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# การศึกษาย้อนหลังการใช้มะระขี้นกในผู้ป่วยเบาหวานในโรงพยาบาลสมเด็จพระยุพราชด่านซ้าย จ.เลย ประเทศไทย

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# Retrospective study on the use of bitter melon for type 2 diabetes at Dansai Crown Prince Hospital, Thailand

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**หลักการและวัตถุประสงค์:** มะระขี้นกเป็นพืชสมุนไพรชนิดหนึ่งที่มีสรรพคุณในการลดระดับน้ำตาลในเลือด แต่ปัจจุบันงานวิจัยที่ศึกษาประสิทธิภาพของการใช้มะระขี้นกในผู้ป่วยเบาหวานมีจำนวนน้อย การศึกษานี้มีวัตถุประสงค์เพื่อประเมินความสามารถลดระดับน้ำตาลในเลือดและผลข้างเคียงของการใช้มะระขี้นกในผู้ป่วยเบาหวานของโรงพยาบาลสมเด็จพระยุพราชด่านซ้าย จังหวัดเลย

**วิธีการศึกษา:** ผู้ทำการศึกษาได้เก็บข้อมูลการใช้มะระขี้นกย้อนหลังจากเวชระเบียนและฐานข้อมูลของผู้ป่วยเบาหวานทั้งหมด เริ่มตั้งแต่เดือนมกราคม ปี พ.ศ. 2544 ถึงกุมภาพันธ์ ปี พ.ศ. 2551 ประกอบด้วยข้อมูลของระดับน้ำตาลในเลือด ผลตรวจทางห้องปฏิบัติการ และผลข้างเคียงต่างๆ ที่ถูกบันทึกไว้ระหว่างการใช้มะระขี้นก

**ผลการศึกษา:** ผู้ป่วยเบาหวานที่ไม่สามารถควบคุมระดับน้ำตาลได้โดยมีระดับน้ำตาลในเลือดสูงน้อยถึงปานกลาง (187.8±47.0 มิลิกรัม/เดซิลิตร) จำนวน 82 คน มีประวัติได้รับมะระขี้นกขนาด 800-1,600 มิลลิกรัมต่อวัน ร่วมกับยาเบาหวานเดิม อาการข้างเคียงที่พบระหว่างการใช้มะระขี้นกมีน้อย ที่พบได้มากที่สุด คือ ภาวะน้ำตาลในเลือดต่ำ ส่วนการประเมินความสามารถลดระดับน้ำตาลในเลือดของมะระขี้นก

**Background and Objective:** Bitter melon (*Momordica charantia*) has been widely used as an herbal medicine for lowering blood glucose levels. To date, there have been very few clinical studies to determine the efficacy of bitter melon in diabetes patients. This study was conducted to describe the use of bitter melon in diabetes patient by evaluating the hypoglycemic effect and adverse events at Dansai Crown Prince Hospital, Thailand.

**Methods:** This retrospective study reviewed medical records and database of type 2 diabetes patients receiving bitter melon from January, 1999 to February, 2008. Fasting plasma glucose levels, laboratory data and adverse events were extracted from existing records.

**Results:** Bitter melon 800-1,600 mg/day was added to the treatment regimens of 82 diabetic patients with mildly to moderately uncontrolled blood glucose levels (187.8±47.0 mg/dL). Adverse events were found in few cases. The most common adverse event was hypoglycemia. The blood glucose lowering effect of bitter melon was assessable in 42 patients. After adding bitter melon to the current regimens of the patients (sulfonylureas ± metformin) for at least 14 days, fasting plasma glucose was reduced by

จะพิจารณาในผู้ป่วยจำนวน 42 คน ที่ขณะใช้มะระขี้นกไม่มีการเปลี่ยนแปลงยาเบาหวานเดิม (ยากลุ่มซัลโฟนิลยูเรียและ/หรือเมทฟอร์มิน) พบว่า หลังจากใช้มะระขี้นกร่วมกับยาเบาหวานเดิมเป็นเวลาอย่างน้อย 14 วัน ระดับน้ำตาลในเลือดก่อนอาหารมีค่าลดลง 26.9±40.8 มิลลิกรัมต่อเดซิลิตร ($p<0.001$) โดยมีผู้ป่วยที่มีระดับน้ำตาลในเลือดก่อนอาหารอยู่ในเกณฑ์เป้าหมาย (≤130 มิลลิกรัมต่อเดซิลิตร) 19 คน (ร้อยละ 45.2)

**สรุป:** ข้อมูลจากการทบทวนการใช้มะระขี้นกในผู้ป่วยเบาหวานย้อนหลังเป็นเวลา 8 ปี แสดงให้เห็นว่า มะระขี้นกอาจเป็นสมุนไพรทางเลือกที่อาจนำมาใช้ร่วมกับยาเบาหวานแผนปัจจุบันในผู้ป่วยเบาหวานที่ไม่สามารถควบคุมได้โดยมีระดับน้ำตาลในเลือดสูงระดับน้อยถึงปานกลาง

**คำสำคัญ:** มะระขี้นก, ระดับน้ำตาลในเลือด, เบาหวาน, ยาลดน้ำตาลในเลือด

26.9±40.8 mg/dL ($p<0.001$). Atter the addition of bitter melon, 19 patients (45.2%) achieved target therapeutic range of FPG levels.

**Conclusion:** The retrospective study for the 8 year usage of bitter melon at Dansai Crown Prince Hospital suggested that bitter melon may be a useful adjunctive treatment to decrease blood glucose levels in patients with mildly to moderately uncontrolled diabetes.

**Key words:** *Momordica charantia*, bitter melon, hypoglycemic effect, diabetes mellitus

ศรีนครินทร์เวชสาร 2552; 24(4): 332-8 • Srinagarind Med J 2009; 24(4): 332-8

## Introduction

Bitter melon (*Momordica charantia*) is a member of Curcurbitaceae family. This plant grows in Thailand and tropical area including Asia, Africa, and South America. It has been widely used as herbal medicine for lowering blood glucose levels[1, 2]. Fruits of bitter melon have been reported to exhibit hypoglycemic effect in normal and diabetic animals[3-6]. The hypoglycemic activity of bitter melon are proposed to act via both pancreatic and non-pancreatic mechanisms including increased insulin secretion,[7] increased glucose uptake in tissues[8] as well as improving liver and muscle glycogen storage[8]. Moreover, the plant has been found to improved the activity of some key enzymes in glycolytic pathway[9] and to regenerate or recover injuried beta-cells[10]. These mechanisms might augment the effects of other hypoglycemic drugs.

Dansai Crown Prince Hospital is located in the north-eastern part of Thailand. This community-based hospital routinely cares for 1,532 patients with diabetes. In its practice, bitter melon had been used as an adjunct to other antidiabetic treatments for 8 years. The retrospective study of the use of bitter melon in this hospital will give additional insights regarding the information of clinical use, hypoglycemic effect and adverse events related to this herbal medicine.

## Methods

Data was collected at Diabetes Clinic, Dansai Crown Prince Hospital, Leuy Province, Thailand. We retrospectively reviewed all cases of patients with diabetes who received bitter melon during the period starting January 1999 through February 2008. The study protocol was approved by Naresuan University Ethics Committee (48 01 04 0012)

Each medical records and computerized pharmacy records were reviewed before and after the first oral bitter melon prescription was filled through discontinuation. Demographic data, blood sugar levels before and after using bitter melon, other laboratory values, dosage regimen of bitter melon prescribing, hypoglycemic drugs and other drug used, and co-morbid diseases were collected. Adherence to the prescribed regimens were evaluated indirectly from the patient's medical records. If there was a note, "took all medications perfectly," or no record of poor compliance such as "had left over medications" or "did not take medications as ordered," the patients were assumed to exhibit good drug adherence. Safety of the herb was determined by reviewing

all reported adverse events in the medical record during the time bitter melon were prescribed.

To evaluate the hypoglycemic activity of bitter melon, we included patients who were maintained on the same dosage regimens of hypoglycemic drugs before and right after the addition of bitter melon, and had no documented problems with drug adherence. A hypoglycemic drug change was defined as (1) a change in dosage of any hypoglycemic drugs, (2) a change of hypoglycemic agent, or (3) an addition of at least one hypoglycemic agent to the existing regimen. Patients who received or took bitter melon for less than 14 days were excluded.

Bitter melon fruit dried powder was ordered from an herbal company. Identification, purification, contamination tests were the responsibility of that company. Filling bitter melon fruit powder to capsules was under supervision of a Dansai Crown Prince Hospital's pharmacist. Each capsule contains 400 mg of bitter melon fruit dried powder.

## Statistical analysis

Nominal and categorical data were described by frequencies and percentages, whereas continuous data were presented as mean ± SD or median (Interquartile (IQ) range). Normal distribution was tested by histogram and normality test. Paired t-test was used to determine the difference between FPG levels before and after receiving bitter melon. A P value of less than 0.05 was considered statistically significant.

## Results

### Patients' Characteristics

Eighty-two patients were included in this study. The mean age was 50.9±12.1 years (range, 27-77 years). Seventy-nine percents (n=65) were female. Fifty-four patients (66%) had no documented co-morbid disease. The mean duration of diabetes mellitus diagnosed prior to the use of bitter melon was 5.5±3.6 years (range 2 months-14 years). All patients were on at least one oral hypoglycemic drug. The mean FPG level before starting bitter melon was 187.8±47.0 mg/dL. (Table 1)

Table 1 Summary of patients' characteristics (n=82)

| Characteristics | |
|---|---|
| Age, years (mean±SD) | 50.9±12.1 |
| Sex (cases) | |
| Male | 17 (20.70%) |
| Female | 65 (79.30%) |
| Weight (kg) (mean±SD) | 56.0±9.4 |
| Body mass index (kg/m$^2$) (mean±SD) | 23.0±3.1 |
| Co-morbid disease(s) (cases) | |
| No | 54 (65.9%) |
| Yes | 28 (31.4%) |
| Hypertension | 15 (53.6%) |
| Dyslipidemia | 15 (53.6%) |
| Ischemic heart disease | 1 (3.6%) |
| Renal failure | 1 (3.6%) |
| Others | 8 (28.6%) |
| Duration of diabetes diagnosed (years) (mean±SD) | 5.5±3.6 |
| History of hypoglycemic drugs before taking bitter melon (cases)* | |
| Glibenclamide | 8 (97.6%) |
| Glipizide | 4 (4.9%) |
| Metformin | 2 (2.4%) |
| Glibenclamide+Metformin | 62 (75.6%) |
| Glipizide+Metformin | 4 (4.9%) |
| FPG level before taking bitter melon (mean±SD) (N=78) | 187.8±47.0 |

* Two pateints'medication records before taking bitter melon were lost.

### Dosage form and administration of bitter melon

Dried fruit of bitter melon was prepared in capsule formulation. Each capsule contained 400 mg of the dried powder of bitter melon fruit. Bitter melon was prescribed by one physician. Fifty-eight percent of the patients began bitter melon at the dose of 1,600 mg/day in combination with one or more oral hypoglycemic drug(s); glibenclamide, glipizide, or metformin. All other patients (42%) started bitter melon at 800 mg/day. Six patients took bitter melon as monotherapy. The most common combination regimen (n=35, 43%) was bitter melon 1,600 mg/day with maximal dose of metformin and glibenclamide. All patients were asked to take bitter melon capsules before meals twice daily (breakfast and dinner) (Table 2).

Table 2 Regimen of bitter melon at beginning (n = 82)

| Regimen | Number of patients (%) | |
|---|---|---|
| | Dose of bitter melon | |
| | 800 mg/day | 1,600 mg/day |
| Bitter melon only | 4 (4.9%) | 2 (2.4%) |
| Bitter melon + Metformin (1,000-3,000 mg/day) | 2 (2.4%) | 1 (1.2%) |
| Bitter melon + Glipizide (5-20 mg/day) | 3 (3.7%) | - |
| Bitter melon + Glibenclamide (20 mg/day) | 3 (3.7%) | 3 (3.7%) |
| Bitter melon + Glipizide (20 mg/day) + Metformin (1,000-3,000 mg/day) | 1 (1.2%) | 2 (2.4%) |
| Bitter melon + Glibenclamide (10-20 mg/day) + Metformin (500-3,000 mg/day) | 21 (25.6%) | 40 (48.8%) |
| Total | 34 (41.5%) | 48 (58.5%) |

## Glycemic control

The hypoglycemic effect of bitter melon fruit was evaluated in 42 patients, who had the same oral hypoglycemic drug regimens before and after adding bitter melon, took bitter melon for at least 14 days, and had no record of non-adherence problems (Fig 1). The average baseline FPG level among these patients was 173.0±27.7 mg/dL. Median duration from baseline measurement at time starting bitter melon until next visit was 35 days (IQ range 28-66 days). The total mean reduction in FPG levels after adding bitter melon was 26.9±40.8 mg/dL ($p<0.001$). The mean reduction of FPG levels was 29.9±39.8 mg/dL in group of patients who were on 1,600 mg/day, and 20.9±43.8 mg/dL among these who received 800 mg/day. (Table 3) Nineteen patients (45.2%) had their FPG levels reduced to meet the target therapeutic level (i.e., less than 130 mg/dL). Median duration of bitter melon use among this group was 189.5 days (IQ range 70-443 days). For patients who were on the maximum doses of metformin and glibenclamide (n=27), mean reduction of FPG level after adding bitter melon was 31.9±42.6 mg/dL ($p<0.001$). Median duration of bitter melon use among these patients was 173 days (IQ range 63-364 days).

## Discontinuation of bitter melon

Among 82 patients, 75 discontinued bitter melon during our data collection period. Median duration of bitter melon use was 156 days (IQ range 77-315 days). Reasons for discontinuation were poor glycemic control (n=42, 56.0%), adverse events (n=21, 28.0%), and lost to follow up (n=12, 16.0%). After discontinuation of bitter melon, 37 patients had their oral hypoglycemic drug regimen adjusted; one patient was switched to pioglitazone after experiencing rash and itching while taking glibenclamide, metformin, and bitter melon; 34 patients received insulin in addition to oral

Table 3 Fasting plasma glucose levels before and after adding bitter melon capsules without changing originally hypoglycemic drug regimens (n=42)

| Data | Mean fasting plasma glucose levels (mg/dL) | | |
|---|---|---|---|
| | Before adding bitter melon | After adding bitter melon | Absolute change |
| Bitter melon 800 mg/day plus | | | |
| Glibenclamide+Metformin (n=9) | 167.1±37.4 | 141.2±38.9 | -22.2±53.1 |
| Others[#] (n=4) | 175.0±52.4 | 144.2±19.4 | -18.0±12.0 |
| Total | 163.1±25.6 | 142.2±33.2 | -20.9±43.8 |
| Bitter melon 1,600 mg/day plus | | | |
| Glibenclamide+Metformin (n=24) | 155.5±33.0 | 141.8±36.3 | -33.1±38.5 |
| Others[#] (n=5) | 152.6±39.9 | 166.8±38.9 | -13.6±46.1 |
| Total | 178.7±26.7 | 149.1±34.3 | -29.6±39.8 |
| Total | 181.0±38.0 | 145.6±34.0 | -26.9±40.8* |

[#] Bitter melon combined with metformin only, glibenclamide only, glipizide only, or glipizide + metformin.

* $p < 0.001$

Table 4 Hypoglycemic regimen after patients discontinued bitter melon

| | Bitter melon (n=75) | | Total |
|---|---|---|---|
| | 800 mg/day | 1,600 mg/day | |
| Dose of sulfonylurea or metformin changed | 16 (21.3%) | 21 (28.0%) | 37 (49.3%) |
| Switched to pioglitazone | - | 1 (1.3%) | 1 (1.3%) |
| Insulin added to oral hypoglycemic drugs | 9 (12.0%) | 25 (33.3%) | 34 (45.3%) |
| Switched to insulin | 1 (1.3%) | 2 (2.7%) | 3 (4.0%) |

Table 5 Number of patients with adverse events leading to stop taking bitter melon combined with oral hypoglycemic drugs.

| | Bitter melon (n=82) | | |
|---|---|---|---|
| Adverse event | 800 mg/day (n=34) | 1,600 mg/day (n=48) | Total |
| Headache | - | 1 | 1(1.2%) |
| Insomnia | - | 1 | 1(1.2%) |
| Muscle pain | 1 | 1 | 2(2.4%) |
| Nausea | 1 | 3 | 4 (4.8%) |
| Vomiting | 2 | 3 | 5 (6.1%) |
| Anorexia | - | 1 | 1(1.2%) |
| Abdominal pain | 1 | - | 1(1.2%) |
| Diarrhea | - | 1 | 1(1.2%) |
| Flatulance | - | 2 | 2 (2.4%) |
| Hypoglycemia | 4 | 7 | 11 (13.4%) |
| Rash | - | 1 | 1(1.2%) |
| Itching | - | 1 | 1(1.2%) |

hypoglycemic drugs; and three patients were switched to insulin therapy only. (Table 4)

During our data collection period, patients were found to be periodically on and off bitter melon—14 patients (2 times), 3 patients (3 times), 1 patient (4 times), and 1 patient (5 times). Two of them experienced good glycemic control, 7 patients had slightly blood glucose decrease, and 5 patients had no response during first time of bitter melon usage. Reason to restart taking bitter melon were hyperglycemia or patients refusing insulin therapy. However, the repetitive use of bitter melon did not bring their blood glucose levels down into target therapeutic range.

### Adverse events

Hypoglycemia was the most frequent adverse event leading to the discontinuation of bitter melon (13.4%, n=11). One patient was reported to have severe hypoglycemia that requiring hospitalization. FPG level and hypoglycemic symptoms were improved after bitter melon and oral hypoglycemic drugs were temporarily discontinued. The percentage of patients experiencing hypoglycemic events among patients who took bitter melon 1,600 mg/day was 8.5 (n=7) and 4.9 (n=4) among patients taking bitter melon 800 mg/day. (Table 5) Other adverse events causing patients to stop taking bitter melon were nausea (n=4), vomiting (n=5), anorexia (n=1), abdominal pain (n=1), flatulance (n=2), diarrhea (n=1), rash (n=1), itching (n=1), muscle pain (n=2), insomnia (n=1) and headache (n=1). During bitter melon using, serum creatinine and levels of alanine aminotranferease (ALT) and aspartate aminotransferase (AST) were measured at least once in 43 and 19 patients, respectively. There was no case report of abnormal renal function and liver enzymes.

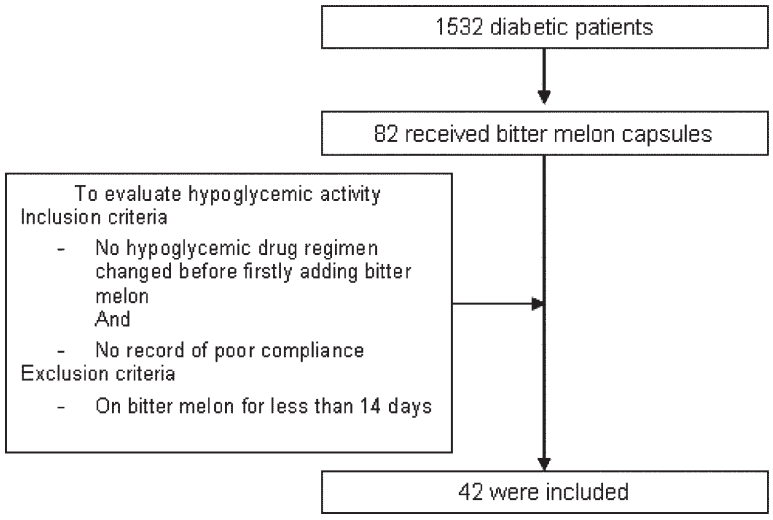


**Fig 1** Flow of glycemic control evaluation

## Discussions

This study demonstrated reduction in FPG levels among patients with type 2 diabetes who received bitter melon as an adjunctive therapy with dietary changes and other antidiabetic medications. Dried powder from the fruits of bitter melon was used alone or in combination with sulfonylureas and/or metformin among patients with mildly to moderately uncontrolled diabetes. We found the mean reduction of FPG levels by 26.7±40.8 mg/dL, which is in agreement with the study of Srivastava and colleagues which demonstrated the reduction of FPG levels by 11 - 48 mg/dL[11]. In contrast, a 4-week randomized, placebo-controlled trial involving 40 patients with type 2 diabetes mellitus failed to show any benefit when bitter melon 6 g/day was added to other oral hypoglycemic drugs[12]. However, the authors suggested that insignificant change in blood sugar levels may due to the dose of bitter melon or related to the process of preparing bitter melon tablets. For another preparation, bitter melon extract (Charantia®) capsules were given to diabetes patients with suboptimal glycemic control by oral hypoglycemic drugs or diet therapy, the results also showed the insignificant difference in percentages of $HbA_{1C}$ and fasting plasma glucose levels when compared with placebo, but this study had less power than the author's expectation[13].

The doses of bitter melon in our report differed from those in previous studies. In our study, doses of bitter melon 800 to 1,600 mg were taken daily, whereas very high doses (6 g/day and 15 g/day) were used in other studies[11, 12]. This different results may be explained by variations in traditional use, planting area, and preparation technique. Thus, standardization of bitter melon preparations is required before the future, prospective studies are conducted.

Even those patients who were on the maximum doses of metformin and glibenclamide experienced a significant reduction in their FPG levels after the addition of bitter melon, bitter melon was continued between two months to one year in the majority of patients, which would imply that patients and the prescribing physician were satisfied with the response. In Thailand, sulfonylureas and metformin are the most common prescribed combination of oral hyperglycemic drugs before adding or switching to insulin[14]. The present study suggested that bitter melon could delay the initiation of insulin therapy in some patients who do not respond adequately to sulfonylureas and metformin. Newer oral hypoglycemic agents such as alpha-glucosidase inhibitors, thiazolidinediones, and miglitinides, are relatively expensive and using such agents would not be affordable in the Thai healthcare system. For this reason, bitter melon could be a reasonable alternative.

However, most of patients had been stopped bitter melon after using it for a period because of uncontrolled blood glucose levels. This might due to patients had progression of diabetes in some patients and of bitter melon's weak hypoglycemic effect which was not enough to controlled blood glucose.

The data demonstrates that bitter melon was reasonably safe. Similar to other antidiabetic medications, hypoglycemia was the most common adverse effect. There was no other serious adverse event reported during our study period.

This study has several limitations. Given the retrospective nature of the data collection, efficacy and safety data was not documented in a systematic way and was not available in all cases. Unfortunately, $HbA_{1C}$, a standard glycemic monitoring to reflect average blood sugar levels over several months, was assessed in very few patients. It is unknown about the impact of dietary changes were on each patient's glycemic control due to a lack of a routine dietary assessment. Finally, there was no control group. Therefore, it is not possible to conclude that observed changes in glycemic control are due to bitter melon only.

## Conclusion

The retrospective study regarding the 8 year usage of bitter melon at Dansai Crown Prince Hospital suggested that bitter melon may be a useful adjunctive treatment for patients with mildly to moderately uncontrolled diabetes. However, prospective double-blind, placebo or active-controlled trials with long-term follow-up and using a standardized dosage formulation are needed before the routine use of bitter melon can be advocated.

### Acknowledgement

This work was financially supported by Naresuan University. We are grateful to thank Dr. Pakdee Seubnukarn, Director of Dansai Crown Prince Hospital, for offering the convenience in data collection.

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