การศึกษาผลลดน้ำตาลในเลือดแบบเฉียบพลันของมะระขี้นก (*Momordica charantia*) ผงแห้ง ฟรีซดราย ในกลุ่มที่มีภาวะทนต่อกลูโคสบกพร่อง

โดย

นางสาวศิริวดี บุญมโหตม์

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาเภสัชศาสตรมหาบัณฑิต

สาขาวิชาเภสัชกรรมคลินิก

บัณฑิตวิทยาลัย มหาวิทยาลัยศิลปากร

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ACUTE HYPOGLYCEMIC EFFECTS OF *MOMORDICA CHARANTIA* FREEZED DRIED POWDER IN IMPAIR GLUCOSE TOLERANCE CASES (IGT)

By

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บัณฑิตวิทยาลัย มหาวิทยาลัยศิลปากร อนุมัติให้วิทยานิพนธ์เรื่อง “การศึกษาผลลดน้ำตาลในเลือดแบบเฉียบพลันของมะระขี้นก(Momordica charantia) ผงแห้ง ฟรีซดราย ในกลุ่มที่มีภาวะทนต่อกลูโคสบกพร่อง” เสนอโดย นางสาวศิริวดี บุญมโหตม์ เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาเภสัชศาสตรมหาบัณฑิต สาขาวิชาเภสัชกรรมคลินิก

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คำสำคัญ: มะระขี้นก / ผลลดน้ำตาลในเลือด / ภาวะทนต่อกลูโคสบกพร่อง / ภาวะก่อนเบาหวาน

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วัตถุประสงค์: เพื่อเปรียบเทียบผลลดน้ำตาลในเลือดของผู้ที่มีภาวะทนต่อกลูโคสบกพร่อง เมื่อรับประทานมะระขี้นกผงแห้งฟรีซดราย ครั้งเดียว และยาหลอก

กลุ่มตัวอย่างและวิธีศึกษา: จากการคัดกรองพบผู้ที่มีภาวะก่อนเบาหวานซึ่งมีความทนต่อกลูโคสบกพร่องเมื่อวัดระดับน้ำตาลในเลือดด้วยวิธีอดอาหาร (IFG; FPG 100-125 มก/ดล) จำนวน 30 คน ถูกคัดเลือกเข้าสู่การศึกษา ในจำนวนนี้ พบว่า เป็นผู้ที่มีความทนต่อกลูโคสบกพร่องเมื่อวัดระดับน้ำตาลในเลือดหลังจากรับประทานกลูโคส 2 ชั่วโมง (IGT subgroup; 2 hr postprandial 140-199 มก/ดล) 14 คน ผู้ถูกศึกษาทั้งหมดถูกสุ่มโดยวิธี randomized, double blind, cross over design ให้ได้รับมะระขี้นกผงแห้ง ฟรีซดรายในขนาด 1,800 มิลลิกรัม/4 แคปซูล และ ยาหลอก ห่างกัน 1 อาทิตย์ ก่อนได้รับสิ่งทดลองผู้ถูกศึกษาจะถูกวัดระดับน้ำตาลในเลือด และหลังจากได้รับสิ่งทดลอง ½ ชั่วโมง ผู้ถูกศึกษาจะต้องรับประทานน้ำตาลกลูโคส 75 กรัม แล้วจึงวัดระดับน้ำตาลในเลือด ทำการวัดซ้ำทุก ½ ชั่วโมง จนกว่าจะครบ 5 ครั้ง ค่าระดับน้ำตาลในเลือดที่วัดได้จะถูกนำมาแสดงเป็นกราฟความทนน้ำตาลของผู้ถูกศึกษาแต่ละราย (OGT curve 0-2½ hr) กลุ่มตัวอย่างจะได้รับการติดตามอาการไม่พึงประสงค์โดยการวัดระดับการทำงานของตับ และ ไต ก่อน และหลังเข้าร่วมการศึกษา และได้รับการติดตามอาการไม่พึงประสงค์ในระหว่างที่ถูกศึกษา

ผลการศึกษา: พบว่าผู้ถูกศึกษา มีค่าพื้นใต้กราฟความทนน้ำตาล (AUC0-2½ hr) และระดับน้ำตาลในเลือดที่เวลา ½, 1, 1½, 2 และ 2½ ชั่วโมง หลังจากรับประทานมะระขี้นกผงแห้ง ฟรีซดรายในขนาด 1,800 มิลลิกรัม แตกต่างจากที่ได้รับยาหลอกอย่างไม่มีนัยสำคัญทางสถิติ ในขณะที่ผู้ที่มีความทนต่อกลูโคสบกพร่องเมื่อวัดระดับน้ำตาลในเลือดหลังจากรับประทานกลูโคส 2 ชั่วโมง มีพื้นที่ใต้กราฟความทนน้ำตาล (AUC0-2½ hr) (408.21 มก ชม/ดล) และระดับน้ำตาล(มก/ดล)ในเลือดที่เวลา 1½ (189.21), 2 (168.14) และ 2½ (133.00) ชั่วโมง ลดลงอย่างมีนัยสำคัญทางสถิติ (P = 0.008, 0.01, 0.04, 0.015)หลังจากรับประทานมะระขี้นกผงแห้ง ฟรีซดรายในขนาด 1,800 มิลลิกรัม เปรียบเทียบกับเมื่อได้รับยาหลอก(AUC = 451.79 มก ชม/ดล, ระดับน้ำตาล = 217.07, 187.00 และ 158.82 มก/ดล ตามลำดับ)

สรุป: พบว่ามะระขี้นกผงแห้ง ฟรีซดรายในขนาด 1,800 มิลลิกรัม/4 แคปซูล รับประทานครั้งเดียวไม่ช่วยให้ความทนต่อน้ำตาลของผู้ที่มีภาวะก่อนเบาหวานดีขึ้น แต่สามารถทำให้ความทนต่อน้ำตาลของผู้ที่มีภาวะก่อนเบาหวานเมื่อวัดระดับน้ำตาลในเลือดหลังจากรับประทานกลูโคส 2 ชั่วโมงดีขึ้น โดยพบว่ามะระขี้นกสามารถลดระดับน้ำตาลในเลือดของผู้ป่วยกลุ่มนี้ได้หลังจากรับประทานยาไปแล้วตั้งแต่ 1½-2 ชม. โดยไม่พบอาการข้างเคียงที่เป็นอันตราย ส่วนกลไกการออกฤทธิ์ที่น่าจะเป็นไปได้ของมะระขี้นก ได้อภิปรายไว้ในการศึกษาครั้งนี้แล้ว ควรมีการศึกษาต่อไปในระยะยาว ทั้งในกลุ่มภาวะก่อนเบาหวาน และผู้ป่วยเบาหวานเพื่อยืนยันผลลดระดับน้ำตาลในเลือด ของมะระขี้นก ว่าสามารถช่วยให้การควบคุมระดับน้ำตาลในเลือดดีขึ้นได้

สาขาวิชาเภสัชกรรมคลินิก บัณฑิตวิทยาลัย มหาวิทยาลัยศิลปากร ปีการศึกษา 2547

ลายมือชื่อนักศึกษา …….....

ลายมือชื่ออาจารย์ผู้ควบคุมวิทยานิพนธ์ ……

K 43550004: MAJOR: CLINICAL PHARMACY

KEY WORD: *MOMORDICA CHARANTIA*/ HYPOGLYCEMIC EFFECTS/ IMPAIR GLUCOSE TOLERANCE/ PREDIABETIC

SIRIWADEE BUNYAMAHOTAMA: ACUTE HYPOGLYCEMIC EFFECTS OF *MOMORDICA CHARANTIA* FREEZED DRIED POWDER IN IMPAIR GLUCOSE TOLERANCE CASES (IGT) THESIS ADVISOR: ASST. PROF. MANAT PONGCHAIDECHA, Ph.D. 122 pp. ISBN 974 – 464 – 668 – 3

OBJECTIVE; The aim of this study was to compare acute hyperglycemic effect between Momordica charantia fruit juice freeze dried capsules single dose and placebo in prediabetic subjects.

RESEARCH DESIGN AND METHODS; 30 prediabetic subjects with impair fasting glucose (IFG; FPG 100-125 mg/dl) was included into the study; in which there were14 subjects with impair glucose tolerance (IGT subgroup; 2 hr postprandial 140-199 mg/dl). Overall subjects completed a randomized, double blind, cross-over trial of *Momordica charantia* fruit juice freeze dried 1,800 mg/4 capsules versus placebo, separated by a 1 week washout period. Before receiving treatment, blood glucose were measured as baseline then subjects were asked to takes intervention. ½ hr later after 75 g glucose loading, blood glucose were measured, then repeated every ½ hr interval for 5 times. Blood glucose levels obtained from the study were plotted as OGTcurve 0-2½ hr. Liver function and renal function test of the subjects were assessed before and the end of study. And adverse events were monitored while studying.

RESULTS; In overall prediabetic subjects, there were found that area under the glucose tolerance curve (AUC0-2½ hr) and blood glucose at any time point showed no statistically significant difference between post dose of *Momordica charantia* fruit juice freeze dried capsules and placebo. When compared in prediabetic with IGT subgroups; *Momordica charantia* demonstrated significantly lower mean values for AUC0-2½ hr (408.21 mg hr/dl, P = 0.008) and blood glucose level (mg/dl) at time 1½ (189.21, P = 0.01), 2 (168.14, P = 0.04), and 2½ (133.00, P = 0.015) hr compare with placebo (AUC = 451.79 mg hr/dl, blood glucose = 217.07, 187.00 และ 158.82 mg/dl respectively). No significant increase in SGOT, SGPT, SAlb and SCr.

CONCLUSIONS; These data show that single dose *Momordica charantia* fruit juice freeze dried 1,800 g/4 capsules did not improve glucose tolerance in the prediabetic cases in general, it did improve glucose tolerance in the prediabetic subgroup with impaired glucose tolerance (IGT), and *Momordica charantia* show hypoglycemic effect at time 1½-2 hr post dose without clinical adverse effect. Expected mechanism of action for *Momordica charantia* was discussed in this study. Longer duration and focus in prediabetic and diabetic patients studies are needed to determine whether this effects are sustained and have a beneficial effect on improving glucose tolerance.

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Student's signature ……

Thesis Advisors' signature ……

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CHAPTER 1

INTRODUCTION

Statement and significance of the problem

Diabetes mellitus (DM) is the commonest endocrine disorder, affecting 173 million adults or about 6% of the world population in the year 2002. Around two thirds of these people live in developing countries (1).

Diabetes is classified by aetiological types. 5-10% of diabetes are type 1 (2), characterized by the processes of β-cell destruction that may ultimately lead to diabetes in which insulin is required for survival. 90-95% of diabetes are type 2 (2), characterized by disorders of insulin action and /or insulin secretion. The third category, "other specific types of diabetes," includes diabetes caused by specific and identified underlying defects such as genetic defects or diseases of the exocrine pancreas (1). Among other clinical classes of DM, impaired glucose tolerance (IGT) and impaired fasting glycaemia (IFG) are intermediate categories between diabetes and normal glucose tolerance, and between higher risk for the future development of type2 diabetes and cardiovascular disease (CVD). An individual falling into the IFG category on the fasting result may also have IGT on the 2-h value or, indeed, diabetes (3)

Most of the consequences of diabetes result from its macrovascular and microvascular complications. The age adjusted mortality, mostly due to coronary heart disease (CHD) in many but not all populations, is 2-4 times higher than in the non-diabetic population. Moreover, people with diabetes have a 2-fold increased risk of stroke. Diabetes is also the leading cause of end stage renal failure in many populations in both developed and developing countries. Lower extremity amputations are at least 10 times more common in people with diabetes than in non-diabetic individuals in developed countries, and more than half of all nontraumatic lower limb amputations are due to diabetes. In developed countries, diabetes is one of the leading causes of visual impairment and blindness. People with diabetes require at least 2-3 times health care resources for people who do not have diabetes. Diabetes care accounts for up to 15% of national healthcare budgets. These may be delayed, lessened or prevented by maintaining blood glucose

close to normal levels. Commonly practiced treatment of diabetes includes lifestyle modification, oral antidiabetics and/or insulin injections. Plant drugs are frequently considered to be less toxic and more free from side effects than synthetic chemicals and may be useful as herbal supplement for checking glucose in diabetics.

In developing countries all over the world 80% of their population continues to use traditional medicine for primary medical problems. In Thailand, Arthorn Riewpaiboon reported, 84% of diabetic patients visiting district hospitals in Nakornpratom province had used herbs to treat their conditions. Surakiat Achanauparp also found 80% of diabetic patients resorted to herbal (4). In the past decade, research has focused on scientific evaluation of traditional drugs of plant origins. *Momordica charantia* L. is one such plant that has been frequently used as medicine and studied on its pharmacological effects (5, 6)

Momordica charantia , a climber belonging to family Cucurbitaceae, is commonly known as bitter gourd or bitter melon in English, karela in Hindi and ma-ra-khee-nok in Thailand. All parts of the plant, including the fruit, taste bitter. The fruit is oblong and resembles a small cucumber, young fruits are emerald green and turn to orange-yellow when ripe. The plant grows in tropical areas of Asia, Amazon, east Africa, and the Caribbean. The raw fruit is commonly available in specialty Asian markets. It is cultivated throughout the world for use as vegetable as well as medicine (7).

Momordica charantia L. has been used traditionally as medicine in developing countries like Brazil, China, Colombia, Cuba, Ghana, Haiti, India Mexico, Malaya, New Zealand, Nicaragua, Panama and Peru. Especially in India, various medicinal properties are claimed for the plant including antidiabetic, abortificient, anthelmintic, contraceptive, antimalarial and laxative. It is also used for treatment of dysmenorrhea, eczema, emmenagogue, galactagogue, gout, jaundice, kidney (stone), leprosy, leucorrhea, piles, pneumonia, psoriasis, rheumatism and scabies. It medicinal uses have become so popular subjects of research that in the last few decades several hundreds of studies on *Momordica charantia* have been carried out, crediting it with antidiabetic, antiviral, antitumor, antileukemic, antibacterial, anthelmintic, antimutagenic, antimycobacterial, antioxidant, antiulcer, anti-inflammatory, hypocholesterolemic, hypotriglyceridemic, hypotensive, immunostimulant, and insecticidal properties (7). For diabetes, the plant has a long history of use for its hypoglycemic effects in Asia, Africa, and Latin America, sometimes being referred as vegetable insulin (8). Ayurveda, one of ancient healing

systems of India has used indigenous remedies in treating diabetes mellitus since the time of Charaka and Sushruta (6th century BC), and *Momordica charantia* has long been used as botanicals in Ayurvedic materials (9, 10). Not only has it been proven to be safe and effective through hundred years of use, but has been also commonly consumed as vegetables.

Studies on the hypoglycemic effects of *Momordica charantia* in vitro, animal, and human has reported its beneficial effects on patients with diabetes mellitus. The aqueous extracts of unripe fruits of *Momordica charantia* have been shown to produce a hypoglycemic effect in experimental model of animals following oral administration (11-20). Animal models in these studies simulates type 2 diabetes. Clinical studies have also confirmed the hypoglycemic action in type 2 diabetic patients(21-26), though most of these studies were poorly designed. Several mechanisms have been proposed for this effect. One is believed to be the inhibition of glucose absorption(27). Another is an insulin secretagogue action. An insulin-like peptide called polypeptide P, or plant insulin, with a pharmacologic effect similar to bovine insulin, has been identified(27, 28). A third potential mechanism is increased utilization of glucose by the liver (29).

The role of *Momordica charantia* on diabetes is of paramount importance as this plant serves various purposes in these patients such as lowering blood glucose, delaying complications (nephropathy, neuropathy, gastroparesis and cataract, athereosclerosis) and being anti-infective (diabetics are known to be more susceptible to infections). Moreover, presently there is no other pharmacological agent that can control diabetic complications. Most importantly, it is cheap and widely available in tropical countries. However, standardization of *Momordica charantia* and its antidiabetic components through controlled clinical trials is needed.

Most of the studies mentioned above were conducted with crude preparations of *Momordica charanti* whose chemical profiles were not mentioned. However, a few studies have demonstrated biological activity of *Momordica charantia* compounds such as charantin, MAP 30, momordin, alpha and beta momorcharins. The compounds from *Momordica charantia* which show hypoglycemic effect are charantin and p-insulin. P-insulin, an insulin-like peptide called polypeptide P, or plant insulin, has been identified for having a pharmacologic effect similar to that of bovine insulin by subcutaneous administration. Therefore, charantin is the component that may take effects through oral intake.

Besides, *Momordica charantia* fruit juice is difficult to prepare for daily use, not to mention its very bitter taste. Additionally, standardization of charantin from *Momordica charantia* has not been reported. For safe utilization of any medicinal plant as a medicine, its standardization is necessary to guarantee its drug authenticity and its content of active principles according to the parameters utilized as quality criteria. Developing water extract of fruit juice to capsule formulation by freeze dried techniques and standardization with charantin marker may be useful for simple administration and qualifying the quality of its content. However, there has been no studies which give proof that freeze dried *Momordica charantia* L. fruit juice can decrease plasma glucose in human subjects. The purpose of this study is to investigate the hypoglycemic effect of *Momordica charantia* L. fruit juice freeze dried capsules .

Objectives of the study

1. To compare mean area under the curve of oral glucose tolerance test:OGTT at 0-2 ½ hours in prediabetic cases receiving *Momordica charantia* fruit juice freeze dried capsules and those receiving placebos.

2. To compare mean blood glucose level increasing from base line at ½ , 1, 1½ and 2 hours time points between prediabetic cases received *Momordica charantia* L. fruit juice freeze dried capsules and placebos

Hypotheses to be tested

1. Mean area under the curve of OGTT at 0-2 ½ hours of prediabetic cases receiving *Momordica charantia* L. fruit juice freeze dried capsules is not different from those receiving placebos.

2. Means blood glucose levels increasing from base line at ½ , 1, 1½ and 2 hours time points of prediabetic cases receiving *Momordica charantia* L. fruit juice freeze dried are not different from those receiving placebos.

Scope of the study

This study limits the scope of acute hypoglycemic effect in prediabetic cases (FPG 100-125 mg/dl)

Limitation of the study

This study is limited to prediabetic cases of ages between 30 and 60 who have no comorbid diseases and do not take any medications.

Definitions

IFG

Subjects who having fasting plasma glucose (FPG) levels ≥100 mg/dl (5.6 mmol/l) but <126 mg/dl (7.0 mmol/l).

IGT

Subjects who 2-h values in the oral glucose tolerance test (OGTT) of ≥140 mg/dl (7.8 mmol/l) but <200 mg/dl. (11.1 mmol/l)

IGT subgroup of prediabetic subjects

Subjects who have FPG 100 mg/dl to 125 mg (5.6 mmol/l /dl-7 mmol/l) and 2-h plasma glucose 140 mg/dl to 199 mg/dl (7.8 mmol/l-11.1 mmol/l).

Prediabetic subjects

Subjects who have FPG 100 mg/dl (5.6 mmol/l) to 125 mg/dl (6.9 mmol/l).

List of abbreviations

BS	=	blood sugar
BG	=	blood glucose
BMI	=	body mass index
BP	=	blood pressure
CBC	=	complete blood count
CNS	=	central nervous system
°C	=	degree Celsius
cm	=	centimeter(s)
dl	=	deciliter (s)
eg.	=	such as
FBS	=	fasting blood sugar
FPG	=	fasting plasma glucose
g	=	gram(s)
GI	=	gastrointestinal
HEPA	=	health enhancing physical activity
HPLC	=	high performance liquid chromatography
hr	=	hour (s)
Ht	=	height
IDDM	=	independent diabetes mellitus or type 1 diabetes
IFG	=	impair fast glucose
IGT	=	impair glucose tolerance
l	=	liter
LD_{50}	=	median lethal dose (dose giving 50% dying)
kcal	=	kilocalorie
kg	=	kilogram(s)
MC	=	*Momordica charantia* L. fruit juice freeze dried capsules
mg	=	milligram(s)
min	=	minute(s)
ml	=	milliliter(s)

mm Hg	=	millimeter thermometer
NIDDM	=	non independent diabetes mellitus or type 2 diabetes
N/V	=	nausea-vomiting
OGT	=	oral glucose tolerance
OGTT	=	oral glucose tolerance test
P	=	placebo
SAlb	=	serum albumin
SCr	=	serum creatinine
SGOT	=	serum glutamic-oxaloacetic transaminease
SGPT	=	serum pyruvic-oxaloacetic transaminease
UA	=	urine analysis
Wt	=	weight
μg	=	microgram(s)

CHAPTER 2

LITERATURE REVIEW

Momordica charantia L.

1. Botanical Information

Momordica charantia L. belongs to the family Cucurbitaceae (gourd family) and genus *Momordica*.

1.1. Synonyms of genus (30)

Momordica balsamica Desc.;

Momordica balsamina Blanco;

Momordica chinensis Sprengel.

Momordica cylindrica Blanco;

Momordica elegans Salisb.

Momordica indica L.;

Momordica humulis Wall.;

Momordica muricata DC.;

Momordica operculata Vahl.;

Momordica senegalensis Lamk.;

Cucumis africana Lindl.

1.2. Thai local name

Ma-ra-Khee-Nok (general), phakha (north-eastern), maha (northern) (31)

1.3. Vernacular name

Bitter gourd, Bitter melon, Balsam pear, Bitter cucumber (English, USA); Paroka (France); Karela, Balsamina, (India); Karawila (Sri Lanka); fu kwa (Chinese); nigai uri, Futoreishi (Japanese); ampalaya (Philipines); Periya laut (Malaysia); Cerasee (Jamaica, Trinidad, Bahamas); Cundeamor (Mexico, Cuba, Puerto Rico); caetano, Melao-de-sao (Brazil); Kakle (East Africa) (32).

1.4. Original and distribution

Original found only in the tropics of the old world, it has been spread by man throughout all the tropical regions of the world and is commonly found on fences and shrubs and in hedgerows (32). In Asia, only 5-7 species occur (31).

1.5. Botanical description

It is a slender-stemmed tendril climber, the older stem often flattened and fluted to six meters or longer (Figure 1-3).

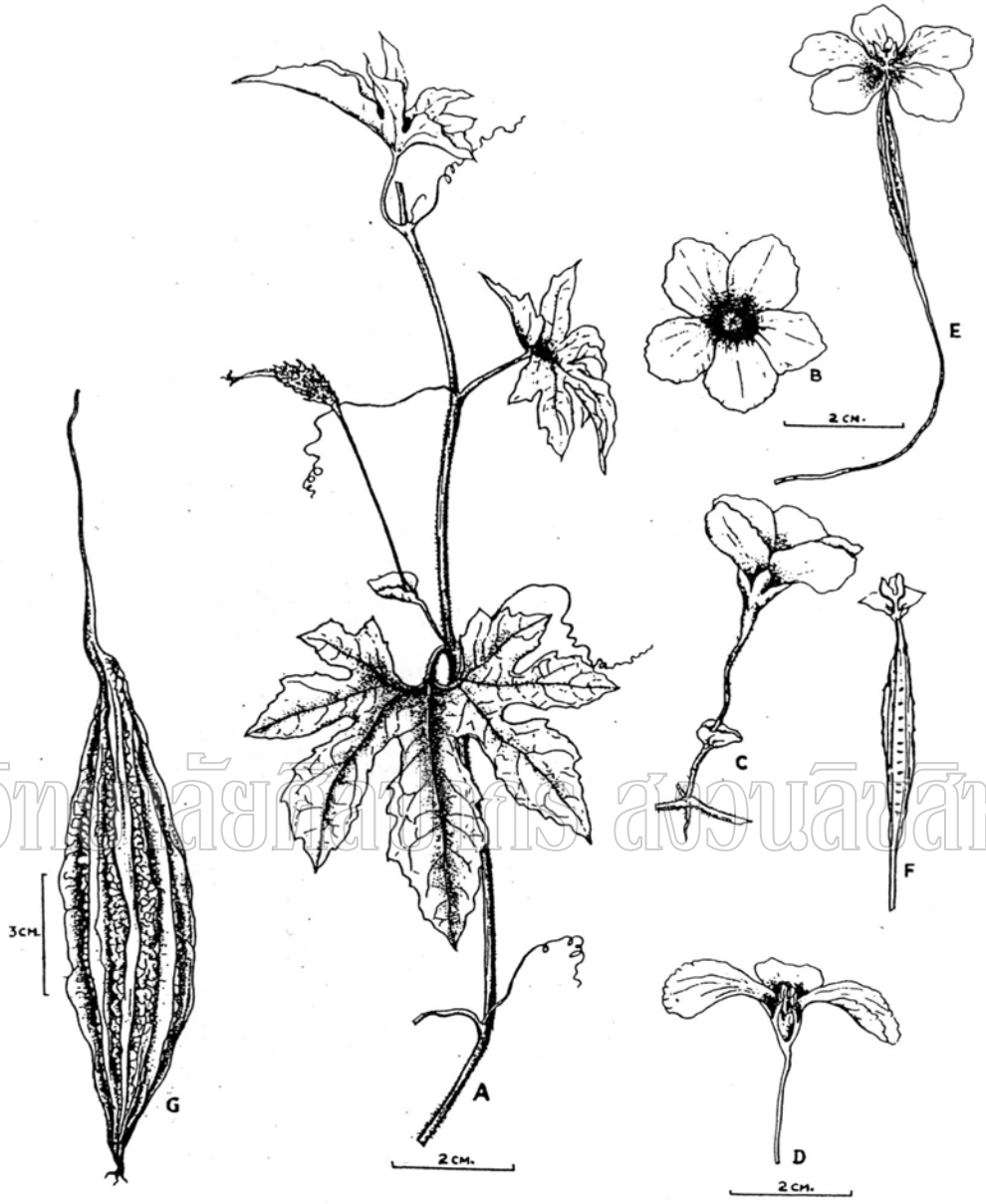


Figure 1 Portion of *Momordica charantia* L.

A; portion of plant with leaves, tendrils and a young fruit.

B; front view of male flower. C; lateral view of male flower.

D; longitudinal section of male flower. E, female flower. F; longitudinal section of female flower.

G; fruit.

A; seed

B; leaves

C; fruits

Figure 2 *Momordica charantia* Linn. A; seed. B; leaves. C; fruits.

MaraKheeNok

MaraChin

Figure 3 Two types of Momordica charantia L. in Thailand.

Leaves, alternate, thin, cut into 5-7 lobes, central lobe the longest, margins irregular, more or less deeply notched or coarsely toothed, petiole up to 7 cm long, shortly pubescent, they produce an offensive smell when crushed (Figure 1-2).

Flowers, monoecious, clear yellow; female flowers solitary in the axils of the leaves, male flowers subtended by a conspicuous kidney- or heart-shaped, long thin flower stalk, corolla about 2.5 cm. Across, 5 petals free (Figure 1).

Fruit, unripe fruit is green, mostly 8.4 cm., but very variable in shape and size, with irregular longitudinal rows of conspicuous warts and many smaller warts between the rows. Ripe fruit is orange-yellow and then becoming softly fleshly and opening to reveal pendulous seeds (Figure 1-3).

Seeds, drip-shaped seeds are covered with red pulp, brown seeds, which have a ridged surface and a thick jagged margin (Figure 2)(33).

1.6. Growth and development

The seed are germinated within 5-7 days, and developed to the vine rapidly. Flowering starts 45-55 days from sowing. The green fruits can be harvested about 2 weeks after anthesis, before ripening. Fruits left on the vine turn orange or yellow and dehisce some 25-30 days after anthesis.

1.7. Other botanical information

The wild and cultivate forms of *Momordica charantia* have been grouped by different mode of classification. There are 2 different varieties of *M. charantia* which is most commonly used. The cultivated form with large fruits (*M. charantia* var.charantia) and the wild variety (var. muricata) with small fruits. The latter is preferred in traditional medicine (31).

In India and South-East Asia, cultivated *M. charantia* is divided into 2 groups, i.e., fruits with diameter less than 5 cm (var. *minima* Williams&Ng) and fruits with diameter larger than 5 cm (var. maxima Williams&Ng). In var. *minima*, all fruits are green and the seed is 13-14.5 mm x 6.8-8.5 mm; cultivars fall into 3 groups: short fruited (6-7.5 cm), medium fruit (8-12 cm) and long fruit (12-22 cm). In var. *maxima*, the fruits are white or green and the seed is 14.8 mm x 8.5 mm; cultivars fall into 2 groups: medium fruited (12-17 cm) with white fruits, and long fruits (about) 20 cm) with green fruits (31).

In Thailand, *M. charantia* L. are found mostly in several region. There are two types. One type has large fruit which is usually called Chinese bitter gourd. The other type has much smaller fruit which is known as Thai bitter gourd or Mara-Khee-Nok. Both types have the same name and species named. Nevertheless, the variety name has not yet been identified (34).

2. Ethnomedical Information of *Momordica charantia* L. fruit

2.1. Ethnomedical uses of *Momordica charantia* fruit.

Traditional usage of *Momordica charantia* fruit as medicine in various countries display summary in Table 1.

Table 1 Ethnobotanical uses of *Momordica charantia* fruit.

Use	Reference
Antidiabetic	(35-40)
Hypoglycemic agent	(41)
Purgative	(42)
Relief of rheumatism, gout	(42)
Flatulence	(43)
Anti-inflammatory	(44)
Fever	(40)
Phlegm	(40)
Remedy for jaundice	(45)
Remedy for leprosy	(45)
Emmenagogue	(45)
Laxative	(45)
Bacillary dysentery	(42)
Treat burn	(42)
Vermifuge	(42)
Abortifacient (entire plant)	(42, 46)

2.2. Folk method for using *Momordica charantia* fruit

There are various folk methods for using *Momordica charantia* fruit, which differ in each local area and are displayed in Table 2

Table 2 Traditional medicinal uses of *Momordica charantia* fruit in various areas (47).

Plant Part / Location	Documented Ethnomedical Use	Type Extract / Route	Used By
Fruit Asia	Traditionally consumed in large amounts for the treatment of diabetes.	Fruit / Oral	Human Adult
Fruit Bimini	Eaten as food.	Fruit / Oral	Human Adult
Fruit Brazil	Used to treat wounds. Fruit juice mixed with ricinus oil in equal parts and serves as an anthelmintic when used internally.	-Hot H2O Ext / External -Juice / Oral	Human Adult Human Adult
Fruit Brazil	Used for tumors.	Not Stated	Human Adult
Fruit + Leaf Brazil	Used as a vermifuge.	Not Stated	Human Adult
Fruit Brazil	Used as an anthelmintic and to lower blood sugar.	Fruit / Oral	Human Adult
Fruit China	Used as a male aphrodisiac.	Decoction / Oral	Human Male
Fruit China	Used as a food.	Fruit / Oral	Human Adult
Fruit China	Used for diabetes mellitus both mild-moderate chronic cases. Used to reduce glucose in the blood and urine and the frequency of urination.	Not Stated / Oral	Human Adult
Fruit Colombia	Used for snakebite.	Infusion/External	Human Adult
Fruit + Leaf Cuba	Used as an emmenagogue.	Hot H2O Ext / Oral	Human Adult(female)
Fruit England	Used for diabetes.	Fruit / Oral	Human Adult
Fruit England	Used for diabetes. Used as an ingredient in curries eaten by immigrants.	Hot H2O Ext / Oral Fruit / Oral	Human Adult
Fruit Fiji	Used for stomach worms, fever, phlegm and diabetes. Fruits are fried or curried.	Fruit / Oral	Human Adult
Fruit	Reported to have hypoglycemic activity.	Not stated	Not Stated

Plant Part / Location	Documented Ethnomedical Use	Type Extract / Route	Used By
Guadeloupe			
Fruit India	Used for diabetes.	Hot H2O Ext / Oral	Human Adult
Fruit India	Used for diabetes.	Decoction / Oral	Human Adult
Fruit India	Used for diabetes.	Decoction / Oral	Human Adult
Fruit India	Used for diabetes.	Hot H2O Ext / Oral	Human Adult
Fruit India	Used for hydrophobia. *Notonia grandiflora* juice is mixed with bitter gourd powder and taken internally.	Powder / Oral	Human Adult
Fruit India	Used as an abortifacient in large doses.	Fruit / Oral	Human (pregnant)
Fruit India	Used as a remedy for diabetes mellitus.	Hot H2O Ext / Oral	Human Adult
Fruit India	Used as an antivenin.	Oil Ext / External or Juice / Not stated	Human Adult
Fruit India	Used for diabetes.	Decoction / Oral	Human Adult
Fruit India	Used as an antileprotic.	Not stated	Human Adult
	Used as an anthelmintic.	Not Stated / Oral	Human Adult
Fruit India	Used as an anthelmintic.	Fruit / Oral	Human Adult
Fruit India	Used as a common vegetable.	Fruit / Oral	Human Adult
Fruit India	Used for jaundice, piles, leprosy, rheumatism and gout. Used as a tonic and laxative, dysmenorrhea and as a emmenagogue.	Not Stated / Oral	Human Adult
Fruit India	Commonly eaten as a vegetable. Used for diabetes mellitus.	Fruit / Oral Juice / Oral	Human Adult Human Adult
Fruit Juice India	Used to treat diabetes. 5 ml of fruit juice mixed with 5 to 10 fruits of black pepper powder is given early in the morning 3-6 weeks.	Fruit Juice / Oral	Human Adult
Fruit Juice India	Used for malarial fevers.	Juice / Oral	Human Adult
Fruit Iraq	Used for leprosy. Used as an anthelmintic.	Not Stated / Not stated Not Stated / Oral	Human Adult Human Adult
Fruit Jamaica	Used for diabetes.	Not Stated / Oral	Human Adult
Fruit Jamaica	Used for diabetes.	Hot H2O Ext / Oral	Human Adult
Fruit Nigeria	Eaten as a pot herb.	Fruit / Oral	Human Adult
Fruit + Leaf Nigeria	Used as a laxative and anthelmintic.	Decoction / Oral	Human Adult

Plant Part / Location	Documented Ethnomedical Use	Type Extract / Route	Used By
Fruit + Leaf Nigeria	Used as an anthelmintic.	Juice / Oral	Human Adult
Fruit Pakistan	Used for diabetes.	Fruit / Oral	Human Adult
Fruit Pakistan	Eaten as a food.	Fruit / Oral	Human Adult
Fruit Juice Panama	Used as a malaria preventative.	Not Stated / Oral	Human Adult
Fruit Peru	-Used as a purgative. -Used for contusions, respiratory conditions and wounds.	Hot H2O Ext / Oral Hot H2O Ext / External	Human Adult Human Adult
Fruit Peru	Used to treat hepatitis. Used as a suppurative. Used as a vermifuge, an emetic and a febrifuge. Used as an emmenagogue.	Infusion / Oral Not Stated / External Not Stated / Oral Not Stated / Oral	Human Adult Human Adult Human Adult Human Female
Fruit Peru	Used for diarrhea and colic.	Juice / Oral	Human Adult / Child
Fruit Saudi Arabia	Used for diabetes, rheumatism, gout, liver disorders, spleen disorders, pyrexia, colic, flatulence and menstrual suppression.	Hot H2O Ext / Oral	Human Adult
Fruit Saudi Arabia	Used for diabetes, rheumatism, gout, liver disorders, spleen disorders, pyrexia, colic and flatulence. Used for menstrual suppression.	Hot H2O Ext / Oral	Human Adult Human Female
Fruit Sri Lanka	Used as a hypoglycemic agent.	Hot H2O Ext / Oral	Human Adult
Fruit Sri Lanka	Used as an anthelmintic.	Not Stated / Oral	Human Adult
Fruit Juice Sri Lanka	Used to treat diabetes mellitus.	Juice / Oral	Human Adult
Fruit Juice Sri Lanka	Used for diabetes.	Hot H2O Ext / Oral	Human Adult
Fruit Thailand	Said to be edible.	Plant / Oral	Human Adult
Fruit Thailand	Used as an anti-inflammatory.	Decoction / Oral	Human Adult
Fruit Thailand	Used for diabetes.	Hot H2O Ext / Oral	Human Adult
Fruit Thailand	Used as a food.	Fruit / Oral	Human Adult
Fruit Turkey	Used as a treatment for peptic ulcers.	Not Stated / Oral	Human Adult
Fruit Turkey	-Used as an antiallergic, antihepatic and antipruritic. -Used as an anti-inflammatory.	Plant / Oral Plant / External	Human Adult Human Adult

Plant Part / Location	Documented Ethnomedical Use	Type Extract / Route	Used By
Fruit Turkey	Used to treat ulcers.	Fruit / Oral	Human Adult
Fruit USA	-Used as a remedy for hemorrhoids. -Used to treat snakebite, leprosy, itching skin, burns and wounds.	Hot H2O Ext / Rectal Plant / External	Human Adult Human Adult
Fruit USA	-Used for bacillary dysentery and to relieve chronic colitis. -Used in large doses as an abortifacient.	Plant / Oral Plant / Oral	Human Adult Human(pregnant)
Fruit Juice USA	-Used to treat burns. -Used for thrush. -Used as a substitute for quinine in intermittent fever, liver and spleen ailments, gout, menstrual difficulties, and rheumatism. -Used as a vermifuge and purgative.	Plant / External Plant / Oral Hot H2O Ext / Oral	Human Adult Human Adult Human Adult
Fruit Virgin Islands	Used for a bad heart and diabetes.	Fruit / Oral	Human Adult
Fruit West Africa	Used as an antidiabetic remedy.	Not Stated / Oral	Human Adult
Fruit West Africa	Used as an abortifacient.	Fruit / Oral	Human (pregnant)
Fruit West Indies	Juice used for diabetes.	Juice / Oral	Human Adult
Fruit Not Stated	-Used as insecticide. -Used to treat colds. Unripe fruit eaten. -Used as a purgative. -Used as an anthelminthic. -Dose in brazil is two or three seeds. Used as an abortifacient.	Fruit / Not stated Fruit / Oral Not Stated / Oral Plant Juice / Oral Not Stated / Oral	Human Adult Human Adult Human Adult Human Adult Human(pregnant)
Fruit Not Stated	Used to treat diabetes.	Not Stated / Oral	Human Adult

The information of the above Table 1-2 show that widely use of *Momordica charantia* as a medication against diabetes was remarkable. Especially in Chinese medicine, *Momordica charantia* (fruit, seeds, leaves, roots) has for a long time played a medicinal role in the treatment of heat-stroke, dysentery, skin ulcers, poisonings and diabetes. In Indian traditional medicine the fruits are mainly used to treat diabetes mellitus, liver disorders, rheumatism and gout.

3. Phytochemical information relating to antidiabetic activity

Momordica charantia contains biologically active chemicals that include glycosides, saponins, alkaloids, fixed oils, triterpenes, proteins and steroids (48, 49). The immature fruits are a good source of Vitamin C and also provide Vitamin A, phosphorus, and iron (50)

Several phytochemicals such as momorcharins, momordenol, momordicilin, momordicins, momordicinin, momordin, momordolol, charantin, charine, cryptoxanthin, cucurbitins, cucurbitacins, cucurbitanes, cycloartenols, diosgenin, elaeostearic acids, erythrodiol, galacturonic acids, gentisic acid, goyaglycosides, goyasaponins, multiflorenol, have been isolated (51-55). These are reported in all parts of the plant (55).

The hypoglycemic chemicals of *M. charantia* are a mixture of steroidal saponins known as charantins, insulin-like peptides and alkaloids (48) and these chemicals are concentrated in fruits of *M. charantia*, therefore fruit of *M. charantia* has shown more pronounced hypoglycemic/antihyperglycemic activity (56). However, (13) differentiated two types of hypoglycemic substances in *M. charantia* with different time dependent effects one with fast antihyperglycemic activity of around 1 hr present in the aqueous and the residue after alkaline chloroform extraction of aqueous extract and another with a slow hypoglycemic activity in acidic wash of the chloroform extract remaining after an alkaline water wash.

The presence of trypsin inhibitors (57-59), elastase inhibitors (58), guanylate cyclase inhibitors (60, 61) and alpha-glucosidase inhibitor like D-(+)-trehalose are reported (62).

Phytochemical relating to antidiabetic activity isolated from *M. charantia* L. fruits are detailed as below

3.1. Protein; P-insulin

It is a polypeptide with molecular weight about 11,000 Dalton, consisted of 166 amino acid. The pharmacological study revealed that the polypeptide-p-$ZnCl_2$ produced blood sugar lowering effect by subcutaneous either in animal and in clinical study (63). Besides the fruits, p-insulin was also found in seeds and tissue culture of *Momordica charantia*.

3.2. Steroids; Charantin

Apart from the lack of randomization, inadequate placebo or control groups and short durations of trials, the lack of standardization of products in previous studies has posed problems in determining effective doses of *Momordica charantia* and thus limited the usefulness of the findings. In view of this handicap, this study puts emphasis on standardizing the study product. Charantin is one of the hypoglycemic compounds which can be isolated from *Momordica charantia* fruit (64). It is a mixture (1:1) of β-D-glucoside of β-sitosterol and stigmast-5, 25-diene-3 β-ol (65) both of which are steroidal saponins. Charantin has been shown to produce hypoglycemic effects by being taken either orally or intravenously (66). Charantin is of highly polar nature and can be found in *Momordica charantia* fruit juice. Hence it is used as the study product marker in this study. Besides, charantin is available in the market and commercially used in *Momordica charantia* products (67-70).

4. Pharmacological properties of the *Momordica charantia* fruit

4.1. Antidiabetic activity

4.1.1. Experimental

Momordica charantia L. is most widely studied with regard to its antidiabetic effect (Table 3) and all parts of the plant (fruit pulp, seed, leaves and whole plant) have shown hypoglycemic activity in normal animals (13, 16, 18, 29, 56, 71, 72); and antihyperglycemic activity in alloxan (20, 23, 38, 41, 73, 74) or streptozotocin-induced (13, 16, 19, 20, 29, 45, 71, 75-80) as well as genetic models of diabetes.

A poly-herbal preparation containing *Momordica charantia* showed a significant reduction in blood glucose, glycosylated haemoglobin, and an increase in plasma insulin and total haemoglobin in animals (17, 73) demonstrated antihyperglycemic activity of *Momordica charantia* fruit that was comparable to glibenclamide in diabetic rats. However, in a recently conducted study, (74) achieved nearly euglycemic state with ethanolic extracts of *Momordica charantia* fruit (250 mg/kg) within 2 weeks of treatment. Chronic treatment with aqueous fruit extract (200 mg/kg, orally) in alloxan diabetic rats caused a significant fall in plasma glucose levels of 64.33, 66.96, 69.7 and 70.53% at 1, 2, 3 and 4 months, respectively, and mean reduction of 15.37, 18.68 and 22.86% in STZ mice at 40, 50 and 60 days, respectively (20).

Momordica charantia has been shown to enhance number of β-cells (77). In another study, it was shown to act like insulin or promote insulin release (22, 76). However, a few studies have also attributed hypoglycemic activity to an extra-pancreatic effect (13, 29), which includes increased glucose transporter protein 4 (GLUT4) of muscles (80), increased glucose utilization in the liver and muscle (29, 81), inhibition of glucose-6-phosphatase & fructose-1, 6-bisphosphatase in liver and stimulation of red-cell and hepatic glucose-6-phosphate dehydrogenase activities (71, 82) attributed the hypoglycemic activity of *Momordica charantia* to inhibition of glucose transport at the brush border of the small intestine. Depressed carbohydrate enzymes activity in liver of diabetic mice was restored with *Momordica charantia* treatment (i.e. hexokinase, glucokinase, phosphofructokinase and substrate glucose-6-phosphate) by 74.8, 29.6, 120.5 and 90.55%, respectively (P<0.05, 0.001, 0.001, 0.001) as compared to control (20).

Table 3 Biological study of *Momordica charantia* L. fruits (49)

Part -Origin	Activity Tested For	Type Extract	Test Model	Dosage	Result	Notes/Organism tested
Fruit India	Antihyperglycemic Activity	Fruit	IG Mouse	Not stated	Active	vs. streptozotocin-induced hyperglycemia.
Fruit India	Antihyperglycemic Activity	Fruit	IG Rat	Not stated	Active	vs. alloxan-induced hyperglycemia.
Fruit India	Antihyperglycemic Activity	Juice	IG Rabbit	Not stated	Active	vs. alloxan-induced hyperglycemia.
Fruit India	Antihyperglycemic Activity	Fruit Juice Powder	Oral Human Adult	Not stated Not statedh Not stated	Active Active Active	Review. Studies in NIDDM and IDDM patients.
Fruit India	Antihyperglycemic Activity	H2O Ext	Mouse	200.0 mg/kg	Active	vs. streptozotocin-induced hyperglycemia. Mean reduction in plasma glucose levels of 15.37% (day 40), 18.68% (day 50) and 22.86% (day 60).
Fruit India	Antihyperglycemic Activity	H2O Ext	Rat	200.0 mg/kg	Active	vs.alloxan-induced hyperglycemia. Mean reduction in plasma glucose levels of 64.33% (1 month), 66.96% (2 months), 69.7% (3 months) and 70.53% (4 months).
Fruit China	Antihyperglycemic Activity	Decoction	IG Rat IP Rat	Not stated Not stated	Active Active	vs. alloxan- and streptozotocin-induced hyperglycemia.
Fruit England	Antihyperglycemic Activity	Fruit	Oral Human Adult	Not stated	Active	A diabetic woman recovered from glycosuria after taking a kind of curry. Karela was believed to be an active ingredient.

Part -Origin	Activity Tested For	Type Extract	Test Model	Dosage	Result	Notes/Organism tested
Fruit India	Antihyperglycemic Activity	Decoction	Oral Human Adult	500.0 mg	Active	
Fruit India	Antihyperglycemic Activity	H2O Ext	IG Rat (Female)	250.0 mg/kg	Active	vs. streptozotocin-induced hyperglycemia.
Fruit India	Antihyperglycemic Activity	H2O Ext	Oral Rat	4.0 gm/day	Active	Dosed for 2 months. Onset of retinopathy retarded. vs. alloxan-induced hyperglycemia.
Fruit India	Antihyperglycemic Activity	Lyophilized Ext	Oral Mouse	200.0 mg	Active	Urine volume decreased, urinary albumin level decreased, renal hypertrophy prevented. vs. streptozotocin induced hyperglycemia.
Fruit India	Antihyperglycemic Activity	Lyophilized Ext	Oral Mouse	200.0 mg	Active	Reduced plasma glucose concentrations by 24.4%.
Fruit India	Antihyperglycemic Activity	Powder	IG Rat	1.0 gm/kg	Active	vs. alloxan-induced hyperglycemia.
Fruit Pakistan	Antihyperglycemic Activity	Fruit	IG Rabbit	1.0 gm/kg	Active	vs. alloxan-induced hyperglycemia.
Fruit Peru	Antihyperglycemic Activity	H2O Ext	Injection Mouse (Male)	100.0 mg/kg	Active Inactive	vs. type 2 diabetic mice. Lowered serum insulin and BG. Non-diabetic mice.
Fruit Saudi Arabia	Antihyperglycemic Activity	Decoction 25% Ext	IG Mouse	0.5 ml	Inactive	Maximal change in blood sugar was 4.33%. vs. alloxan-induced hyperglycemia.
Fruit Saudi Arabia	Antihyperglycemic Activity	Hot H2O Ext 25% Ext	Gastric Intubation Mouse	0.5 ml	Inactive	vs. alloxan-induced hyperglycemia.

Part -Origin	Activity Tested For	Type Extract	Test Model	Dosage	Result	Notes/Organism tested
Fruit Thailand	Antihyperglycemic Activity	Hot H2O Ext Hot H2O Ext	Rabbit Rabbit	10.20 mg/kg Not stated	Active Inactive	Diabetic rabbits used. Diabetic rabbits used.
Fruit Thailand	Antihyperglycemic Activity	Lyophilized Ext Lyophilized Ext	Rabbit Rabbit	1.2 gm/kg 400 mg/kg	Inactive Inactive	vs. alloxan-induced hyperglycemia. vs. alloxan-induced hyperglycemia.
Fruit United Arab Emirates	Antihyperglycemic Activity	Juice	IG Rat (Male)	10.0 ml/kg	Active	vs. streptozotocin-induced type-1 diabetes.
Seed India	Antihyperglycemic Activity	H2O Ext	Oral Rabbit	3.0 ml/kg	Inactive	vs. alloxan-induced hyperglycemia.
Fruit India	Antihyperglycemic Activity	Fruit	IG Rat	15.0 gm	Active	vs. alloxan-induced hyperglycemia.
Fruit India	Antihyperglycemic Activity	Fruit	Oral Human Adult	Not stated	Active	
Fruit India	Antihyperglycemic Activity	H2O Ext	IG Rat	1.0 gm	Active	Reduction of initial blood sugar level after 3 week s from 220m g to 105mg. vs. alloxan-induced hyperglycemia.
Fruit India	Antihyperglycemic Activity	Hot H2O Ext	IG Rat	4.0 gm	Active	vs. alloxan-induced hyperglycemia. Inhibited cataract formation (dependent on blood sugar levels).
Fruit India	Antihyperglycemic Activity	Juice	IG Rabbit	6.0 ml/kg	Active Active	vs. alloxan-induced hyperglycemia. vs. glucose-induced hyperglycemia.

Part -Origin	Activity Tested For	Type Extract	Test Model	Dosage	Result	Notes/Organism tested
Fruit India	Antihyperglycemic Activity	H2O Ext	Oral Human Adult (Male)	1.0 gm	Active	The subjects included (433) severe to mild (260) diabetics, aged 42 to 70 years. Blood sugar estimated 2,3,4 & 7 weeks of treatm ent. Overall fall in blood sugar was 54%. vs.alloxan-induced hyperglycemia.
Fruit Kenya	Antihyperglycemic Activity	H2O Ext	IG Mouse	16.0 gm/kg	Active	vs. streptozotocin-induced hyperglycemia.
Fruit Sri Lanka	Antihyperglycemic Activity	Juice	IG Rat	10.0 ml/kg	Inactive	Daily dosing for 30 days. vs. streptozotocin-induced hyperglycemia.
Fruit Sri Lanka	Antihyperglycemic Activity	Juice	Oral Human Adult	100.0 ml	Not stated	Improved glucose tolerance in 73% of patients with maturity onset diabetes. Juice was given 30 minutes before oral glucose load in the glucose tolerance test.
Fruit Turkey	Antihyperglycemic Activity	H2O Ext	IG Mouse (Male)	0.5 gm/kg	Active	Significant decrease in nonfasting blood glucose levels of hyperglycemia induced mice. Results significant at $p < 0.01$ level.
Fruit England	Antihyperglycemic Activity	Fruit	Oral Human Adult	0.23 kg/day	Active Improved glucose tolerance in diabetic patients. Treatment for 8 to 11 weeks. Results significant at $p < 0.05$ level.	
Pulp Barisal	Antihyperglycemic Effect	Aqueous homogenized suspension	Human Adult	Not stated	Active	Reduction ($p<0.001$) of fasting and post-prandial serum glucose leve ls seen in 86% of non-insulin dependent diabetic subjects after oral glucose intake.
Fruit Pulp Bangladesh	Antihyperglycemic Activity	Juice MEOH Ext	IG Rat IG Rat	2.5 gm/kg 2.5 gm/kg	Inactive Active	vs. streptozotocin-induced hyperglycemia.

Part -Origin	Activity Tested For	Type Extract	Test Model	Dosage	Result	Notes/Organism tested
Fruit Pulp Japan	Antihyperglycemic Activity	H2O Ext	IG Rat	100.0 mg/kg	Active	vs. streptozotocin-induced hyperglycemia.
Roasted Fruit Pulp Japan	Antihyperglycemic Activity	H2O Ext	IG Rat	100.0 mg/kg	Active	vs. streptozotocin-induced hyperglycemia.
Fruit Egypt	Antihyperglycemic Activity	Juice	IG Rat	Not stated	Active	
Fruit Juice India	Antihyperglycemic Activity	Hot H2O Ext	Oral Rat (Male)	5.0 ml/kg	Equivalent	vs. anterior pituitary extract-induced hyperglycemia.
Fruit Juice England	Antihyperglycemic Activity	Juice	Oral Human Adult	50.0 ml	Active	Improved glucose tolerance in diabetic patients. Treatment for 8 to 11 weeks. Results significant at $p < 0.01$ level.
Fruit Juice India	Antihyperglycemic Activity	Juice	IG Mouse (Male)	10.0 ml/kg	Active	vs. streptozotocin-induced hyperglycemia.
Fruit Juice India	Antihyperglycemic Activity	Juice	IG Rat (Male)	5.0 ml/kg	Active	A glucose tolerance test was used.
Fruit Juice Sri Lanka	Antihyperglycemic Activity	Hot H2O Ext	IG	Not stated	Active	vs. glucose-induced hyperglycemia.
Fruit Juice Sri Lanka	Antihyperglycemic Activity	Hot H2O Ext	Oral Human Adult	Not stated	Active	Maturity onset diabetics. 73% improved glucose tolerance. vs. glucose-induced hyperglycemia.
Fruit Juice China	Antihyperglycemic Activity	-Juice -Lyophilized Ext	IG Mouse	Not stated Not stated	Active Active	vs. alloxan-induced hyperglycemia.

Part -Origin	Activity Tested For	Type Extract	Test Model	Dosage	Result	Notes/Organism tested
Fruit Juice India	Antihyperglycemic Activity	Juice	IG Rabbit	5.0 ml/kg	Active	vs. alloxan-induced hyperglycemia.
Pulp Juice Bangladesh	Hypoglycem ic Activity	Juice	IG Rat	150 mg	Active	Lowered fasting blood glucose levels in non-diabetic rats; ($p<0.05$ at 120 m in).
Pulp Juice Bangladesh	Hypoglycem ic Activity	Juice	IG Rat	150 mg	Inactive	IDDM model rats in fasting or postprandial states.
Fruit Juice India	Hypoglycem ic Activity	Juice	IG Rabbit	2.0 ml/kg	Equiv	
Fruit Juice Sri Lanka	Hypoglycem ic Activity	Hot H2O Ext	IG	Not stated	Active	
Fruit Juice India	Hypoglycem ic Activity	Juice	IG Rabbit	500.0 mg	Inactive	
Fruit Pulp Sri Lanka	Hypoglycem ic Activity	Juice	Gastric Intubation Rat	10.0 ml/kg	Active	
Fresh Fruit Egypt	Hypoglycem ic Activity	Juice	IG Rat	Not stated	Active	
Fruit Pulp Bangladesh	Hypoglycem ic Activity	Juice	IG Rat	2.5 mg/kg	Active	Extract fed 45 minutes before the oral glucose load.
Fruit Pulp Bangladesh	Hypoglycem ic Activity	Juice	IG Rat	2.5 mg/kg	Inactive	IDDM rats.

Part -Origin	Activity Tested For	Type Extract	Test Model	Dosage	Result	Notes/Organism tested
Fruit + Leaf + Stem Trinidad	Hypoglycem ic Activity	Decoction	IP Mouse (Male)	0.3 ml	Active	1.0 ml of extract was equ ivalent to 10 gm of dried plant material. Following a single dose of the extract, basal plasma glucose concentrations were reduced after 4 and 8 hours. Glucose tolerance was also improved 8 hr after dosing. Plasm a insulin levels were unaffected by the extract.
Fruit + Leaf + Stem Trinidad	Hypoglycem ic Activity	Decoction in Drinking Water	Mouse (Male)	0.2%	Inactive Daily dosing of the extract for 13 days followed by IP glucose tolerance. Plasma glucose and plasma insulin were measured. There was no significant alteration of body weight, food intake, fluid intake or plasma concentrations of glucose or insulin. Glucose tolerance, measured on day 13, was improved by treatment.	
Fruit Pakistan	Hypoglycem ic Activity	Fruit	IG Rabbit	0.5 gm/kg	Active	
Fruit India	Hypoglycem ic Activity	Fruit	IG Mouse	Not stated	Active	
Fruit India	Hypoglycem ic Activity	Juice	IG Rat	Not stated	Active	vs. ant.pituitary extract-induced hyperglycemia.
Fruit China	Hypoglycem ic Activity	Not stated Juice	-IV Rabbit -Gastric Intubation Rabbit	12.0 microcuries/ kg	Active Active	vs. alloxan-induced hyperglycemia.
Fruit India	Hypoglycem ic Activity	Decoction	IG Rabbit	200.0 mg/kg	Active	
Fruit India	Hypoglycem ic Activity	H2O Ext	Rat (Female)	250.0 mg/kg	Active	Potentiation effect if used with C. longa and E. officin alis.

Part -Origin	Activity Tested For	Type Extract	Test Model	Dosage	Result	Notes/Organism tested
Fruit India	Hypoglycem ic Activity	H2O Ext	Oral Rabbit	10.0 mg/kg	Active	Drop in blood sugar of 15 mg rela tive to inert-treated control.
Fruit Jamaica	Hypoglycem ic Activity	Hot H2O Ext	Gastric Intubation Dog	200.0 ml	Weak Activity	Dose = 20 gm of air-dried plant material.
Fruit Thailand	Hypoglycem ic Activity	-Glycoside Mixture -Lyophilized Ext -Lyophilized Ext	Rabbit Rabbit Rabbit	10.0 mg/kg 1.2 gm/kg 400.0 mg/kg	Active Inactive Inactive	
Fruit Thailand	Hypoglycem ic Activity	Hot H2O Ext	Rabbit	5 mg/kg 10 mg/kg 20 mg/kg	Inactive	
Fruit Japan	Hypoglycem ic Activity	Powder Powder	Oral Rat (Male)	1.0 % of diet 1.0 % of diet	Active Inactive	Serum vs. fed cholesterol-free diets. Serum vs. fed cholesterolenriched diets.
Fruit India	Hypoglycem ic Activity	Fruit	Oral Human Adult	15.0 gm/day	Equiv	The dose was given for 21 days. The fall in blood sugar was 25% of the initial level; however statistically is insignificant. The overall fall in blood sugar was 25%.
Fruit India	Hypoglycem ic Activity	Juice	IG Rabbit	6.0 ml/kg	Active	

Part -Origin	Activity Tested For	Type Extract	Test Model	Dosage	Result	Notes/Organism tested
Fruit Israel	Glucose Absorption Inhibition	Aqueous High Speed Supernatant	Rat (Intestine, small)	50.0 mcl	Active	
Fruit Brazil	Glucose Absorption Inhibition	Aqueous High Speed Supernatant	Rat (Adipocytes)	50.0 mcl	Inactive	
Fruit Kenya	Glucose Absorption Inhibition	H2O Ext	IG Mouse	16.0 gm	Inactive	vs. streptozotocin-induced hyperglycemia.
Fruit Peru	Glucose Uptake Induction	H2O Ext	Injection Mouse (Male)	100.0 mg/kg	Active	Muscle content of GLUT4 transporter was increased ($p<0.01$).
Fruit India	Glucose Uptake Induction	Juice	Diaphragm	Not stated	Active	
Fruit Sri Lanka	Glucose Uptake Induction	Juice	Gastric Intubation Rat	10.0 ml/kg	Active	Results significant at $p < 0.001$ level.
Pulp Juice Bangladesh	Insulin Release Stimulation	Not stated	Mouse (Islets)	Not stated	Active	
Fruit India	Insulin Level Increase	Not stated	Human Adult Mouse Pig	Not stated Not tated Not stated	Active Active Active	
Fruit India	Insulin Potentiating Effect	ETOH(100%) Ext H2O Ext	IG Rat IG Rat	400.0 mg 400.0 mg	Active Active	

Part -Origin	Activity Tested For	Type Extract	Test Model	Dosage	Result	Notes/Organism tested
Fruit India	Glucose Absorption Inhibition	-ETOH(95%) Ext -H2O Ext	Intestine (small)	Not stated Not stated	Active Active	
Fruit Juice Sri Lanka	Glucose Uptake Induction	Hot H2O Ext	Not stated	Not stated	Active	
Fruit Sri Lanka	Insulin Induction	H2O Ext	Cell Culture (Pancreatic islets)	1.0 mg/ml	Active	
Fruit India	Insulin Release Stimulation	H2O Ext	Islets of Langerhan	Not stated	Active	
Fruit India	Gluconeogenesis Inhibition	-Juice -ETOH(95%) Ext	Kidney Liver	Not stated Not stated	Equivalent Active	
Fruit Juice Sri Lanka	Gluconeogenesis Inhibition	Hot H2O Ext	Kidney	Not stated	Inactive	
Fruit Juice Sri Lanka	Liver Glycogen Increase	Hot H2O Ext	Liver	Not stated	Active	Muscle glycogen levels also increased.
Fruit India	Enzyme Modulation	H2O Ext	Rat Mouse	200 mg	Active	In streptozotocin-induced diabetic mice and alloxanized-induced diabetic rats, momordica restored hepatic and skeletal m uscle glycogen content, hepatic glucokinase, hexokinase, glucose- 6-phosphate and phosphofructokinase.

Part -Origin	Activity Tested For	Type Extract	Test Model	Dosage	Result	Notes/Organism tested
Fruit Brazil	Glucose Oxidase Inhibition	Supernatant	Rat (Adipocytes)	50.0 mcl	Active	
Fruit Brazil	Glucose Oxidase Inhibition	Supernatant	Rat	50.0 mcl	Active	Liver homogenates.
Fruit Brazil	Hexokinase Inhibition	Supernatant	Rat	50.0 mcl	Active	Liver homogenates.
Fruit Sri Lanka	Liver & Muscle Glycogen Increase	Juice	GI Rat	10.0 ml/kg	Active	Results significant at $p < 0.01$ level.
Fruit Juice United Arab Emirates	Miscellaneous Effects	Fruit Juice	IG Rat (Male)	10.0 ml/kg	Active	Study of the effect of fruit juice on the increase of alpha, beta, and gamma cells in pancreas of streptozotocin-induced diabetic rats. There was a significant increase in beta and delta cells.
Fruit India	Glycogen Content Increased	Juice	Liver	Not stated	Active	
Fruit Juice India	Apoptosis Inhibition	Juice	Cell Culture	0.1%	Active	vs. RIN cells. vs. .streptozotocin-induced hyperglycemia.
Fruit United Arab Emirates	Hepatic Enzyme Modulating Activity	Juice	Oral Rat (streptozotocin- induced diabetes)		Active	Reversed 50-100% increase in aniline hydroxylase and ethoxyresorufin-O-deethylase activity. Reversed the 17-20% decreased activity of aminopyrene N-demethylase and ethoxycoumarin-O-deethylase. Normalized a reduced cytosolic glutathione concentration. Increased (20-30%) GST activity.
Fruit Juice Sri Lanka	Gamma-glutam yl Transferase Induction	Fruit Juice (unripe)	IG Rat (Male)	10.0 ml/kg	Active	Results significant at $p < 0.001$ level.

Part -Origin	Activity Tested For	Type Extract	Test Model	Dosage	Result	Notes/Organism tested
Fruit Juice Sri Lanka	Gamma-glutam yl Transferase Induction	Not stated	IG Rat (Male)	10.0 ml/kg	Active	Results significant at p <0.001 level.

BG=Blood glucose GI = Gastric Intubation IG = Intragastric IP =Intraperitoneally IV = Intravenously SC = Subcutaneous IM = Intramuscular

4.1.2. Clinical study

Momordica charantia has been observed decrease serum glucose levels in animal experiments and in a few methodologically weak human studies. These investigations were neither randomized nor blinded, and dosage, toxicity, and adverse effects have not been systematically assessed. Preparation techniques varied, and potency and chemical constituents may have varied accordingly. Nonetheless, the human, animal, and in vitro evidence collectively suggest a moderate hypoglycemic effect of *Momordica charantia* and some of its crude extracts. Reductions in serum glucose levels may occur as soon as 30 minutes after ingestion, peak at 4 hours, and persist for at least 12 hours.

In a clinical trial, Leatherdale et al.(21) conducted a case-series of nine patients with type 2 diabetes mellitus, of whom eight were taking concomitant sulfonylureas. The subjects underwent a baseline glucose tolerance test (GTT), a GTT after ingestion of 50 mL of *Momordica charantia* juice (obtained from approximately 200 g of fresh fruit), and then another GTT after 8-11 weeks of daily ingestion of 0.23 g of fried bitter melon fruit. The GTT performed after the period of fried-fruit ingestion revealed a mean decrease in glucose levels of approximately 6% after one hr. This result does not appear to have been statistically significant. The GTT after juice consumption showed a significant decline in glucose of approximately 12% after one hour. In addition, consumption fried bitter melon for 8-11 weeks reduced glycosylated hemoglobin (Hb_{AIC}) levels 8% from baseline. Because of methodological weakness, including a lack of controls, failure to describe patients baseline characteristic, and inadequate explanation of statistical methods, firm conclusions cannot be drawn.

Welihinda et al. (22) reported a case-series study involving 18 patients with newly diagnosed type 2 diabetes mellitus. The subjects were each given 100 ml of *Momordica charantia* juice 30 minutes before glucose loading for a OGTT. The results were compared with the subjects' own responses to a OGTT on a previous day, when water was administered as control. 73% of the patients showed moderate, significant improvements in OGTT results after taking *Momordica charantia*. It is not clear what baseline difference might have existed in the five nonresponders. Although suggestive, these results cannot be considered conclusive. Even with patients serving as their own controls, the lack of true controls or randomization increases the possibility of confounding. Again, the study was not blinded, and patients baseline characteristics were poorly defined.

Srivastava (26) conducted a case series study involving 12 patients with type 2 diabetes mellitus over 21 days. The patients were not using other treatments, aside from diabetic diets. Each subject received one to two *Momordica charantia* preparations: 1) an aqueous extract, prepared by boiling 100 g of chopped bitter melon in 200 ml of water until the volume was reduced to 100 ml, given daily as a single morning dose, and 2) 5 g of dried fruit powder given three times daily. After three weeks of therapy in the powder group (n=5) showed a non-significant 25% reduction in the mean blood glucose level. In the aqueous extract group (n=7), a significant 54% reduction in the mean blood glucose level was observed, and the mean HbA1C level fell from 8.37% to 6.95% ($p<0.01$). Once again, this study was poorly designed and written. The statistical analysis was not properly described, and controls, a description of the patients' baseline characteristics, and a measurement of fasting glucose levels were absent.

In another clinical study of Ahmed et al.(24), a homogenized suspension of the vegetable pulp of *Momordica charantia* given to 100 cases of moderate NIDDM subjects caused a significant reduction ($P<0.001$) of post-prandial serum glucose in 86% cases and fasting glucose in 5% cases

In a controlled clinical trial, Baldwa et al.(83) studied the effects of bitter melon on blood sugar levels in patients with diabetes. Nineteen subjects were enrolled, including 14 patients with type 1 or type 2 diabetes mellitus. An extraction method was performed to isolate vegetable insulin, which was suspended in sterile water and made available in a subcutaneous form with a concentration of 1.8 mg of vegetable insulin (p-insulin) per 40 unit dose. Nine of the diabetic patients (six with juvenile, one with maturity onset and two with chemical diabetes) were placed on a sliding scale to receive 10 units of this suspension if the fasting blood glucose concentration was <180 mg/dl, 20 units for>250 mg/dl. Five diabetic patients and five healthy volunteers received placebo. a single subcutaneous injection of pure protein (p-insulin) from *Momordica charantia* to nine patients produced a mean decrease in serum glucose levels for the diabetic patients, with effects noted as early as 30 minutes (a 21.5% decrease from a mean baseline glucose concentration of 295 mg/dl), a maximum reduction at a 4 hours (a 49.2% drop), and persistent effects after 12 hours (a 28% drop). In contrast, a mean decrease in serum glucose of about 5% was seen during the study period in both the diabetic patients and the healthy controls. Although these results appear promising, no statistical analysis was performed, and the study was not blinded or randomized. The diabetic patients who received *Momordica charantia* had a

substantially different mean baseline serum glucose concentration from the placebo group (295 versus 210 mg/dl, respectively). Furthermore, both type 1 and type 2 diabetes mellitus were represented in the study; these disease have different etiologies and mechanisms. As a result of these weakness, the results can be considered only preliminary.

In another controlled clinical study, an antihyperglycemic peak effect between 4–8 hr was achieved with subcutaneous polypeptide P adminstration to nineteen juvenile and maturity diabetics patients (63).

Further clinical work is required to be undertaken before these isolated, purified compounds can be marketed. However, in the developing countries, to cut down costs, intake of *Momordica charantia* fruit in form of vegetable should be encouraged as the same has also shown to clinically effective. Keeping the above findings in mind, NIDDM patients should be encouraged to consume *Momordica charantia* as it can reduce the blood sugar and more importantly it can keep them away from developing complications associated with diabetes. At the same time safety is assured as the same has been consumed in diet for centuries.

4.2. Effect on diabetic complications

Complications are frequently encountered in diabetes and these are associated with irreversible functional and structural changes in various organs particularly the kidneys, eyes, nerves and blood vessels.

Momordica charantia has shown promising effects in prevention as well as delay in progression of diabetic complications (nephropathy, neuropathy, gastroapresis, cataract and insulin resistance) in experimental animals (79, 84-87).

Diabetic patients are 17 times more prone to kidney disease and diabetes is now the leading cause of end stage renal disease. With a view to assessing the effect of *Momordica charantia* treatment on development of nephropathy in diabetic animals certain renal functions parameters were measured. STZ diabetic mice had several times higher mean values of serum creatinine (50.0 μmol/l), urinary albumin (1411.3 μg/24 h), urine volume (31.9 ml/24 h) and renal weight (0.59 gm) compared to normal mice. However, in parallel, these values were significantly less (47.5 μmol/l, 1072 μg/24 h, 20.0 ml/24 h & 0.51 g, respectively) in *Momordica charantia* treated animals (84).

The most frequent and disabling complication of DM is diabetic neuropathy, which causes limb pain, sexual dysfunction along with gastrointestinal, genitourinary and cardiovascular symptoms. In one study, to evaluate the effect of *Momordica charantia* on diabetic neuropathy, an aqueous extract of *Momordica charantia* (200 mg/kg) was given to diabetic animals for 50 days. The treatment caused reduction in tail flick latency by 43.6% in comparison to diabetic control animals where it increased by 73.6% compared to normal animals (79).

Diabetic enteropathy results in dyspepsia, heartburn, nausea, vomiting, abdominal pain, constipation, diarrhea and fecal incontinence, a syndrome that is typically seen in NIDDM. These symptoms were found in 76% of diabetic outpatients evaluated at a tertiary referral center (88). In experimental work, gastric transit ratio in STZ (150 mg/kg i.p.) diabetic mice was reduced 83.00% to that of in normal mice and an aqueous extract of *Momordica charantia* (200 mg/kg) normalized this transit time to 90.28%of normal, in addition to causing reduction of plasma glucose (79).

Insulin resistance is another important feature of diabetes has been linked to obesity, hypertension, dyslipidemia and atherosclerosis which, together are responsible for substantial morbidity and premature mortality (89). A fructose rich diet in rats has been shown to induce syndrome X constituting hyperglycemia associated with hyperinsulinemia, hypertriglyceridemia and obesity (90). Oral administration of aqueous *Momordica charantia* extract (400 mg/day for 15 days) to rats fed a fructose rich diet substantially prevented hyperglycemia (63.5 mg/dl versus 75.4 mg/dl in controls; $P<0.001$) and hyperinsulinemia (7.78 ng/dl versus 15.04 ng/dl in controls, $P<0.01$) in comparison with fructose control rats (91).

Diabetes mellitus has been consistently identified in many studies as the most important risk factor for cataract in Western countries (92-94). Although surgery is effective, strategies aimed to prevent or delay development of cataract remains the preferred approach to confront the global problem.

In Rathi et al. experiments, *Momordica charantia* treatment (aqueous extract 200 mg/kg) of alloxan diabetic rats inhibited development of cataract (observed up to 120 days) that was otherwise seen in non-treated diabetic rats at 100 days (85).

In another study, daily administration of a high dose (4 gm/kg) of *Momordica charantia* fruit for 2 months to alloxanized diabetic rats (120 mg/kg) delayed development of cataract to 140–180 days in comparison to 90–100 days in the controls (95).

4.3. Another effects benefit to diabetes mellitus treatment

A few preliminary studies have shown various other pharmacological properties of the plant.

4.3.1. Hypotensive and anti prothrombin activity

Wang et al. (96) observed mild hypotensive response with Momordin. In another study, *Momordica charantia* prolonged prothrombin time by inhibiting activation of factor X by factor VIIa-tissue factor complex or factor IXa (97).

4.3.2. Hypocholesterolemic and anti-oxidant potential

Several experimental studies carried out in normal as well as diabetic animals have shown hypo-cholesterolemic effect by *Momordica charantia* (38, 72, 78, 98-100). Feeding of conjugated octadecatrienoic fatty acid isolated from *Momordica charantia* seed for 4 weeks significantly lowered the plasma lipid peroxidation and erythrocyte membrane lipid peroxidation as well as nonenzymatic liver tissue lipid peroxidation, in sunflower oil fed rats (101). However, in another study, total lipids as well as phospholipid concentrations in heart and brain were significantly higher when karela oil was given compared with linseed oil administered rats (102).

5. Adverse effects

No large-scale studies have been undertaken to establish the safety of *Momordica charantia*. The most commonly reported adverse effects are discussed here.

5.1. Endocrine system

Momordica charantia has been found to lower blood glucose levels in animal studied and in several methodological weak human trials. Proposed mechanisms include insulin-like effects, stimulation of pancreatic insulin secretion, decreased hepatic glucogenesis, increased hepatic glycogen synthesis, and increased peripheral glucose oxidation. Two case reports have documented hypoglycemic coma and convulsions in children after administration of a *Momordica charantia* tea (8).

5.2. Gastrointestinal system

The seeds and outer rind of *Momordica charantia* contain a toxic lectin that inhibits protein synthesis in the intestinal wall. However, this has not been correlated with clinical signs or symptoms in humans (8).

5.3. Genitourinary system

The fertility rate of mice fed with daily bitter melon juice dropped from 90% to 20% in one study. Spermatogenesis was inhibited in dogs fed a bitter melon fruit extract for 60 days. Studies of MAP30 have not shown an effect on human sperm mortality in vitro (8).

5.4. Hematologic system

Individuals with glucose-6-phosphate dehydrogenase deficiency are at risk of developing favism after ingesting bitter melon seeds. Favism is defined by the onset of hemolytic anemia and other symptoms, including headache, fever, stomach pain, and coma. The glycosidic compound vicine, a favism-including chemical, has been isolated from *Momordica charantia*. Glucose-6-phosphate dehydrogenase deficiency and favism are most common in persons of Mediterranean and Middle Eastern lineage (8).

5.5. Hepatic system

Significant increases in γ-glutamyltranferase and alkaline phosphatase have been observed in animals after oral administration of *Momordica charantia* fruit juice and seed extract. These increases have not, however, been associated with significant histopathologic changes in the liver. The clinical relevance in humans has not been studied; caution is warranted, particularly in patients with underlying liver disease (8). Hepatological effects study of *Momordica charantia* are showing in Table 4

5.6. Neurologic system

Headaches have been reported after the ingestion of bitter melon seeds, but detailed information about headache severity and duration is not available (8).

Table 4 Hepatic function study of *Momordica charantia* L. fruits (49)

Part -Origin	Activity Tested For	Type Extract	Test Model	Dosage	Result	Notes/Organism tested
Fruit In dia	Cytochrom e B-5 Increase	H2O Ext	External Mouse	100.0 mcl	Active	
Fruit In dia	Cytochrom e B-5 Increase	H2O Ext	IG Mouse (Liver)	100.0 mcl	Active	Activity was passed translactationally to pups of dams treated with extract for 14 days.
Seed India	Cytochrom e B-5 Increase	H2O Ext	External Mouse	100.0 mcl	Active	
Fruit Pulp India	Cytochrom e B-5 Increase	H2O Ext	Externa Mouse	100.0 mcl	Inactive	
Fruit Pulp India	Cytochrom e B-5 Increase	H2O Ext	IG Mouse (Female) (Liver)	100.0 mcl	Inactive	
Fruit Peel India	Cytochrom e B-5 Increase	H2O Ext	External Mouse	100.0 mcl	Active	
Fruit Peel India	Cytochrom e B-5 Increase	H2O Ext	IG Mouse (Female)	100.0 mcl	Active	Liver activity was passed translactationally to pups of dams treated with extract for 14 days.
Seed India	Cytochrom e B-5 Increase	H2O Ext	IG Mouse (Female) (Liver)	100.0 mcl	Active	
Fruit Peel India	Cytochrome P450 Induction	H2O Ext	IG Mouse (Female)	100.0 mcg	Active	Liver activity was passed translactationally to pups of dams treated with extract for 14 days.
Seed India	Cytochrome P450 Induction	H2O Ext	IG Mouse (Female) (Liver)	100.0 mcl	Active	
Fruit Pulp India	Cytochrome P450 Induction	H2O Ext	IG Mouse (Female) (Liver)	100.0 mcl	Inactive	
Fruit In dia	Cytochrome P450 Induction	H2O Ext e)	IG Mouse (Femal	100.0 mcl	Active	Liver activity was passed translactationally to pups of dams treated with extract for 14 days.
Fruit China	Cytochrome P450 Inhibition	Fruit	Oral Mouse	15.0 % of diet	Inactive	Microsomes-rat-liver.
Fruit Thailand	Cytochrome P450 Inhibition	Fruit	Oral Rat (Male)	12.5 % of diet	Inactive	Microsomes-rat-liver.

5.7. Reproductive system

Studies on male fertility showed α-momorcharin as well as β-momorcharin did not affect luteinizing hormone-induced testosterone production in isolated rat Leydig cells or corticotropin-induced corticosterone production in isolated rat adrenal decapsular cells (103). An alcohol extract of MC seeds (25 mg/100 g body weight) showed potent antispermatogenic, antisteroidogenic and androgenic activities in rats (104). MAP30 had no effect on the motility and vitality of spermatozoa (105).

In conclusion (7), *Momordica charantia* was shown to be safe (no signs of nephrotoxicity and hepatotoxicity and any adverse influence on the food intake, growth organ weights and hematological parameters) in experimental animals when ingested in low doses up to 2 months (17, 98). However, relatively low toxicity of all parts of this plant are also reported when ingested, although toxicity and even death, in laboratory animals has been reported when extracts in high doses were administered intravenously or intraperitoneally (106). Traditionally as well as in experiment *Momordica charantia* has shown abortifacient activity. The fruit and seeds demonstrated greater toxicity than the leaf or aerial parts of the plant. Documented adverse effects of *Momordica charantia* are hypoglycemic coma and convulsions in children, reduced fertility in mice, a favism-like syndrome, increases in gamma-glutamyltransferase and alkaline phosphatase levels in animals, and headaches (8).

6. Use in pregnancy and lactation

Momordica charantia should not be consumed during pregnancy. Several experimental studies demonstrated abortifacient properties of *Momordica* proteins (107-111). Momorcharins produced abortifacient activity in early and midterm pregnancy (109-111) and it was attributed to its inhibitory effect on the differentiating endometrium. Law et al. and Tam et al.(108, 112) attributed abortifacient activity of protein to the effect on implantation of embryos to endometrium, in mouse given on days 4 and 6 of pregnancy. β-Momorcharin was shown to have inhibitory effect on decidualization and endometrium & myometrium cell proliferation of pseudopregnant mouse uterus. In addition, β-Momorcharin also inhibited the biosynthetic activity of the cultured endometrial cells (110). The abortifacient activity of β-momorcharin is seen via (a) blockage of the hatching of embryos from the zona pellucida; (b) decrease in

attachment of the blastocyst; (c) reduction in the trophoblast outgrowth and (d) disruption of inner cell mass development (109).

However, α- and β-momorcharins treatment prior to pregnancy do not affect follicular recruitment & maturation and the animals underwent pregnancy resulting in a litter size similar to that of controls (113).

Teratogenic effect of momorcharins was seen in the cultured mouse embryos at early organogenesis stage (111).

In conclusion, experimental studies demonstrated their ability to induce abortions in rats and mice. Thus, *Momordica charantia* produced antifertility in females as well as male animals sperm production declined, though other studies have shown *Momordica charantia* to be safe during pregnancy. Thus, it is important to undertake detailed work on teratogenic and abortifacient effects of this plant before recommending its use in pregnancy.

7. Drug interactions

Momordica charantia may have additive effects when taken concomitantly with other blood glucose-lowering agents. In a poorly described case-series study, additive glucose-lowering effects (measured with GTTs) were seen in eight of nine subjects when bitter melon juice or fried fruit was taken concomitantly with sulfonylureas (21). A 40-year-old woman with type 2 diabetes mellitus experienced additive glucose-lowering effects when ingesting both the sulfonylurea when ingesting both the sulfonylurea chlorpropamide and a curry-containing *Momordica charantia* and garlic preparation(25). Garlic has been said to have hypoglycemic properties, although human evidence is limited. In rats, oral *Momordica charantia* juice has been found to potentiate the glucose-lowering effects of the sulfonylurea tolbutamide .

8. Dosage and administration

Because of the wide variations in preparations techniques, the optimum dosage of *Momordica charantia* has not been determined. In the available studies, *Momordica charantia* was sometimes administered as a fruit juice doses of 50 ml (21) or 100 ml (22). Juice formulations have been reported to have more potent effects on blood sugar and HbA1C levels than the powder of the sun-dried fruit.(26). However, safety and efficacy have not been established for any specific dosage of *Momordica charantia*.

Subcutaneous administration of *Momordica charantia* has been studied in humans. When used subcutaneously, Baldwa et al. (83) used a sliding scale for vegetable insulin isolated from the bitter melon fruit. The safety, efficacy, and optimum dosage for this formulations and route have not been established.

Data on pediatric dosages are lacking. Extreme caution is warranting in view of the two case reports of hypoglycemic coma in children who were given *Momordica charantia* tea (8, 48).

9. Conclusion

Over the years scientists have verified many of the traditional uses of this bitter plant that continue to be an important natural remedy for various diseases. Concentrated fruit or seed extracts can be found in various herbal preparations (capsules and tablets) that are marketed today. *Momordica charantia* preparations are becoming more widely available in the U.S as well as rest of the world and are employed by practitioners of natural health for treatment of diabetes.

Momordica charantia is used medicinally mainly for the treatment of type 2 diabetes mellitus. Some preliminary evidence suggests that the consumption of *Momordica charantia* as whole fruit, extract, or dried powder may reduce blood sugar levels. Most trials have been small, brief, and poorly designed and reported. Since diabetes mellitus is a chronic condition requiring long-term treatment, a longer and better trial is needed to assess safety and clinical efficacy. Such a study could also help in creating a standard dosage form and dosage schedule.

Role of *Momordica charantia* in diabetes is of paramount importance as this plant serves various purposes in these patients lowers blood sugar, delays complications (nephropathy, neuropathy, gastroparesis and cataract, athereosclerosis) and is anti-infective (diabetics are known to be more susceptible to infections). Moreover till now there is no pharmacological agent that can control diabetic complications. Most importantly it is cheap and easily available in tropical countries. However, standardization of *Momordica charantia* and its antidiabetic component followed by a controlled clinical trial is needed.

Most of the mentioned studies have been conducted using crude preparation of *Momordica charantia* and the chemical profile was not mentioned. However, few studies have demonstrated biological activity of *Momordica charantia* compounds such as charantin, MAP 30, momordin, α and β momorcharins (7).

Diabetes Mellitus

1. Definition and description of diabetes mellitus (2)

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels.

Several pathogenic processes are involved in the development of diabetes. These range from autoimmune destruction of the β-cells of the pancreas with consequent insulin deficiency to abnormalities that result in resistance to insulin action. The basis of the abnormalities in carbohydrate, fat, and protein metabolism in diabetes is deficient action of insulin on target tissues. Deficient insulin action results from inadequate insulin secretion and/or diminished tissue responses to insulin at one or more points in the complex pathways of hormone action. Impairment of insulin secretion and defects in insulin action frequently coexist in the same patient, and it is often unclear which abnormality, if either alone, is the primary cause of the hyperglycemia.

Symptoms of marked hyperglycemia include polyuria, polydipsia, weight loss, sometimes with polyphagia, and blurred vision. Impairment of growth and susceptibility to certain infections may also accompany chronic hyperglycemia. Acute, life-threatening consequences of uncontrolled diabetes are hyperglycemia with ketoacidosis or the nonketotic hyperosmolar syndrome.

Long-term complications of diabetes include retinopathy with potential loss of vision; nephropathy leading to renal failure; peripheral neuropathy with risk of foot ulcers, amputations, and Charcot joints; and autonomic neuropathy causing gastrointestinal, genitourinary, and cardiovascular symptoms and sexual dysfunction. Patients with diabetes have an increased incidence of atherosclerotic cardiovascular, peripheral arterial, and cerebrovascular disease. Hypertension and abnormalities of lipoprotein metabolism are often found in people with diabetes.

The vast majority of cases of diabetes fall into two broad etiopathogenetic categories (discussed in greater detail below). In one category, type 1 diabetes, the cause is an absolute

deficiency of insulin secretion. Individuals at increased risk of developing this type of diabetes can often be identified by serological evidence of an autoimmune pathologic process occurring in the pancreatic islets and by genetic markers. In the other, much more prevalent category, type 2 diabetes, the cause is a combination of resistance to insulin action and an inadequate compensatory insulin secretory response. In the latter category, a degree of hyperglycemia sufficient to cause pathologic and functional changes in various target tissues, but without clinical symptoms, may be present for a long period of time before diabetes is detected. During this asymptomatic period, it is possible to demonstrate an abnormality in carbohydrate metabolism by measurement of plasma glucose in the fasting state or after a challenge with an oral glucose load.

The degree of hyperglycemia (if any) may change over time, depending on the extent of the underlying disease process (Figure 4). A disease process may be present but may not have progressed far enough to cause hyperglycemia. The same disease process can cause impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) without fulfilling the criteria for the diagnosis of diabetes. In some individuals with diabetes, adequate glycemic control can be achieved with weight reduction, exercise, and/or oral glucose-lowering agents. These individuals therefore do not require insulin. Other individuals who have some residual insulin secretion but require exogenous insulin for adequate glycemic control can survive without it. Individuals with extensive β-cell destruction and therefore no residual insulin secretion require insulin for survival. The severity of the metabolic abnormality can progress, regress, or stay the same. Thus, the degree of hyperglycemia reflects the severity of the underlying metabolic process and its treatment more than the nature of the process itself.

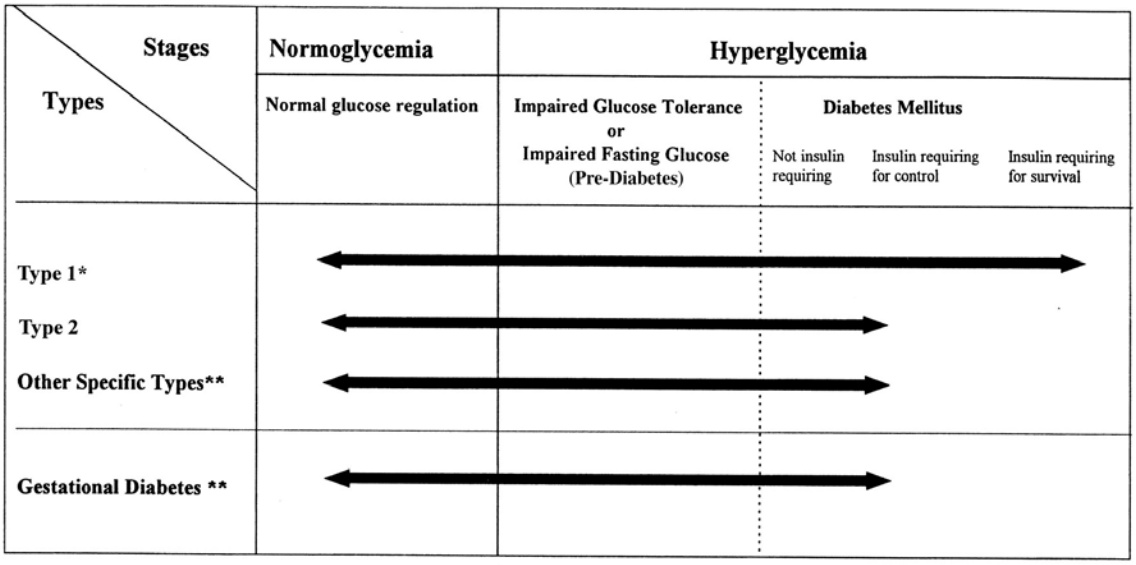


Figure 4 Disorders of glycemia: etiologic types and stages. *Even after presenting in ketoacidosis, these patients can briefly return to normoglycemia without requiring continuous therapy (i.e., "honeymoon" remission); **in rare instances, patients in these categories (e.g., Vacor toxicity, type 1 diabetes presenting in pregnancy) may require insulin for survival.

2. Classification of diabetes mellitus and other categories of glucose regulation (2)

Assigning a type of diabetes to an individual often depends on the circumstances present at the time of diagnosis, and many diabetic individuals do not easily fit into a single class. For example, a person with gestational diabetes mellitus (GDM) may continue to be hyperglycemic after delivery and may be determined to have, in fact, type 2 diabetes. Alternatively, a person who acquires diabetes because of large doses of exogenous steroids may become normoglycemic once the glucocorticoids are discontinued, but then may develop diabetes many years later after recurrent episodes of pancreatitis. Another example would be a person treated with thiazides who develops diabetes years later. Because thiazides in themselves seldom cause severe hyperglycemia, such individuals probably have type 2 diabetes that is exacerbated by the drug. Thus, for the clinician and patient, it is less important to label the particular type of diabetes than it is to understand the pathogenesis of the hyperglycemia and to treat it effectively.

2.1. Type 1 diabetes (ß-cell destruction, usually leading to absolute insulin deficiency)

2.1.1. Immune-mediated diabetes.

This form of diabetes, which accounts for only 5–10% of those with diabetes, previously encompassed by the terms insulin-dependent diabetes (IDDM), type I diabetes, or juvenile-onset diabetes, results from a cellular-mediated autoimmune destruction of the ß-cells of the pancreas. Markers of the immune destruction of the ß-cell include islet cell autoantibodies, autoantibodies to insulin, autoantibodies to glutamic acid decarboxylase (GAD_{65}), and autoantibodies to the tyrosine phosphatases IA-2 and IA-2ß. One and usually more of these autoantibodies are present in 85–90% of individuals when fasting hyperglycemia is initially detected.

2.1.2. Idiopathic diabetes.

Some forms of type 1 diabetes have no known etiologies. Some of these patients have permanent insulinopenia and are prone to ketoacidosis, but have no evidence of autoimmunity. Although only a minority of patients with type 1 diabetes fall into this category, of those who do, most are of African or Asian ancestry. Individuals with this form of diabetes suffer from episodic ketoacidosis and exhibit varying degrees of insulin deficiency between episodes. An absolute requirement for insulin replacement therapy in affected patients may come and go.

2.2. Type 2 diabetes (ranging from predominantly insulin resistance with relative insulin deficiency to predominantly an insulin secretory defect with insulin resistance)

This form of diabetes, which accounts for ~90–95% of those with diabetes, previously referred to as non-insulin-dependent diabetes, type II diabetes, or adult-onset diabetes, encompasses individuals who have insulin resistance and usually have relative (rather than absolute) insulin deficiency At least initially, and often throughout their lifetime, these individuals do not need insulin treatment to survive. There are probably many different causes of this form of diabetes. Although the specific etiologies are not known, autoimmune destruction of ß-cells does not occur, and patients do not have any of the other causes of diabetes listed above or below.

Most patients with this form of diabetes are obese, and obesity itself causes some degree of insulin resistance. Patients who are not obese by traditional weight criteria may have an increased percentage of body fat distributed predominantly in the abdominal region. Ketoacidosis seldom occurs spontaneously in this type of diabetes; when seen, it usually arises in association with the stress of another illness such as infection. This form of diabetes frequently goes

undiagnosed for many years because the hyperglycemia develops gradually and at earlier stages is often not severe enough for the patient to notice any of the classic symptoms of diabetes. Nevertheless, such patients are at increased risk of developing macrovascular and microvascular complications. Whereas patients with this form of diabetes may have insulin levels that appear normal or elevated, the higher blood glucose levels in these diabetic patients would be expected to result in even higher insulin values had their ß-cell function been normal. Thus, insulin secretion is defective in these patients and insufficient to compensate for insulin resistance. Insulin resistance may improve with weight reduction and/or pharmacological treatment of hyperglycemia but is seldom restored to normal. The risk of developing this form of diabetes increases with age, obesity, and lack of physical activity. It occurs more frequently in women with prior GDM and in individuals with hypertension or dyslipidemia, and its frequency varies in different racial/ethnic subgroups. It is often associated with a strong genetic predisposition, more so than is the autoimmune form of type 1 diabetes. However, the genetics of this form of diabetes are complex and not clearly defined.

2.3. Other specific types of diabetes

2.3.1. Genetic defects of the ß-cell.

Several forms of diabetes are associated with monogenetic defects in ß-cell function. These forms of diabetes are frequently characterized by onset of hyperglycemia at an early age (generally before age 25 years). They are referred to as maturity-onset diabetes of the young (MODY) and are characterized by impaired insulin secretion with minimal or no defects in insulin action.

2.3.2. Genetic defects in insulin action.

There are unusual causes of diabetes that result from genetically determined abnormalities of insulin action. The metabolic abnormalities associated with mutations of the insulin receptor may range from hyperinsulinemia and modest hyperglycemia to severe diabetes.

2.4. Gestational diabetes mellitus (GDM)

GDM is defined as any degree of glucose intolerance with onset or first recognition during pregnancy. The definition applies regardless of whether insulin or only diet modification is used for treatment or whether the condition persists after pregnancy. It does not exclude the possibility that unrecognized glucose intolerance may have antedated or begun concomitantly

with the pregnancy. Deterioration of glucose tolerance occurs normally during pregnancy, particularly in the 3rd trimester.

2.5. Impaired glucose tolerance (IGT) and impaired fasting glucose (IFG)

An intermediate group of subjects whose glucose levels not meeting criteria for diabetes, are nevertheless too high to be considered normal. This group is defined as having

- fasting plasma glucose (FPG) levels ≥100 mg/dl (5.6 mmol/l) but <126 mg/dl (7.0 mmol/l) or
- 2-h values in the oral glucose tolerance test (OGTT) of ≥140 mg/dl (7.8 mmol/l) but <200 mg/dl (11.1 mmol/l).

Thus, the categories of FPG values are as follows:

FPG <100 mg/dl (5.6 mmol/l) = normal fasting glucose;

FPG 100–125 mg/dl (5.6–6.9 mmol/l) = IFG (impaired fasting glucose);

FPG >126 mg/dl (7.0 mmol/l) = provisional diagnosis of diabetes (the diagnosis must be confirmed, as described below).

The corresponding categories when the OGTT is used are the following:

2-h postload glucose <140 mg/dl (7.8 mmol/l) = normal glucose tolerance;

2-h postload glucose 140–199 mg/dl (7.8–11.1 mmol/l) = IGT (impaired glucose tolerance);

2-h postload glucose ≥200 mg/dl (11.1 mmol/l) = provisional diagnosis of diabetes (the diagnosis must be confirmed, as described below).

Patients with IFG and/or IGT are now referred to as having "pre-diabetes" indicating the relatively high risk for development of diabetes in these patients. In the absence of pregnancy, IFG and IGT are not clinical entities in their own right but rather risk factors for future diabetes as well as cardiovascular disease. IFG and IGT are associated with the metabolic syndrome, which includes obesity (especially abdominal or visceral obesity), dyslipidemia of the high-triglyceride and/or low-HDL type, and hypertension. It is worth mentioning that medical nutrition therapy aimed at producing 5–10% loss of body weight, exercise, and certain pharmacological agents have been variably demonstrated to prevent or delay the development of diabetes in people with IGT; the potential impact of such interventions to reduce cardiovascular risk has not been examined to date.

Note that many individuals with IGT are euglycemic in their daily lives. Individuals with IFG or IGT may have normal or near normal glycated hemoglobin levels. Individuals with IGT

often manifest hyperglycemia only when challenged with the oral glucose load used in the standardized OGTT.

3. Pathogenesis of diabetes

In order to better understand the role of each drug class in the treatment of diabetes, it is important to have a basic understanding of the pathogenesis of diabetes (Figure 5) and the interplay between insulin and glucose at different sites . Postprandial elevations in serum glucose levels stimulate insulin synthesis and release from pancreatic β-cells. Insulin secreted into the systemic circulation binds to receptors in target organs (skeletal muscle, adipose tissue, liver). Insulin binding initiates a cascade of intracellular signal transduction pathways that inhibits glucose production in the liver, suppresses lipolysis in adipose tissue and stimulates glucose uptake into target cells (muscle and fat) by mechanisms such as the translocation of vesicles that contain glucose transporters to the plasma membrane.

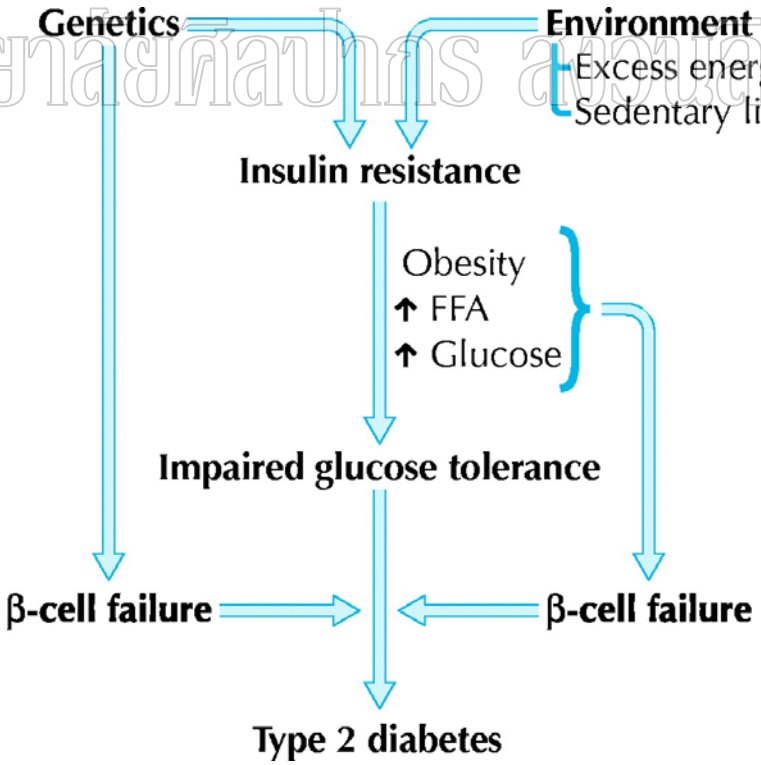


Figure 5 Overveiw of the pathogenesis of type 2 diabetes mellitus. FFA = free fatty acids.

Type 2 diabetes is a metabolic disorder that results from complex interactions of multiple factors and is characterized by 2 major defects: decreased secretion of insulin by the pancreas and resistance to the action of insulin in various tissues (muscle, liver and adipose), which results in impaired glucose uptake. The precise molecular mechanism of insulin resistance is not clearly understood, but deficits in the postinsulin receptor intracellular signaling pathways are believed to play a role. Insulin resistance, which is usually present before the onset of diabetes, is determined by a number of factors, including genetics, age, obesity and, later in the disease, hyperglycemia itself. Excess visceral adiposity, dyslipidemia and hypertension often accompany insulin resistance. Other findings may include impaired fibrinolysis, increased platelet aggregation, vascular inflammation, endothelial dysfunction and premature atherosclerosis. The inability to suppress hepatic glucose production is a major contributor to the fasting hyperglycemia seen in diabetes.

The increase in lipolysis by adipose cells that are resistant to insulin and the subsequent increased levels of circulating free fatty acids also contribute to the pathogenesis of diabetes by impairing β-cell function, impairing glucose uptake in skeletal muscles and promoting glucose release from the liver. In addition to its role as a source of excess circulating free fatty acids, adipose tissue has emerged in the last decade as an endocrine organ. Adipose tissue is a source of a number of hormones (adipo-cytokines or "adipokines") that appear to regulate insulin sensitivity (e.g., adiponectin, resistin), as well as appetite regulation (e.g., leptin), inflammation (e.g., tumour necrosis factor-α , interleukin-6) and coagulability (e.g., plasminogen activator inhibitor-1). Recent evidence suggests that the inflammatory cytokines are derived from infiltrating macrophages within adipose tissue beds rather than from the adipocytes themselves..

The initial response of the pancreatic β cell to insulin resistance is to increase insulin secretion. Elevated insulin levels can be detected before the development of frank diabetes. As the disease progresses, pancreatic insulin production and secretion decreases, which leads to progressive hyperglycemia. Postprandial hyperglycemia can precede fasting hyperglycemia. Hyperglycemia itself exacerbates insulin resistance and impairs insulin secretion so called "glucotoxicity." The cause of progressive pancreatic β-cell failure is not completely understood, but it appears to result from a number of factors, including genetic determinants, chronic

inflammation, glucotoxicity and the deleterious effects of elevated levels of free fatty acids on β - cell function so called "lipotoxicity." (114).

4. Treatment of type II diabetes mellitus

The interacting defects in multiple organs muscle, liver, adipose tissue and pancreas generate the pathogenic milieu that results in diabetes. Various classes of oral hypoglycemics agents are now available that target the different pathophysiologic factors contributing to diabetes Figure 6:

- α-glucosidase inhibitors to delay intestinal carbohydrate absorption,

- biguanides to target hepatic insulin resistance,

- insulin secretagogues to increase pancreatic insulin secretion,

- insulin sensitizers or thiazolidinediones to target adipocyte and muscle insulin resistance,

- intestinal lipase inhibitor or orlistat to inhibit fat absorption and promote weight loss in obese patients (114).

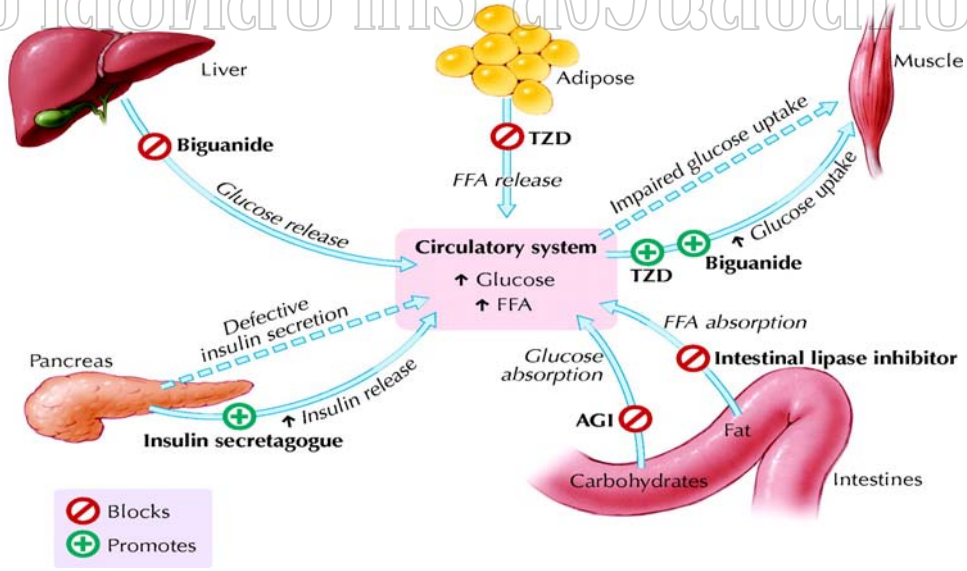


Figure 6 Major target organs and actions of orally administered antihyperglycemic agents in type 2 diabetes mellitus. TZD = thiazolidinedione; FFA = free fatty acid; AGI = α-glucocidase inhibitor.

Blood sugar tests

1. Definition

Blood sugar tests include several different tests that measure the amount of sugar (glucose) in a person's blood. These tests are done either on an empty stomach, or after consuming a meal or premeasured glucose drink. Blood sugar tests are done primarily to diagnose and evaluate a person with diabetes mellitus.

2. Purpose

The body uses sugar, also called glucose, to supply the energy it needs to function. People get sugar from their diet and from their body tissues. Insulin is made by the pancreas and affects the outer membrane of cells, making it easy for glucose to move from the blood into the cells. When insulin is active, blood glucose levels fall. Sugar from body tissues is stored in the form of glycogen. When glycogen is active, blood glucose levels rise.

After a meal, blood glucose levels rise sharply. The pancreas responds by releasing enough insulin to take care of all the newly added sugar found in the body. The insulin moves the sugar out of the blood and into the cells. Only then does the blood sugar start to level off and begin to fall. A person with diabetes mellitus either does not make enough insulin, or makes insulin that does not work properly. The result is blood sugar that remains high, a condition called hyperglycemia.

3. Description

There are a variety of ways to measure a person's blood sugar.

3.1. Whole blood glucose test

Whole blood glucose testing can be performed by a person in his or her home, and kits are available for this purpose. The person pricks his or her finger (a finger stick) with a sterile sharp blade from the kit. A single drop of blood is placed on a strip in a portable instrument called a glucometer. The glucometer quickly determines the blood sugar and shows the results on a small screen in usually a few seconds.

3.2. Fasting plasma glucose test

The fasting plasma glucose test is done on an empty stomach. For the eight hours before the test, the person must fast (nothing to eat or drink, except water). The person's blood is drawn

from a vein by a healthcare worker. The blood sample is collected into a tube containing an anticoagulant. Anticoagulants stop the blood from clotting. In the laboratory, the tube of blood spins at high speed within a machine called a centrifuge. The blood cells sink to the bottom and the liquid stays on the top. This straw-colored liquid on the top is the plasma. To measure the glucose, a person's plasma is combined with other substances. From the resulting reaction, the amount of glucose in the plasma is determined.

3.3. Oral glucose tolerance test

The oral glucose tolerance test is done to see how well the body handles a standard amount of glucose. This test measures the amount of glucose in a person's plasma before and two hours after drinking a large premeasured beverage containing glucose. The person must eat a consistent diet, containing at least 150 grams of carbohydrates each day, for three days before this test. For eight hours before the test, the person must fast. A healthcare provider draws the first sample of blood at the end of the fast to determine the glucose level at the start of the test. The healthcare provider then gives the person a beverage containing 75 g of glucose. Two hours later, the person's blood is drawn again. These blood samples are centrifuged and processed in the laboratory. A doctor can then compare the before and after glucose levels to see how well the body processed the sugar. patient should intake carbohydrate intake at least 150 g and fasting at least 10-12 hr before the OGT test.

3.4. Two-hour postprandial blood glucose test

The two-hour postprandial blood glucose test measures the amount of glucose in plasma after a person eats a specific meal containing a certain amount of sugar. Although the meal follows a predetermined menu, it is difficult to control many factors associated with this testing method .

CHAPTER 3

METHOD OF STUDY

Research Design

A randomized, double-blind, placebo-controlled cross over study was undertaken. The first 15 subjects were initially assigned to take placebo and another 15 were assigned to take *Momordica charantia* fruit juice freeze dried capsules 1 dose (Period 1). After a 1 week washout period, the participants received the alternative treatment (Period 2). The *Momordica charantia* fruit juice freeze dried capsules preparation 1 dose contained the *Momordica charantia* fruit juice freeze dried powder 1,800 mg which is equivalent to 100 ml of fresh fruit juice and 300 g of fresh pulp. The randomization was performed by the pharmacist who has nothing to do in this study with a random number generating table. A copy of the randomization code was kept secure by the hospital pharmacy and was available to the investigator only in emergency.

Subjects

The subjects of present study were screened from people in Tambon Saensook, Amphur Muang, Chonburi. A total of 86 cases were screened for inclusion in the study by criteria

- FPG range 100-125 mg/dl and were considered to be prediabetes
- age between 30 to 60 years old
- untreated with any antihyperglycemic agents.

They were excluded from the study if:

1. Found any disease that may be harmful to their health or had any cause of hyperglycemia such as:
   - liver disorder
   - renal disorder
   - endocrinologic disorder such as thyroid disease
   - gastrointestinal disorder that affect gastrointestinal absorption e.g. short bowel syndrome

- cardiovascular disorder
- metabolic disorder

2. Current or previous (in the preceding 2 weeks before eligible to the study) use of drugs or herbs that affect blood glucose level

- Antihypertensive agents; Diuretics eg. thaizide, furosemide

β-adrenergic blockers

α_2-agonist

Ca^{2+} channel blockers

- Anti-inflammatory agents; Glucocorticoid

Nonsteroidal antiinflamatory agents

- Others; Estrogen/Progesterone or any contraceptives

Phenytoin

Pantamidine

Nicotinic acid

Antituberculous agents

smoking

3. Found diabetic complication sign
4. Being pregnant and planning to be

At the end, a total of 30 subjects were eligible to participate in this study.

Research Instruments

1. Materials

1.1. Momordica charantia L. fruit juice freeze dried capsules

1.1.1. Preparation

Momordica charantia L. fruit juice freeze dried capsules were prepared by Herbal product R&D Devision, ChaophyaAbhaibhubejhr hospital Foundation, Prachinburi with following procedures:

1. Fresh unripe fruits of Momordica charantia L. were obtained from the Prachinburi province market, washed well and removed the seed.

2. The freshly part was then cut into thin slide and grinded by electronic machine.

3. To obtain the juice, the pulp was then squeezed in a 4 layers of filter cloth.

4. Then the juice was centrifuged at 8,000 g for 10 minutes

5. The supernatant was decanted and the crude extract was lyophilized and kept at 4°C.

6. Then filled lyophilized powder into capsule No. 0. Each capsule contained 450 mg, obtained from 25 ml of fresh fruit juice which from 75 g of fresh pulp.

7. Then gave 4 capsules for 1 dose, which was equivalent to 100 ml of fresh fruit juice and 300 g of fresh pulp.

1.1.2. Quality Control

1. Material

- Study product: lyophilized *Momordica charantia* L. 450 mg. capsule

- Chemicals: Solvents were Sulfuric acid AR, Methanol AR, Dichloromethane AR and absolute ethanol AR

Spraying reagent was 10% sulfuric acid in ethanol

- Reference compound was charantin, which was isolated from fruit of *M. charantia* L. and identified as a mixture of sitosteryl glucoside and clerosteryl glucoside.

- Instrument: High performance thin layer chromatography (HPTLC):

Stationary phase was TLC aluminium sheets of silica gel GF254, precoated, 20x20 cm, layer thickness 0.25 nm, Merck (No. 5554)

- Equipment: Centrifugator (Sorvall, USA)

TLC-tank size 13 x 13x 5 cm (CAMAG, Germany)

Spraying bottle

Blender

2. Methods

- Preparation of standard solution

A charantin was accurately weighed, 1 mg into a 10 ml volumetric flask. Added 2 ml of dichloromethane – methanol (1:1, v/v) and mixed until the clear solution was obtained. Adjusted to volume with methanol and mixed. The final concentration of standard solution was 0.1 mg/ml.

- Preparation of sample solution

Accurately weighed 500 mg of sample was mixed with methanol 10 ml and filtered with filter paper. Piped 5 ml into evaporating dish and dried on water bath. Added 1 ml of methanol.

- High performance thin layer chromatography (HPTLC)

Stationary phase : TLC plates silica gel GF_{254} 10 x10 cm

Sample application : The standard solution and sample solution were applied by CAMAG Linomat 5. The volume of standard solution (0.2, 0.4, 0.6, 0.8 and 1 μl) and 2 μl of sample solution were applied to adsorbent.

Mobile phase: Dichloromethane-methanol (85:15)

Detection: Spraying with 10% sulfuric acid in ethanol spraying agent and UV absorption at 390 nm. The chromatogram and retention time was recorded.

- Quantitative analysis of charantin in sample

The determination of the content of charantin in sample was performed by the standard calibration curve. The standard calibration plot was constructed by the least square linear regression of the peak area of charantin versus amount. Each determination was carried out in triplicate.

3. Results

The concentrations of standard solution were prepared in the range 0.2 to 1 μg/ml. The calibration curve of charantin was shown. The result of regression coefficient (r^2) was 0.9988. The linear regression equation was y = 7,807.8x – 301.61 (Figure 7). The standard curve was established and used for the determination of charantin in sample from fruit of *M. charantia* L. Table 4.

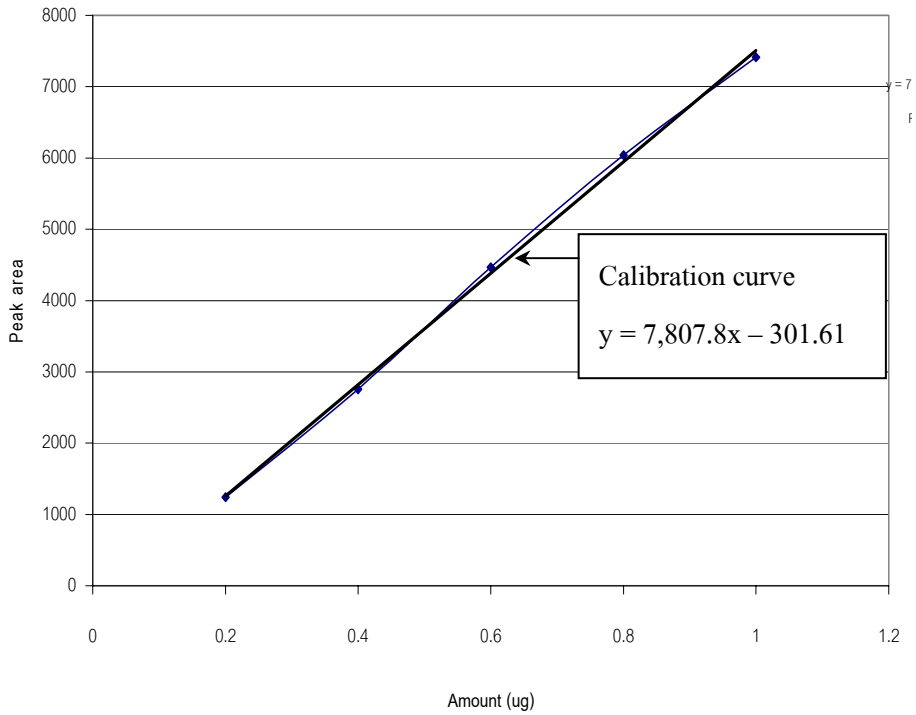


Figure 7 The calibration curve of charantin

Table 5 Shows percent yield (w/w) of charantin amount in *Momordica charantia* fruit juice freeze dried capsules

Sample	Percent yield of Charantin in lyophilized *M. charantia* fruit juice			Statistic	
	Track 1	Track 2	Track 3	Mean	SD
Freeze dry 1st time	0.0436	0.0426	0.0429	0.0430	0.0005
Freeze dry 2nd time	0.0422	0.0419	0.0431	0.0424	0.0006

In each dose, the subject took 4 capsules of 450 mg *Momordica charantia* fruit juice freeze dried powder, which contained charantin about 0.774 mg (0.043 x 4.5 x 4; Table 5)

1.2. Placebo

The control supplement was consisted of 350 g of corn starch, which had no significant caloric content.

2. Study measurements

2.1. Oral glucose tolerance test

After an overnight fast at least 12 hrs, oral glucose tolerant test was performed by the following steps:

- At time 0 hr, fasting blood sugar was measured as baseline (BS0) then subjects in group 1 were asked to take *Momordica charantia* fruit juice frozen dried capsules and group 2 were asked to take 4 capsules of placebo.

- At time ½ hr after *Momordica charantia* fruit juice freeze dried capsules or placebo eating, the subjects took 75 g of oral glucose then blood sugar were measure as BG1

- At time 1 to 2 ½ hrs, measured blood sugar every ½ hr until finish at time of 2 ½ hr. the obtained blood sugar levels were labeled as BG2, BG3, BG4 and BG5 respectively.

Capillary blood sample were obtained by fingertip puncture using needle (ACCU-CHEK® Softclix) and the blood glucose levels were estimated by oxygen-insensitive electrochemical biosensor (ACCU-CHEK®Advantage) that use glucose dehydrogenase enzyme method as a test strip (Advantage II®).

Blood glucose concentrations were estimated as area under the glucose tolerance curve (AUC) from 0 to 2 ½ hrs. of time point by NCSS test and PASS test software

2.2. Safety assessment

Subject obtained laboratory tests for safety assessment during screening (before OGTT of period 1), and 1 week after OGTT of period 2, those tests were

- SGOT, SGPT, serum albumin (SAlb) for examine liver function.

- Serum creatinin (SCr) for renal function examinination.

In addition, adverse events were monitored through out the study.

2.3. Twenty four hours diet recall (24 hrs diet recall)

Subjects were asked to recall the exact food eaten during the previous 24 hours, or the preceding day before performing the OGTT. Details description of foods, beverages, and snacks consumed were recorded by interviewers by using food record shown in Appendix B.

Food data was converted into raw weight by using Food Code ND.2, handbook for modifying the 24-hour dietary recall into the quantity of food intake. Then bring the data to analyze for food composition by using INMUCAL V.4.0, the computerized program from Nutrition Research Institute, Mahidol University. The dietary analysis through computer indicated the intake of carbohydrate, protein, and fat amount (g) and then calculated to energy intake (kcal) (Appendix B).

2.4. Physical activity assessment

Participants were asked by interviewer for recording in physical activity questionnaires. The classification of activity was determined by using scoring protocol shown in Appendix C.

Study Procedures

1. Subject selection

Selected the volunteers by screening the people from Tambon Saensook, Amphur Muang, Chonburi, with the following requirements:

- Prediabetic cases (FPG 100-125 mg/dl)
- Age between 30-60 years old
- Untreated with any hypoglycemic drugs

2. Inform and consent

Selected volunteers from item 1, and informed them about the details of this study showing in consent form in Appendix A. Then they were asked to consent of participation in this study and signed in consent form (Appendix A)

3. History review and physical examination

Selected cases from item 2 to conducted physical examination and to review individual history, then recorded the results as base line information. The following items were recorded:

- Physical examination results; blood pressure (BP), pulse rate, weight (wt), height (ht)
- Liver function test; SGOT, SGPT and SAlb
- Renal function test; SCr
- Lipid profile; Cholesterol, Triglyceride, HDL and LDL
- Physical activity assessment by using physical activity questionnaires (Appendix C).

4. Exclusion from study

After physical examination, subjects who met the exclusion criteria (showing in subjects item) were excluded from the study.

5. Random allocation

30 Subjects were divided into 2 groups by randomization within subjects trial method for simple cross over design:

- Group 1; 15 subjects were treated by placebo for the first time, and followed by *Momordica charantia* fruit juice freez dried capsules for the second time
- Group 2; The rest of 15 subjects were treated by *Momordica charantia* fruit juice freez dried capsules for the first time, and followed by placebo in the second time.

Each subject received individual code for intervention.

6. Subject preparation

Participants were made the first appointment and asked to do the followings:

- Not to drink or eat anything after 20.00 o'clock before the appointment date.
- But before 20.00 o'clock, participants should eat enough food especially in carbohydrate group which should not take less than 150 g/d.
- Record the exact food eaten during the previous 24 hours, or the preceding day before performing the OGTT into food record form showing in Appendix B.

7. The first appointment

Step 1; When the volunteers arrived at the hospital, they were measured the fasting blood sugar (define as BG10).

Step 2; Asked volunteers to take the first experiment capsules.

Step 3; Waited for 30 min

Step 4; Had volunteers to take glucose for 75 g

Step 5; After volunteers took glucose, measured and recorded their blood glucose level and then repeated every 30 min for 5 times (define as BG11-15). While waiting for measuring blood glucose, subjects were interviewed to recall their 24 hr diet.

Step 6; Made the second appointment 1 week later.

8. The second appointment

Conducted the same processes like the first appointment (item 6) but defining each time blood glucose to be BG20-25 instead of BG10-15 and then made the third appointment at 1 week later.

9. The third appointment

Conducted the following examinations:

- Physical examination
- Liver function test; SGOT, SGPT and SAlb
- Renal function test; SCr

And completed collecting data

10. Collecting the data

Gathered the subject's data as the following

1. Subject's characteristic data

- Age
- Gender
- Weight (kg), height(cm) and body mass index (BMI) calculated from weight(kg) and height (m).
- Physical examination result such as blood pressure and pulse rate.
- Amount of carbohydrate consumed (g), calories intake from carbohydrate consumed and total calories intake (kcal) before the test for 24 hrs.

2. Study variables

- Blood glucose level of each time (0, ½, 1, 1½, 2 and 2½ hrs.) point as the BG10-BG15 for the first period and BG20-BG25 for the second period respectively.
- Area under the curve as AUC1 for period 1 and AUC2 for period2 of glucose tolerance curve

3. Safety outcome

- Liver function test as SGOT1, SGPT1 and SAlb1 before the study and SGOT2, SGPT2 and SAlb2 at the end of the study
- Renal function test as SCr1 before the study and SCr2 at the end of the study

Statistical Analysis

Results from subjects completing both treatments were analyzed by followings:

1. Computerized SPSS version 13 demo was used to analyze the descriptive statistics of the data including percentage, means, and standard deviation.

2. AUC of OGT curve of individual subjects were calculated from 0 to 2 ½ hrs of time point by NCSS test and PASS test software

3. Mean AUC and BG1, 2, 3, 4, 5 at ½ , 1, 1½ and 2 hrs time points respectively, which obtained from OGTT when treated with *Momordica Charantia* fruit juice freez dried capsules, compared with the results when obtained the placebo by Cross over analysis using NCSS test and PASS test computerized program.

4. Carbohydrate intake before period 1 and period 2 obtained from 24 hrs diet recall in IGT subgroup of group 1 compared with carbohydrate intake in group 2 by Nonparametric two Independent samples test using SPSS computerized program

5. Safety values such as SGOT, SGPT, SAlb, and SCr before and after study were compared by Pair samples T test using SPSS computerized program

6. Using two-sided 5% significance level and the results were considered significant if the two-tailed P value was <0.05.

7. NCSS test and PASS test software was used for estimate power to detect a mean difference of 5 of the observe result. The data given a common standard deviation about 20 to 70 when samples per group were 15 cases .

CHAPTER 4

RESULTS

Characteristics data

The 30 subjects were eligible for inclusion in the study were randomized into 2 groups

1. Group 1 were treated with placebo in period 1 then MC in period 2. This sequence define as P-MC

2. Group 2 were treated with MC in period 1 then placebo in period 2. This sequence define as MC-P

The characteristics of subjects in this study have been summarized in Table 6. As a group, the study subjects had a number of female (83.3 %) more than male (16.7 %), and tended to be obesity (70 %).

Table 6 Subjects' characteristic data

Characteristic data	Total subjects		IGT Subgroup	
	Subjects	Range or %	Subjects	Range or %
Gender				
- No. of male	5	16.7 %	3	21.4 %
- No. of female	25	83.3 %	11	78.6 %
Mean age (year)$\pm$ SD	45.67 $\pm$ 8.04	30-60	42.86 $\pm$ 7.93	30-60
Mean weight (kg) $\pm$ SD	66.65 $\pm$ 10.06	45.6-86.3	68.01 $\pm$ 11.22	52-86.3
Mean height (cm) $\pm$ SD	157.1 $\pm$ 7.04	143-175	158.57 $\pm$ 7.85	149-175
Mean BMI (kg/m^2) $\pm$ SD	27.07 $\pm$ 3.62	20.9-33.82	27.16 $\pm$ 4.46	20.9-33.82
BMI classification				
- No.of normal cases	5	16.7 %	4	28.6%
- No. of overweight cases	4	13.3 %	1	7.1%
- No. of obesity cases	21	70 %	9	64.3%

Characteristic data	Total subjects		IGT Subgroup	
	Subjects	Range or %	Subjects	Range or %
Systolic BP (mm Hg)	120.7 ± 15.15	96-159	118.71±17.33	100-152
Diastolic BP(mm Hg)	77.03 ± 11.03	53-94	76.5 ± 8.73	68-90
Pulse rate (beats/min)	78.67 ± 8.15	68-99	78.07 ± 7.54	68-96
FPG (mg/dl)	104 ± 5.79	100-123	105.93 ± 6.91	100-123
Physical activity				
- No. of inactive cases	19	63.3 %	10	71.4
- No. of minimally active	11	36.7 %	2	28.6
Average energy intake/d (kcal/d)	2,595.66 ± 871.82	1,249.8-4,477.75	2,791.25±	1,249.8-3,785.1
Number of subjects	30		14	
- Group 1	15		7	
- Group 2	15		7	

a value = mean ± SD

Research outcome measurement

A total of 30 prediabetic subjects diabetes completed the entire cross-over study. Outcome measured show in following.

1. Effects on glycemic control

The research results showing in Table 7-8 and Figure 8-21

1.1. Overall subjects analysis

1.1.1. Area under the blood glucose concentration-time curve ($AUC_{0\text{-}2½\ hr}$)

As display in Table 7 and Figure 9. The mean AUC obtained from placebo and *Momordica charantia* L fruit juice freeze dried capsules (MC) treatment in a 2x2 cross-over study are not significantly different at the 0.05 significance level (the actual significance level was 0.18). The design had 15 subjects in sequence 1 (P-MC) and 15 subjects in sequence 2 (MC-P). The average response to placebo was 401.67 mg hr/dl and the average response to MC was 388.03 mg hr/dl. Therefore taking of MC had no significant effects in decreasing AUC that instead of glucose concentration after their single 1800 g dose intake compare with the placebo.

A preliminary test failed to reject the assumption of equal period effects at the 0.05 significance level (the actual significance level was 0.30), and failed to reject the assumption of equal carryover effects at the 0.05 significance level (the actual significance level was 0.62). Therefore no period effect or carryover effect were identified for the observed result.

1.1.2. Blood glucose at time 0, ½, 1, 1½, 2, 2½ hr

As display in Table 7 and Figure 10-14. The means blood glucose at time ½, 1, 1½, 2, 2½ hr obtained from placebo and MC treatment in a 2x2 cross-over study are not significantly different at the 0.05 significance level (the actual significance level was 0.59, 0.98, 0.08, 0.27, and 0.31 mg/dl respectively). The design had 15 subjects in sequence 1 (P-MC) and 15 subjects in sequence 2 (MC-P). The average response to placebo treatment was 152.13, 185.30, 185.67, 160.33 and 131.40 mg/dl respectively) and the average response to treatment MC was 148.47, 185.43, 172.87, 153.37 and 124.77 mg/dl respectively). Therefore taking of MC had no significant effects in decreasing blood glucose at time ½, 1, 1½, 2, 2½ hr that instead of glucose tolerance in the cases after their single 1,800 g dose intake compare with the placebo.

For mean blood glucose at time ½, 1, 2½ hr, a preliminary test failed to reject the assumption of equal period effects at the 0.05 significance level (the actual significance level was 0.37, 0.52 and 0.13 respectively). Therefore no period effect were identified for the observed results. But at time 1½, 2 hr displayed in Figure 12-13, test rejected the assumption of equal period effects at the 0.05 significance level (the actual significance level was 0.04 and 0.03). So it may be interpreted that there is a direct-by-period interaction. This literally means that the difference between the placebo and MC treatments in period 1 and 2 depends on the period in which they were administered

A preliminary test also failed to reject the assumption of equal carryover effects at the 0.05 significance level (the actual significance level was 0.37, 0.43, 0.97, 0.88, and 0.75) at time ½, 1, 1½, 2, and 2½ hr. Therefore no carryover effect were identified for the observed results.

Table 7 Effects of *Momordica charantia* L.fruit juice freeze dried capsules (MC) versus placebo on glycemic control in overall prediabetic subjects

Glycemic control	Placebo (n=30)	MC (n=30)	Treatment difference (*P* value)	Period effect (*P* value)	Carryover effect (*P* value)
Mean AUC[a](mg hr/dl)	401.67	388.03	0.18	0.30	0.62
- group 1	401.27±69.05	377.07±59.33			
- group 2	402.07±79.87	399.00±60.63			
Mean blood glucose at ½ hr[a] (BG1) (mg/dl)	152.13	148.47	0.59	0.37	0.37
- group 1	142.8±34.66	145.4±31.41			
- group 2	161.47±31.41	151.53±40.29			
Mean blood glucose at 1 hr (BG2)[a] (mg/dl)	185.30	185.43	0.98	0.52	0.43
- group 1	178.33±36.5	182±38.45			
- group 2	192.27±47.26	188.87±32.04			
Mean blood glucose at 1½hr (BG3)[a] (mg/dl)	185.67	172.87	0.08	0.04	0.97
- group 1	193±52.17	165±48.78			
- group 2	178.33±50.35	180±44.15			
Mean blood glucose at 2 hr (BG4)[a] (mg/dl)	160.33	153.37	0.27	0.03	0.88
- group 1	168.33±40.02	147±34.47			
- group 2	152±37.59	159.47±39.46			

Glycemic control	Placebo (n=30)	MC (n=30)	Treatment difference (*P* value)	Period effect (*P* value)	Carryover effect (*P* value)
Mean blood glucose at 2½hr (BG5)[a] (mg/dl)	131.40	124.77	0.31	0.13	0.75
- group 1	138.04±29.22	121.27±21.33			
- group 2	124.73±40.83	128.27±34.22			

a least squares means are created by taking the simple average of their component means, not by taking the average of the raw data. For example, if the mean of the 20 subjects in period 1 sequence 1 is 50.0 and the mean of the 10 subjects in period 2 sequence 2 is 40.0, the least squares mean is (50.0 + 40.0)/2 = 45.0. That is, no adjustment is made for the unequal sample sizes. Also note that the standard deviation and standard error of some of the subgroups are not calculated, values in group 1 and 2 are mean ± SD

b Means AUC and BG1-5 when treated with MC, compared with the results when obtained the placebo by Cross over analysis using NCSS test and PASS test computerized program, P <0.05

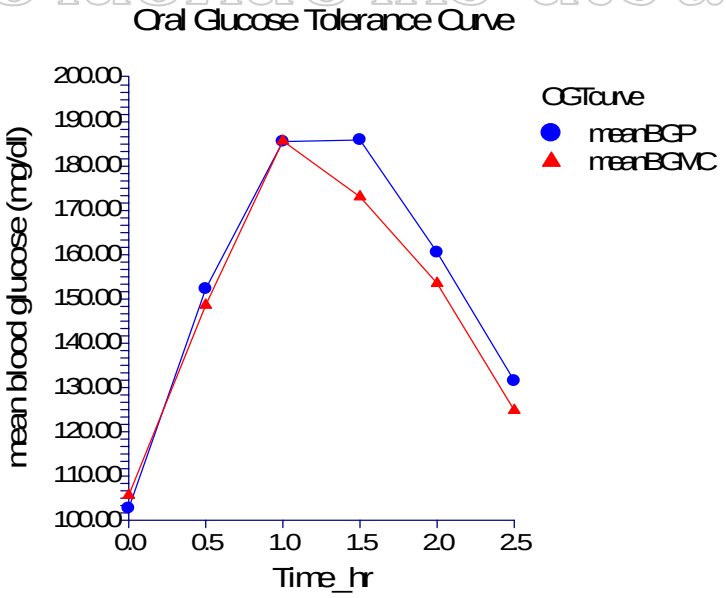
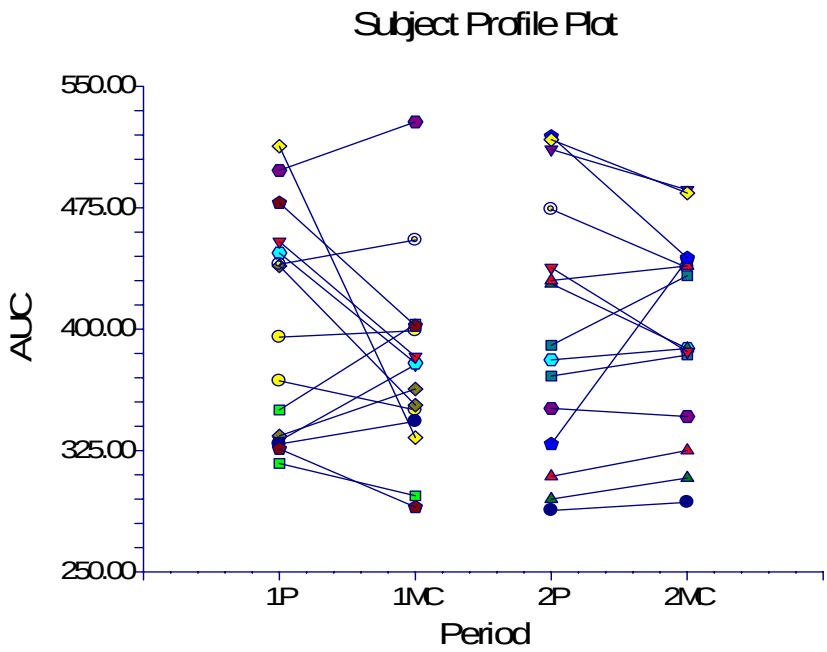


Figure 8 Means blood glucose concentration-time profile after receiving single oral dose of MC versus placebo in all prediabetic subjects show no statistically significant difference



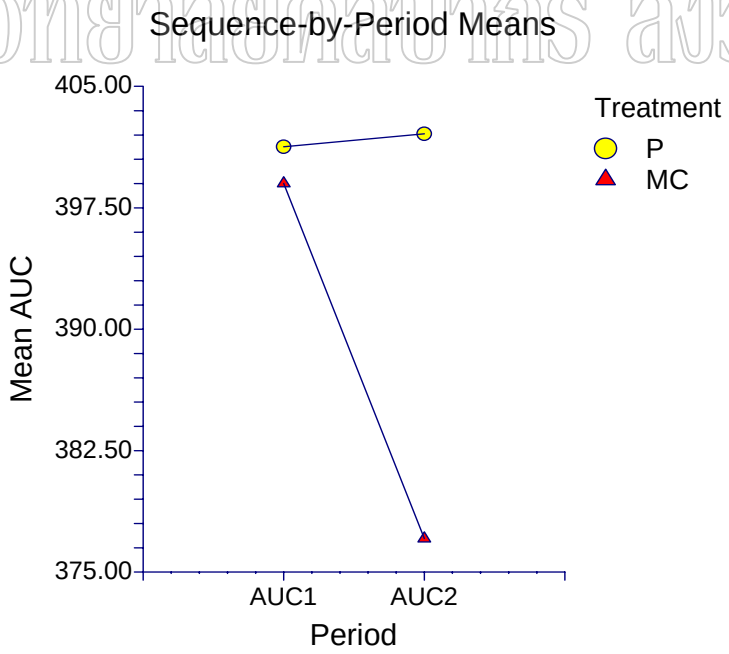
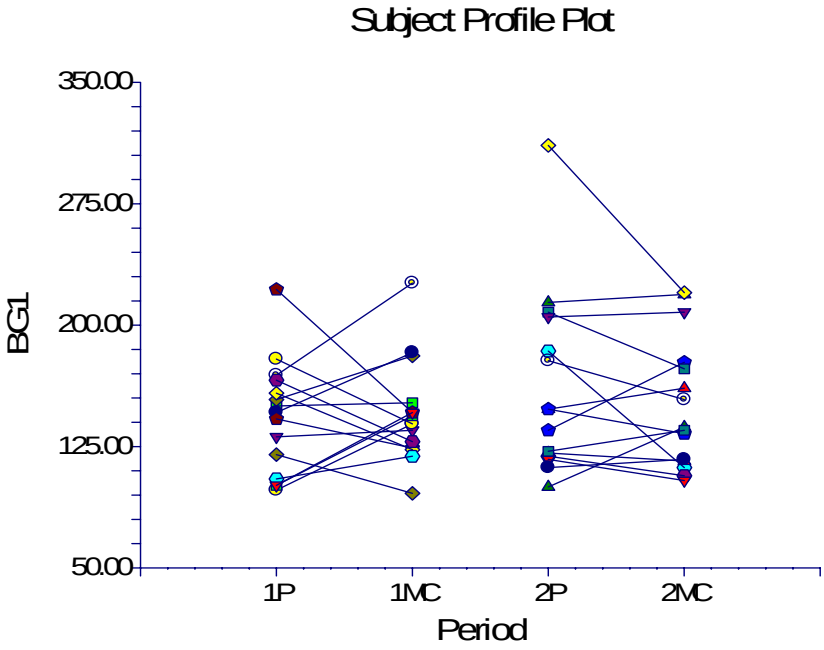


Figure 9 AUC and means after treatment with MC versus placebo in overall prediabetic subjects



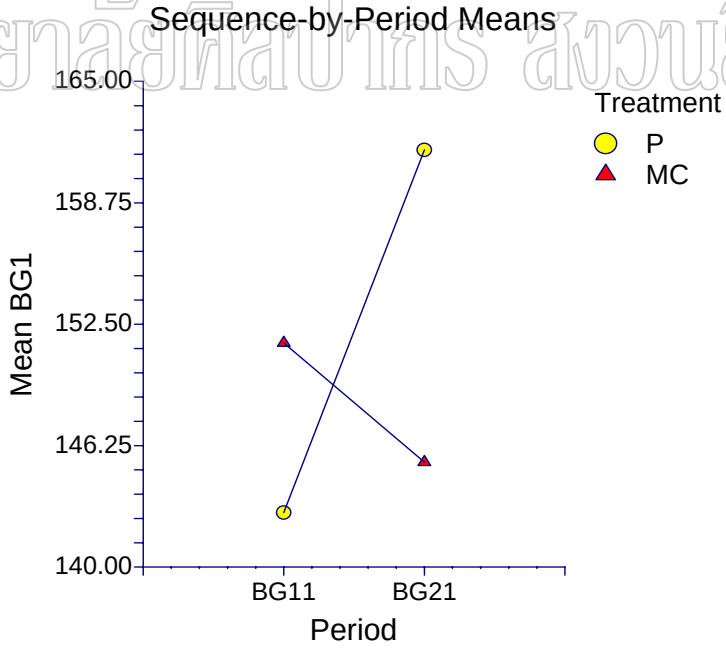
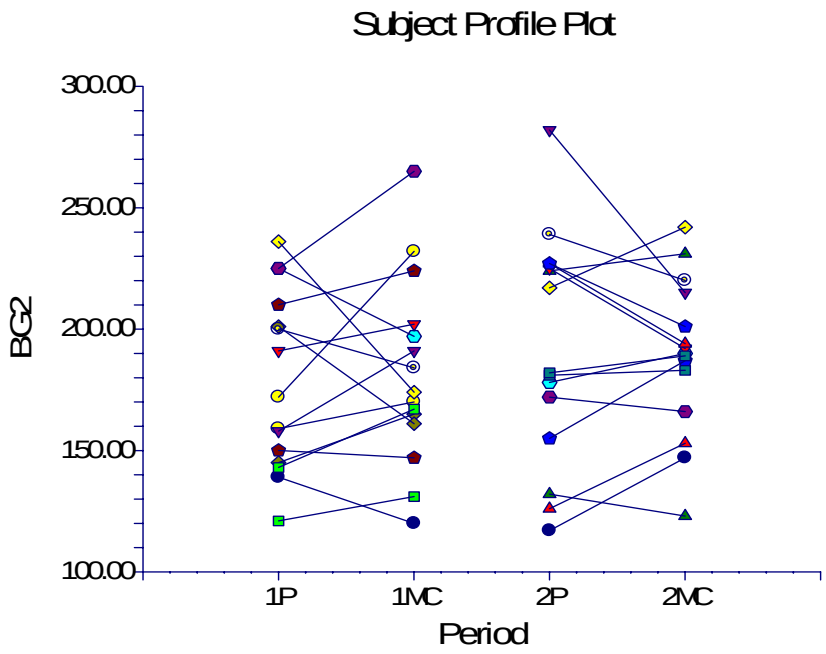


Figure 10 Blood glucose and means (BG1) at ½ hr after treatment with MC versus placebo in overall prediabetic subjects.



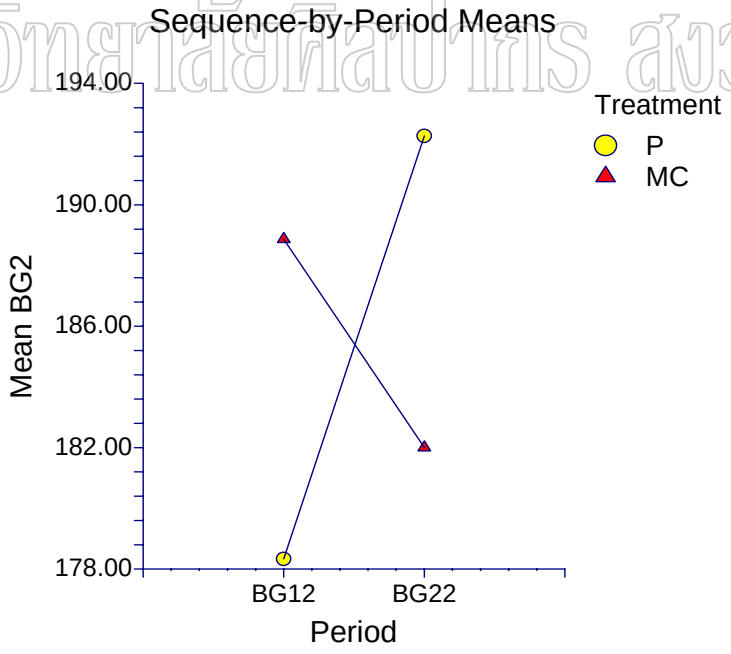
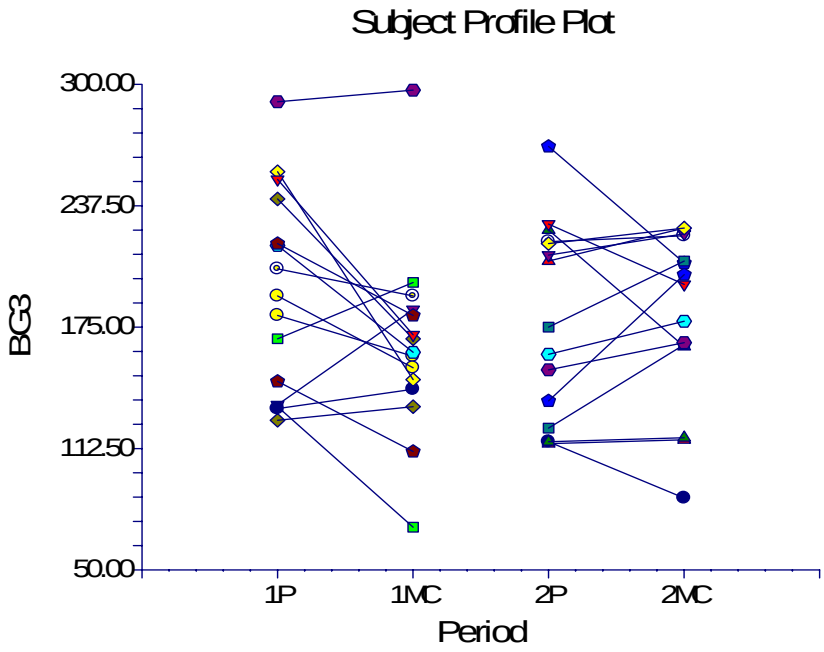


Figure 11 Blood glucose and means at 1 hr (BG2) after treatment with MC versus placebo in overall prediabetic subjects.



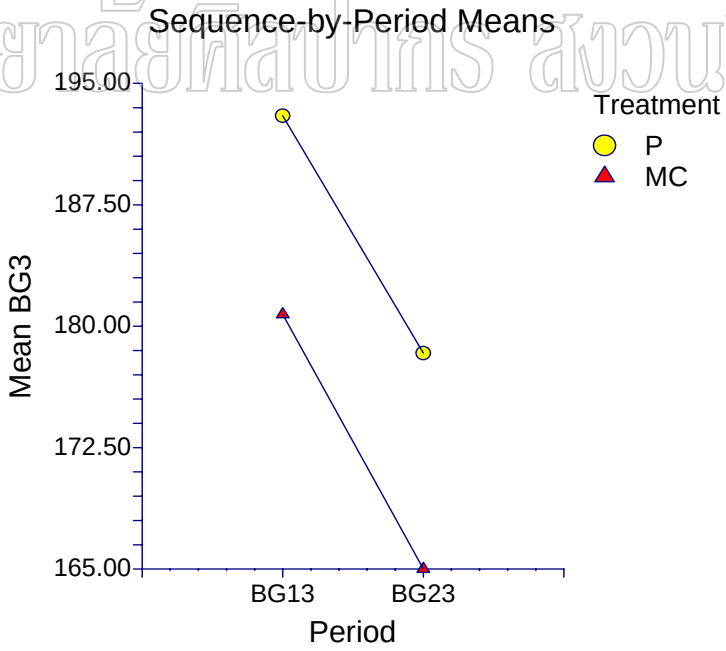
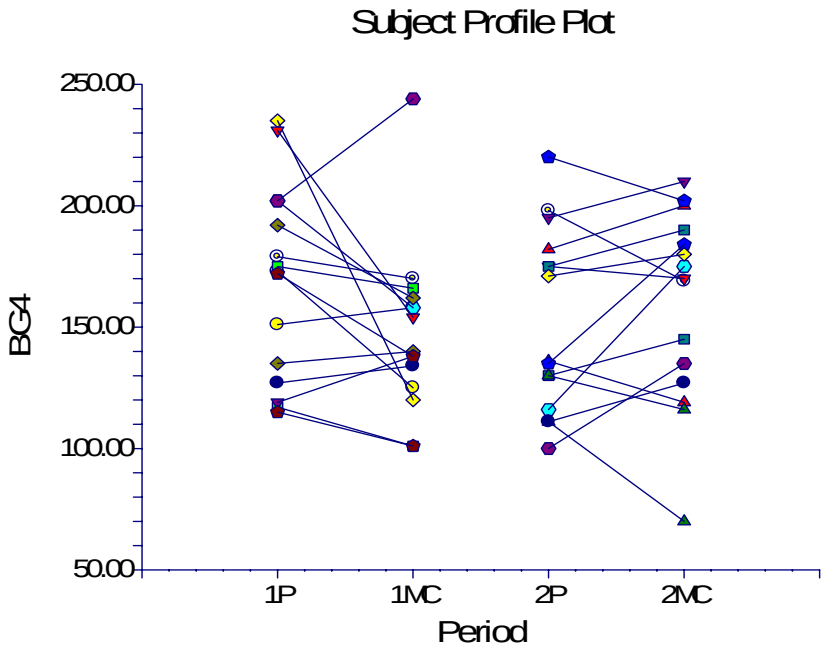


Figure 12 Blood glucose and means (BG3) at 1½ hr after treatment with MC versus placebo in overall prediabetic subjects.



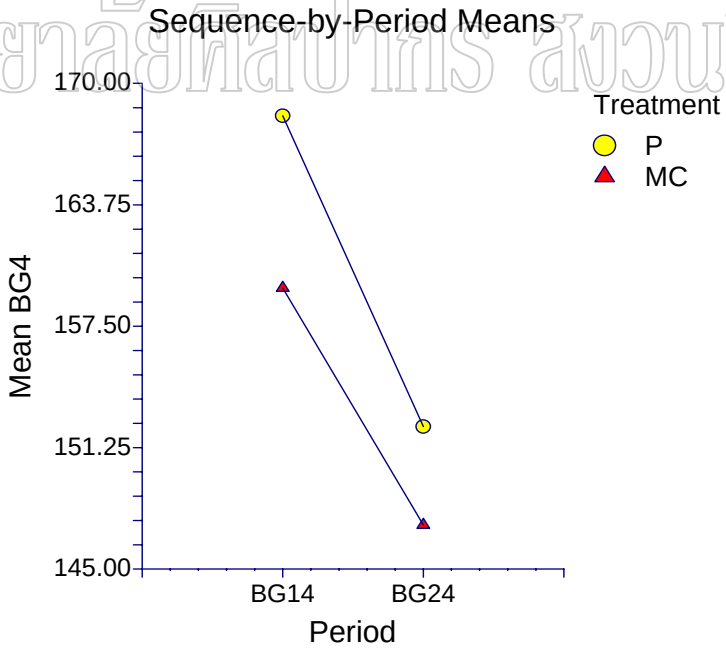
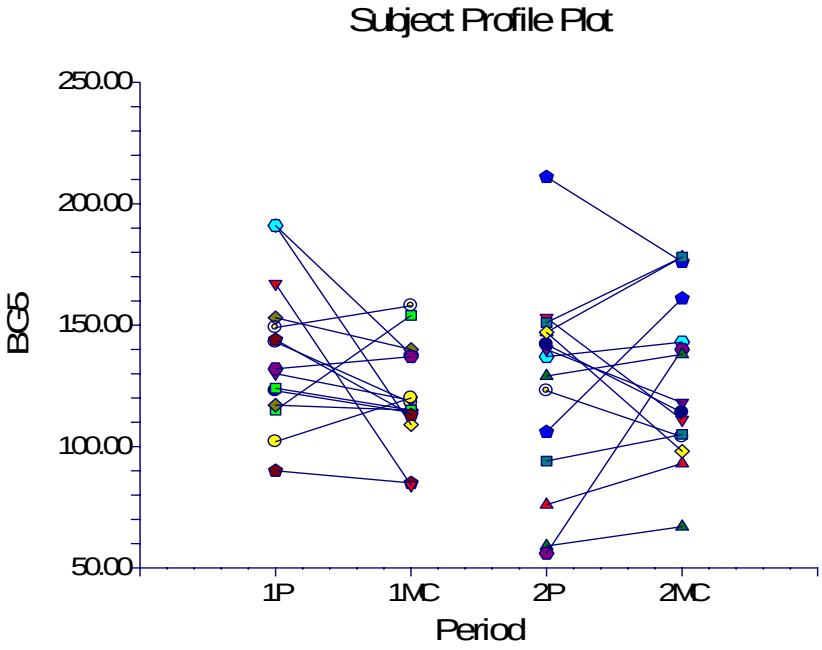


Figure 13 Blood glucose and means at 2 hr (BG4) after treatment with MC versus placebo in overall prediabetic subjects



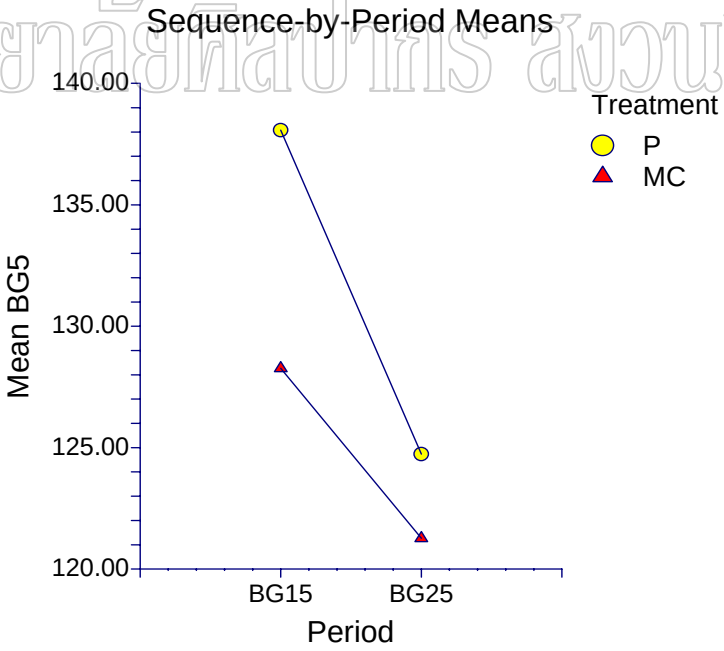


Figure 14 Blood glucose and means at 2½ hr (BG5) after treatment with MC versus placebo in overall prediabetic subjects.

Although overall subject analysis had no statistic significant different between MC and placebo treatment, but the results differentiate in select subjects who had blood glucose level more than 140 mg/dl at time 2 hr after glucose load of OGTT (define as IGT subgroup of prediabetic subjects). The analysis of results in selected subjects was the following

1.2. IGT subgroup of prediabetic subjects analysis

1.2.1. Area under the blood glucose concentration-time curve ($AUC_{0\text{-}2½\ hr}$)

As displayed in Table 8 and Figure 16, The mean AUC obtained from placebo and MC treatment in a 2x2 cross-over study are significantly different at the 0.05 significance level (the actual significance level was 0.01). The design had 7 subjects in sequence 1 (P-MC) and 7 subjects in sequence 2 (MC-P). The average response to treatment placebo was 451.79 mg hr/dl and the average response to treatment MC was 408.21 mg hr/dl. So taking of MC had significant effects in decreasing AUC after their single 1800 g dose compare with the placebo in the subgroup with IGT.

A preliminary test failed to reject the assumption of equal period effects at the 0.05 significance level (the actual significance level was 0.09), and failed to reject the assumption of equal carryover effects at the 0.05 significance level (the actual significance level was 0.15). Therefore no period effect or carryover effect were identified for the observed results.

1.2.2. Blood glucose at time 0, ½, 1, 1½, 2, 2½ hr

As displayed in Table 8 and Figure 17-21, The means blood glucose at time ½ and 1 hr obtained from placebo and MC treatment in a 2x2 cross-over study are not significantly different at the 0.05 significance level (the actual significance level was 0.36 and 0.07 respectively). The design had 7 subjects in sequence 1 (PMC) and 7 subjects in sequence 2 (MCP). The average response to placebo treatment was 155.79 and 211.43 mg/dl respectively) and the average response to treatment MC was 144.50 and 195.36 mg/dl respectively). Therefore taking of MC had no significant effects in decreasing blood glucose at time ½ and 1 hr in IGT subgroup of prediabetic cases after their single 1,800 g dose intake compare with the placebo.

For mean blood glucose at time ½ and 1 hr results, a preliminary test failed to reject the assumption of equal period effects at the 0.05 significance level (the actual significance level was 0.25 and 0.966 respectively) and failed to reject the assumption of equal carryover effects at the

0.05 significance level (the actual significance level was 0.46 and .17 respectively). Therefore no period effect or carryover effect were identified for the observed result.

The means blood glucose at time 1½, 2 and 2½ hr obtained from placebo and MC treatment in a 2x2 cross-over study are significantly different at the 0.05 significance level (the actual significance level was 0.01, 0.04, 0.015 respectively). The design had 7 subjects in sequence 1 (P-MC) and 7 subjects in sequence 2 (MC-P). The average response to treatment placebo was 217.07, 187.00 and 158.86 mg/dl respectively) and the average response to treatment MC was 189.21, 168.14 and 133.00). So taking of MC had significant effects in decreasing means blood glucose at time 1½, 2 and 2½ hr post their single 1800 g dose compare with the placebo in the subgroup with IGT.

For means blood glucose at time 1½ and 2 hr results illustrated in Figure 19-20, a preliminary test rejected the assumption of equal period effects at the 0.05 significance level (the actual significance level was 0.01 and 0.002). So they can be interpreted that there are a direct-by-period interaction that affect the response. Some possible reasons are those;

- Carbohydrate intake conducted prior OGTT among 2 groups decreased in period 2 which push down response in this period too. From 24 hr diet recall record, there is no statistically significant difference between carbohydrate intake either before period 1 and period 2 (P = 0.225, 0.338 respectively). So there is insufficient evidence to prove this expectation.
- Psychological effect such as stress situation was more likely to be experienced in period 1 than in period 2 as the subjects got used to lab staff and equipment. Stress measurement on the subjects could help determine its intervening effects.

But at time 2½ hr, failed to reject the assumption of equal period effects at the 0.05 significance level (the actual significance level was 0.15). Therefore no period effect were identified for the observed results at time 2½ hr.

For carryover effects test of mean blood glucose at time 1½, 2 and 2½ hr results, found that failed to reject the assumption of equal carryover effects at the 0.05 significance level (the actual significance level was 0.20, 0.30, and 0.57 respectively). Therefore no carryover effect were identified for theses observed results.

Table 8 Effects of *Momordica charantia* L. fruit juice freeze dried capsules versus placebo on glycemic control in IGT subgroup of prediabetic subjects

Glycemic control	Placebo (n=14)	MC (n=14)	Treatment difference (*P* value)	Period effect (*P* value)	Carryover effect (*P* value)
Mean AUC[a](mg hr/dl)	451.79	408.21	0.008	0.09	0.15
- group 1	448.43±44.17	379.29±40.73			
- group 2	455.14±60.13	437.14±40.17			
Mean blood glucose at ½ hr (BG1) [a] (mg/dl)	155.79	144.50	0.36	0.25	0.46
- group 1	139.00±46.17	142.14±41.03			
- group 2	172.57±69.83	146.86±47.30			
Mean blood glucose at 1 hr (BG2[a]) (mg/dl)	211.43	195.36	0.07	0.966	0.17
- group 1	203.14±24.88	187.43±21.74			
- group 2	219.71±34.60	203.29±19.30			
Mean blood glucose at 1½hr (BG3) [a] (mg/dl)	217.07	189.21	0.01	0.01	0.20
- group 1	224.00±26.69	168.86±14.16			
- group 2	210.14±35.08	209.57±17.69			
Mean blood glucose at 2 hr (BG4) [a] (mg/dl)	187.00	168.14	0.04	0.002	0.30
- group 1	197.71±26.37	146.71±19.22			
- group 2	176.29±31.52	189.57±15.10			

Glycemic control	Placebo (n=14)	MC (n=14)	Treatment difference (*P* value)	Period effect (*P* value)	Carryover effect (*P* value)
Mean blood glucose at 2½hr (BG5) [a] (mg/dl)	158.86	133.00	0.015	0.15	0.57
- group 1	162.57±20.98	122.86±24.23			
- group 2	155.14±25.27	143.14±34.67			

a least squares means are created by taking the simple average of their component means, not by taking the average of the raw data. For example, if the mean of the 20 subjects in period 1 sequence 1 is 50.0 and the mean of the 10 subjects in period 2 sequence 2 is 40.0, the least squares mean is (50.0 + 40.0)/2 = 45.0. That is, no adjustment is made for the unequal sample sizes. Also note that the standard deviation and standard error of some of the subgroups are not calculated, values in group 1 and 2 are mean ± SD

b Means AUC and BG1-5 when treated with MC, compared with the results when obtained the placebo by Cross over analysis using NCSS test and PASS test computerized program, *P* <0.05

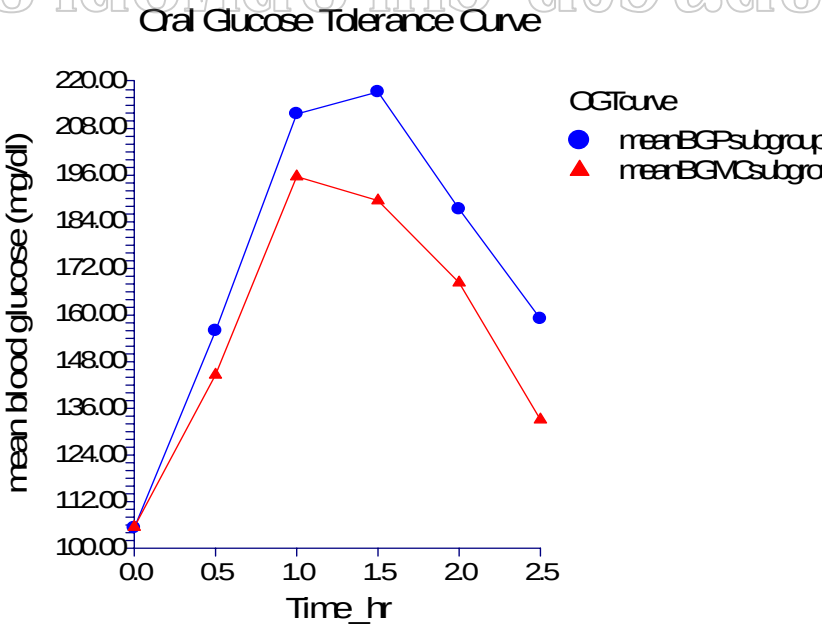
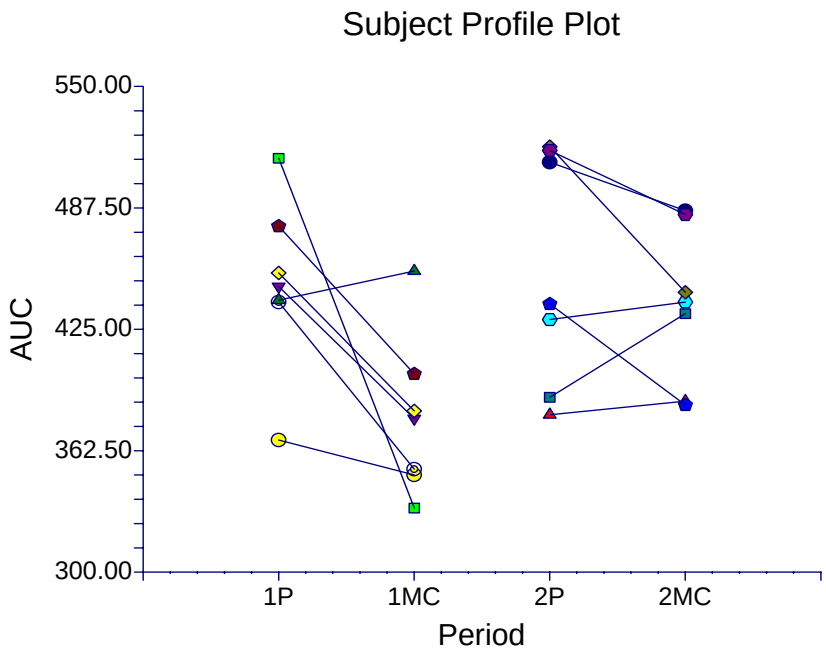


Figure 15 Means blood glucose concentration-time profile after receiving single oral dose of MC versus placebo in IGT subgroup of prediabetic cases show statistic significant different from 1½-2½ hr post dose.



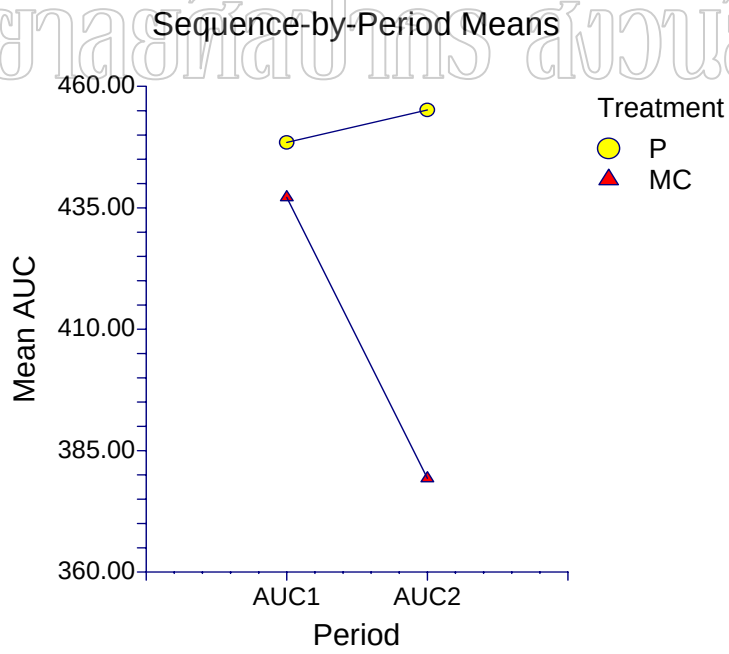
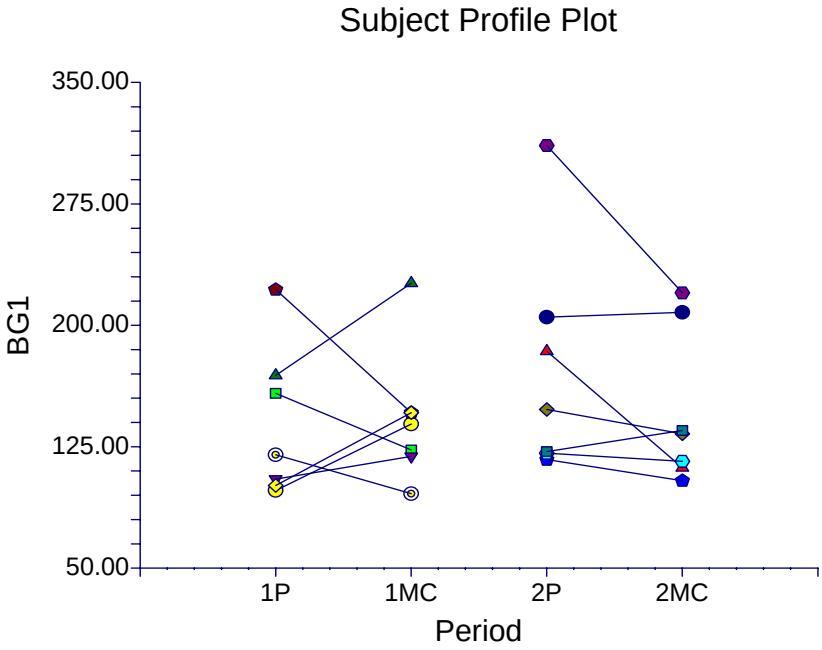


Figure 16 AUC and means after treatment with MC versus placebo in IGT subgroup of prediabetic subjects



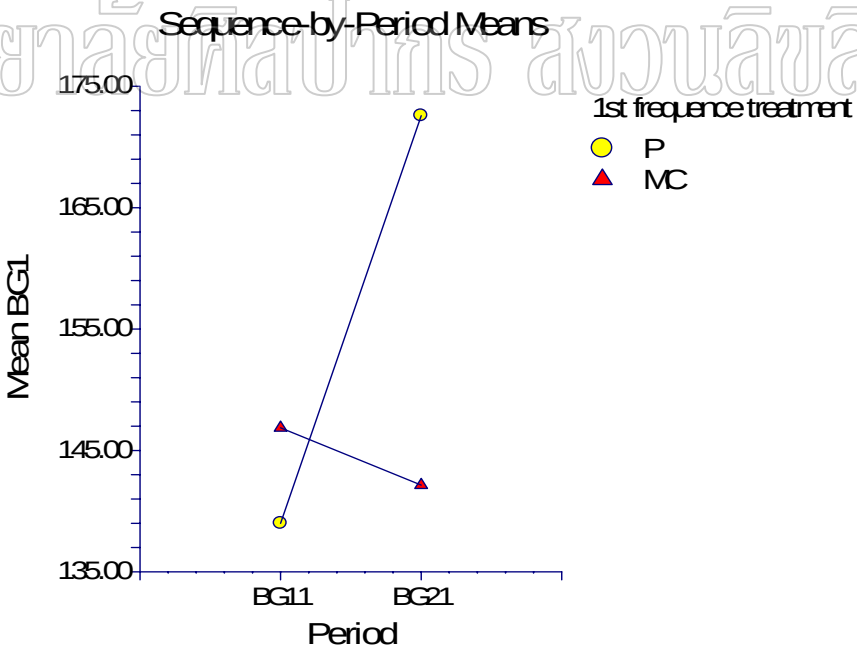


Figure 17 Blood glucose and means at ½ hr (BG1) after treatment with MC versus placebo in IGT subgroup of prediabetic subjects

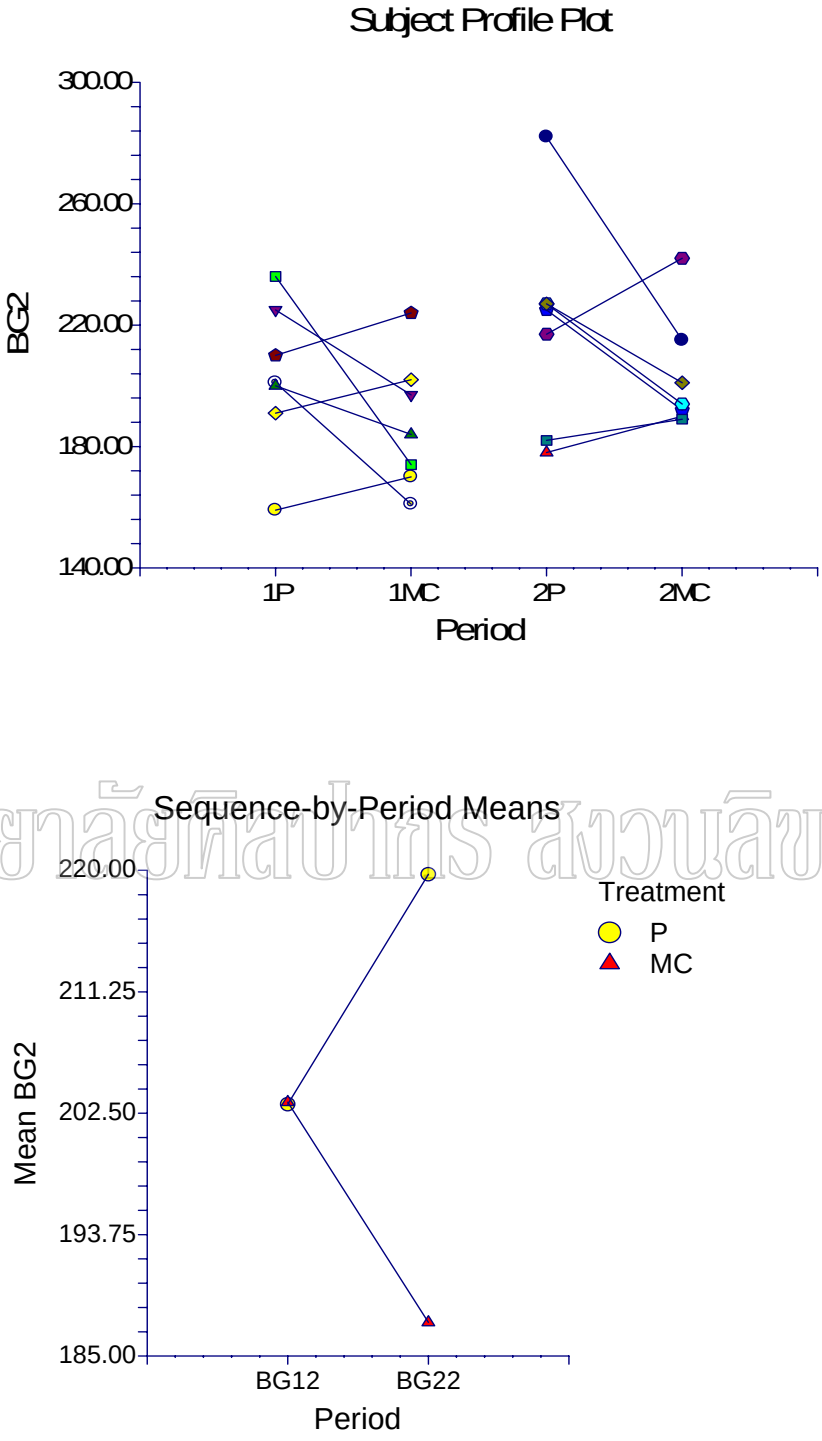
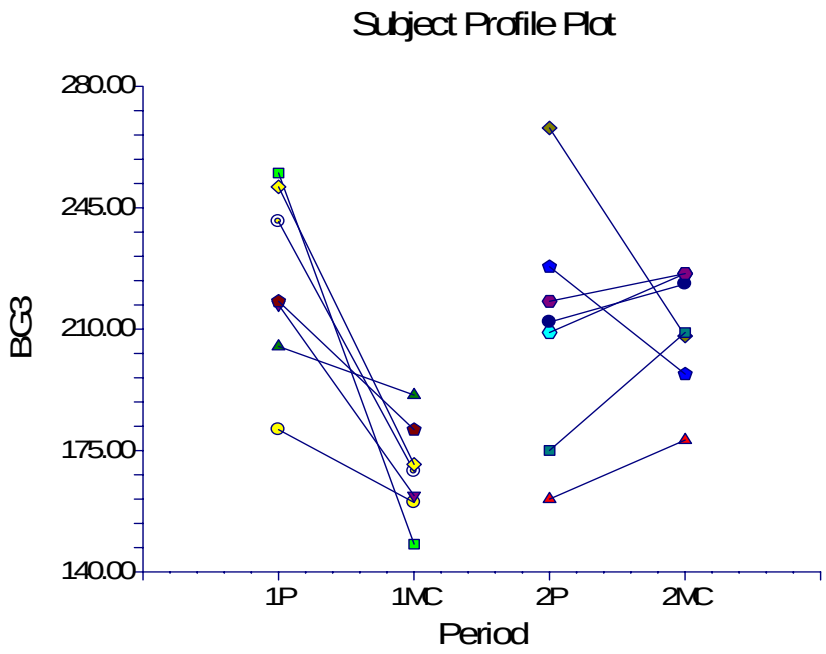


Figure 18 Blood glucose and mean at 1 hr (BG2) after treatment with MC versus placebo in IGT subgroup of prediabetic subjects



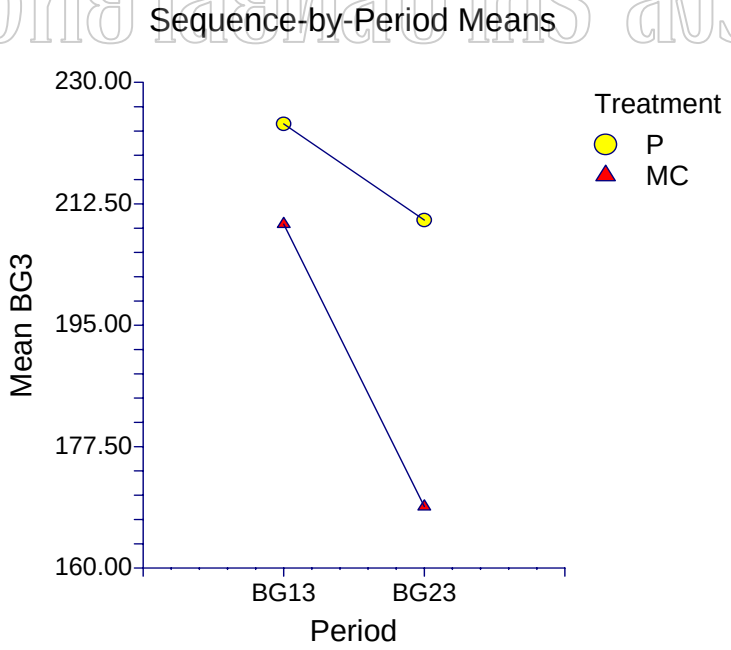
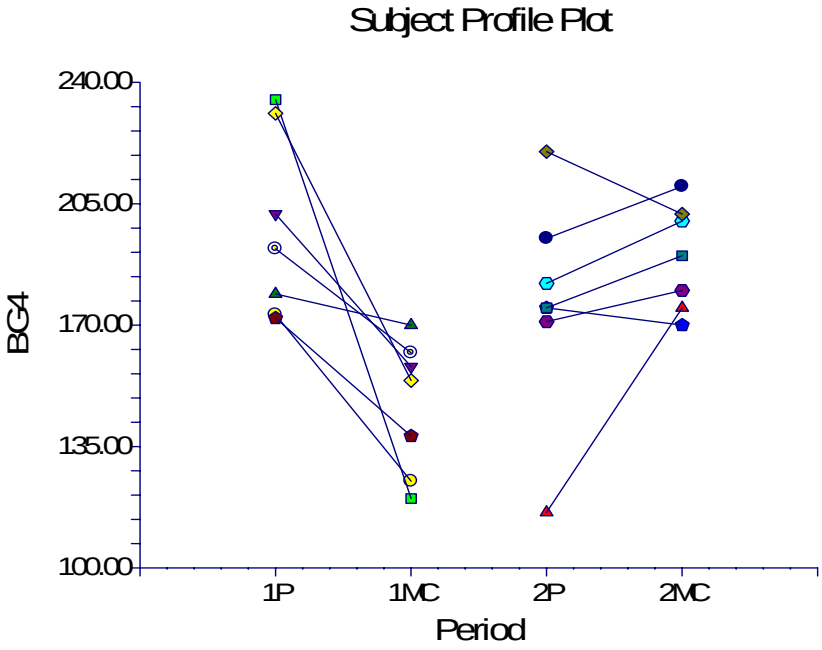


Figure 19 Blood glucose and mean at 1½ hr (BG3) after treatment with MC versus placebo in IGT subgroup of prediabetic subjects



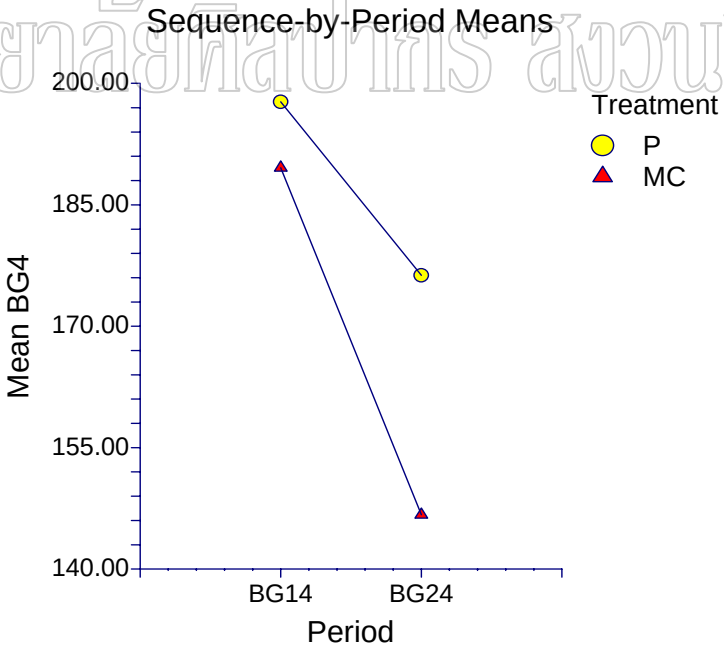
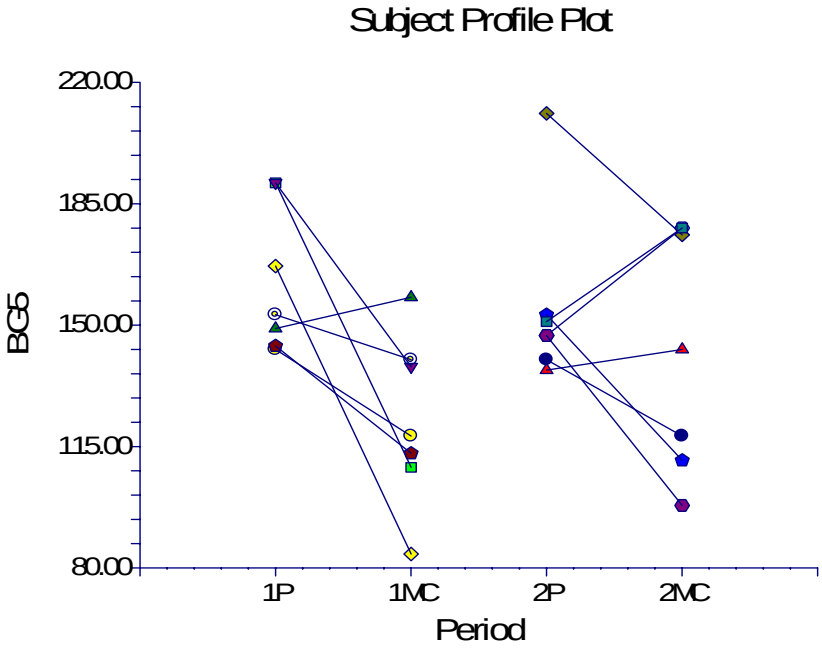


Figure 20 Blood glucose and means at 2 hr (BG4) after treatment with MC versus placebo in IGT subgroup of prediabetic subjects



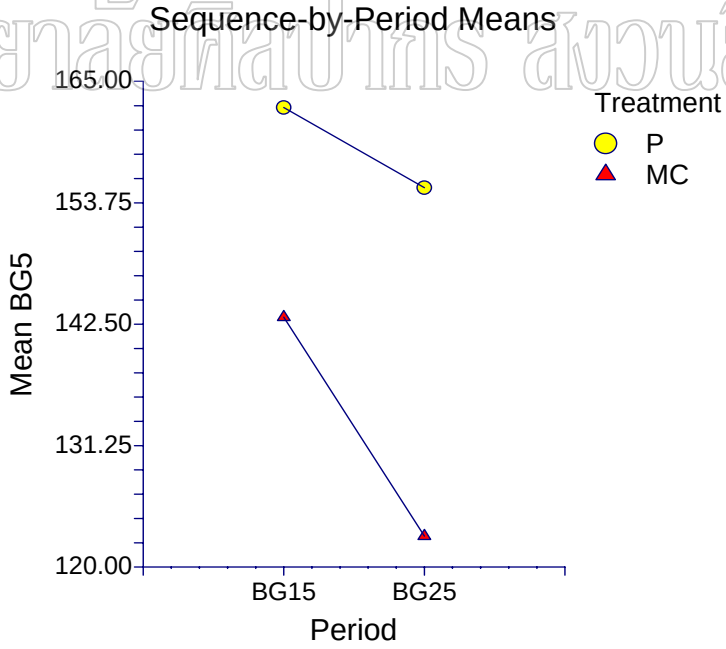


Figure 21 Blood glucose and mean at 2½ hr (BG5) after treatment with MC versus placebo in IGT subgroup of prediabetic subjects

2. Adverse effects

As displayed in Table 9, the liver function tests (as measured by SGOT and SGPT) are not significantly different at the 0.05 significance level (the actual significance level was 0.880 and 0.658). at the end of the study compared with baseline. Safety values, including renal function (as measured by SCr), and SAlb decreased at the end of study, and this difference was significant when compared with baseline (P = 0.010 for SAlb and 0.018 for SCr). These results denote that MC were no increase either liver function and renal function.

During the study, 1, 2 and 1 subjects complained of headache dizziness and nausea-vomiting (N/V) respectively after MC treatment whereas placebo also complained of dizziness and N/V each in 1 subjects.

Table 9 Display safety value and adverse events of the study

Mean safety value	Baseline (n=30)	End of study (n=30)	Mean different	P value
SGOT (U/l)[a]	23.30±6.50	23.13±8.14	.167	0.880
SGPT (U/l)[a]	21.23±11.80	20.70±10.40	.533	0.658
SAlb (g/dl)[a]	4.443±0.29	3.960±1.006	.483	0.010
SCr (mg/dl)[a]	0.717±0.20	0.690±0.206	.027	0.018
Averse events	placebo	%	MC	%
No. of headache (subject)	0	0	1	3.33
No. of dizziness (subject)	1	3.33	2	6.67
No. of nausea-vomitting (subject)	1	3.33	1	3.33

a values at baseline and the end of study were compared by pair-T test, P <0.05

CHAPTER 5

DISCUSSION

The objective of this research is to study the acute hypoglycemic effect of *Momordica charantia* L. fruit juice freeze dried capsules (MC) in prediabetic cases. In this study MC was administered in the form of freeze dried fruit juice contained capsules with the recommended dose of 1,800 mg. Corresponding trials with placebo were used for comparison. It is found that the taking of MC had no significant effects in decreasing glucose concentration and blood glucose levels as at any point of time from ½ to 2 ½ hours after the intake. While the result shows that MC did not improve glucose tolerance in the prediabetic subjects in general as hypothesized, it did improve glucose tolerance in the subgroup with impaired glucose tolerance (IGT).

A clinical study by Welihinda et al (22) showed that *Momordica charantia* L. fruit juice improved glucose tolerance in maturity onset diabetes (NIDDM) after a single taking. Similarly, Ahmed et al (115) found that *Momordica charantia* L. fruit juice could lower fasting blood sugar and postprandial blood sugar in NIDDM when it was taken just once. Both studies were undertaken in NIDDM or type-2 diabetic patients. Previous studies demonstrate that *Momordica charantia* L. causes effects through the following mechanisms:

- Promote insulin release by stimulation of insulin secretion of β-cell (22, 76)
- Act like insulin (22, 76).
- Enhance number of beta cells (77).

And hypoglycemic activity to an extra-pancreatic effect (13, 29), which includes

- Increased GLUT4 transporter protein of muscles (80).
- Increased glucose utilization in the liver and muscle (29, 81)
- Inhibition of glucose-6-phosphatase & fructose-1, 6-bisphosphatase in liver and stimulation of red-cell and hepatic glucose-6-phosphate dehydrogenase activities (71, 82).
- Attributed the hypoglycemic activity of *Momordica charantia* to inhibition of glucose transport at the brush border of the small intestine.

- Depressed carbohydrate enzymes activity in liver of diabetic mice was restored with *Momordica charantia* treatment (i.e. Hexokinase, glucokinase, phosphofructokinase and substrate glucose-6-phosphate) (20).

Its stimulation of insulin secretion by β-cell of pancreas in particular is likely to be an important mechanism to improve glucose tolerance in case studies on its acute effects (116).

30 subjects were originally selected for this study. They were considered prediabetic cases for their fasting plasma glucose (FPG) fell in the 100-125 mg/ml range. The fact that some of these subjects had FPG closer than others to the upper borderline of people with normal glucose tolerance may explain why initial analysis showed no discernible hypoglycemic effect of MC in the entire group. A possible explanation is that in the subjects with higher glucose tolerance their bodies in normal state can maintain blood glucose at acceptable levels by reducing insulin secretion from pancreas, lowering the production of glycogen by liver and decrease in skeletal muscle uptake of glucose (114). This finding suggests that the use of MC in non-diabetics would not lead to hypoglycemia and be safe to eat.

Subgroup analysis was then taken, using OGTT to determine those with impaired glucose tolerance (IGT; 2 hr postprandial > 140 mg/dl) (2). As a result, 14 subjects met the criterion. In this subgroup MC was found to significantly decrease blood glucose concentration (AUC) and postprandial glucose.

In the subjects with IGT, the study found that blood glucose levels of those taking MC were significantly lower than those of the group receiving placebo at 1½ to 2½ hrs times after the intake. The result indicates that MC could begin effect about from 1½ hr closely as suggested by previous studies (21).

Figure 19-21 shows that in the group being given placebo in period 1 and MC in period 2, the lowering effect of MC on the subjects' means blood glucose level and means AUC is more distinct than that of the other group, for which the prescription was reversed. The difference suggests interference by some period factors may be responsible for making the effect of MC less discernible in the latter group.

One of the factors could be stress from subjecting to tests or from other reasons such as lack of sleep. Stress was more likely to be experienced in period 1 than in period 2 as the subjects

got used to lab staff and equipment. Stress measurement on the subjects could help determine its intervening effects.

Lifestyle adjustments could take place between test periods following the subjects' awareness of their prediabetic state. Some could become more cautious in eating food high in carbohydrate and sugar. However, tests for carbohydrate intake conducted prior to OGTT in period 1 and 2 on the subjects with impaired glucose tolerance showed no significant differences.

Although the hypotheses on the effect of MC in prediabetic cases in general are not supported by the findings, the absence of clear hypoglycemic effects could be dose-related. The dose of the study product was decided following the doses generally recommended by previous studies (86, 117). It is possible that increased doses may produce different results regarding the hypoglycemic effect of *Momordica charantia* L.

For safety evaluation, MC were no increase either liver function and renal function and gastrointestinal side effect such as nausea-vomiting were similar during both treatment phases. CNS side effect that is headache and dizziness were predominantly, and developed in 3 subjects after MC treatment and one subjects while on placebo. This findings agrees with a previous study (17, 98) that short term use of MC is no clinical adverse effect and safety to use in human.

This study has a few limitations that should be noted here.

; First, the use of a single FPG alone as the key inclusion criterion may be inadequate in selecting prediabetic subjects of mature state. When this criterion applied, the subjects eg. with lacking of sleep, stress or eating food high in carbohydrate and sugar before screening are likely to include some prediabetic cases whose FPG are close to the lower border line or glucose tolerance are lower than mature cases. Consequently, the effect of *M. charantia* in reducing blood glucose failed to show clearly among the subject group. To select the "real" mature state prediabetic subjects, FPG should be taken at least twice on the subjects, or cross checked with 2 hr postprandial glucose.

; Secondly, although diabetic patients may clearly show hypoglycemic effect, this study excluded from the subjects diabetic patients using hypoglycemic or other drugs with effects on blood glucose because they would be required to suspend their drug treatment and taking OGTT are limit for them whose FPG more than 140 mg/dl. These two procedures, however, were against ethical considerations and standard treatment practice for the patients would run a risk of

hyperglycemia. With this exclusion, diabetic patients who were qualified for being recruited were those whose conditions were mild or not in serious need for the use of drugs. Changes in lifestyle and diet may be sufficient for many in this group to reduce blood glucose. Only a few would visit hospitals for regular checks and treatment, making the pool of qualified patients rather small. The effort to recruit a larger number of subjects was also hindered by time limits.

; The last, this research was designed to study the short-term effects of MC by giving the subjects a single dose. MC's long-term safety and effects on liver and renal functions needs studied and followed up for extended use of the medicine.

CHAPTER 6

CONCLUSION AND RECOMMENDATION

Conclusion

In summary, present study shown that single 1,800 g dose of *Momordica charantia* L.fruit juice freeze dried capsules did not improve glucose tolerance in the prediabetic cases in general, but it did improve glucose tolerance in the subgroup with impaired glucose tolerance (IGT). Its hypoglycemic effect initiate at 1½ hr post dose without clinically meaning adverse effect.

Suggestions for further study

1. Further studies about acute hypoglycemic effect should be performed as the following;

- Control confounders by reduce and assess stress of the subjects while measure main outcome and maintain life style such as diet until stable before study to avoid life style change effect.

- Dose variation both in prediabetic and type 2 diabetes.

- For discernible of hypoglycemic effect of *Momordica charantia* L., Subject closely to Type 2 Diabetes Mellitus or mild Type 2 Diabetes Mellitus should be selected into study.

- Increase number of subject for raise power of test in general prediabetic subjects.

- Tests for carbohydrate intake conducted prior to OGTT such as 24 hr diet recall should be emphasized the importance of sugar consumption when interviewing subjects. Sugar consumption may affect the outcome measurement of blood glucose control if subjects eat it much more.

- Selecting appropriate dietary assessment methods are needed for diet lifestyle adjustments. So repeated 24-hr recall at least 3 days (1 day of weekend and 2 days of working day) may better represent average usual intake of a group in all days of the week (118).

- Another parameters which relate to glycemic control of *Momordica charantia* should be evaluated as secondary outcome such as plasma insulin. Plasma insulin help to expect mechanism of action because it is secreted from β-cell of pancrease.

2. Studies in type 2 diabetes and longer duration are needed to determine whether these effects are sustained and have a beneficial effect on blood glucose control.

3. Study on methods for standardization of *Momordica charantia* L. fruit juice freeze dried capsules (MC) products to improve accuracy in tests on their effectiveness in lowering sugar levels in blood.

Although a mixture of steroidal saponins known as charantin has been used as the marker for studies on the effects of *Momordica charantia* on blood glucose levels, other substances, namely glycosides such as vicine, insulin-like peptides, alkaloids and inorganic materials found in the plant, could probably contribute to the same effect. Findings suggest that much greater quantities of charantin might be required if it is used alone to get desired sugar-lowering results. In one study, charantin could reduce hyperglycemia in rabbits by 42 percent only when it was administered in a 50mg/kg dose. Another study found water-extracted *Momordica charantia* was more effective than alcohol-extracted one. Since charantin is a crystalline fraction obtained from an alcoholic extract of the fruit, the result suggests the effects of substances other than charantin in the former. To gain further understanding of the effects of *Momordica charantia*, methods for standardization have to be developed by using additional sugar-lowering substances as multiple markers.

4. Study on the effects of *Momordica charantia* taken by other means or product forms which will promote domestic production capacity and self-reliance among the public.

This study introduced a standardization method for preparation of *Momordica charantia* products which would yield basic information of the marker for further study. To obtain 1 kg. of *Momordica charantia* juice for preparing the products, 3 kg. of fresh *Momordica charantia* fruit meat is blended and strained through fine cloth, leaving a large amount of residue which may sill contain active ingredients. For a patient to take *Momordica charantia* juice directly, 20 fruits are needed to get 300 mg of fruit meat which will yield a recommended dose of 100 ml. of juice.

Further study to determine quantities of *Momordica charantia* needed for preparation and appropriate methods is called for. A study by Ahmad et,al. (115) employed a homogenized

suspension of the vegetable pulp of *Momordica charantia*, the amount of which was calculated by using the formula: body weight (in kg) of the given patient x 2 g. Then add some water to make the mixture 100-120 cc. in volume when blended. The mixture was found to be effective in reducing post-prandial serum glucose and fasting glucose. Around 120 g. of *Momordica charantia* fruit meat is needed for this method, which is far less than the straining method. As for the freeze dried preparation, the method may not be commercially viable because of its time-consuming process, high costs and form instability. The freeze dried product would melt in humidity and has to be kept in desiccators. *Momordica charantia* products presently available in the market as registered traditional medicine is contained in 500-mg capsules. They are officially approved for reducing fever and cool down internal heat, but a large number of users take them for diabetes. *Momordica charantia* can be taken by other means: a dose of 50-100 ml of fresh juice or 3-15 g. of dried powder daily (70). The effectiveness of *Momordica charantia* products available should be subject to research based on standardization and randomization as proposed in this study to ensure objectivity.

5. Study on the production process of *Momordica charantia* plant materials from varieties, breeding, planting, harvesting, post-harvesting treatment and quality control measures.

6. Study on development of *Momordica charantia* products from standardized extracts to promote industrial production capacity.

Suggestions for Policy Development

The Thai government should actively promote research and development of herbal medicine for diabetes, hypertension and high cholesterol in blood levels, which are among major chronic diseases which have been increasingly affected Thai people and created higher demand for medicine. Unless the government embarks on a drive toward self-reliance in domestic medicine production soon, the mounting costs for importing expensive patented drugs will drain the country of much needed foreign exchange. Vigorous support for integrated, clinical research on herbal medicine is vital if the knowledge is to be put to use for the benefits of the people and steer the country toward self-reliance in domestic medicine production.

Development of herbal medicine should be comprehensively implemented to promote its use from household planting and use, production in local communities up to teaching and practicing in medical schools with an aim to test, learn and gain more experience for knowledge-based development of herbal use.

The government has an important role to play in building an information base gathered locally and globally from persons, direct experiences, clinical studies, etc. This information base should provide easy access to resources for practical uses as well as further research.

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APPENDIX

Appendix A

Consent form

ข้อมูลสำหรับผู้ป่วย

การศึกษาทางคลินิก; การศึกษาผลลดน้ำตาลในเลือดแบบเฉียบพลันของมะระขี้นก(*Momordica charantia*) ผงแห้ง ฟรีซดราย ในผู้ที่มีภาวะทนต่อกลูโคสบกพร่อง

เรียน ผู้เข้าร่วมโครงการทุกท่าน

ท่านเป็นผู้ที่ได้รับเชิญจากคณะผู้วิจัยให้เข้าร่วมการศึกษาทางคลินิกเพื่อดูว่ามะระขี้นกแคปซูลจะมีผลต่อระดับน้ำตาลในเลือดหลังการกินอาหารหรือไม่ ก่อนที่ท่านจะตกลงเข้าร่วมการศึกษาดังกล่าว ขอชี้แจงให้ท่านทราบถึงเหตุผล และรายละเอียดของการศึกษาวิจัย ดังนี้

1. คำชี้แจงเกี่ยวกับโรคที่ท่านได้รับการวินิจฉัย การรักษา และเหตุผลที่ต้องทำการศึกษาวิจัย

ในผู้ที่มีความทนทานต่อกลูโคสบกพร่องคือมีระดับน้ำตาลในเลือด 100-126 mg/dl ยังไม่จัดว่าเป็นโรคเบาหวาน แต่ก็มีโอกาสสูงที่จะเป็นโรคเบาหวาน หรือเกิดโรคเกี่ยวกับหลอดเลือดเช่นเดียวกับผู้ป่วยเบาหวาน จึงจำเป็นที่จะต้องได้รับการรักษาที่เหมาะสม โดยการปรับนิสัยในการบริโภคอาหาร ร่วมกับการออกกำลังกายอย่างเหมาะสม ส่วนผู้ป่วยเบาหวานชนิดที่ 2 ที่มีระดับน้ำตาลในเลือด 126-140 mg/dl จัดเป็นกลุ่มผู้ป่วยเบาหวานที่สามารถให้การรักษาเบื้องต้นด้วยการปรับนิสัยในการบริโภคอาหาร ร่วมกับการออกกำลังกายอย่างเหมาะสม เช่นเดียวกับผู้ที่มีความทนทานต่อกลูโคสบกพร่อง ทั้งสองกลุ่มดังที่กล่าวมามักจะมีระดับน้ำตาลในเลือดหลังการกินอาหารสูงกว่าในคนปกติ

ในผู้ที่มีความทนต่อกลูโคสบกพร่อง และผู้ป่วยเบาหวานชนิดที่ 2 ที่ยังไม่ต้องใช้ยาลดระดับน้ำตาลในเลือดนั้น นอกจากการปรับนิสัยในการบริโภคอาหาร และการออกกำลังกายอย่างเหมาะสมแล้ว การใช้สมุนไพรเช่น มะระขี้นก อาจมีส่วนช่วยในการควบคุมระดับน้ำตาลในเลือดของผู้ป่วยได้

การศึกษาครั้งนี้จะช่วยยืนยันว่ามะระขี้นกแคปซูลสามารถลดระดับน้ำตาลในเลือดได้หรือไม่ โดยการดูระดับน้ำตาลในเลือดหลังกินอาหารทุกครึ่งชั่วโมง เป็นเวลา 2 ชั่วโมงครึ่ง หลังจากที่ท่านได้กินมะระขี้นก 4 แคปซูล (ประมาณ 3-4 ผลของมะระขี้นก) เทียบกับหลังจากกินเม็ดแป้งแคปซูลที่ไม่มีผลต่อระดับน้ำตาลในเลือด

2. คำชี้แจงเกี่ยวกับผลลดระดับน้ำตาลในเลือด การเตรียมเป็นแคปซูล และผลข้างเคียงของมะระขี้นก

จากการศึกษาที่ผ่านหลายๆการศึกษา พบว่าน้ำคั้นมะระขี้นกสามารถลดระดับน้ำตาลในเลือดหลังการกินอาหารได้ทั้งในสัตว์ทดลองหลายชนิด เช่น หนูชนิดต่างๆ กระต่าย เป็นต้น และในคน โดยมีการศึกษาผลลดระดับน้ำตาลในเลือดมาแล้วทั้งในคนที่เป็นเบาหวาน และคนปกติ นอกจากนี้ยังมีตำรับยาโบราณหลายตำรับนำมะระมาใช้เป็นยารักษาโรคเบาหวาน เช่น ตำรับยาทางอายุรเวชของอินเดีย, ตำรับยาโบราณของไทย และจีน เป็นต้น ผลมะระขี้นกในขนาดที่คณะผู้วิจัยนำมาทำการศึกษาในครั้งนี้ได้รับการทดสอบแล้วพบว่ามีความปลอดภัย แต่ก็มีการศึกษาวิจัยพบว่าเมล็ดของมะระเป็นสาเหตุสำคัญที่ทำให้เกิดการแท้ง และทารกพิการในหนูได้ ซึ่งในการเตรียมเป็นยาคณะผู้วิจัยก็ได้เอาส่วนของเมล็ดออก

มะระขี้นกแคปซูลที่ใช้ในการศึกษาครั้งนี้เตรียมจากน้ำคั้นมะระขี้นกซึ่งมีการศึกษาแล้วว่าสามารถลดระดับน้ำตาลในเลือดได้ นำมาทำให้เป็นผงแห้งด้วยความเย็นซึ่งเชื่อว่าจะทำให้สารสำคัญในน้ำคั้นมะระขี้นกยังคงอยู่เหมือนเดิม แล้วบรรจุผงมะระขี้นกดังกล่าวในแคปซูลเพื่อให้สามารถกินได้สะดวก และง่ายขึ้น

3. คำชี้แจงเกี่ยวกับการตรวจร่างกาย และวิธีวัดระดับน้ำตาลในเลือด

ก่อนและหลังการเข้าร่วมโครงการ ท่านจะได้รับการตรวจร่างกายโดยแพทย์ และได้รับเจาะเลือดเพื่อดูการทำงานของตับ ไต ระดับไขมัน และโปรตีนในเลือด ว่ามีความผิดปกติหรือไม่

การวัดระดับน้ำตาลในเลือดที่ท่านจะได้รับการตรวจวัด เป็นวิธีตรวจเพื่อดูว่าหลังจากกินอาหารที่เวลาต่างๆ ระดับน้ำตาลในเลือดของท่าน สูงขึ้นเท่าไหร่ โดยผู้วิจัยจะขอเจาะเลือดจากปลายนิ้วท่านก่อนกินมะระแคปซูลหรือเม็ดแป้ง 1 ครั้ง หลังจากนั้นอีกครึ่งชั่วโมงท่านจะต้องกินน้ำตาล 75 กรัม(ประมาณ 15 ช้อนกาแฟที่มีขนาดประมาณนิ้วหัวแม่มือของผู้หญิง) และจะต้องถูกเจาะเลือดจากปลายนิ้วทุก ครึ่งชั่วโมง อีก 5 ครั้ง

การตรวจด้วยวิธีนี้เป็นวิธีทางการแพทย์ที่ใช้ตรวจเพื่อยืนยันว่าเป็นเบาหวานหรือไม่ ในผู้ที่มีผลการตรวจระดับน้ำตาลแบบที่ใช้กันทั่วไป(FPG)เป็นปกติ แต่ก็มีบางครั้งที่พบว่า อยู่ในช่วง 100-140 mg/dl และเป็นการตรวจที่ได้รับคำแนะนำให้ทำได้ในผู้ที่มีระดับน้ำตาลในเลือดไม่เกิน 140 mg/dl

4. คำชี้แจงเกี่ยวกับประโยชน์ที่ท่านจะได้รับในการเข้าร่วมโครงการวิจัย

ประโยชน์ที่จะได้รับเมื่อเข้าร่วมโครงการวิจัยในครั้งนี้ คือ ท่านจะได้รับทราบผลการตรวจร่างกาย และการตรวจทางห้องปฏิบัติการเพื่อดูการทำงานของ ตับ ไต ความผิดปกติของระบบเลือด และระดับไขมันในเลือด โดยไม่ต้องเสียค่าใช้จ่ายใดๆ สำหรับท่านที่มีผลการตรวจ ระดับ

น้ำตาลในเลือดแบบปกติทั่วไปอยู่ลักษณะก้ำกึ่งว่าจะเป็นเบาหวานหรือไม่ วิธีวัดระดับน้ำตาลในเลือดหลังกินน้ำตาลจะเป็นการตรวจเพื่อช่วยยืนยันได้ว่าความสามารถในการลดน้ำตาลในเลือดหลังอาหารของท่านใกล้เคียงคนปกติหรือคนเป็นเบาหวานมากกว่ากัน และเป็นการตรวจที่ช่วยยืนยันได้ชัดเจนยิ่งขึ้นว่าท่านเป็นเบาหวานหรือไม่ นอกจากนี้ยังทำให้ทราบว่ามะระแคปซูลช่วยให้การควบคุมระดับน้ำตาลในเลือดหลังกินอาหารของท่านดีขึ้นจริงหรือไม่

5. คำชี้แจงเกี่ยวกับวิธี และขั้นตอนในการศึกษา

หากท่านเข้าร่วมในการศึกษานี้ คณะผู้วิจัยจะขออนุญาตทำการตรวจร่างกาย และเจาะเลือดเพื่อตรวจดูว่าร่างกายของท่านมีอะไรผิดปกติหรือไม่ ท่านจะต้องงดน้ำ และอาหารใดๆหลัง 2 ทุ่ม ถ้าไม่พบอะไรผิดปกติ ท่านก็จะได้รับการคัดเลือกให้กินมะระแคปซูล หรือเม็ดแป้งแคปซูล คณะผู้วิจัยจะนัดท่านมาอีก 2 ครั้ง โดยทุกครั้งท่านจะต้องงดน้ำ และอาหารใดๆหลัง 2 ทุ่มของคืนก่อนที่จะมาโรงพยาบาลเช่นเดียวกับครั้งแรก เมื่อท่านมาถึงโรงพยาบาลในตอนเช้าคณะผู้วิจัยจะขออนุญาตเจาะเลือดเพื่อวัดระดับน้ำตาลในเลือดครั้งที่ 1 หลังจากนั้นจะให้ท่านกินยาที่เตรียมไว้ให้ ซึ่งอาจเป็นเม็ดแป้งธรรมดา หรือเป็นมะระขี้นกแคปซูลก็ได้ แล้วให้ท่านนั่งพักประมาณครึ่งชั่วโมง หลังจากนั้นก็จะให้ท่านกินน้ำตาลกลูโคสละลายน้ำ 1 แก้ว แล้วทำการเจาะเลือดท่านทุกครึ่งชั่วโมง ทั้งหมด 5 ครั้งเพื่อวัดระดับน้ำตาลในเลือดที่เวลาต่างๆหลังจากกินน้ำตาลเป็นอันเสร็จสิ้นการศึกษาในวันแรก ท่านจะต้องมาโรงพยาบาลอีกครั้งในอาทิตย์ต่อมาเพื่อทำการศึกษาเช่นเดียวกับครั้งแรก แต่คณะผู้วิจัยจะให้ท่านกินยาสลับกันกับวันแรก เช่นถ้าวันแรกได้รับมะระขี้นกแคปซูล วันที่ 2 ก็จะได้รับผงแป้งแคปซูลแทน ปริมาณเลือดที่จะขออนุญาตท่านเจาะไปตรวจจะมีขนาดประมาณครึ่งช้อนชาต่อครั้ง ซึ่งจะไม่ทำให้เกิดอันตรายใดๆ นอกจากนี้คณะผู้วิจัยจะขอสัมภาษณ์ท่านเกี่ยวกับการกินอาหารโดยที่ไม่ได้บอกให้ท่านทราบล่วงหน้าได้ ในระหว่างที่ท่านเข้าร่วมการศึกษาทั้งที่โรงพยาบาล และที่บ้านหากท่านมีอาการผิดปกติใดก็สามารถบอกโดยตรง หรือโทรศัพท์มาปรึกษาได้ตลอดเวลา และเพื่อความปลอดภัยหลังจากการศึกษาคณะผู้วิจัยจะทำการตรวจร่างกายให้ท่านอีกครั้งเพื่อดูว่ามีสิ่งผิดปกติใดเกิดขึ้นหรือไม่ และถ้าพบว่ามีความผิดปกติใดๆที่เป็นผลข้างเคียงจากการเข้าร่วมโครงการในครั้งนี้คณะผู้วิจัยจะแจ้งให้ท่านทราบและให้การดูแลรักษาเป็นอย่างดีตามความเหมาะสมจนกระทั่งหายเป็นปกติ

ในช่วงของการศึกษาคณะผู้วิจัยจะเป็นผู้รับผิดชอบค่าใช้จ่ายของผู้เข้าร่วมโครงการในการตรวจร่างกาย การตรวจทางห้องปฏิบัติการต่างๆ ตามที่ได้กล่าวถึงข้างต้น รวมทั้งค่าใช้จ่ายในการเดินทางมาโรงพยาบาลตามนัดครั้งละ 500 บาท

<u>หากท่านตกลงจะเข้าร่วมการศึกษานี้ นั่นคือท่านยินยอมกินมะระขี้นกแคปซูล และเม็ดแป้งแคปซูล รวมทั้งอนุญาตให้คณะผู้วิจัยทำการเจาะเลือด และเก็บข้อมูลจากท่านเพื่อการศึกษาวิจัยนี้</u>

โดยเป็นการสมัครใจเท่านั้น หากท่านไม่เข้าร่วมในการศึกษานี้จะไม่มีผลกระทบใดๆ ต่อการดูแลรักษาตามปกติที่ควรจะได้รับจากโรงพยาบาลที่นี่และที่อื่นๆ หากท่านตัดสินใจเข้าร่วมในการศึกษานี้ท่านสามารถขอยุติการเข้าร่วมในการศึกษานี้เมื่อใดก็ได้ที่ต้องการ โดยไม่มีผลกระทบใด ๆ เช่นกัน

หากท่านมีปัญหา หรือข้อสงสัยประการใด กรุณาติดต่อ

ภญ.ศิริวดี บุญมโหตม์

ฝ่ายเภสัชกรรม ศูนย์วิทยาศาสตร์สุขภาพ มหาวิทยาลัยบูรพา

หมายเลขโทรศัพท์ (038) 390324 ต่อ 114-5

ซึ่งยินดีให้คำตอบแก่ท่านทุกเมื่อ

ขอขอบพระคุณในความร่วมมือของท่านมา ณ ที่นี้

ใบยินยอมเข้าร่วมการวิจัย

โครงการวิจัยเรื่อง การศึกษาผลลดน้ำตาลในเลือดแบบเฉียบพลันของมะระขี้นก(*Momordica charantia*) ผงแห้ง ฟรีซดราย ในผู้ที่มีภาวะทนต่อกลูโคสบกพร่อง

วันที่ให้คำยินยอม วันที่.....เดือน.....พ.ศ. .....

ก่อนที่จะลงนามในใบยินยอมให้ทำการวิจัยนี้ ข้าพเจ้าได้รับการอธิบายจากผู้วิจัยถึงวัตถุประสงค์ของการวิจัย วิธีการวิจัย อันตราย หรืออาการที่อาจเกิดขึ้นจากการวิจัย หรือจากยาที่ใช้รวมทั้งประโยชน์ที่จะเกิดขึ้นจากการวิจัยอย่างละเอียด และมีความเขาใจดีแล้ว

ผู้วิจัยรับรองว่าจะตอบคำถามต่างๆ ที่ข้าพเจ้าสงสัยด้วยความเต็มใจไม่ปิดบังซ่อนเร้นจนข้าพเจ้าพอใจ

ข้าพเจ้ามีสิทธิที่จะบอกเลิกการเข้าร่วมในโครงการวิจัยนี้เมื่อใดก็ได้ และเข้าร่วมโครงการวิจัยนี้โดยสมัครใจ และการบอกเลิกการเข้าร่วมการวิจัยนี้จะไม่มีผลต่อการรักษาโรคที่ข้าพเจ้าจะพึงได้รับต่อไป

ผู้วิจัยรับรองว่าจะเก็บข้อมูลเฉพาะเกี่ยวกับตัวข้าพเจ้าเป็นความลับ และจะเปิดเผยได้เฉพาะในรูปที่เป็นสรุปผลการวิจัย การเปิดเผยข้อมูลเกี่ยวกับตัวข้าพเจ้าต่อหน่วยงานต่างๆ ที่เกี่ยวข้องกระทำได้เฉพาะกรณีจำเป็นด้วยเหตุผลทางวิชาการเท่านั้น

ผู้วิจัยรับรองว่าหากเกิดอันตรายใดๆจากการวิจัยดังกล่าว ข้าพเจ้าจะได้รับการรักษาพยาบาลโดยไม่คิดมูลค่า และจะได้รับการชดเชยรายได้ที่สูญเสียไประหว่างการรักษาพยาบาลดังกล่าวตลอดจนเงินทดแทนความพิการที่อาจเกิดขึ้นตามความเหมาะสม

ข้าพเจ้าได้อ่านข้อความข้างต้นแล้ว มีความเข้าใจดีทุกประการ และได้ลงนามในใบยินยอมนี้ด้วยความเต็มใจ

ลงนาม……..…..ผู้ยินยอม

(…….)

ลงนาม……..…..พยาน

(…….)

ลงนาม……..…..ผู้ทำวิจัย

(…….)

ข้าพเจ้าไม่สามารถอ่านหนังสือได้ แต่ผู้วิจัยได้อ่านข้อความในใบยินยอมนี้ให้แก่ข้าพเจ้าฟังจนเข้าใจดีแล้ว ข้าพเจ้าจึงลงนามหรือประทับลายนิ้วหัวแม่มือขวาของข้าพเจ้าในใบยินยอมนี้ด้วยความเต็มใจ

ลงนาม……ผู้ยินยอม

(……)

ลงนาม……พยาน

(……)

ลงนาม……ผู้ทำวิจัย

(……)

Appendix B

Food Record Form for 24 hr Diet Recall

ชื่อ.....วันที่.....

ข้อแนะนำในการบันทึก

1. บันทึกอาหารทุกมื้อทุกชนิดรวมทั้งขนม และเครื่องดื่มที่ท่านรับประทานตลอดวัน ตั้งแต่ท่านตื่นนอนจนเข้านอน(เฉพาะส่วนที่ท่านรับประทานเท่านั้น)

2. บันทึกอาหารที่รับประทานทั้งที่บ้านและนอกบ้านถ้าเป็นมื้อพิเศษให้ระบุด้วย เช่น งานเลี้ยงแต่งงาน เป็นต้น

3. ข้อความต่อไปนี้เป็นสิ่งจำเป็นในการบันทึก

- ระบุเครื่องประกอบของอาหารแต่ละชนิด พร้อมทั้งปริมาตร โดยของแข็งให้ระบุเป็นช้อนตวงหรือทัพพี ส่วนของเหลวให้ระบุเป็น ซี.ซี. หรือระบุตามที่ตวง วัด ที่ใช้อยู่ในบ้านถ้าไม่สามารถประมาณปริมาณได้ ให้พยายามบันทึกในรูปขนาด เช่น ขนาดเล็ก, กลาง, ใหญ่ หรือขนาดกว้างยาวของอาหารที่ใช้ เช่น ผัดเปรี้ยวหวานต้องระบุว่ารับประทานแตงกวาประมาณ 4 ช้อนโต๊ะ เนื้อหมู 2 ช้อนโต๊ะ หรือระบุว่ารับประทานแตงกวาประมาณครึ่งลูกใหญ่ มะเขือเทศ 1 ลูกเล็ก เนื้อหมู 5 ชิ้น ขนาดชิ้นละ 1x2 ซม. เครื่องดื่มควรระบุเป็นปริมาตรหรือขนาดเช่น โคล่า 1 ขวดกลาง หรือ 290 ซี.ซี. เป็นต้น

- อาหารที่รับประทานปรุงอย่างไร เช่น ปลาทูทอด ไก่ย่าง เป็นต้น

- การเติมน้ำตาล น้ำเชื่อม ลงในเครื่องดื่ม อาหาร ของหวาน ชนิดต่างๆ ให้ระบุปริมาณด้วย เช่น น้ำตาล 2 ช้อนชา ในกาแฟ 1 แก้ว

ตัวอย่างการบันทึกอาหาร

วันที่ .....

มื้ออาหารและสถานที่	เวลา	ชนิดอาหาร	ส่วนประกอบ	ปริมาณ
เช้า ที่บ้าน	7.00 น.	ข้าวมันไก่	ข้าวมัน เนื้อไก่ น้ำซุป น้ำจิ้ม (เต้าเจี้ยว, ขิง, กระเทียม, น้ำตาล, น้ำส้ม, ซีอิ๊วดำ)	1 ถ้วยตวง 7 ชิ้น (1x2 ซม.) 1 ถ้วย 1 ช้อนโต๊ะ
		กุนเชียงทอด	กุนเชียง น้ำมันพืชกุ๊ก	2 ช้อนโต๊ะ 1 ช้อนโต๊ะ
		กาแฟ	กาแฟ น้ำตาล นมสด	1 ช้อนชา 2 ช้อนชา 2 ช้อนโต๊ะ
อาหารว่างเช้า ที่ทำงาน	10.00 น.	สาคูเปียก – เผือก	สาคู เผือก น้ำตาล กะทิ	1 ถ้วยตวง 1 ช้อนโต๊ะ 1 ช้อนโต๊ะ 1 ช้อนโต๊ะ
กลางวัน ทำงานที่	12.00 น.	ก๋วยเตี๋ยว ลูกชิ้นเนื้อสด	เส้นก๋วยเตี๋ยว ถั่วงอก เนื้อสด ลูกชิ้น น้ำมันกระเทียมเจียว น้ำตาลทราย(ปรุงรส)	1 ทัพพี 2 ช้อนโต๊ะ 2 ช้อนโต๊ะ 5 ลูก 2 ช้อนชา 2 ช้อนชา
		ปอเปี๊ยะทอด	แป้งปอเปี๊ยะ กุนเชียง	3 แผ่น 2 ช้อนชา

มื้ออาหารและสถานที่	เวลา	ชนิดอาหาร	ส่วนประกอบ	ปริมาณ
			เต้าหู้ ถั่วงอก เนื้อปู น้ำราด(รสค่อนข้างหวาน)	2 ช้อนโต๊ะ 2 ช้อนโต๊ะ 1 ช้อนโต๊ะ 1 ช้อนโต๊ะ
		สับปะรด	สับปะรดขนาด 2x3 นิ้ว น้ำตาล	1 ชิ้น 1 ช้อนชา
		Coke	Coke ขวดกลาง	290 ซี.ซี.
อาหารว่าง บ่าย ที่ทำงาน	15.00 น.	กล้วยบวชชี	กล้วยน้ำว้า(1 ลูก ผ่า 4) น้ำกะทิ น้ำตาล	4 ชิ้น 4 ช้อนโต๊ะ 2 ช้อนโต๊ะ
อาหารเย็น ที่บ้าน	18.00 น.	ข้าวสวย ต้มยำไก่, เห็ด	ข้าว เนื้อไก่ เห็ดฟาง น้ำตาล	2 ทัพพี 2 ช้อนโต๊ะ 2 ช้อนโต๊ะ 2 ช้อนชา
		ผัดคะน้าหมูกรอบ	ผักคะน้า หมูกรอบ น้ำมันพืช	2 ถ้วยตวง 2 ช้อนโต๊ะ 1 ช้อนโต๊ะ
		ไข่เจียวหมูสับ	ไข่ หมูสับ น้ำมันพืช	1 ฟอง 1 ช้อนโต๊ะ 2 ช้อนโต๊ะ
		ส้มเขียวหวาน	ส้มเขียวหวานขนาดกลาง	2 ลูก
อาหารว่าง ก่อนนอน	23.00 น.	นมสด	นมสดหนองโพ ชนิดหวาน	1 กล่อง

แบบบันทึกรายการอาหารที่รับประทาน

วันที่ .....

มื้ออาหารและสถานที่	เวลา	ชนิดอาหาร	ส่วนประกอบ	ปริมาณ

Example for Conversion Food Data by Using Food Code

มื้ออาหาร และ สถานที่	เวลา	ชนิด อาหาร	ส่วนประกอบ	ปริมาณ	น้ำหนัก (กรัม)	food code
เช้า ที่บ้าน	7.00 น.	ข้าวมันไก่	ข้าวมัน เนื้อไก่ น้ำซุป น้ำจิ้ม (เต้าเจี้ยว, ขิง, กระเทียม, น้ำตาล, น้ำส้ม, ซีอิ๊วดำ)	1 ถ้วยตวง 7 ชิ้น (1x2 ซม.) 1 ถ้วย 1 ช้อนโต๊ะ	200 35 10 10 (3,1,1,2,2,1)	14 2435 - - (1236,1609,1684, 440, 3221, 1216)

การคำนวณปริมาณสารอาหารที่ได้รับแต่ละวัน

เมื่อได้ข้อมูลการบริโภคอาหารในแต่ละมื้อ ของแต่ละคนจนครบ 1 วัน ดังตารางที่ได้แสดงไว้เป็นตัวอย่าง เช่น มื้อเช้า นาย ก รับประทานข้าวมันไก่ ประมาณ 1 ถ้วยตวงมีส่วนประกอบเป็นอะไรบ้าง จากส่วนประกอบที่แยกออกมาได้ ของอาหารมื้อเช้าซึ่งเป็นข้าว เนื้อไก่ น้ำซุบ และน้ำจิ้ม ซึ่งน้ำจิ้มยังแยกออกเป็นส่วนประกอบต่างๆได้อีก จากส่วนประกอบที่ได้ จะนำมาคำนวณเป็นปริมาณสารอาหารที่ได้บริโภคโดยใช้ค่าอ้างอิงจากตารางแสดงคุณค่าอาหารไทยในส่วนที่กินได้ 100 กรัม ของกรมอนามัย กระทรวงสาธารณสุข ตัวอย่างเช่น เนื้อไก่ หรือ ข้าวสุกหนัก 100 กรัมจะมีสารอาหารที่เป็น พลังงาน ไขมัน เกลือแร่ โปรตีน วิตามินต่างๆ ฯลฯ อยู่เท่าไร ส่วนที่นาย ก รับประทานไปในมื้อเช้า จะคำนวณได้ว่า นาย ก จะได้รับสารอาหารเท่าไร เมื่อรวมกันครบ 3 มื้อ หรือที่รับประทานใน 1 วัน จะได้เท่าไร

ในการคำนวณปริมาณสารอาหารที่บริโภคในปัจจุบันนี้มีโปรแกรมคอมพิวเตอร์สำเร็จรูปโดยการใส่ข้อมูลของสารอาหารหลายชนิดจากตารางแสดงคุณค่าอาหาร (ของกรมอนามัย) ซึ่งได้ทำการวิเคราะห์ปริมาณสารอาหารแต่ละชนิดเอาไว้แล้ว ลงในโปรแกรมคอมพิวเตอร์ พร้อมรหัส (food code) เก็บเอาไว้เป็นข้อมูลอ้างอิง เมื่อสำรวจได้ว่า นาย ก รับประทานอาหารอะไรบ้าง ในแต่ละมื้อ มีส่วนประกอบเป็นอาหารแต่ละชนิดกี่กรัม ผู้คำนวณเพียงแต่ใส่ปริมาณอาหารแต่ละชนิดให้ตรงกับรหัสของอาหารที่มีอยู่ในโปรแกรมแล้วให้ถูกต้อง ตัวโปรแกรมจะทำการคำนวณค่าเฉลี่ยของสารอาหารที่ได้รับประทานต่อมื้อ ต่อวัน หรือต่อคน ออกมาได้เองโดยอัตโนมัติ อย่างไรก็ตามสิ่งสำคัญที่จะต้องคำนึงถึง คือ ผู้ประเมินจะต้องทราบถึงตำรับ และวิธีปรุงอาหารเพื่อที่จะแยกอาหารแต่ละมื้อ ออกเป็นส่วนประกอบที่เป็นอาหาร และเครื่องปรุงย่อยๆได้อย่างถูกต้อง เช่น น้ำจิ้มข้าวมันไก่ จะประกอบด้วย กระเทียม ขิง เต้าเจี้ยว น้ำตา ล น้ำส้ม ซีอิ๊วดำ เป็นต้น

Appendix C

Physical Activity Questionare

แบบสอบถามการออกกำลังกาย

ชื่อ.....วันที่.....

กาเครื่องหมาย ☑ ในหัวข้อที่ตรงกับท่านมากที่สุด

1. ท่านออกกำลังกายด้วยวิธีใด หรือ มีกิจกรรมอะไร ที่ทำเป็นประจำ บ้าง(ตอบได้มากกว่า 1 อย่าง)

.....

.....

2. ท่านออกกำลังกาย หรือทำกิจกรรมดังกล่าว ตามข้อ 1.มานานเท่าไหร่

.....

.....

3. หลังออกกำลังกาย หรือทำกิจกรรมท่านรู้สึกอย่างไร ?

.....

.....

แต่ละกิจกรรมให้ตอบเป็น 3 ระดับ ดังนี้

4. เหนื่อยเล็กน้อย และยังสามารถร้องเพลงไปด้วยได้
5. เหนื่อย และยังสามารถพูดไป และออกกำลังกาย หรือ ทำกิจกรรมไปด้วยได้
6. เหนื่อยมาก จนหอบ และต้องหายใจแรงๆ ขณะพูด

4. ท่านใช้เวลาในการออกกำลังกาย หรือทำกิจกรรมแต่ละชนิดนานแค่ไหน ?

กิจกรรม

.....☐ <10 นาที ☐ 10-19 นาที ☐ 20-30 นาที ☐ >30 นาที

.....☐ <10 นาที ☐ 10-19 นาที ☐ 20-30 นาที ☐ >30 นาที

.....☐ <10 นาที ☐ 10-19 นาที ☐ 20-30 นาที ☐ >30 นาที

.....☐ <10 นาที ☐ 10-19 นาที ☐ 20-30 นาที ☐ >30 นาที

5. ท่านออกกำลังกาย หรือทำกิจกรรมบ่อยแค่ไหน ?

.....☐ เดือนละ1-ไม่กี่ครั้ง☐ 1-2ครั้ง/สัปดาห์ ☐ 3-5ครั้ง/สัปดาห์ ☐ เกือบทุกวัน

.....☐ เดือนละ1-ไม่กี่ครั้ง☐ 1-2ครั้ง/สัปดาห์ ☐ 3-5ครั้ง/สัปดาห์ ☐ เกือบทุกวัน

.....☐ เดือนละ1-ไม่กี่ครั้ง☐ 1-2ครั้ง/สัปดาห์ ☐ 3-5ครั้ง/สัปดาห์ ☐ เกือบทุกวัน

……..☐ เดือนละ1-ไม่กี่ครั้ง☐ 1-2ครั้ง/สัปดาห์ ☐ 3-5ครั้ง/สัปดาห์ ☐ เกือบทุกวัน

The scoring protocol for Physical Activity Questionare

Categorical Score- three levels of physical activity are proposed

1. Inactive (category 1)

This is the lowest level of physical activity. Those individuals who not meet criteria for categories 2 or 3 ar considered inactive.

2. Minimally Active (category 2)

Any one of the following 3 criteria

• 3 or more days of vigorous activity of at least 20 minutes per day OR

• 5 or more days of moderate-intensity activity or walking of at least 30 minutes per day OR

• 5 or more days of any combination of walking, moderate-intensity or vigorous intensity activities achieving a minimum of at least 600 MET-min/week.

3. HEPA Active (category 3)

Any one of the following 2 criteria

• Vigorous-intensity activity on at least 3 days and accumulating at least 1500 MET-minutes/week OR

• 7 or more days of any combination of walking, moderate-intensity or vigorous intensity activities achieving a minimum of at least 3000 MET-minutes/week the intensity of certain activities is commonly characterized as light, moderate, or vigorous (119).

Measuring Physical Activity Intensit by Talk Test

The talk test method of measuring intensity is simple. A person who is active at a *light* intensity level should be able to sing while doing the activity. One who is active at a *moderate* intensity level should be able to carry on a conversation comfortably while engaging in the activity. If a person becomes winded or too out of breath to carry on a conversation, the activity can be considered *vigorous*.

Appendix D

Table show classifications for BMI

Classification	BMI (kg/m2)
Underweight	< 18.5
normal	18.5-24.9 (18.5-22.9[a])
Overweight	25.0-29.9 (23.0-25 [a])
Obesity (Class 1)	30.0-34.9
Obesity (Class 2)	35.0-39.9
Obesity (Class 3)	≥ 40

[a] use for Asian people

Biograhy

NAME	Miss Siriwade Bunyamahotama
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