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Hypoglycemic efficacy and safety of *Momordica charantia* (bitter melon) in patients with type 2 diabetes mellitus

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ABSTRACT

Introduction: *Momordica charantia* (bitter melon) is widely used for its glucose-lowering effects. This study was conducted to assess the efficacy and safety of *M. charantia* as an adjuvant treatment in patients with type 2 diabetes.

Methods: We performed a randomized, placebo-controlled study. Blood glucose levels, lipid profile, and adverse events were investigated after 12 weeks of treatment. Ninety subjects were included in the final analysis for glucose lowering efficacy of bitter melon.

Results: There were no differences in age, sex, or glycated hemoglobin (HbA1c) levels between the bitter melon extract and placebo groups. After treatment with bitter melon extract for 12 weeks, the HbA1c levels of the bitter melon and placebo groups remained unchanged; however, the average fasting glucose level of the bitter melon group decreased ($p = 0.014$). No serious adverse events were reported during the treatment period.

Conclusions: Our data showed that bitter melon has effects of glucose lowering in patients with type 2 diabetes.

1. Introduction

The prevalence of type 2 diabetes mellitus in Korea has increased, as it has in many other countries.[1] Type 2 diabetes is often accompanied by long-term microvascular and macrovascular complications. It is important to maintain optimal glucose levels to reduce the diabetic complications. However, current treatments are unsatisfactory,[2] and various alternative and complementary treatments have emerged among the population of Asia. Studies have shown that such as green tea,[3] aloe,[4] citrus fruits,[5] and beans,[6–9] have glucose lowering effect and hypolipidemic effects in animals and human studies. With the increase in popular reporting and advertisements about the beneficial effects of various alternative and complementary treatments on glucose control, many patients with diabetes use alternative and complementary treatments to improve their glucose levels or reduce diabetic complications.[10]

Momordica charantia (MC), known as bitter melon, has been reported to have antiviral, antibacterial, anti-cancer, and immune-modulating properties.[11] It has been widely used as a complementary or alternative therapy for treating diabetes mellitus in many countries, including Korea.

Experimental animal studies have shown that bitter melon has hypoglycemic effects by stimulating glucose uptake into skeletal muscle cells or by increase in insulin secretion.[12–14] However, it is important to prove the glucose lowering effects and safety of bitter melon in humans. A few clinical studies have reported the glucose lowering efficacy of bitter melon in patients with type 2 diabetes mellitus.[15–19] However, most of these studies except few studies[17,19] were not randomized, lacked proper controls, were of short duration, used small sample sizes, and inconsistent findings. Furthermore, wide use of alternative and complementary medicine needs to be examined the glucose lowering efficacy and adverse events of bitter melon through human study. Thus, randomized double blind placebo controlled studies are necessary for assessing the glucose-lowering efficacy and safety of bitter melon as a complementary treatment in patients with type 2 diabetes. For this purpose, we conducted study to determine the anti-diabetic and hypolipidemic effects of bitter melon in patients with type 2 diabetes.

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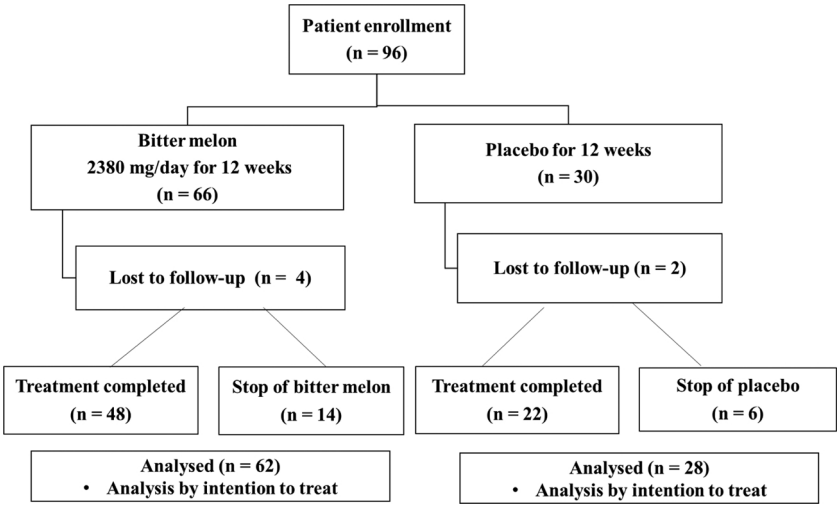

Fig. 1. Patient enrollment, study design, and follow-up.

2. Methods

2.1. Study design and subject

This was a single-center, randomized, double blind, placebo-controlled study. The study protocol was reviewed and approved by the Ethics Committee of Gyeongsang National University School of Medicine in Jinju, Korea. We enrolled 96 Korean patients with type 2 diabetes and allocated them randomly to either the group receiving bitter melon extract (twice a day, total 2380 mg daily) or the control group (placebo capsules) in a 2:1 ratio using block randomization for 12 weeks.

Bitter melon powder was given in the form of capsules. The dosage of bitter melon used in this study is based on levels previously reported to improve blood glucose in clinical trials.[11] We investigated blood glucose levels, body weight, lipid profiles, and adverse events after 12 weeks of treatment.

The inclusion criteria were as follows: 1) a confirmed diagnosis of type 2 diabetes, 2) no changes in treatment for 3 months prior to the start of the study, 3) a glycosylated hemoglobin (HbA1c) level no greater than 7.5 %, 4) age between 20 and 70 years, 5) submission of a completed consent form for participation in this study. Exclusion criteria were as follows: 1) treatment with α-glucosidase inhibitors, 2) liver dysfunction (aspartate transaminase and alanine transaminase levels > 3× the upper standard values), 3) treatment with steroids or immunosuppressive agents, 4) renal impairment (serum creatinine level > 1.3 mg/dL in men and > 1.2 mg/dL in women), and 5) pregnancy or lactation. The homeostasis model assessments of β-cell function (HOMA-β) and insulin resistance (HOMA-IR) were calculated to determine basal insulin secretion and insulin resistance, respectively.

2.2. Outcome measurements

The primary efficacy outcome was the mean change in HbA1c over 12 weeks. The secondary outcomes were the mean changes in fasting glucose and lipid profiles. Safety was monitored by assessing patient-reported symptoms, physical examination findings, vital signs, and laboratory tests (liver function test, complete blood cell count, blood urea nitrogen, and serum creatinine). Patients reported adverse events when they returned to the clinic after 12 weeks, or by phone at any time during the study (n = 6). Six patients did not visit the outpatient clinic three months later, so they could not perform the test. However, it was confirmed by phone whether adverse events occurred. Therefore, a total of 96 patients were included for analysis of the occurrence of adverse events.

2.3. Preparation of standardized extract of Momordica charantia

Three batches (No. DHP20160217-20160219) of standardized Momordica charantia extract (MCE) containing 0.1 % γ-Aminobutyric acid (GABA) as a marker compound were manufactured and verified by Daeho Corporation Co., Ltd. (Hwaseong, Korea). Briefly, the dried unripe fruit of Momordica charantia (Hamyang, Korea/Cheonryung Foods Co., Ltd.) was shattered and extracted by heating at 70 °C twice (4 h and 2 h) using 70 % ethanol. The extract was then filtered and concentrated (Busung Tech, Ansung, Korea) to 15–20 degrees Brix at 65 °C. The concentrated extract was spray dried (Mehyun Engineering, Anyang, Korea) at inlet temperature 175 ± 10 °C and outlet temperature 80 ± 5 °C adding dextrin (49 %) and lecithin (1%). The extraction yield was approximately 34 % (w/w). Placebo capsule was consisted of maltodextrin (57 %, about 1.36 g per day), Microcrystalline Cellulose (36 %), and other ingredients.

2.4. Data analysis

Intention-to-treat statistical analysis was carried out. Data are presented as means ± standard deviations, or as medians (25th to 75th percentile). Comparisons between the two groups were performed using the chi-squared or Fisher's exact tests for categorical variables and the Mann–Whitney *U* test for continuous variables. The effects of bitter melon on blood glucose control (fasting plasma glucose, HbA1c) and lipid profiles were compared by analysis of variance (ANOVA) and multiple regression analysis.

All statistical analyses were performed using PASW 18.0 software (SPSS, Inc., Chicago, IL, USA). A two-sided p-value < 0.05 indicated statistical significance.

3. Results

3.1. Patient basal characteristics

A total of 96 patients were enrolled in the study. Thirty patients were randomized to the placebo group and 66 patients to the bitter melon group. Two placebo group patients and 4 bitter melon group patients did not follow up after 3 months (Fig. 1). Six placebo group patients and 14 bitter melon group patients stopped taking of

Table 1
Baseline clinical characteristics of enrolled patients.

	Bitter melon (n = 62)	Placebo (n = 28)	*P* value
Age (year)	58.1 ± 6.9	60.3 ± 7.6	0.162
Sex (M:F)	38;24	12;16	0.103
Body mass index (kg/m^2)	25.3 ± 3.8	26.6 ± 5.1	0.226
HbA_{1C} (%)	7.0 ± 0.5	6.9 ± 0.4	0.442
Fasting glucose (mg/dL)	145.9 ± 34.5	131.0 ± 24.2	0.047
HOMA-β	30.7 (14.7–46.3)	38.6 (23.7–52.9)	0.111
HOMA IR	2.4 (1.3–3.5)	1.9 (1.3–3.7)	0.782
Total cholesterol (mg/dL)	155.4 ± 28.6	159.0 ± 27.3	0.542
Triglyceride (mg/dL)	137.1 ± 83.3	116.4 ± 55.8	0.436
HDL-C (mg/dL)	49.3 ± 12.1	54.1 ± 11.5	0.073
LDL-C (mg/dL)	94.9 ± 26.0	94.2 ± 24.8	0.842
Sulfonylurea (%)	15 (24.2 %)	6 (21.4 %)	0.774
Metformin (%)	53 (85.5 %)	25 (89.3 %)	0.623
DPP4-inhibitors (%)	37 (59.7 %)	15 (53.6 %)	0.587
Thiazolidinedione (%)	3 (4.8 %)	3 (10.7 %)	0.301
Hypertension (%)	30 (42.2 %)	8 (28.6 %)	0.078
Cardiovascular disease (%)	5 (8.1 %)	4 (14.3 %)	0.362
Dyslipidemia (%)	28 (45.2 %)	19 (67.9 %)	0.046
Cerebrovascular disease	3 (4.8 %)	3 (10.7 %)	0.301

Dipeptidyl Peptidase-4 (DPP-4).

medication due to adverse events or non-compliance. There were no significant differences in drug discontinuation rate between groups ($p = 0.655$). So the final analysis included the 62 patients in the bitter melon group and 28 patients in the placebo group (Fig. 1).

There were no significant differences in age, sex, body mass index (BMI), HbA1c, or lipid profiles at baseline (Table 1). There were no significant differences in the medication of oral hypoglycemic agents and comorbidity except for dyslipidemia between two groups (Table 1).

3.2. Glycemic control after the 12-week study period

Compared with baseline levels, the patients in the bitter melon group showed no difference in mean HbA1c levels. However, in the placebo group, HbA1c levels increased significantly compared to baseline (Table 2). After adjusting for baseline HbA1c, age, and sex, a significant correlation was found between bitter melon intake and HbA1c level after 12 weeks ($p = 0.022$, Table 3).

Table 2
Effects of bitter melon on $HbA1_C$, fasting glucose, and lipid profile after 12 weeks.

	Baseline	After 12 weeks	*P* value
HbA_{1C} (%)			
Bitter melon group (n = 62)	7.0 ± 0.5	7.0 ± 0.7	0.235
Placebo group (n = 28)	6.9 ± 0.4	7.2 ± 0.9	0.024
Fasting glucose (mg/dL)			
Bitter melon group	145.9 ± 34.5	140.5 ± 31.9	0.014
Placebo group	131.0 ± 24.2	155.1 ± 53.0	0.006
HOMA-β			
Bitter melon group	30.7 (14.7–46.3)	28.3 (17.1–46.2)	0.331
Placebo group	38.6 (23.7–52.9)	26.0 (16.6–54.6)	0.122
HOMA IR			
Bitter melon group	2.4 (1.3–3.5)	1.8 (1.3–2.8)	0.017
Placebo group	1.9 (1.3–3.7)	2.0 (1.4–3.1)	0.767
Total cholesterol (mg/dL)			
Bitter melon group	155.4 ± 28.6	154.6 ± 35.2	0.690
Placebo group	159.0 ± 27.3	160.4 ± 24.7	0.597
Triglyceride (mg/dL)			
Bitter melon group	137.1 ± 83.3	128.9 ± 76.9	0.680
Placebo group	116.4 ± 55.8	143.2 ± 81.4	0.037
HDL- C (mg/dL)			
Bitter melon group	49.3 ± 12.1	48.6 ± 14.1	0.589
Placebo group	54.1 ± 11.5	51.3 ± 13.3	0.097
LDL-C (mg/dL)			
Bitter melon group	94.9 ± 26.0	95.0 ± 26.0	0.563
Placebo group	94.2 ± 24.8	95.6 ± 22.0	0.611

Table 3
Factors for HbA1c level and fasting glucose level after 12 weeks in multivariate regression model.

Variable	Beta-coefficient for HbA1c level after 12 weeks	P-value	Beta-coefficient for fasting glucose level after 12 weeks	P-value
Intake of bitter melon	−0.203	0.022	−0.312	0.001
Age, year	−0.083	0.339	−0.067	0.438
Sex	0.097	0.269	−0.013	0.883
Baseline HbA1c	0.604	0.001		
Baseline fasting glucose			0.601	0.001

*by multiple regression analysis.
Model 1: adjusted for age, sex, HbA1c or fasting glucose level at baseline.

Fasting glucose levels improved in the bitter melon group, and were exacerbated in the placebo group. Fasting glucose after 12 weeks was also associated with baseline fasting glucose, and bitter melon intake (Table 3).

The HOMA-IR was improved in the bitter melon group and there was no change in the placebo group (Table 2). There was no difference in HOMA-β in both groups.

There was no significant change in lipid profile in the bitter melon group; however, the serum triglyceride level was increased after 12 weeks in the placebo group (Table 2).

3.3. Adverse events

All 96 enrolled patients, including those who dropped out, were analyzed for adverse events. Bitter melon was well tolerated, and there was no difference in the overall rate of adverse events ($p = 0.356$).

The reported adverse events were gastrointestinal symptoms, including anorexia, nausea, abdominal discomfort, and soreness; foamy urine; and skin rashes (Table 4). Gastrointestinal complaints were the most common adverse events in both the bitter melon group and the placebo group. There were no clinically serious adverse events. There were no changes in liver enzymes or serum creatinine after the 12-week study period.

4. Discussion

This randomized double blind placebo-controlled clinical trial demonstrated an association between the intake of bitter melon for 12 weeks and improved fasting glucose levels and insulin resistance index in patients with type 2 diabetes mellitus.

Bitter melon is widely consumed in Korea as an adjuvant treatment for diabetes, because it is known that bitter melon has glucose-lowering effects in patients with type 2 diabetes or those in a pre-diabetic state.[20] Animal studies have shown that the fruits, seeds, and leaf extracts of this plant have glucose-lowering effects. Several animal studies reported that bitter melon improves insulin resistance and suppresses

Table 4
Adverse events of bitter melon during 12 weeks of study period.

	Bitter melon (n = 66)	Placebo (n = 30)
Gastrointestinal tract		
Anorexia/ Nausea	2 (3.0 %)	1 (3.3 %)
Abdominal discomfort	3 (4.5 %)	2 (6.6 %)
Epigastric soreness	–	1 (3.3 %)
Diarrhea	1 (1.5 %)	–
Constipation	2 (3.0 %)	–
Renal		
Foamy urine	1 (1.5 %)	1 (3.3 %)
Dermatological		
Skin rashes	1 (1.5 %)	1 (3.3 %)

postprandial hyperglycemia. [12,21,22]

Compared with animal studies, human studies of bitter melon are inconclusive. Many previous clinical trials found bitter melon juice, fruit, and dried powder to have hypoglycemic effects [15,17–19,23] Tongia et al. studied the effects of bitter melon for 7 days after dose reductions of oral hypoglycemic agents (OHAs) in patients with type 2 diabetes mellitus.[23] Oral intake of bitter melon lowered blood glucose levels. The bitter melon extract potentiated OHAs in patients with type 2 diabetes. However, the size of these studies were small, and others were not randomized or double-blinded. Marisol et al. conducted the randomized, double-blinded, placebo-controlled study.[19] They reported MC administration reduced $HbA_{1C,}$ and improved insulin secretion. However, the HbA_{1C} was also improved in the control group, and the enrolled patients are smaller than ours. Recently, a prospective, randomized, double blind, placebo controlled study was conducted and reported a significant improving of HbA_{1C} level after 4 months of bitter melon treatment.[24] On the contrary, another studies reported that bitter melon had no significant effects on HbA1c, fasting glucose levels, or lipid profiles [16,18] John et al. conducted randomized, placebo-controlled trials.[18] The subjects were randomized into a control group or treatment groups that took 4 g of dry bitter melon daily for 2 or 4 weeks. All subjects continued with OHAs during study period. There were no significant changes in fasting glucose levels or fructosamine in either the controls or treatment groups at the end of the study. We observed improvements in fasting glucose levels and insulin resistance index after 12 weeks of bitter melon treatment in our study. However, there was no change in HbA1c levels in the treatment group. These conflicting results between human studies may be due to differences in the preparation of the bitter melon treatment, study duration, sample size, or study design, ethnic differences. [18,19]

In our study, we observed increased HbA1c levels in the control group ($p = 0.024$). We speculate that the reason of HbA1c levels did not change in the treatment group but were exacerbated in the control group was the study period. Our study was conducted from October to March. There are four seasons in Korea, and HbA1c levels exhibit seasonal variation, with the highest levels during the cold season.[25] Our study started at the beginning of the cold season and ended at the end of the cold season. The cold season may have affected HbA1c in both groups, and the mean HbA1c level in the treatment group did not changed ($p = 0.235$).

Various studies have investigated the mechanisms underlying the glucose-lowering effects of bitter melon. The reported mechanisms involve stimulating pancreatic secretion,[26] decreasing hepatic gluconeogenesis, and increasing hepatic glycogen synthesis [27] Charantin, vicine, and polypeptide-P are the components of bitter melon thought to have glucose-lowering effects [28] Polypeptide-P is an unidentified insulin-like peptide that has been isolated from bitter melon fruit and seeds.[29] However, there was no increase plasma insulin concentration in rat models, and it revealed that bitter melon stimulates glycogen synthesis.[28] Furthermore, bitter melon stimulates glucose uptake into skeletal muscles.[30] Our study showed that insulin resistance index improved after bitter melon intake, which could explain the decrease in fasting glucose level. It needed the further study to clarify the mechanism of glucose lowering effects of bitter melon.

As for the safety of bitter melon, animal studies have shown significant increases in gamma glutamyl transferase and alkaline phosphatase, and reduced fertility, in rats [30–32] However, toxicity and infertility have not been reported in humans, despite widespread use of bitter melon. In human studies, the most common adverse events are abdominal pain and diarrhea. [33] The most common adverse events in our study were also gastrointestinal-related symptoms. The subjects complained of anorexia, nausea, abdominal discomfort, diarrhea, and constipation. However, there was no significant difference in adverse events between the bitter melon and placebo groups.

There is still insufficient evidence to draw definitive conclusions about the efficacy of bitter melon for the treatment of diabetes; however, it appears to be generally safe.

Our study did not show improvements in HbA1c levels; however, fasting glucose levels and the insulin resistance index were lowered after intake of bitter melon for 12 weeks. Thus, bitter melon may have additive effects when taken with other glucose-lowering agents.

The limitation of our study is that the short-term duration of study, and high drop-out rates due to poor adherence to medication. Larger, randomized, placebo-controlled trials are needed in order to appropriately advise to patients about safety and glucose lowering effects of bitter melon.

5. Conclusion

Bitter melon has potential anti-diabetic effects in humans. Thus, bitter melon may be a useful option as adjuvant treatment in patients with type 2 diabetes.

Declaration of competing interest

None.

Authorship statement

We confirmed that all listed authors meet the authorship criteria, and all authors are in agreement with the content of the manuscript.

K.S. K and J.R.H designed the present study. J.H.J. and J.J identified and screened the included randomized controlled trials. N. Y., G.S.R, and S.S K. analyzed and evaluated the data. K.S.K wrote the draft of the manuscript and J.R. H. revised the manuscript. All authors approve the final version for submission. All authors are in agreement with the content of the manuscript.

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No competing financial interests exist.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ctim.2020.102524.

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