The MOCHA DM study: The Effect Of *MOmordica CHArantia* Tablets on Glucose and Insulin Levels During the Postprandial State Among Patients with Type 2 Diabetes Mellitus*

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Abstract

Background: The worldwide prevalence of diabetes is rising both in developed and developing countries like the Philippines where 4.6% of the population has the disease. Because of the high cost of medications, the use of dietary supplements has also increased. *Momordica charantia* (ampalaya), is a well known plant with glucose-lowering properties which have been demonstrated by previous clinical studies. Its mechanism of action and pharmacologic properties are not yet well understood, and hence continues to be used as a supplement rather than as a standard drug for the treatment of Type 2 diabetes.

Objective: To compare the effect of *Momordica charantia* (MC) and placebo on insulin and glucose among type 2 diabetic patients using different doses

Methodology: A double-blind, placebo-controlled, randomized trial was conducted on 40 diabetic subjects who randomly received single oral doses of either: a) 60 mg/kg/day, b) 80 mg/kg/day, c) 100 mg/kg/day MC tablets, and d) placebo. Subjects were fasted for 8 hours and given standardized meal after taking assigned drug. Fasting blood sugar and plasma insulin were determined at 0 minute, 15 minutes, 30 minutes, 1 hour, 2 hours, and 4 hours after the given dose. Statistical analysis was done using analysis of variance (ANOVA), Kruskal-Wallis, Bonferroni and Ranksum pairwise comparison tests.

Results: 40 participants completed the study with no adverse events. There is significantly higher insulin levels (p value = 0.0756) and significantly lower plasma glucose levels (p value = 0.024) for the 100 mg/kg/day ampalaya group (but not with the other dose groups) versus placebo after 15 minutes.

Conclusion: In this single dose study in type 2 diabetic patients, 100 mg/kg/day of ampalaya showed incremental dose effect and provided more rapid and shorter-lived stimulation of insulin secretion than placebo, resulting in lower meal-related glucose excursions.

Introduction

Diabetes mellitus is the new epidemic. The prevalence of diabetes for all age groups worldwide was estimated to be 2.8% in 2000, and to rise to 4.4% by the year 2030.[1] The total number of people with diabetes is projected to increase from 171 million in 2000 to 366 million in 2030, with the Philippines ranking 9th among the top most countries with the greatest number of diabetic patients.[1] According to local data, the prevalence rate of diabetes in the Philippines is 4.6%, based on fasting blood sugar (FBS) > 125 mg/dL or a previous history of diabetes.[2]

Many patients develop microvascular and macrovascular complications that can cause significant morbidity and mortality.[3,4] The prevention or slowing down of these complications are possible by adequate control of blood glucose using different pharmacologic agents.

There are currently many classes of pharmacological agents for type 2 diabetes mellitus such as sulfonylureas, biguanides, thiazolidinediones and alpha glucosidase inhibitors. However, these drugs have also shown adverse effects, including hypoglycemia, lactic acidosis, and diarrhea.[5] Studies of functional food components with blood glucose-controlling effects are in progress, and many useful components have been discovered in plants.[6-7] In the Philippines, and other Asian and developing countries, the uses of natural drugs, such as plants and herbal remedies to treat diseases is very common. These populations are linked with the use of traditional medicines, due to their efficacy or due to the high cost of pharmaceutical production.[5-7]

The annual prevalence of dietary supplement use increased from 14.2% in 1998 – 1999 to 18.8% in 2002 based on data from the United States.[8] In a local study done by Tanchoco et al., it was estimated that 23% use nutraceutical products,[9] and ampalaya supplements are among the top five of the most commonly used herbal medication.[10,11,12,13,14]

Momordica charantia, is a well known plant for its glucose-lowering properties.[15,16] However, the sample sizes of the investigations were small, with vaguely described

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statistical analysis. Some of the researches did not even have control groups. There were no randomized trials that were included. Subsequently, no conclusions on effectiveness were made.

The mechanism of action of the hypoglycemic effect brought about by *Momordica charantia* has been variedly described. According to experimental evidence, whole plant-aqueous extract contains a hypoglycemic principle, which is an insulin-like peptide (polypeptide p-insulin) or an alkaloid, variously called foetidin, momordicin, or charantin.[17] It is hypothesized that this plant extract mimics or improves insulin action at the cellular level, and may even have an extra-pancreatic mode of action. [17] Theoretical mechanisms have also been proposed. These include increased insulin secretion, tissue glucose uptake, liver muscle glycogen synthesis, glucose oxidation, and decreased hepatic gluconeogenesis.[15]

The leaves of *Momordica charantia*, particularly of the Makiling variety, produced the most consistent hypoglycemic properties with acceptable safety profiles compared to other parts of the plant.[18-19] It has undergone several clinical trials.[18, 20, 21] Based on these studies, it was determined that the mean difference in fasting blood sugar of 40.8% from baseline compared to 36.8% for the glibenclamide group at 12 weeks using a dose of 100mg/kg/day of ampalaya tablets. Mean HbAic also showed a 4.8% decrease from baseline using *Momordica charantia*, compared to 4.2% for the glibenclamide group.[21]

Clinical Significance

Despite these clinical trials however, the joint position statement of the Philippine Society of Endocrinology and Metabolism, Philippine Diabetes Association, Institute for Studies on Diabetes Foundation, and Philippine Center for Diabetes Education Foundation still does not consider ampalaya-derived products as part of the standard care for diabetes in the absence of more research data. The pharmacodynamics of the *Momordica charantia* tablets has not been determined, especially as it relates to blood glucose and insulin levels at different doses. It has only been shown that *Momordica charantia* has insulin-like properties without the documentation of the actual levels of insulin. It is the purpose of this study to provide physicians with significant data on the comparative efficacy of *Momordica charantia* tablets and placebo as glucose lowering agents among subjects, emphasizing its effect on blood glucose and insulin levels. This research seeks to integrate the existing data on *Momordica charantia* and offer additional inputs to fill in the gaps in knowledge, thereby improving its clinical use.

Objectives

The objective of this study was to compare the effect of *Momordica charantia* tablets and placebo on insulin secretion and glucose excursions among type 2 diabetic patients using different doses. Specifically, this study aimed to: a) indirectly demonstrate the mechanism of action of *Momordica charantia* by determining its effect in insulin levels since theoretically, ampalaya extracts have been shown to improve insulin levels; and b) determine the time of peak effect and onset of efficacy of *Momordica charantia* tablets versus placebo using different doses of 60 mg/kg/day, 80 mg/kg/day and 100 mg/kg/day among patients with type 2 diabetes mellitus during the postprandial state. This will be significant in establishing the dosage intervals of *Momordica charantia* tablets in maximizing its medical use.

Methodolgy

Research Design

This study was a double-blind, placebo-controlled, randomized trial conducted in the Philippine General Hospital, from June to December 2008.

Study population

Subjects were recruited from the outpatient clinics of the University of the Philippines-Philippine General Hospital and were enrolled to the study after fulfilling the following inclusion criteria:

1. Type 2 diabetes mellitus based on the American Diabetes Association (ADA) Criteria for Diabetes Mellitus, 2007 (APPENDIX B)
2. Newly diagnosed diabetes mellitus AND is drug naïve OR is NOT on anti-diabetic agents for the past 3 months
3. Glycemic criteria: Glycosylated hemoglobin (HbA1c) ≥ 6.5% and ≤ 9.0% and fasting blood glucose of ≥126 mg/dL but ≤ 205 mg/dL
4. Patient is ≥ 21 years old but ≤ 65 years old

Exclusion criteria included:

1. Unstable co-morbidities
2. Significant acute illness in the previous 2 weeks before the start of the study
3. History of diabetic emergency
4. History of corticosteroid use, herbal medications or any other drugs that may affect glucose metabolism within the preceding 6 months
5. Hypersensitivity to the drug
6. Presence of conditions affecting compliance, e.g., drug or alcohol abuse or psychiatric illness
7. Recipient of another investigational drug during and preceding 6 months
8. Pregnancy
9. Unwillingness to participate in the study

Materials and Methods

1. Data collection

a. *Determination of clinical data.* Volunteers were asked to sign a written consent after explaining the objectives and procedures involved in the study. They were then interviewed upon entry to the study for demographic data, risk factors

for coronary artery diseases such as smoking, family history of diabetes, presence or absence of sedentary lifestyle (being on his/her feet for <4 hours a day), and frequency of regular exercise (30 minutes of exercise 3-4x/week).

b. *Physical examination and determination of baseline measurements.* Subjects underwent a standard physical examination. Vital signs were measured, including the blood pressure.

A non-elastic tape measure was used to measure waist circumference at the level of the iliac crest, and hip circumference at the level of the largest circumference or the greater trochanters. The waist-to-hip ratio was used as an index of upper-body versus lower-body adiposity. Body mass index (BMI) was calculated as weight (in kilograms) divided by height (in meters) squared.

c. *Screening laboratory tests.* Blood was extracted for baseline serum HbAic, FBS, blood urea nitrogen (BUN), creatinine, AST, ALT, complete blood count (CBC) levels and were analyzed using the COBAS Integra 400 Plus Chemistry Analyzer.

2. Randomization. Random allocation was done using a computer-generated sequence of random numbers (Stata® version 6.0). To conceal allocation, medications were prepared by a third party. The treatment and placebo tablets were matched in appearance and packaged in unpackaged blisters.

3. Study Proper

a. *Test Drug. Momordica charantia* tablets, from dried ampalaya leaves of the Makiling variety, was obtained from a local licensed pharmacy in Manila. Commercially, it is available as Amargozin tablets. The dosage form was 500 mg/tablet. The dummy placebo tablets were formulated by an industrial pharmacy to simulate the 500 mg *Momordica charantia* tablets.

b. *Study Protocol.* The study was conducted at the Medical Research Laboratory of UP-PGH under the supervision of trained personnel. Volunteers were randomly allocated to one of four groups according to single oral doses of *Momordica charantia* tablets at 60, 80, or 100 mg/kg/day and placebo. Subjects were fasted for 8 hours before each treatment period. At time 0, they were given either one of the three doses of *Momordica charantia* or placebo after which they were then given a standard meal consisting of 56.6 g carbohydrate, 19.5 g protein, 11.5 g fat and 395 kcal. The subjects were permitted only water and minimal physical activity for 4 hours.

c. *Study evaluations.* Plasma glucose and insulin concentrations were measured at multiple time-doses from pre-dose to 4 hours post-dose: namely 0 minute, 15 minutes, 30 minutes, 1 hour, 2 hours, and 4 hours after the given dose. Fasting blood sugar and blood insulin levels were determined using standardized kits.

d. *Discontinuation of testing.* Study therapy was immediately discontinued for the following reasons:

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Hypoglycemia

- defined as symptoms suggestive of hypoglycemia (e.g. sweating, shaky, increased heart rate, confusion, dizziness, lightheadedness, or hunger) in the absence of environmental factors known to contribute to hypoglycemia (i.e. excess physical activity, concurrent illness, or missed or delayed meal) and/or documented fasting blood glucose values ≤ 50mg/dL (2.8 mmol/L)

Outcome measures

1. The primary outcome was the change in glucose and insulin level 4 hours after administration of treatment.
2. Adverse events were monitored and recorded based on spontaneous reporting by subjects and direct interview both of which will be conducted by the investigating physician (Appendix C). Tolerability parameters and tablet acceptability by subjects was based on the organoleptic qualities of the tablet and ease of swallowing conducted by the physician-investigator (Appendix D). Subjects were evaluated upon entry to the study, and at the end of the study.

Statistical analysis. The intent-to-treat analysis was the primary analysis for this study. Only protocol-compliant subjects were included in the secondary analysis. The primary variables for the study were change in glucose and insulin levels. The end points were summarized using proportions and analyzed using one way and repeated measures ANOVA and Kruskal Wallis tests. Bonferroni and Ranksum pairwise comparison tests were also used for the statistical analyses.

Ethical considerations. Ethical approval for this study was obtained from the Ethics Committee of the University of the Philippines (Research Implementation and Development Office, College of Medicine-Philippine General Hospital, University of the Philippines).

The main ethical issue for this study was the possible adverse effects of the intervention of *Momordica charantia* tablets. Based on the previous toxicity studies done in animal and human subjects[17-21], the following adverse effects were noted: gastric pain, nausea, vomiting, diarrhea, dyspnea, headache, dizziness, and rashes. These adverse effects were observed during the third week of the study with no interventions or medical treatment being needed to address the adverse effects.

Any adverse event that was incurred during the study period, was addressed immediately and was compensated by the investigators.

Results

A total of 40 Filipino healthy Type 2 diabetic patients participated in the study, of which 18 males and 22 females.

Table I. Baseline demographic characteristics of the subjects in the study population. University of the Philippines-Philippine General Hospital, 2009 (N = 40).

Variable (Mean, S.D.)	Placebo (n = 10)	Momordica charantia 60mg/kg (n = 10)	Momordica charantia 60mg/kg (n = 10)	Momordica charantia 100mg/kg (n = 10)	p value
Age (years)	55.7 ± 4.9	55.3 ± 5.0	57.8 ± 4.8	57.8 ± 4.8	0.74
Weight (kg)	60.9 ± 5.7	63.1 ± 7.0	62.4 ± 7.7	65.5 ± 7.6	0.74
Height (m)	1.55 ± 0.08	1.57 ± 0.07	1.58 ± 0.10	1.59 ± 0.11	0.40
Waist circumference (cm)	90.4 ± 6.8	93.45 ± 7.0	90.2 ± 6.2	93.85 ± 6.5	0.86
Waist-to-hip ratio	0.94 ± 0.05	0.96 ± 0.03	0.95 ± 0.03	0.95 ± 0.05	0.33
Body Mass Index (BMI) (kg/m2)	25.55 ± 2.05	25.60 ± 2.25	25.60 ± 2.25	26.00 ± 2.4	0.15
HbAic (%)	7.72 ± 0.8	7.44 ± 1.0	8.08 ± 0.8	7.86 ± 1.1	0.83
Fasting blood sugar (mg/dl)	174.8 ± 8.8	171.9 ± 16.7	172 ± 20.4	170.1 ± 16.5	0.14
Serum insulin (uIU/ml)	22.12 ± 11.7	22.45 ± 6.7	25.11 ± 6.5	24.65 ± 9.6	0.27

Table II. Analysis of variance of average insulin levels of subjects using different doses of *Momordica charantia* tablets and placebo 4 hours after treatment.

Group	Average Insulin Levels					
	Baseline (uIU/ml)	15 mins (uIU/ml)	30 mins (uIU/ml)	1 hr (uIU/ml)	2 hr (uIU/ml)	4 hr (uIU/ml)
Placebo	22.12	38.81	45.82	44.26	40.12	28.93
60 mg/kg/day	22.45	37.29	46.63	42.55	38.65	29.97
80 mg/kg/day	25.11	40.3	51.09	42.92	40.55	31.82
100 mg/kg/day	24.35	48.49	53.43	45.71	39.72	29.11
Kruskal Wallis p-value	0.8109	0.0402 *	0.2657	0.3365	0.3151	0.2852

*Significant difference across groups if p-value < 0.05

The mean age of the participants is 56.6 ± 1.28 years with majority being overweight or obese with mean body weight of 62.98 ± 1.92 kg, BMI of 25.6 ± 0.23 kg/m^2 and WHR of 0.95 ± 0.01, respectively. Baseline HbA1c, FBS and insulin levels were also determined as follows: 7.78 ± 0.27 %, 172.2 ± 1.8 mg/dl, and 23.51 ± 1.52 uIU/ml. Table 1 summarizes the other demographic characteristics of the subjects.

Table 1 shows no significant difference in the baseline characteristics of the subjects. All 40 participants completed the study. No clinically meaningful changes in vital signs were reported during the study or at the end-of-study evaluations. No reports of adverse events were noted. The placebo and ampalaya tablets were generally acceptable and well-tolerated by the subjects.

All active drug treatments increased plasma insulin levels in response to a standardized breakfast relative to placebo. During the initial 15-minute postmeal interval, 100 mg/kg/day dose of *Momordica charantia* tablets significantly produced a more increased induction of insulin secretion than 80 mg/kg/day, 60 mg/kg/day and placebo ($p \leq 0.10$) (Table 2), with mean rates of rise in insulin secretion of 48.49 ± 9.26, 40.3 ± 6.28, 37.29 ± 6.47, and 38.81 ± 16.76 uIU/ml, respectively.

Table 2 shows that there is a significant difference in average insulin levels across the four groups at the 15 minute observation point. The pairwise comparison test showed that the insulin levels using the 100 mg/kg/day dose are significantly higher than that of the 60 mg/kg/day dose (Ranksum test p value = 0.0091) at 5% level of significance. There is also significantly higher insulin levels for the 100 mg/kg/day group versus placebo (Ranksum test p value = 0.0756) at 10% level of significance. In analyzing the insulin levels, Kruskal Wallis test was used rather than ANOVA because the variances across groups are significantly different at 5% level of significance for each observation period.

Mean plasma insulin concentrations peaked at 30 minutes postdose for both the placebo and the three treatment groups. After reaching the peak concentrations, mean plasma insulin decreased in all groups and was similar to placebo by 1 hour postdose (Figure 1).

The rapid effects of the 100 mg/kg/day dose of ampalaya tablets resulted in significantly higher average plasma insulin over the early 0- to 0.25-h postdose intervals (36.42 ± 15.40 uIU/ml) compared with ampalaya doses of 80 mg/kg/day (32.70 ± 9.96 uIU/ml), 60 mg/kg/day (29.87 ± 9.95

Figure 1. Mean plasma insulin concentrations after treatments with 60 mg/kg/day, 80 mg/kg/day, 100 mg/kg/day ampalaya tablets and placebo administered postprandially.

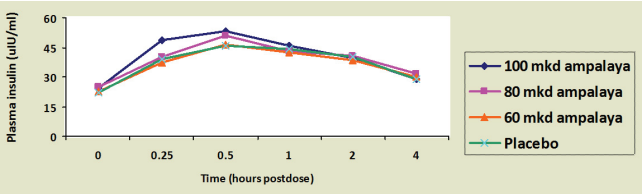
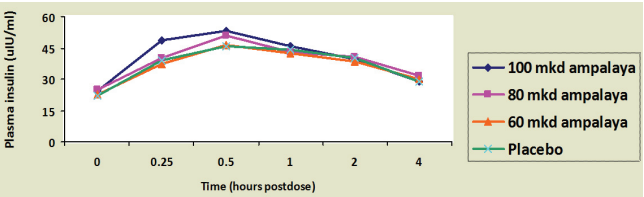


Figure 2. Mean plasma glucose concentrations after treatments with 60 mg/kg/day, 80 mg/kg/day, 100 mg/kg/day ampalaya tablets and placebo administered postprandially.



uIU/ml) and placebo (30.46 ± 16.48 uIU/ml). Late average plasma insulin levels (1 – 4 hour postdose) after *Momordica charantia* at all doses were similar to levels observed with placebo. The average insulin response over the entire 0- to 4- hour postdose interval was 8.6% higher with ampalaya tablets using the 100 mg/kg/dose than placebo (40.14 ± 14.10 vs 36.68 ± 26.05 uIU/ml).

Mean plasma glucose concentrations rose after breakfast and reached peak levels 1 hour postdose after all treatments and placebo (Table 3).

Table 3 shows that there is a significant difference in average plasma glucose levels after 15 minutes. The 100 mg/kg/day group has the lowest average plasma glucose levels after 15 minutes. The Bonferroni Pairwise comparison test shows that doses at 100 mg/kg/day and 60 mg/kg/day (p value = 0.048), 100 mg/kg/day and placebo (p value = 0.024) are significantly different.

The peak of the mean glucose postdose concentration was significantly lower with the 100 mg/kg/day dose of *Momordica charantia* tablets (210.50 ± 51.61 mg/dl) than with either the 80 mg/kg/day (232.50 ± 39.16 mg/dl) or 60 mg/kg/day doses (239.80 ± 20.61 mg/dl) and placebo (240.10 ± 67.91 mg/dl) (Figure 2). Plasma glucose concentrations relatively returned to predose levels by 4 hours with ampalaya treatment using the 80 mg/kg/day and 100 mg/kg/day, whereas the 60 mg/kg/day dose ampalaya-treated groups and placebo did not reach the predose glycemic levels.

Compared with ampalaya tablets at 80 mg/kg/day, 60 mg/kg/day, and placebo, *Momordica charantia* at 100 mg/kg/day produced lower average plasma glucose concentrations (188.48 ± 35.97 mg/dl) over the 0- to 4-hour postdose interval (Figure 2; 197.83 ± 33.88 mg/dl versus 80 mg/kg/day dose, 204.27 ± 31.39 mg/dl versus 60 mg/kg/day dose at 207.03 ± 43.82 mg/dl versus placebo).

Discussion

Recently, emerging data have looked into the significance of meal time glycemia on overall glycemic control and cardiovascular risk for mortality.[22, 23] Studies show that early insulin secretion plays a critical role in maintaining normal glucose homeostasis.[24] Thus, loss of early insulin secretion initially leads to post-prandial hyperglycemia which, as the disease progresses, worsens to clinical hyperglycemia.[25] Strategies that enhance early insulin secretion improve glucose tolerance and represent a novel and more physiologic approach to improving glycemic control in patient with type 2 diabetes mellitus. However, most oral anti-diabetic agents have little or no effect on meal-related glucose excursions.[26] In contrast, this study shows that *Momordica charantia* tablets appear to increase the first phase of insulin secretion in response to a meal.

The results of this study compared the effects *Momordica charantia* tablets at different doses versus placebo on the early and extended profiles of mealtime insulin secretion in individuals with type 2 diabetes mellitus, as well as the associated effects on the glycemic response to a meal. In

Table III. Analysis of variance of average plasma glucose levels of subjects using different doses of Momordica charantia tablets and placebo 4 hours after treatment.

Group	Average plasma glucose levels							
	Baseline (uIU/ml)	15 mins (uIU/ml)	30 mins (uIU/ml)	1 hr (uIU/ml)	2 hr (uIU/ml)	2 hr (uIU/ml)	Diff Base -	Diff Base-
Placebo	174.8	200.1	224.2	240.1	218.1	184.9	25.3	49.4
60 mg/kg/day	171.9	198	221.1	239.8	214.3	180.5	26.1	49.2
80 mg/kg/day	172	184.8	208.4	232.5	207.6	179	12.8	36.4
100 mg/kg/day	170.1	175.5	196	210.5	200.9	177.9	5.4	25.9
Anova F p-	0.933	0.0121*	0.036*	0.4804	0.8206	0.9255	0.0032*	0.0338*

*Significant difference across groups if p-value < 0.05

these subjects, ampalaya tablets using the 100 mg/kg/day dose showed higher insulin levels compared to lower doses of ampalaya and placebo. Plasma insulin concentrations also comparatively returned to pre-prandial levels more promptly with the 100 mg/kg/day dose of ampalaya, resulting in lower overall insulin exposure relative to lower doses and placebo.

The ampalaya tablets showed a consistent effect with the onset of action within 15 to 60 minutes. This is similar to previous studies done on extracts of *Momordica charantia*.[19] However, the relative increase in insulin levels was short-lived as it was only able to significantly increase insulin levels during the first 15 minutes with an increasing trend until the 1st hour postdose, as compared with the duration of 4 to 12 hours noted in other studies.[27,28] But it is worth mentioning that the substances used in the previous studies were that of plant extracts from different parts of the ampalaya plant and not in a constituted tablet form solely from the leaves of *Momordica charantia*.

The importance of early insulin secretion in the control of mealtime glucose excursions was evident in the early postdose glycemic profiles and the average overall glucose exposure resulting from each drug treatment. Aside from demonstrating greater overall insulin levels, 100 mg/kg/day dose of ampalaya was more effective than lower doses of *Momordica charantia* and placebo in reducing mealtime glycemic excursions within the 4 hour postdose, with a more rapid return to pretreatment plasma glucose levels.

Conclusion

In conclusion, in this study involving 40 adult type 2 diabetics, *Momordica charantia* tablet given as a single dose using the 100 mg/kg/day dose (12 tablets of 500 mg/tab), showed an incremental dose effect and provided a more rapid (15 minutes) and shorter-lived (30 minutes) stimulation of insulin secretion than placebo, resulting in lower meal-related glucose excursions. This herbal product has the potential to be used for reducing post-meal hyperglycemia.

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