Glucose-Lowering Efficacy of Water Extract of *Malvastrum coromandelianum* in Type 2 Diabetes Subjects: A Double Blind, Randomized Controlled Trial

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Background: *Water extract from Malvastrum coromandelianum (Linn.) Garcke (MC) has been shown to have glucose lowering effect, short- and long-term safety in animal studies. A preliminary study in human reveals safety and its potential use as an adjunctive treatment to antihyperglycemic medications.*
Objective: *To investigate the glycemic-lowering efficacy of MC in type 2 diabetes subjects.*
Material and Method: *A multicenter randomized, double-blind, placebo-controlled trial was conducted. Seventy-one diabetes subjects, who were treated with either diet control or single oral anti-diabetic drug (sulphonylurea or biguanide) with HbA1C between 6.5-9%, were recruited. Subjects were randomized to take MC tablets in a total dose of 1,200 mg/day or placebo for 12 weeks. Clinical parameters, glycemic control, HOMA-IR and HOMA-β were assessed.*
Results: *Both MC (n = 34) and placebo (n = 37) groups had comparable baseline characteristics with a mean baseline HbA1C of 7.6±0.82 vs. 7.5±0.8%, respectively. During the study, HbA1C did not differ statistically after 4, 8 and 12 weeks of treatment (7.7±0.97 vs. 7.6±1.0, 7.9±1.09 vs. 7.8±1.03 and 7.8±1.1 vs. 7.6±1.1%, respectively). The body weight, insulin resistance and insulin secretion were also similar between groups (p>0.05). No episode of hypoglycemia was reported.*
Conclusion: *MC in a dosage of 1,200 mg/day does not have glucose lowering efficacy in type 2 diabetes.*

Keywords: *Type 2 diabetes, Malvastrum coromandelianum, Water extract, HbA1C*

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Malvastrum coromandelianum (Linn.) Garcke (MC) is an annual crop in the *Malvaceae* family. Its common names are False Mallow, Broom weed, Clock plant and Prickly malvastrum. In Thailand, MC is called Ya-Tevada, Ya-kradumtong and Daikhad. Water extract of its leaves composed of alkaloids, tannins, amino acid proteins and carbohydrate, while petroleum ether extract finds β-sitosterol[1]. MC has anti-inflammatory, anti-dysenteric, analgesic[2], wound healing property and anti-antibacterial activity against *Staphylococcus aureus*[3,4]. Moreover, MC has been anecdotal used as an antihyperglycemic agent in Thailand and Mexico[5]. Previous studies in diabetogenic rats and rabbits revealed its glycemic-lowering property equivalents to insulin injection and chlorpropamide[6,7]. Acute and chronic toxicity in animal study ensure the MC safety up to 400 times of therapeutic dosage[8,9].

Phase 1 study in human does not find acute toxicity of MC water extract in form of dried powder 1,000 mg/day[9]. A single-arm, small study in type 2 diabetes subjects reveals a significant decrement of

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mean fasting plasma glucose at 2nd to 8th week after MC ingestion. In contrast, there is no significant reduction of HbA1c at the 3rd month of treatment[9]. The present study aimed to evaluate glycemic-lowering efficacy of MC in type 2 diabetes subjects, who were currently treated with life style modification alone or with antihyperglycemic drug monotherapy.

Material and Method

A double blind, randomized, placebo controlled trial was conducted in Thammasat University Hospital, Khlong Laung Hospital, Nong Suea Hospital, Bang Rachan Hospital, Singburi General Hospital, Chandrakasem Clinic, Government Pharmaceutical Organization Clinic and Provincial Waterworks Authority Clinic. To attain 80 percent power to detect 1 percent of HbA1c difference between two groups plus 20 percent dropout, we had to include at least 35 subjects in each arm. This study consisted of a 1-month life style modification run-in period and a 12-week double blind treatment. The inclusion criteria were type 2 diabetes subjects aged more than 18-years-old, had been treated with either diet control or single oral anti-diabetic drug (sulphonylurea or metformin), fasting plasma glucose less than 250 mg/dl and HbA1c level of 6.5-9% after run-in period. Current antihyperglycemic agents were continued throughout the study. Subjects with pregnancy, overt nephropathy, chronic kidney disease, history of cardiovascular diseases within 6 months prior enrollment, chronic liver disease, malignancy, poor controlled hypertension (blood pressure >180/110 mmHg), receiving other herbal remedies or medication that interfere with glycemic control e.g. steroid, atypical antipsychotic drugs, nicotinic acid, megastrol acetate were excluded. Eligible subjects were randomly assigned to receive 1,200 mg/day of MC (300 mg/tablet; 2 tablets twice a day before meal) or placebo. Randomization to treatment groups was in 1:1 ratio stratified by body mass index (18-24.9 and 25-35 kg/m^2), using random permuted blocks of four. Both care providers and subjects were blinded to the treatment allocation. Clinical data, glycemic control and safety information were collected at 2nd, 4th, 8th and 12th weeks after randomization. The authors also measured insulin level before and at the end of the study by solid-phase, enzyme-labeled chemi-luminescent-immunometric assay (IMMULITE/IMMULITE 1000®). Insulin resistance and beta cell function were evaluated by HOMA-IR and HOMA-β. During the study, subjects would be withdrawn if they had fasting plasma glucose more than 300 mg/dl and HbA1c >10%, encountered hyperglycemic episode, lost to follow-up, compliance was less than 80% or more than 120% or had MC intolerance. Current antihyperglycemic medication would be adjusted if subjects had hypoglycemia (glucose less than 70 mg/dl) or hyperglycemia (plasma glucose more than 250 mg/dl). Our primary outcome was glycemic control assessed by fasting plasma glucose and HbA1c. The secondary outcome was the body weight change, number of hypoglycemic episodes, HOMA-IR and HOMA-β[10]. All biochemical results were obtained from the central laboratory.

MC extract preparation

Dried leaf, stem and root of MC were ground and boiled in water. Water extract of MC was dried by evaporator and dried to be powdered with spray dry instrument which used the inlet temperature 160°C and exhaust temperature 90°C. Spray-dried MC yield 8-18%. Hydroxypropylmethyl-cellulose (HPMC) was used to make 300 mg film-coated tablets. The stability of tablet was tested by high performance liquid chromatography (HPLC) fingerprint (HPLC Agilent LC 1200®) at day 0 and one year after manufacture. The MC extract did not change chromatogram. Microbial limit test was assured by development unit, Government Pharmaceutical Organization (GPO). Placebo composed of Tapioca starch, talcum, Di Calcium phosphate, Mg sterate and Povidone K30. Both study drugs had the same features. This clinical trial has been approved by Human Research Ethics Committee of Thammasat University No.1 (Faculty of Medicine) (MTU-E-1-12/52). All subjects provided written informed consent.

Statistical analysis

The authors analyzed data with SPSS program (SPSS Inc. Chicago, USA version 11.5). Data were expressed in mean $\pm$ SD for categorical variables, and number with percentage for continuous variables. Mean difference and proportion difference of outcomes between 2 groups were analyzed with unpaired Student t-test and Chi-square test respectively. Non-normal distribution data was analyzed with Mann Whitney U test. Analysis of covariance (ANCOVA) was used to compare the mean of primary and secondary outcomes between two groups, adjusted for baseline glycemic control, sex, and body mass index.The statistical significance of analyses were $p<0.05$.

Results

One hundred and eighty-four subjects were

screened. There were 71 subjects eligible for the study (n = 37 in MC and 34 in placebo group). Baseline characteristics were similar (Table 1) except more female in placebo group than in MC group (68% and 38% respectively). The mean age was 53 years old (minimum-maximum: 39-73 years old). Most of them were obese and have been recently diagnosed diabetes with the baseline mean HbA1c of 7.6±0.82% in MC group and 7.5±0.8% in placebo group (p = 0.573). Both groups had good compliance (97 vs. 94% in MC and placebo group, respectively). During the study, 7 subjects (2 in MC and 5 in placebo group) were withdrawn due to side effects (n = 4), poor compliance (n = 1) and loss to follow (n = 2). However, there were 32 subjects per group remained until the end of the study (Fig. 1).

During the study, both groups had similar glycemic control (Table 2). At 12 weeks, the mean fasting plasma glucose and HbA1c were 159±53 vs. 146±44 mg/dl (p = 0.475) and 7.8±1.1 vs. 7.6±1.1% (p = 0.934) in MC and placebo group, respectively. Eleven subjects in MC and 12 subjects from placebo group achieved HbA1c ≤7% at the end of the study (odd ratio = 0.95,

Table 1. Showed baseline characteristics of participants

Characters	MC (n = 34)	Placebo (n = 37)	*p*-value
Age (years)	53.5±7.98	53.8±5.49	0.848
Female sex (%)	13 (38)	23 (68)	0.044
Diabetes duration (months)	33±26	37±40	0.648
Body weight (kg)	72.6±14.5	68.8±11.7	0.234
Body mass index (kg/m^2)	27.61±0.8	27.4±0.5	0.813
Concomitant diseases:			
Hypertension (%)	21 (62)	22 (65)	0.84
Dyslipidemia (%)	22 (65)	26 (76)	0.62
Complications:			
Retinopathy	3	3	0.914
Peripheral neuropathy	3	4	0.779
Diabetes nephropathy	1	1	0.952
Stroke	0	1	0.334
Coronary artery disease	3	3	0.914
Antihyperglycemic medication:			
No antihyperglycemic medication	13	18	0.377
Biguanide	16	15	0.580
Sulfonylurea	5	4	0.622
Antihypertensive medication:			
Angiotensin converting enzyme (ACEI)	12	16	0.494
Angiotensin receptor blocker (ARB)	1	3	0.346
Beta-blocker	7	12	0.260
Diuretics	6	7	0.890
Statin	19	20	0.877
Aspirin	9	8	0.632
Laboratory results:			
Fasting plasma glucose (mg/dl)	152±30	148±27	0.690
A1c (%)	7.6±0.82	7.5±0.8	0.573
Cr (mg/dl)	0.93±0.2	0.82±0.3	0.072
Cholesterol (mg/dl)	203±35	195±42	0.399
Triglyceride (mg/dl)	171±140	157±94	0.617
High density lipoprotein (HDL) (mg/dl)	49±11	47±8.6	0.313
Low density lipoprotein (LDL) (mg/dl)	124±34	121±38	0.718

MC stands for *Malvastrum coromandelianum* (Linn.) Garcke.
Data were expressed in mean ± SD for categorical variables, and number with percentage for continuous variables.
p<0.05 defined a statistical significant.

95% CI 0.49-1.8, $p = 0.868$). There were 6 subjects (4 vs. 2 in MC and placebo group, respectively) received increasing dose of metformin up to 500 mg/day. Subgroup analysis revealed similar glycemic control regardless of types of oral antihyperglycemic agents ($p>0.05$), obesity status ($p = 0.12$) and diabetes duration ($p = 0.95$). HOMA-β and HOMA-IR was not different between groups.

There was no significant difference of blood pressure, lipid profiles and body weight between and within groups. Hypoglycemia did not occur. Adverse events have been reported in MC group which were transient nausea (n = 1) and eye pain suspected from glaucoma (n = 1). Three subjects in placebo group had transient elevation of liver enzymes (≥3 times of upper normal limit). The possible causes were concomitant herbal preparation (n = 1), Dengue fever (n = 1) and unknown cause (n = 1). All of them were withdrawn from this study. Of note, there was no significant hepatitis in MC group (Table 3).

Table 2. Showed glycemic control in *Malvastrum coromandelianum* (Linn.) Garcke compared with placebo group during 12 weeks of treatment

Glycemic control	MC (n = 34)	Placebo (n = 37)	*p*-value
Fasting plasma glucose (mg/dl)			
2nd week	157±34	149±32	0.253
4th week	152±32	148±34	0.596
8th week	146±25	146±30	0.995
12th week	159±53	146±44	0.475
HbA1c (%)			
4th week	7.7±0.97	7.6±1.0	0.507
8th week	7.9±1.09	7.8±1.03	0.882
12th week	7.8±1.1	7.6±1.1	0.934

MC stands for *Malvastrum coromandelianum* (Linn.) Garcke.
Analysis of covariance (ANCOVA) was used to compare the mean between two groups, adjusted for baseline glycemic control, sex, and body mass index.

Table 3. Showed number of adverse events in *Malvastrum coromandelianum* (Linn.) Garcke group compared with placebo group

Adverse events	MC	Placebo
Eye pain	1	0
Hepatitis	0	3
Lower urinary tract infection	0	1
Nausea	1	0

MC stands for *Malvastrumcoromandelianum* (Linn.) Garcke.

Discussion

The extract of MC possesses glucose lowering efficacy along with short term and long-term safety in animal studies[6-9]. A phase 1 and 2 clinical studies also revealed short term safety and its potential use as an adjunctive treatment to antihyperglycemic medications[9].

This double blind, randomized phase 2 clinical study conducted in type 2 diabetes subjects, who were inadequately controlled with life style modification and/or antihyperglycemic agent monotherapy (sulfonylurea or metformin). Subjects in MC and placebo group had comparable baseline characteristics except more female in the placebo group. Most subjects in the MC group had been receiving metformin while most of the placebo group did not receive any antihyperglycemic agents. However, glycemic control was similar between groups throughout the study. Subgroup analysis comparing different glucose control methods also revealed similar glycemic control, so drug interaction should not be the concern of this study. The assessment of insulin sensitivity and insulin secretion were not different between groups, thus mechanism of action of MC is still unknown. Body weight, blood pressure, lipid profiles and renal function were stable. This study confirmed the safety of the study drug in 12-week period. The ineffectiveness of MC for glucose-lowering might be the results of inadequate dosage, different effect between animal and human, or insulin resistance issue.

Conclusion

Malvastrum coromandelianum extract in a dosage of 1,200 mg/day does not have glucose lowering efficacy in type 2 diabetes. Trials in the future should be conducted in less obese type 2 diabetes subjects, given more dosage of MC or step back to study in insulin resistant animals. A trial in type 1 diabetes as an adjunctive treatment to insulin is also in attention.

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Potential conflicts of interest

None.

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ประสิทธิผลการลดน้ำตาลในเลือดของสมุนไพรดายขัดในผู้ป่วยโรคเบาหวานชนิดที่ 2: การศึกษาแบบสุ่มปกปิด

ทิพาพร ธาระวานิช, กัมมาล กุมาร ปาวา, ภูริทัต เมืองบุญ, พิชญ์วรา พันธุ์พิทย์แพทย์, สุธน พรธิสาร, วิโรจน์ ตั้งเจริญดี, อดิศว์ ทัศณรงค์, กาญจนพิมล ฤทธิเดช, สุกัญญา เจษฎานนท์

ภูมิหลัง: สารสกัดด้วยน้ำของสมุนไพรดายขัด (Malvastrum coromandelianum (Linn.) Garcke) มีประสิทธิภาพในการลดระดับน้ำตาลในเลือด มีความ ปลอดภัยในระยะสั้นและระยะยาวในสัตว์ทดลอง การศึกษาเบื้องต้นในคนพบว่าสมุนไพรชนิดนี้มีความปลอดภัยและอาจสามารถนำมาใช้ร่วมกับการรักษาแผนปัจจุบันเพื่อลดระดับน้ำตาลในเลือดในผู้ป่วยเบาหวานชนิดที่ 2

วัตถุประสงค์: เพื่อศึกษาประสิทธิผลของสมุนไพรดายขัดต่อการลดระดับน้ำตาลในเลือดของผู้ป่วยเบาหวานชนิดที่ 2

วัสดุและวิธีการ: การวิจัยแบบสุ่มไปข้างหน้าปกปิดสองทางในหลายสถาบัน การศึกษาทำในผู้ป่วยเบาหวานที่ควบคุมอาหาร โดยไม่ได้รับประทานยาเบาหวานหรือรับประทานยาเบาหวานชนิดเดี่ยวในกลุ่ม sulfonylurea หรือ biguanide และมีระดับน้ำตาลสะสมเอวันซีเท่ากับ 6.5-9% จำนวน 71 คน ผู้ป่วยได้รับการสุ่มให้รับประทานสมุนไพรดายขัดแบบเม็ดขนาด 1,200 มก./วัน หรือยาหลอกเป็นระยะเวลา 12 สัปดาห์มีการประเมินข้อมูลลักษณะทางคลินิก ระดับน้ำตาล HOMA-IR และ HOMA-β เป็นระยะ

ผลการศึกษา: ผู้ได้รับสารสกัดสมุนไพรดายขัดจำนวน 34 คนและยาหลอกจำนวน 37 คนมีลักษณะพื้นฐานไม่แตกต่างกัน ระดับน้ำตาลสะสมเอวันซีก่อนเริ่มให้สมุนไพร 7.6±0.82 และ 7.5±0.8% ในกลุ่มสารสกัดสมุนไพรดายขัดและยาหลอกตามลำดับหลังจากได้รับสารสกัดสมุนไพรพบว่าระดับน้ำตาลสะสมเอวันซีในระยะเวลา 4, 8 และ 12 สัปดาห์ของกลุ่มทั้งสองไม่ต่างกัน (7.7±0.97 vs 7.6±1.0, 7.9±1.09 vs 7.8±1.03 และ 7.8±1.1vs 7.6±1.1% ในกลุ่มสารสกัดสมุนไพรดายขัดและยาหลอกตามลำดับ) นอกจากนี้น้ำหนัก ความดื้อต่ออินซูลิน (ประเมินจาก HOMA-IR) และความสามารถในการหลั่งอินซูลิน (ประเมินจาก HOMA-β) ไม่มีความแตกต่างระหว่างกลุ่ม ($p>0.05$) ไม่พบภาวะน้ำตาลต่ำรุนแรงในทั้งสองกลุ่มการรักษา

สรุป: การศึกษานี้แสดงให้เห็นว่าสารสกัดสมุนไพรดายขัดในขนาด 1,200 มก./วัน ไม่มีประสิทธิภาพในการลดระดับน้ำตาลในผู้ป่วยเบาหวานชนิดที่ 2