h PP were tested every week. The tablet of MC contained 20 mg of the polypeptide from the dried juice of the whole fruit. The dose given was four to six tablets/day, half an hour before meals (t.d.s.).

The pretreatment levels of FBS and 2 h PP for each patient was taken as his or her own control. The post-test treatment levels of FBS and 2 h PP for patients was taken as a mean of their weekly FBS and 2 h PP readings.

Statistical analysis

As this experiment is a case study, each one was discussed with normal standards.

Results

The results are summarized in Tables 1 and 2.

The patients' age ranged from 25–70 years, but most of them were 40 years or older. Seven of the 18 patients were not on any hypoglycemic treatment; three patients were on insulin and the rest were on conventional oral hypoglycemic. Eight of 18 patients (44.4%) (four ♀ and four ♂) showed improvement in their FBS (range 17.2–61.2) and 2 h PP glucose levels (range 31.2–65.3%) (cases no. 1, 2, 3, 7, 8, 12, 13, 17). Three of 18 patients (two ♂ and one ♀) showed mild improvement (cases no. 9, 10, 11). Two of 18 patients (one ♀ and one ♂) showed improvement in PP blood sugar only (cases no. 4, 14). Four of 18 patients (three ♀ and one ♂) showed no improvement or deterioration in significance (cases no. 4, 5, 16, 18). Three patients had hyperlipidemia, two had elevated liver functions tests, and two were traced for only 1 week. One of 18 patients (a ♀) showed no improvement at 3 weeks, but showed improvement at 6 weeks (case no. 15).

Discussion

To date, close to 100 *in-vivo* studies have demonstrated the blood sugar lowering effect of bitter gourd fruit (MC). The fruit has also been shown to have the ability to enhance cell uptake of glucose to promote insulin release and to potentiate the effect of insulin.

MC has been ethnomedically used worldwide as a hypoglycemic — in Brazil, China, Cuba, India, Mexico, Nicaragua, Panama, Peru, etc. [13].

Substantial work has been carried out and documented on the positive hypoglycemic activity of MC on normal and diabetic laboratory animals [8,14–20]. However, relatively few reports are available on its activity in humans.

Table 1 Clinical and laboratory data of the studied cases

Number	Sex/age	Weight/kg	BP ≤140/90	FBS 80–120 mg (%)	2 h PP ≤140 mg (%)	Glycated Hb ≤6.4 (%)	LFT_s	Lipogram	Pretest treatment	Duration of treatment (weeks)	Results
1	♂27	75	√	B = 253A = 170	B = 375A = 150	B = 11A = 8	↑	√	–	4	Improvement
2	♂35	60	√	B = 175A = 116	B = 40A = 140	B = 10A = –	↑↑	√	–	4	Improvement
3	♀65	75	√	B = 115A = 100	B=145A = 135	–	√	–	Insulin cidophage	8	Same state but insulin stopped gradually. Therefore, improvement
4	♀50	78	↑	B = 135A = 166	B = 160A = 110	–	√	–	Amaryl	4	Improvement in PP only
5	♀70	100	√	B = 175A = 205	B = 208A = 265	9.4	↑	↑	Amaryl	1	No improvement
6	♀52	81	↑	B = 120A = 140	B = 251A = 260	10.9	√	↑↑	–	1	No improvement
7	♂34	80	√	B = 140A = 116	B = 240A = 120	–	√	√	–	4	Improvement
8	♂–	–	↑	B = 259A = 163	B = 362A = 245	8.2	√	√	–	4	Improvement
9	♀55	58	↑	B = 141A = 133	B = 239A = 208	11	√	√	–	4	Mild improvement
10	♂54	87	√	B = 115A = 113	B = 156A = 130	6.5	√	√	Novonorm avenida	4	Mild improvement
11	♂55	110	↑	B = 180A = 157	B = 377A = 330	8.4	√	√	Diamicron	2	Mild improvement
12	♀40	85	√	B = 309A = 120	B = 418A = 166	10	↑		Diamicron cidophage	6	Improvement
13	♀70	78	√	B = 188A = 198	B = 188A = 198	8.3	√	√	Glucobay	3	No improvement
14	♂43	100	↑	B = 226A = 213	B = 400A = 259	–	√	√	Diamicron cidophage	1	Improvement in PP
15	♀70	61	√	B = 360A = 375A = 141	B = 478A = 480A = 195	–	↑	↑	Insulin	36	No improvementImprovement
16	♂32	83	√	B = 143A = 170	B = 402A = 350	8.5	↑	↑↑	–	3	Mild improvement in PP
17	♀55	57	↑	B = 141A = 133A = 91	B = 239A = 208A = 124	11	√	√	Diamicron	26	Mild improvementImprovement
18	♀25	66	√	B = 342	B = 381	8.1	√	↑	Insulin	4	No Improvement (verbal)

Blood picture and kidney function are all normal; 2 h PP, 2 h postprandial blood sugar; A, after treatment; B, before treatment; BP, blood pressure; FBS, fasting blood sugar; LFTs, liver functions tests.

Table 2 Summary of patients' result

Time after treatment (weeks)	Number of cases studied	Improvement	Mild improvements	Improvements in PP	Improvement in fasting	No improvement
1	3			1		2
2	2		2			
3	3			1		2
4	8	4	2	1		1
5	3	3				
6	1	1				

PP, postprandial.

This clinical trial dealt with 18 cases of type 2 diabetes mellitus. It was based on the long-lived, consistent, and updated role of MC as a hypoglycemic in experimental animals (rats and mice) and in individuals with type 2 diabetes mellitus. A study in 1982 [21] documented eight patients with uncomplicated diabetes mellitus, who were given 50 mg/kg body weight of MC powder in milk, twice per day. They were on diet but not on any other treatment. They showed significant hypoglycemic effect, with no side effects at 1/2, 1, 1.5, and 2 h after glucose tolerance test.

The present study used 20 mg tablet from formulated dried juice of the whole fruit given at four to six tablets/day, half an hour before meals, t.d.s.

In 1986, Welihinda *et al.* [22] reported an improved glucose tolerance of 73% in a patient on MC. Kirti *et al.* [23] described early studies (1950–1974) in which karela's antidiabetic activity was observed. In a comprehensive review in King college, London, it was concluded that limited studies on humans have shown that karela fruit juice reduces fasting blood glucose tolerance on acute administration and that prolonged administration causes a lowering of glycosylated hemoglobin and decreases glucosuria and basal glycemia. This effect was also noticed in the present study, which recommends a treatment of 4 weeks or greater with MC [12].

An insulin secretagogue insulin mimetic activity of the fruit has been shown *in vitro* in animal experiments but not *in vivo*.

The review also provided data on a polypeptide insulin from the fruit that produces hypoglycemic effects in humans and animals on subcutaneous injection through the oral activity, which is questionable. Similarly, liver and reproductive system side effects recorded in animals have not been reported in humans despite the widespread use of the fruit medicinally.

In a study conducted in India, a significant fall (54%) in blood sugar was observed after treatment of rats for 3 weeks with an aqueous extract of the fruit, whereas the dried fruit showed a nonsignificant 25% fall [11].

In humans, the hypoglycemic effect was found to be highly significant ($P < 0.01$) at the end of the trial, but it was cumulative and gradual unlike that produced by insulin. The authors also believe in the adaptogenic properties of the fruit, indicated by the delay in appearance of the cataract, the secondary complication of diabetes mellitus, and relief of the neurological symptoms even before hypoglycemia occurs [11].

The present study used the dried juice and not the aqueous extract or dried fruit and recommends its use for 4 weeks or more for satisfactory results.

An analysis made in Bangladesh recorded a significant reduction ($P < 0.001$) in both FBS and PP serum glucose levels in 86% of cases, whereas 5% of cases showed lowering of FBS only. The present analysis revealed a decrease in FBS and 2 h PP in 44% of cases, mild improvement in 16% of cases, and decrease in PP only in 11% of cases (two cases) [24].

A study on the hypoglycemic action of MC among type 2 diabetic patients was conducted by Rosales and Fernando [25]. They successfully tested the hypoglycemic effect of MC.

It was believed that the active ingredients in MC given orally to rats has neither insulin-like nor insulin-releasing activity, but they act by suppressing the transfer of glucose from the stomach to the small intestine and by inhibiting glucose transport to the brush border of the latter [14].

In Japan, the aqueous extract of MC was investigated, and a decrease in the blood glucose levels of mice 3 weeks after oral administration, and significantly lowered serum insulin were documented. They suggest that the antidiabetic effect of MC is derived at least in part, from a decrease in insulin resistance because of the noticed significant increase in GLUT4 protein in the plasma membrane of muscles. The present

Figure 1

Momerdica charantia can be used as an effective oral adjunct hypoglycemic with no reportable clinical side effects. Treatment must continue for 4 weeks.

Figure 2

Momordica charantia.

work did not assess insulin levels in the patients studied [16].

A research by Virdi *et al.* [17] in India concluded that the aqueous extract of powdered, fresh, unripe whole fruit of MC (as used in the present study) appears to be a safe alternative to reduce blood sugar, with no nephrotoxicity or hepatotoxicity by histological, biochemical parameters.

Basch *et al.* [26] reviewed the critical trials on different properties of MC, including hypoglycemic effects. They concluded that data are not sufficient to recommend its use in the absence of careful supervision and that monitoring of side effects and drug interactions, such as hypoglycemic coma, dropped fertility, and elevated liver enzyme, are necessary; this fact has been denied by the experiments of Raman and Lau [12].

The present trial agrees that elevated liver enzymes may interfere with the action of MC if not taken care of and properly controlled.

A review in India on the potential use of MC noted that there are only few reports on its clinical use in diabetes mellitus that have shown promising results [27].

Yibchok Anun *et al.* [20] documented in experimental STZ-induced diabetic rats, a slow-acting protein extract from the fruit pulp of MC, with insulin secretagogue, insulin mimetic activities to decrease blood glucose *in vivo* and enhance glucose uptake in lymphocytes and adipocytes.

In the Institute of Nutritional Science in Germany, it was reported that the hypoglycemic, metabolic effect of bitter gourd in cell culture, animal, and human studies were reported, although the mechanism of action is still under debate [28].

In a recent review conducted in Korea [29], MC has been reported to be beneficial in the treatment of type 2 diabetes (Figs. 1 and 2).

Conclusion

On the basis of this individualized trial, it can be preliminarily concluded that MC can be used as an effective oral adjunct hypoglycemic with no reportable clinical side effects. It is advised to continue treatments for more than 4 weeks for possible tapering of the conventional hypoglycemics. In one case included in the experiments, it has been possible to stop insulin therapy in 7 weeks time. It is also concluded that hyperlipidemia and impaired liver function tests have to be carefully monitored and controlled before or during MC treatment.

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Conflicts of interest

There are no conflicts of interest.

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