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Original Article

Pilot study: Hypoglycemic and antiglycation activities of bitter melon (*Momordica charantia* L.) in type 2 diabetic patients

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ABSTRACT

Background/Objectives: Bitter melon (*Momordica charantia* L., MC) has been used as a traditional remedy in diabetics due to its hypoglycemic activity. However, its antihyperglycemic effect and antiglycation activity have been demonstrated *in vitro* and in animal experiments, but not in a long-term clinical study. The aim of this study was to investigate the effect of bitter melon on long-term glycemic control and glycation status in type 2 diabetic patients.

Methods: This study was a two-arm, parallel, randomized, double-blinded, placebo-controlled trial in which type 2 diabetic patients were randomized to continuously take either 6 g/day of MC dried-fruit pulp containing 6.26 ± 0.28 mg of charantin ($N = 19$) or placebo ($N = 19$) for 16 weeks.

Results: After 8 and 16 weeks of the treatment, the reduction of A1C from baseline in the MC group was greater than that of the placebo group (0.25 ± 0.12%, $P = 0.042$ and 0.31 ± 0.15%, $P = 0.044$, respectively). In addition, the MC group showed a significant decline of total advanced glycation endproducts (AGEs) in serum after 16 weeks of the intervention. The mean difference between both groups was $8.22 \pm 3.58 \times 10^3$ AU/g protein ($P = 0.028$). The levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and serum creatinine (Cr) did not change from baseline in each group and were not different between the two groups. None of participants experienced serious adverse events.

Conclusions: It is possible that this herb is beneficial not only on glycemic control, but also on potential systemic complications of type 2 diabetes mellitus.

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1. Introduction

Type 2 diabetes mellitus (T2DM) and its complications put great impact on global health and economic consequences. Bitter melon (*Momordica charantia* L., MC, family Cucurbitaceae) has been used as a traditional remedy with hypoglycemic activity particularly in tropical areas.[1,2] *In vitro* and experimental animal studies have demonstrated its hypoglycemic activity as well as possible mechanisms of action as alpha-glucosidase inhibition, insulin-like properties, insulin secretagogue, pancreatic beta-cell function preservation, increase of GLUT-4 in skeletal muscle cell and reduction of hepatic gluconeogenesis.[1,3–5] To date, the potency of MC dried-fruit pulp is widely claimed, but the scientific results in diabetic patients were inconsistent. Most previous clinical studies were not randomize, unclear of specification of the investigational products, and not long-term studies.[2,6–9] Majority of previous results did not show significant glucose lowering effect, but Fuangchan et al demonstrated that significantly reduced of fructosamine from baseline of Thai bitter melon recently. However, the studied- dosage and duration were only 2 g/day and 4 weeks, respectively.[2] Hence, it is important that investigations with sufficient dose and longer studied period are needed to clarify the hypoglycemic effect of this herb. Generally, clinical outcome relies on blood glucose measurement; however, advanced glycation endproducts (AGEs) are now considered the more meaningful parameter in diabetic evaluation. AGEs are heterogeneous substances generated from sugars and proteins *via* Hodge pathway or Wolf and Namiki pathways. Amadori's product, such as A1C and fructosamine, are produced in the early phase of Hodge pathway. This phase remains blood glucose dependent and partially reversible while the late phase to generate AGEs is blood glucose independent and irreversible.[10,11] AGEs accumulation correlates with long term diabetic microvascular complications as retinopathy and nephropathy.[12–16] These substances may enhance diabetes complications through endothelial cell damage and intracellular protein dysfunction, leading to cell and organ deterioration.[17–21] Kubola and colleagues reported the reduction of AGEs by MC fruits in an *in vitro* experiment,[22] but this action has not been studied in human.

Since there has been no study of MC dried-fruit pulp on long-term glycemic control including antiglycation activity in type 2 diabetic patients. The present pilot study aimed to investigate the effects of this herb on these issues.

2. Material and methods

2.1. Bitter melon preparation

Bitter melon or Mara-kheenok (in Thai) was cultivated in Suphan Buri and Kanchanaburi provinces, Thailand, and harvested during April–June 2010. The voucher specimen (WTR-002) was deposited at Department of Pharmacognosy, Faculty of Pharmacy, Silpakorn University, Thailand. Unripe fruits with seeds removed were collected and dried under the sun light for 6 h and in hot air oven at 60 °C for another 6 h. MC and placebo capsules were manufactured at U-Thong Hospital, Suphan Buri, Thailand. Each MC capsule contained 400 mg of dried fruit pulp. Placebo was made of microcrystalline cellulose grade 102 (Flocel® 102, Gujarat Microwax Private Limited, India). Charantin, an analytical marker of MC, was analyzed by HPLC method with modification from Ref.[23] at Faculty of Pharmacy, Mahidol University, Bangkok, Thailand. The content of charantin was 0.42 ± 0.02 mg/capsule. Capsules were tested for weight variation. Contaminations of pesticide residues, heavy metals and microorganisms of finished product were analyzed by Medicinal Plant Research Institute, Department of Medical Science, Ministry of Public Health, Thailand. All tests were acceptable with respect to the criteria of Thai Herbal Pharmacopoeia (THP) 2000 and Supplement to Thai Herbal Pharmacopoeia (THP Supplement) 2004.[24,25]

2.2. Clinical trial

A two-arm, parallel, randomized, placebo-controlled trial was conducted at Ramathibodi Hospital, Mahidol University, Bangkok, Thailand. The protocol was approved by the Ethics Committee of Faculty of Medicine, Ramathibodi Hospital, Mahidol University.

2.2.1. Patients

Eligible volunteers were T2DM patients with at least 20 years of age, A1C $\geq$ 6.5%, and informed consents were provided. Patient with any of the following conditions were excluded: type 1 diabetes mellitus, being treated with insulin, history of allergy to MC or members of Cucurbitaceae, pregnancy or lactation, liver disease (aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $>$ 3 times the upper limit of normal values), renal impairment (serum creatinine (Cr) $>$ 1.5 mg/dL), unstable diabetes or concomitant illness requiring medicine adjustment, history of other disorders of oxidative status, currently smoking, history of taking supplements or functional foods or herbal medicines within 8 weeks prior to the beginning of the study, presence of conditions affecting compliance such as psychiatric problems. The flow chart describing patient enrollment and follow up is shown in Fig. 1.

2.2.2. Study procedure

At initial visit, all eligible patients were requested to maintain behavior according to the criteria of the study from the run-in period (2 weeks) and during the intervention (16 weeks). These criteria were: not taking other source of bitter melon except the assigned product in this study, maintaining usual dietary intake/medications/physical activities, not taking any supplements and herbal medicines which may affect glucose level or oxidative status, and not smoking. After the run-in period, participants were randomized to take either 6 g/day of MC dried fruit pulp in 3 divided doses 30 min before meals or placebo. Block randomization using a block size of four was employed. In the present experiment, 6 g of dried pulp was derived from 4 fresh fruits of Thai MC which did not exceed usual daily intake as food in general. The patients were followed up every 4 weeks. Laboratory investigation, anthropometric assessment, and physical examination were performed at the first visit (baseline, week 0) as well as after 8 weeks and 16 weeks of the treatment. Blood and urine

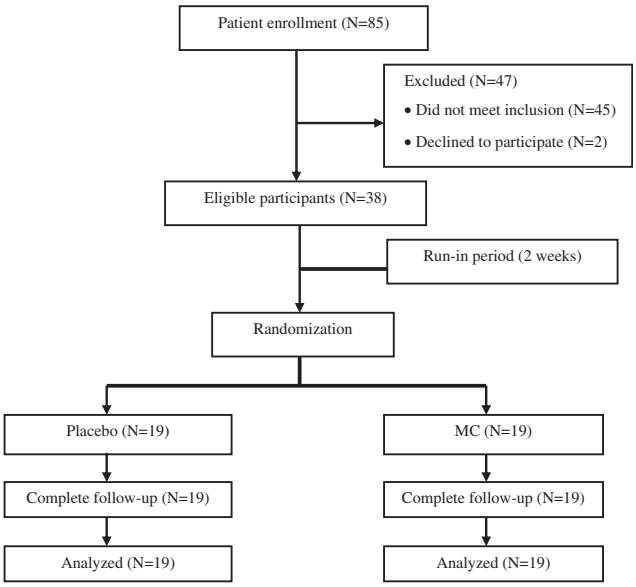

Fig. 1 – The flow chart describing patient enrollment and follow up.

sampling was taken after fasting for 8 h. At each visit, data of adverse events (AEs), 3-day food record and compliance checking by capsule count were collected.

2.2.3. *Outcome measurement*

The primary efficacy outcome was the change of A1C (immunoturbidimetric assay, Cobas Integra 800, Roche Diagnostics) from baseline at 8 weeks and 16 weeks after the initiation of the intervention. Secondary efficacy outcomes included the changes of serum AGEs, FPG (hexokinase, Architech ci 4001 analyzer, Abbott Laboratories), and urine albumin to creatinine ratio (UACR) (turbidimetric assay, Cobas Integra 800, Roche Diagnostics). Safety monitoring was performed by interviews, physical examination, biochemical assessment i.e. Cr (Kinetic Jaffe, Dimension RXL, Siemens), AST and ALT (International Federation of Clinical Chemistry method, Dimension RXL, Siemens). Definition and severity of AEs were based on the category of Common Terminology Criteria for Adverse Events (CTCAE) version 4.02.[26] Dietary intake data were analyzed by INMUCAL-N version 2.0 software (Institute of Nutrition, Mahidol University).

Measurement of serum AGEs was modified from Kaluousava et al.[11] Serum was diluted 1:20 to 1:10 with phosphate buffer saline (PBS) pH 7.4 (Sigma). AGEs fluorescence intensity was measured at 350/440 (Ex/Em) nm with a spectrofluorometer (Shimadzu Model RF-1501, Shimadzu). Serum total protein (TP) was measured by Biuret method (Dimension RXL, Dade Behring). Serum AGEs was expressed as a ratio of AGEs fluorescence intensity to total protein (AGEs/TP ratio). All analyses were performed in triplicates.

2.2.4. *Statistical analysis*

Data analysis was carried out as per protocol (PP) principle. Data were expressed as number of patients (*N*), mean ± SD or mean difference ± SE of difference. The differences between baseline and after intervention were expressed as change values (Δ) at week 8 and week 16. Discrete data were evaluated by Pearson's Chi-square or Fisher's Exact test. Two factor repeated measures analysis of variance (RM-ANOVA) with multiple comparisons by Bonferroni or Friedman test were used to assessed the effects of treatment, time, and their interaction. Independent *t*-test or Mann–Whitney test was utilized in comparing the effect between 2 groups at each time point. Paired *t*-test or Wilcoxon Signed Rank test was applied to compare the change values after 8 weeks and 16 weeks of treatment within group. The 2-sided hypothesis was used in all tests and $P < 0.05$ was considered statistically significant.

3. Results

Thirty-eight T2DM patients were completely participated in this study. They were randomized to continuously take either 6 g/day of dried-fruit powder of MC equivalent to 6.26 ± 0.28 mg of charantin ($N = 19$), or placebo ($N = 19$) for 16 weeks. All baseline characteristics at week 0 between the 2 groups did not differ (Table 1). Mean dietary intake at the same period of the time was not different between groups, and all nutrient intakes of each group did not alter throughout the study (Table 2). This indicated that food consumption of all patients was maintained throughout the study. Percentage of ingested capsules did not differ between the MC and placebo groups (96.11 ± 3.07% and 94.50 ± 3.11%, respectively) indicating that both groups had good compliance. None of patient was non-adherent which defined as failure to take assigned investigational product (less than 80% base upon capsule counting).

Laboratory and physical assessments at baseline and mean change from baseline at week 8 and week 16 were shown in Table 3. All parameters at baseline of the MC and placebo groups were not different. Body weight, body mass index (BMI) and blood pressure (BP) did not differ between groups and did

Table 1 – Baseline characteristics of patients.

Parameter	Placebo ($N = 19$)	MC ($N = 19$)	P-value[a]
Age (years)	58.7 ± 7.0	57.2 ± 8.8	0.543
Gender (*N*), male/female	8/11	3/16	0.074
Body weight (kg)	68.91 ± 16.50	63.21 ± 12.94	0.243
BMI (kg/m^2)	26.37 ± 6.04	25.04 ± 3.69	0.419
Past smoker (*N*)	5	2	0.405
Diabetes duration (years)	8.11 ± 6.53	6.95 ± 5.03	0.544
Antidiabetic medicine taking (*N*), yes/no	14/5	15/4	1.000
Hypertension (*N*)	15	13	0.461
A1C (%)	7.32 ± 0.70	7.47 ± 1.03	0.606
FPG (mg/dL)	118.37 ± 16.36	117.63 ± 32.14	0.511
AGEs/TP (x 10^3 AU/g protein)	93.99 ± 17.67	85.50 ± 16.21	0.132

Data expressed as number of patient (*N*) or mean ± SD.

[a] *P*-values were obtained *via* Independent *t*-test, Mann–Whitney test, Pearson's Chi-square or Fisher's Exact test.

Table 2 – Dietary intake during run-in and treatment periods.

Parameter	Run-in period	P-value between groups[a]	Treatment (16 weeks)	P-value between groups[a]	P-value within group[b]
Energy (kcal/day)					
Placebo group	1864 ± 406		1915 ± 379		0.084
MC group	1775 ± 359	0.483	1816 ± 324	0.393	0.135
Carbohydrate (% of energy)					
Placebo group	52.82 ± 2.75		53.83 ± 3.95		0.574
MC group	53.19 ± 3.47	0.367	53.50 ± 4.60	0.817	0.545
Protein (% of energy)					
Placebo group	15.34 ± 1.91		15.54 ± 2.01		0.645
MC group	15.19 ± 1.75	0.746	15.61 ± 1.83	0.471	0.767
Fat (% of energy)					
Placebo group	31.84 ± 2.60		30.63 ± 3.36		0.710
MC group	31.62 ± 2.82	0.220	30.89 ± 3.59	0.490	0.591
Dietary fiber (g)					
Placebo group	11.99 ± 3.60		12.65 ± 1.72		0.314
MC group	12.10 ± 4.34	0.933	12.43 ± 3.30	0.799	0.455

Data expressed as mean ± SD.

[a] $P < 0.05$ indicated significantly different between MC and placebo groups at the same period of time (Independent *t*-test).

[b] $P < 0.05$ indicated significantly different between the values at run-in period and treatment period of each group (Paired-*t* test).

not alter throughout the trial. The results showed that mean decrement of A1C was significantly different between the groups and between each time point of the intervention. After 8 weeks of the treatment, the mean reduction from baseline of A1C of the MC group (−0.27 ± 0.30%) was more than that of the placebo group (−0.02 ± 0.43%), and the mean difference was 0.25 ± 0.12% ($P = 0.042$). In addition, the mean decrement of A1C from baseline after consumption of MC for 16 weeks (−0.50 ± 0.45%) was significantly greater than that of the placebo group (−0.20 ± 0.45%), and the mean difference between them was 0.31 ± 0.15% ($P = 0.044$). Mean changes of A1C from baseline after MC ingestion for 8 weeks and 16 weeks were significantly different (mean difference: −0.23 ± 0.26%, $P = 0.001$). In addition, the mean change from baseline after 16 weeks of treatment in MC group was significantly lower than that of the placebo group ($-5.69 \pm 9.72 \times 10^3$ AU/g protein and $2.53 \pm 12.20 \times 10^3$ AU/g protein, respectively). The mean difference between both groups was $8.22 \pm 3.58 \times 10^3$ AU/g protein ($P = 0.028$).

The level of ALT, AST and Cr after treatment did not significantly change from baseline in each group. All of these parameters were not different between the 2 groups. None of participants experienced the signs and symptoms of hepatitis. Fifteen adverse events were reported (Table 4). None was serious adverse event, and subjects were well tolerated. Adverse events included gastrointestinal complaints: diarrhea and flatulence. Frequency of diarrhea and flatulence in the MC group was significantly higher than the placebo group ($P = 0.046$ and $P = 0.027$, respectively). These symptoms were transient. Severity of all events was classified as grade 1 (mild) according to CTCAE. No participant dropped out from the study due to adverse events.

4. Discussion

Six gram per day of MC dried fruit pulp (containing 6.26 ± 0.28 mg/day of charantin) had anti-glycation activity, not only reduced the reversible glycation product (A1C) but also decreased the level of irreversible glycation products (serum AGEs). Level of A1C was significantly reduced up to 16 weeks of treatment. Though the lowering of FPG was not statistically significant, FPG is a blood glucose level after fasting for 8–12 h and contributes about 30% of the total glucose change while A1C is an integrated measurement of fasting and postprandial blood glucose levels covering the rest of glycemic change during the previous 6–8 week period.[27] UKPDS has shown long-term lowering of A1C 1% reduces microvascular complications up to 37%.[28] Addition of MC could reduce A1C by 0.3% in our subjects over the placebo group. Furthermore, MC did not increase appetite. Recently, Fuangchan and colleagues in shorter study found that intake of 2 g/day of dried-fruit pulp Thai MC (contained 0.8–1 mg/day of charantin and grown at Phitsanulok, Thailand) could also cause a significant reduction from baseline of fructosamine (−10.2 μmol/L; 95% CI, −19.1, −1.3 μmol/L) whereas 0.5–1 mg/day of Thai MC had no benefit.[2] It is notable that 2 g of Thai MC may be a minimum effective dose. The present work evaluated glucose lowering effect of Thai MC with the higher dose and covered longer study period (16 weeks). The results demonstrated a tendency of long term glycemic control of this herb. Although some previous studies on other cultivars of MC found that MC had no anti-hyperglycemic effect,[6–8] this study and Fuangchan's work showed the potential for glycemic control of Thai MC dried-fruit pulp. It is possible that even at the nearly equal weight of dried powder, the quantity of active ingredients of MC, e.g. charantin, is due to the variation of cultivar and planted area, leading to the difference in their hypoglycemic effect.

Previous data indicated that renal structures e.g. basement membranes, mesangial cell, endothelial cell and tubules of patients with diabetic nephropathy are susceptible to accumulation of AGEs. This is not the case with normal kidney.[29] Moreover, AGEs have been localized in retinal blood vessels in T2DM patients, and are also correlated with the degree of retinopathy.[13,18] The present work was the first human study

Table 3 – Laboratory and physical assessments of placebo and MC groups.

Parameter	Baseline	Δ at week 8	Δ at week 16	P within group[a]	P between groups[b]	
					At 8 weeks	At 16 weeks
A1C (%)						
Placebo group	7.32 ± 0.70	−0.02 ± 0.43	−0.20 ± 0.45	0.153		
MC group	7.47 ± 1.03	−0.27 ± 0.30	−0.50 ± 0.45	0.001	0.042	0.044
FPG (mg/dL)						
Placebo group	118.37 ± 16.36	−2.84 ± 10.78	−3.79 ± 17.77	0.904		
MC group	117.63 ± 32.14	−7.11 ± 13.92	−11.16 ± 17.05	0.231	0.148	0.156
AGEs/TP ($\times 10^3$ AU/g protein)						
Placebo group	93.99 ± 17.67	5.41 ± 18.51	2.53 ± 12.20	0.434		
MC group	85.50 ± 16.21	−3.49 ± 7.94	−5.69 ± 9.72	0.103	0.066	0.028
UACR (mg/g creatinine)						
Placebo group	30.21 ± 87.04	−6.62 ± 19.04	−6.76 ± 30.27	0.778		
MC group	36.61 ± 103.88	−8.29 ± 24.83	−15.03 ± 59.03	0.629	0.827	0.474
AST (U/L)						
Placebo group	19.58 ± 6.59	1.74 ± 8.00	2.68 ± 5.95	0.506		
MC group	24.74 ± 12.41	−0.42 ± 11.53	−3.68 ± 13.74	0.091	0.507	0.072
ALT (U/L)						
Placebo group	38.00 ± 11.34	−1.63 ± 8.25	1.00 ± 6.38	0.156		
MC group	39.00 ± 21.39	−2.32 ± 16.22	−2.37 ± 21.00	0.980	0.871	0.508
Cr (mg/dL)						
Placebo group	0.95 ± 0.20	0.00 ± 0.09	−0.01 ± 0.09	0.574		
MC group	0.84 ± 0.16	−0.01 ± 0.06	−0.02 ± 0.07	0.587	0.486	0.584
Body weight (kg)						
Placebo group	68.91 ± 16.50	−0.02 ± 0.46	−0.18 ± 0.42	0.225		
MC group	63.21 ± 12.94	−0.07 ± 0.30	−0.11 ± 0.21	0.602	0.708	0.472
BMI (kg/m^2)						
Placebo group	26.37 ± 6.04	−0.01 ± 0.18	−0.07 ± 0.17	0.249		
MC group	25.04 ± 3.69	−0.03 ± 0.13	−0.04 ± 0.08	0.708	0.691	0.486
SBP (mmHg)						
Placebo group	125.74 ± 12.32	−1.03 ± 6.29	−0.76 ± 2.39	0.331		
MC group	125.87 ± 13.87	−0.21 ± 4.71	1.03 ± 5.87	0.064	0.182	0.428
DBP (mmHg)						
Placebo group	75.45 ± 7.88	−0.89 ± 4.94	−1.21 ± 3.00	0.359		
MC group	76.08 ± 8.43	−0.24 ± 4.67	−0.74 ± 2.46	0.816	0.704	0.568

Data expressed as mean ± SD.
The change values of A1C and AGEs/TP showed significantly different for time or treatment effects (two factor RM-ANOVA) at $P < 0.05$.
[a] $P < 0.05$ indicated significantly different of change values between MC and placebo groups at the same period of time (Independent *t*-test or Mann–Whitney test).
[b] $P < 0.05$ indicated significantly different of change values after 8 weeks and 16 weeks of treatment in each group (Paired *t*-test or Wilcoxon Signed Rank test).

to demonstrate the beneficial effect of this herb on irreversible glycation product, serum AGEs. Hence, it is possible that Thai MC would have beneficial effect on potential systemic complications of T2DM.

To reduce the risk or to slow down the progression of diabetic nephropathy, appropriate glycemic control is recommended. The present work is the pilot study to address the beneficial effect of this herb on early microvascular complication of diabetes, nephropathy. Although there was not the statistically significant difference of UACR reduction between MC and placebo group, the positive trend was shown. The sample size and study period might be not enough to see the significant effect. Larger sample size with longer period of study is necessary to confirm the result on this issue.

Table 4 – Frequency of adverse events.

Events	Placebo (N = 19)	MC (N = 19)	P-value[a]
Diarrhea, N (%)	0 (0.0)	5 (26.3)	0.046
Flatulence, N (%)	2 (10.5)	8 (42.1)	0.027

Data expressed as number of patients (%).
[a] $P < 0.05$ indicated significantly different between MC and placebo groups (Pearson's Chi-square or Fisher's Exact test).

A daily dose of 6 g of MC was well tolerated and conformed to previous reports that diarrhea and flatulence were common side effects.[2,30] These symptoms were mild and transient. Levels of AST, ALT and Cr in T2DM patients with normal liver and kidney functions showed no alteration in their functions throughout the treatment period. These results suggested that MC was safe within the 16 weeks of this study. However, taking this herb in patient with liver/kidney disease or abnormal liver/kidney function was not recommended.

In conclusion, the current pilot study presented preliminary clinical evidence that MC is beneficial on the

glycemic control and potential systemic complications of T2DM. However, a larger clinical trial to confirm the results of this pilot study is required.

Conflicts of interest

All authors have none to declare.

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