Momordica charantia Administration Improves Insulin Secretion in Type 2 Diabetes Mellitus

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ABSTRACT An improvement in parameters of glycemic control has been observed with *Momordica charantia* in patients with type 2 diabetes mellitus (T2DM). It is unknown whether this improvement is through a modification of insulin secretion, insulin sensitivity, or both. We hypothesized that *M. charantia* administration can improve insulin secretion and/or insulin sensitivity in patients with T2DM, without pharmacological treatment. The objective of the study was to evaluate the effect of *M. charantia* administration on insulin secretion and sensitivity. A randomized, double-blinded, placebo-controlled, clinical trial was carried out in 24 patients who received *M. charantia* (2000 mg/day) or placebo for 3 months. A 2-h oral glucose tolerance test (OGTT) was done before and after the intervention to calculate areas under the curve (AUC) of glucose and insulin, total insulin secretion (insulinogenic index), first phase of insulin secretion (Stumvoll index), and insulin sensitivity (Matsuda index). In the *M. charantia* group, there were significant decreases in weight, body mass index (BMI), fat percentage, waist circumference (WC), glycated hemoglobin A1c (A1C), 2-h glucose in OGTT, and AUC of glucose. A significant increase in insulin AUC ($56,562 \pm 36,078$ vs. $65,256 \pm 42,720$ pmol/L/min, $P = .043$), in total insulin secretion (0.29 ± 0.18 vs. 0.41 ± 0.29 , $P = .028$), and during the first phase of insulin secretion (557.8 ± 645.6 vs. 1135.7 ± 725.0 , $P = .043$) was observed after *M. charantia* administration. Insulin sensitivity was not modified with any intervention. In conclusion, *M. charantia* administration reduced A1C, 2-h glucose, glucose AUC, weight, BMI, fat percentage, and WC, with an increment of insulin AUC, first phase and total insulin secretion.

KEYWORDS: • insulin secretion • insulin sensitivity • *Momordica charantia* • nutraceutical • type 2 diabetes mellitus

INTRODUCTION

DIABETES MELLITUS (DM) is a serious global health problem with an expected increase in the prevalence of 415 million in 2015 to 642 million in 2040.¹ This metabolic disorder is increasing rapidly around the world and is considered an important source of morbidity in developed and developing countries.

There are several pharmacological options available for the treatment of type 2 diabetes mellitus (T2DM), including metformin as first-line treatment.² Despite this, the use of complementary and alternative medicine (CAM) is still common among patients with DM. About 30% of patients with DM use CAM as an alternative to traditional Western medicine.³

Momordica charantia, also known as bitter melon, is a traditional plant used for the treatment of DM among the

indigenous populations of Asia, East Africa, India, South America, and the Caribbean.³ There are a number of active ingredients such as charantin, insulin-like peptide, cucurbitane glycosides, momordicin, and oleanolic acids that are reported to be present in *M. charantia*.⁴

Several studies conducted in animal models have demonstrated the hypoglycemic potential of *M. charantia*.^{4–6} Favorable results have also been observed in blood pressure,^{7,8} lipid profile,^{4,9} and weight.^{10,11} Although a decrease in the concentration of glucose,^{12,13} glycated hemoglobin A1c (A1C),¹² and fructosamine¹⁴ has been observed in clinical trials in patients with T2DM, the results have been inconsistent. Furthermore, whether the improvement observed within the glycemic control parameters is through a modification of insulin secretion, insulin sensitivity, or both is unknown. To date, few clinical trials have evaluated the effect of *M. charantia* administration on these pathophysiological alterations.^{15,16}

Our hypothesis for the research was that *M. charantia* administration can improve insulin secretion and/or insulin sensitivity in patients with T2DM, without pharmacological treatment. The aim of this study was to evaluate the effect of *M. charantia* administration on insulin secretion and insulin

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sensitivity in patients with T2DM, without pharmacological treatment. The results of this study can contribute to the understanding of how this nutraceutical therapy exerts its hypoglycemic effect, thus generating more knowledge about a possible dietary supplement for the patient with T2DM.

MATERIALS AND METHODS

A randomized, double-blinded, placebo-controlled, clinical trial was carried out in 24 patients with newly diagnosed T2DM according to the American Diabetes Association criteria.²

Selection criteria

Eligible patients were those with diagnosis of T2DM of less than 5 years and without pharmacological treatment for at least 3 months before entering the study. All individuals were nonsmokers, 35–60 years old, stable body weight for at least 3 months before the study, and body mass index (BMI) between 25.0 and 34.9 kg/m², with fasting serum glucose <11.6 mmol/L and A1C between 7% and 9%. Subjects were selected through campaigns for the timely detection of diabetes from the same residential area and socioeconomic status, within the metropolitan area of the city of Guadalajara, México. Participants did not engage in heavy physical activity or were extremely sedentary. Women of child-bearing age had to use a birth control method for at least 3 months before the study.

Patients were excluded if they had any of the following characteristics: pregnant or suspected pregnant women, breastfeeding women, subjects taking medications known to affect the metabolism of glucose and insulin, personal history of liver or renal disease, hypertension, thyroid or decompensated cardiovascular disease, total cholesterol (TC) ≥ 6.20 mmol/L, triglycerides (TG) ≥ 4.48 mmol/L, liver transaminases ≥ 2.5 the upper normal limit, or glomerular filtration rate ≤ 60 mL/min/1.73 m².

Pharmacological intervention

The dried powder of the fruit pulp was purchased from Shanghai Kangxi Biotechnology Co. of Shanghai (China). Identification, purification, and pollution tests were performed by the company. Each capsule contained 500 mg of *M. charantia* fruit powder. Calcined magnesium was used as placebo.

The allocation was done by simple randomization using a list of numbers, 12 patients received *M. charantia* (2000 mg/day), two capsules orally of 500 mg twice daily before breakfast and dinner for 12 weeks. The other 12 patients received placebo in the same pharmacological presentation. All patients received medical nutritional therapy and were instructed to continue with their normal physical activity.

Clinical and laboratory determinations

Patients completed five visits during the study. An oral glucose tolerance test (OGTT) was performed before and after the intervention. Subjects drank 75 g of anhydrous

glucose dissolved in 200 mL of water within 5 min and blood samples were collected by a heparinized catheter before and at 30-min intervals (30, 60, 90, and 120 min) during the OGTT. Clinical determinations (weight, BMI, waist circumference [WC], body fat percentage, and blood pressure), as well as compliance and adverse events, were evaluated at each visit. Pill counting was used to evaluate drug compliance. Lifestyle recommendations were also reinforced during all visits. Patients were instructed to record adverse events in their diary and return to the clinic in case of any abnormal event. A month after the cessation of the intervention, a follow-up telephone call was made.

Before testing, an isocaloric diet of at least 250 g of carbohydrate per day was followed for 3 days. Women were in the first phase of their menstrual cycle (3–8 days) during the realization of the tests. Laboratory tests were performed at 8:00 a.m. after a 10- to 12-h overnight fast. Weight was registered with the subjects wearing light clothing. To record height, subjects were asked to remove their shoes and stand with their feet together; measurements were rounded off to the nearest centimeter. WC was taken at the midpoint between the highest point of the iliac crest and the lowest rib in the midaxillary line to the nearest centimeter. The BMI was calculated as weight (kg) divided by height (m²). A digital sphygmomanometer was used to evaluate blood pressure, and the mean value of three measurements was recorded after a 5-min resting period.

Venous blood samples were obtained and kept at room temperature for 30 min. The samples were centrifuged and the serum was placed in an aliquot that was immediately used for the measurement of glucose, TC, TG, high-density lipoprotein cholesterol (HDL-c), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and creatinine by spectrophotometry. The glucose oxidase technique (Beckman Instruments, Inc., Brea, CA, USA) was used to determine serum glucose with an intra- and interassay coefficient of variation of <1%. Serum lipid levels were measured enzymatically and determinations were performed with commercially available kits (Ortho-Clinical Diagnostics, Rochester, NY, USA) with an intra- and interassay coefficient of variation of <3%.

The Friedewald formula was used to calculate low-density lipoprotein cholesterol (LDL-c) levels as follows: LDL-c (mmol/L) = TC (mmol/L) – HDL-c (mmol/L) – [TG (mmol/L)/2.2] and very low-density lipoprotein (VLDL) with the proportion of TG (mmol/L)/2.2. For the determination of A1C, a liquid chromatography method was used (Bio-Rad Laboratories, Hercules, CA, USA) with an intra- and interassay coefficient of variation of 0.4% and 1.6%, respectively. Insulin concentrations were measured with a chemiluminescent immunoassay technique (Beckman Coulter, Fullerton, CA, USA) with an intra- and interassay coefficient of variation of 3.8 and 4.2, respectively.

The polygonal formula was used to calculate area under the curve (AUC) of glucose and insulin. The insulinogenic index (δ AUC insulin/ δ AUC glucose) and Stumvoll index ($1283 + 1.829 \times \text{ins } 30' - 138.7 \times \text{glucose } 30' + 3.772 \text{ insulin } 0'$) were used to estimate total insulin secretion and the first phase of insulin secretion, accordingly. Insulin sensitivity

was evaluated with the Matsuda index $[10,000/\sqrt{(\text{glucose } 0' \times \text{ins } 0') (\text{mean glucose OGTT} \times \text{mean insulin OGTT})}]^{17,18}$. Calculations were made from the OGTT.

Statistical analysis

Sample size was calculated using a formula for mean differences¹⁹ with a statistical confidence of 95%, statistical power of 80%, standard deviation (SD) of 0.27 for insulin secretion and 1.5 for insulin sensitivity,²⁰ and an expected between-group difference of at least 0.35 for insulin secretion and 2.1 for insulin sensitivity. A total of 12 patients for each group, including 20% of expected loss was obtained. Values were converted to the International System of Units and presented as mean $\pm$ SD. Shapiro–Wilk test was used to evaluate normal distribution. Intention to treat statistical analysis was carried out. Intra- and intergroup differences were tested by the Wilcoxon signed-rank and Mann–Whitney *U* test, respectively. A $P \leq .05$ was considered statistically significant. Statistical analysis was conducted using IBM SPSS® 18.0 for Windows.

Ethical considerations

The study protocol was reviewed and approved by the Bioethics Committee of the University Center of Health Sciences of the University of Guadalajara (DF/CBO41/13). Written informed consent was obtained from all volunteers. The protocol was registered at ClinicalTrials.gov. NCT02397447.

RESULTS

A total of 96 subjects were screened, of which 24 patients were included in the study and 20 patients completed the intervention; during the study, two patients from each study group withdrew for reasons unrelated to the interventions (lost to follow-up), refer to Figure 1. The female sex represented 58% (7/12) for the *M. charantia* group and 75% (9/12) for the placebo group, while the male sex represented 42% (5/12) and 25% (3/12) for the *M. charantia* and placebo groups, respectively; ($P = .386$). There was no significant difference in age between *M. charantia* and placebo groups (50.1 ± 7.3 vs. 47.0 ± 7.4 years, respectively; $P = .347$). Likewise, there were no significant differences in clinical and laboratory characteristics at baseline between study groups (Table 1).

In the *M. charantia* group, there were significant decreases in weight, BMI, fat percentage, WC, A1C, 2-h glucose in OGTT, and AUC of glucose. A significant increase in AUC of insulin, total insulin secretion, and first phase of insulin secretion was observed after *M. charantia* administration (Table 1). Insulin sensitivity was not modified with any intervention. There was a significant increase in creatinine in the placebo group after the intervention (Table 1).

Adverse events during the intervention were not significantly different between groups ($P > .05$). In the *M. charantia* group, the most common adverse events were headache and dizziness (33.3%), followed by nausea (16.7%), vomiting (8.3%), and constipation (8.3%). In the placebo group, headache (25%), constipation (16.7%), abdominal distension (16.7%), dizziness (8.3%), and nausea (8.3%) were reported. In no case was it necessary to discontinue the interventions.

FIG. 1. Flow diagram.

TABLE 1. CHARACTERISTICS BEFORE AND AFTER THE INTERVENTION

	Placebo		Momordica charantia	
	Baseline n = 12	12 Weeks n = 10	Baseline n = 12	12 Weeks n = 10
Body weight, kg	73.6 ± 11.1	73.4 ± 10.8	79.4 ± 9.2	78.0 ± 9.2**
BMI, kg/m ²	28.8 ± 3.9	28.9 ± 3.6	29.1 ± 2.4	28.3 ± 1.9**
Fat mass, %	35.2 ± 8.1	35.8 ± 6.9	36.7 ± 7.8	36.3 ± 7.6*
WC, cm	97 ± 11	98 ± 10	106 ± 12	104 ± 11*
SBP, mmHg	116.5 ± 10.8	115.4 ± 9.8	119.5 ± 8.9	119.6 ± 9.5
DBP, mmHg	74.2 ± 5.5	72.6 ± 4.7	75.0 ± 4.7	75.1 ± 6.5
A1C, %	7.6 ± 0.6	7.1 ± 1.1	7.8 ± 0.8	7.1 ± 1.3*
FSG, mmol/L	7.1 ± 1.9	7.2 ± 2.3	8.2 ± 1.4	7.4 ± 2.9
2-h serum glucose, mmol/L	14.9 ± 4.7	14.3 ± 4.3	17.1 ± 3.7	13.2 ± 4.3**
AUC-glucose, mmol/L/min	1670 ± 380	1663 ± 363	1840 ± 295	1576 ± 391*
AUC-insulin, pmol/L/min	41,334 ± 22,356	41,310 ± 20,292	56,562 ± 36,078	65,256 ± 42,720*
Insulinogenic index	0.23 ± 0.14	0.23 ± 0.12	0.29 ± 0.18	0.41 ± 0.29*
Stumvoll index	419.3 ± 769.1	309.0 ± 776.5	557.8 ± 645.6	1135.7 ± 725.0*
Matsuda index	3.8 ± 4.6	2.3 ± 1.0	2.4 ± 1.4	2.1 ± 1.6
Total cholesterol, mmol/L	4.41 ± 0.75	4.39 ± 0.52	4.89 ± 0.73	4.68 ± 1.02
Triglycerides, mmol/L	2.19 ± 0.76	2.02 ± 0.56	2.31 ± 1.25	1.93 ± 0.92
HDL-c, mmol/L	1.04 ± 0.23	1.09 ± 0.27	1.13 ± 0.18	1.05 ± 0.31
LDL-c, mmol/L	2.35 ± 0.64	2.41 ± 0.48	2.69 ± 0.80	2.75 ± 0.96
VLDL, mmol/L	7.86 ± 2.7	7.22 ± 1.98	8.26 ± 4.48	6.92 ± 3.32
Creatinine, mmol/L	61.88 ± 8.84	79.56 ± 0.00*	70.72 ± 8.84	70.72 ± 35.36
ALT, U/L	36 ± 19.7	38.2 ± 18.9	35.4 ± 24.4	28.1 ± 19.4
AST, U/L	23.1 ± 11.3	24.4 ± 6.7	29 ± 22.4	23.9 ± 16.5

* $P < .05$, ** $P < .01$; between baseline and 12-week measurement intragroup (Wilcoxon rank test).

There were no significant differences in characteristics at baseline between groups (Mann-Whitney U test).

BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; A1C, glycated hemoglobin A1c; FSG, fasting serum glucose; AUC, area under the curve; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; VLDL, very low-density lipoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

DISCUSSION

T2DM is the most prevalent form of diabetes and is due to a progressive loss of β cell insulin secretion and the presence of insulin resistance.² The decrease in insulin secretion is associated with a significant loss of β cell mass.

It has been reported in the literature that *M. charantia* can regenerate β cells in pancreatic islets, increase pancreatic islet size, total β cell area, and the number of β cells in rats with DM induced by streptozotocin.^{21–24} In normal and diabetic rats, the protein extract of the fruit pulp of *M. charantia* raised plasma insulin concentrations by twofold, 4 h following subcutaneous administration.²⁵ To the best of our knowledge, only one study has evaluated the effect of *M. charantia* administration on insulin secretion among T2DM patients.

In a double-blinded clinical trial, 40 diabetic subjects were randomly allocated to one of four groups according to single oral doses of *M. charantia* tablets at 60, 80, or 100 mg/kg/day and placebo. Insulin concentrations were measured at 0, 15, 30 min, 1, 2, and 4 h after the given dose. At min 0, patients received a dose of *M. charantia* or placebo, followed by a standard meal. All *M. charantia* groups increased plasma insulin levels in response to a standardized breakfast relative to placebo. During the initial 15-min postmeal interval, 100 mg/kg/day dose of *M. charantia* tablets

produced an increased induction of insulin secretion than the other doses and placebo. The study showed that *M. charantia* appears to increase the first phase of insulin secretion in response to a meal.¹⁵

These data are consistent with our results, after 12-weeks of intervention with *M. charantia*, a significant increase of AUC of insulin and first phase and total insulin secretion was observed. However, we cannot establish that the increase in insulin secretion has been related to a primary effect of *M. charantia* on the β cell, because the study design does not fit this purpose.

Insulin resistance precedes and plays a key role in the development of T2DM. It has been described that *M. charantia* can improve insulin sensitivity through various mechanisms reported in animal models, such as the increase in the rate of phosphorylation of the insulin receptor substrate^{26,27} and the increase in adenosine monophosphate-activated protein kinase (AMPK) activity.^{28–30} Activation of AMPK could be directly or through adiponectin and thyroxine since *M. charantia* has been reported to increase levels of these hormones and both hormones activate AMPK.

AMPK is an enzymatic complex that acts as a metabolic switch and exerts insulinotropic effects by increasing the biogenesis of glucose transporter type 4 receptors and translocation, and this results in an increase in glucose

uptake and an improvement in insulin sensitivity.^{28–30} Adiponectin also activates peroxisome proliferator-activated receptors alpha and gamma (PPAR α , PPAR γ), which are fundamental in lipid and glucose homeostasis. Stimulation of PPAR γ improves glucose tolerance and insulin sensitivity.³¹ It has also been reported that *M. charantia* can inhibit the action of protein tyrosine phosphatase 1B (PTP-1B) in skeletal muscle in db/db mice; this is a physiological antagonist of the insulin receptor and its signal.⁶

Only one clinical trial has evaluated the effect of *M. charantia* administration on insulin sensitivity, however, it was conducted in patients with metabolic syndrome, and different indexes to assess insulin sensitivity were used. After 1 to 3 months of *M. charantia* supplementation (4.8 g/day), insulin resistance indicators, logHOMA, McAuley, and QUICKI, showed ameliorated trends that did not reach statistical significance.¹⁶ Insulin sensitivity was also not modified in the present study. An interesting perspective would be to evaluate if an increase in the dose or a longer period of administration can modify this variable.

It is important to mention that the gold standard to assess insulin secretion and insulin sensitivity is the glucose/insulin clamp technique. In this study, we used the insulinogenic, Matsuda, and Stumvoll indexes from a 2-h OGTT to evaluate insulin secretion and insulin sensitivity. This could be considered a limitation of the study; nevertheless, these indexes have a very good correlation with the gold standard.³²

Several clinical trials have reported the hypoglycemic effect of *M. charantia* in patients with T2DM. Reductions in blood glucose concentrations as well as in glycemic control indicators, such as A1C and fructosamine, have been observed.^{12–14} These results could be explained by multiple mechanisms. *In vitro* and animal studies have shown that *M. charantia* decreases the absorption of glucose by inhibiting α -glucosidase, reduces Na⁺/K⁺-dependent absorption of glucose by the intestinal mucosa, upregulates PPAR α , stimulates the glycolytic pathway, decreases hepatic gluconeogenesis, increases hepatic glycogen synthesis, and suppresses disaccharidase activity in the intestine.³⁰ The increase in insulin secretion observed with *M. charantia* could also have an important effect on reducing postprandial glucose concentrations.¹⁵

Our study showed that *M. charantia* administration significantly reduced A1C, 2-h serum glucose, and AUC of glucose. Although a reduction in fasting blood glucose of about 0.8 mmol/L was observed, it was not statistically significant. The results of our study have a clinically relevant impact since 50% of patients reached fasting glucose concentrations <7.2 mmol/L and 30% of patients had 2-h serum glucose levels <10 mmol/L in the OGTT after the intervention with *M. charantia*. Furthermore, 60% of patients had a percentage of A1C less than 7%. In general, 30% of patients achieved all three glycemic control goals.

A 5% reduction of initial body weight in overweight and obese patients with T2DM is associated with an improvement in glycemic control.² In this study, *M. charantia* administration significantly reduced weight, BMI, fat percentage, and WC. These additional beneficial effects of *M. charantia* on

these anthropometric variables are important in the context of integral care of a patient with T2DM and the cardiovascular morbi-mortality reduction.²

The findings in the present study are consistent with those reported in the literature; in patients with T2DM after 10 weeks of *M. charantia* administration, a significant reduction in body weight was observed (−3.1 kg),¹² while in patients with metabolic syndrome, 3 months of administration of *M. charantia* significantly decreased WC (−2.09 cm).¹⁶ The possible mechanisms responsible for these effects include an increase in the expression of uncoupling proteins (UCP) 1 and 3,^{11,30} the inhibition of preadipocyte differentiation, increased lipolysis in adipocytes, or through PPAR γ expression in adipose tissue.³³

Although positive results on blood pressure and lipid profile have been reported in patients with T2DM,¹² these parameters were not modified with our intervention. *M. charantia* was well tolerated by patients, and the adverse events reported were in general transient, of mild-to-moderate intensity, and consistent with those reported in previous studies.

An increase in creatinine was observed in the placebo group. We do not have an explanation for this increment given that calcined magnesina has been used as placebo in previous studies in our investigation group without a modification in this parameter. Our study has internal validity, however, further randomized, placebo-controlled, clinical trials with different types of populations and for a longer period of time are necessary to confirm our results.

In conclusion, our study demonstrated that *M. charantia* administration can modify insulin secretion by increasing the AUC of insulin and first phase and total insulin secretion, in addition to significantly decreasing A1C, 2-h serum glucose, AUC of glucose, and various anthropometric variables (weight, BMI, fat percentage, and WC).

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AUTHOR DISCLOSURE STATEMENT

No competing financial interests exist.

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