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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