Clinical application of Momordica charantia (Bitter Melon) for reducing blood sugar in type 2 diabetes mellitus

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Running Title

Bitter melon for type 2 diabetes

Review Article

Open Access &

Peer-Reviewed Article

DOI: 10.14302/issn.2379-7835.ijn-23-4737

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Keywords:
Bitter melon, glycemic control, hypoglycemic effect, *momordica charantia*, non-insulin dependent diabetes mellitus, type 2 diabetes mellitus.

Received: August 29, 2023

Accepted: October 07, 2023

Published: October 19, 2023

Academic Editor:
Sasho Stoleski, Institute of Occupational Health of R. Macedonia, WHO CC and Ga2len CC

Citation:
Ashley Dahlquist, Dana Jandali, Mirielle C. Nauman, Jeremy J. Johnson (2023) Clinical application of Momordica charantia (Bitter Melon) for reducing blood sugar in type 2 diabetes mellitus. International Journal of Nutrition - 7 (4):8-26. https://doi.org/10.14302/issn.2379-7835.ijn-23-4737

Abstract

Bitter melon is a popular fruit cultivated in Southeast Asia and other tropical climate regions. Bitter melon has been used in traditional medicine because of its numerous medicinal benefits, including having hypoglycemic effects. This has an indication for diabetic patients, and several clinical trials have provided evidence that orally administered bitter melon extract can reduce A1C and blood sugar levels in diabetes patients. *In vitro and in vivo* mechanistic studies suggest that bitter melon's anti-diabetic actions work through intra- and extra-pancreatic mechanisms. Herein we summarize and highlight these mechanistic and clinical studies that have demonstrated the hypoglycemic effects of bitter melon in type 2 diabetes patients.

Introduction

Momordica charantia, commonly known as bitter melon or bitter gourd, is a climbing plant that belongs to the Cucurbitaceae family[1]. The plant is cultivated in tropical and subtropical regions, such as India, Malaysia, Thailand, Singapore, Vietnam, China, Japan, New Zealand, parts of eastern Africa, Brazil, Colombia, Cuba, Haiti, Mexico, Nicaragua, Panama, and in the Middle East [2]. The plant's fruit is referred to as "bitter melon" or "bitter gourd" due to its sour or bitter taste and has been used for thousands of years for its medicinal benefits. Significant pharmacologic activities have been reported, including hypoglycemic, anti-cancer, anti-inflammatory, antimicrobial, antimutagenic, antioxidant, anti-helminthic, anti-hyperlipidemic, anti-obesity, and immunomodulatory effects [3, 4]. Recent efforts have gone into studying bitter melon for use in type 2 diabetes patients due to its hypoglycemic activities.

Diabetes mellitus (DM) is a metabolic disorder that results from hyperglycemia and abnormalities in carbohydrate, fat, and protein metabolism [5, 6]. DM can lead to chronic microvascular, macrovascular, and/or neuropathic complications [7].

Type 1 DM (T1DM), accounting for approximately 5-10% of all DM cases, is a genetic disease caused by the autoimmune destruction of pancreatic β-cells resulting in absolute insulin deficiency. Insulin therapy is the main treatment for T1DM [8]. Type 2 DM (T2DM), accounting for approximately 90% of all DM cases, is referred to as non–insulin-dependent diabetes (NIDDM) and can result from a wide variety of causes, such as insulin resistance, defective insulin secretion, or hyperglycemia [9]. Pharmacological treatment for T2DM varies and largely depends on the patient and the progression of the disease, though metformin is typically considered the first line standard of care for obese T2DM patients [10].

Metformin improves the body's sensitivity to insulin by decreasing hepatic glucose production and decreasing intestinal absorption of glucose [11]. Metformin is efficacious and relatively inexpensive, however, 30% of patients experience gastrointestinal side effects including abdominal discomfort, upset stomach, and diarrhea [8, 12]. Additionally, if target blood sugar or A1C levels are not reached after treatment with metformin, additional pharmacologic therapies may be added to the regimen; which is common in many patients within 5 years of treatment initiation [10, 13]. While there is a large need for

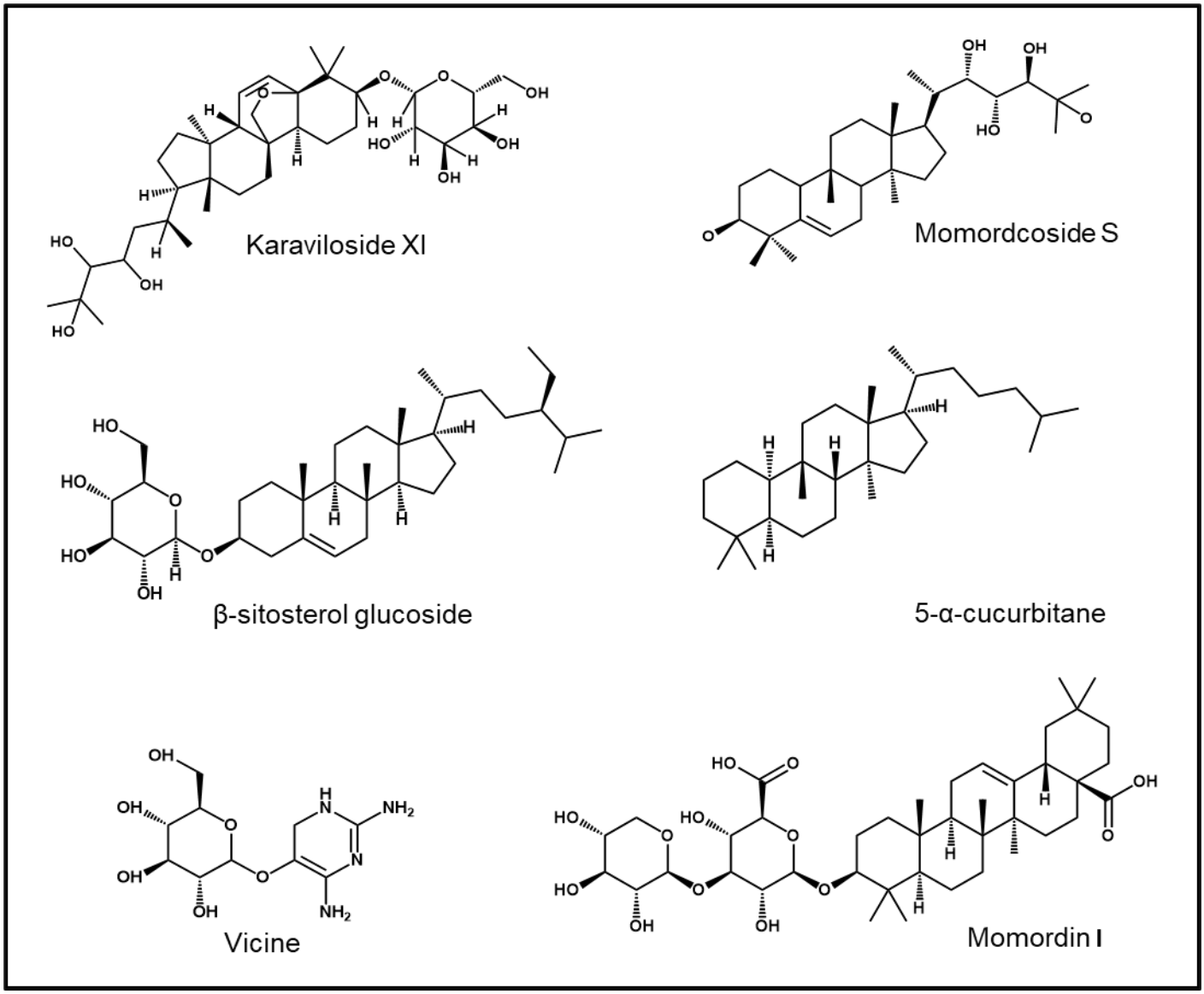

Figure 1. Structures of bitter melon phytochemical constituents

pharmacological novelties for diabetic patients, there are several vitamins, minerals, and botanicals that have been reported to lower blood sugar levels and could improve people with diabetes quality of life.

Several clinical trials have investigated bitter melon's ability to achieve glycemic control in T2DM patients [14]. Bitter melon contains a unique mixture of steroidal saponins, insulin-like peptides, triterpenoids, flavonoids, and alkaloids that may be responsible for its antidiabetic effects. Some phytochemicals worth noting include cucurbitanes, saponins, charantins, momoridins, karaviloside XI, momordicoside S, polypeptide-p, and vicine (**Figure 1**) [1, 11, 15]. The fruit and seeds contain the highest concentration of phytochemicals and the fruit has been reported to have the most pronounced anti -diabetic activity [16]. In this review, we evaluate the current clinical evidence for bitter melon as a strategy for type 2 diabetes mellitus control.

Mechanism of Action

Many different organs are affected by T2DM, including the heart, kidneys, and pancreas, and several mechanisms of action have been suggested that may contribute to the hypoglycemic effect of bitter melon extracts [17, 18]. Polypeptide-p is one of the bioactive constituents of bitter melon that has been suggested to structurally resemble bovine insulin, thereby rendering an informal name of plant insulin (p-insulin) [19]. One clinical study reported that a subcutaneous injection of p-insulin significantly decreased blood glucose levels in patients with diabetes [20]. Another active constituent of bitter melon, compound K16, a cucurbitane type triterpenoid, has been shown to restore the levels of insulin receptors and insulin receptor substrates and upregulate the expression of several proteins involved in insulin signaling, including AMPKα1 and GLUT4 *in vivo* [21]. Compound K16 effectively reduced blood glucose and serum lipid levels and improved glucose tolerance in a murine model [3].

Insulin resistance

Insulin resistance is a physiologically altered state characterized by reduced responsiveness of insulin targeting tissues to high insulin levels. It is considered a main driver of many diseases, one being type 2 diabetes mellitus[22]. In many cases, insulin resistance occurs when insulin levels increase to meet normal physiologic demands which leads to hyperinsulinemia, hyperglycemia-induced beta cell failure and eventually to type 2 diabetes mellitus. There are several proposed mechanisms of insulin resistance, one being abnormal insulin and downstream PI3K/Akt signal pathways. These pathways aid in the modulation of glucose transport, glycogen synthesis, glycolysis, and protein synthesis. Insulin signaling pathways can be suppressed via several inhibitory molecules such as the protein tyrosine phosphatase 1 B (PTP-1B), suppressor of cytokine signaling-3 (SOCS-3), and c-Jun N-terminal kinase (JNK). However, proinflammatory cytokines such as TNF-alpha and IL-6 activate these inhibitory molecules and suppress the insulin signaling pathways leading to insulin resistance. In a 2017 study, investigators looked at *Momordica charantia* effects on T2DM rats. *M. charantia* has been shown to have hypolipidemic, weight loss and anti-inflammatory activities. The results shown that in type 2 diabetic rats, *M. charantia* ethanol extracts ameliorated insulin resistance. This was attributed to the dose dependent decreases in the expressions of MAPK signaling proteins observed, including JNK and SOCS-3 [23].

Extra pancreatic effects

A feature of T2DM is the relatively high Na^+, K^+-ATPase-dependent absorption of glucose in the

intestine compared that of healthy individuals [24]. Both *In vitro* and *in vivo* studies using either bitter melon extracts in everted intestines or bitter melon juice administered daily to rats showed a reduction in intestinal absorption of glucose [25-27]. Furthermore, bitter melon flavonoids inhibit intestinal glucose transport by acting as glucosidase inhibitors, specifically to sodium glucose co-transporters and fructose transporters like SGLT1 and GLUT5 which are key transporters responsible for diabetes-associated postprandial hyperglycemia [13, 28]. Another study shows that bitter melon powder can inhibit intestinal maltase, sucrose, and pancreatic lipase activities in diabetic rats, therefore suppressing the absorption of disaccharides and lipids and reducing hyperglycemia [29].

T2DM is also known to alter the expression of glucose transporters, contributing to insulin resistance, and bitter melon may reverse this resistance by increasing GLUT4 expression, a crucial glucose transporter. Miura. et al's study found an increased number of GLUT4 transport proteins in KK-ay mice (genetically engineered diabetic mice) after administering bitter melon aqueous extract for 30 days [30]. Another study by Tan et al. showed that cucurbitane glycosides, momordicosides, and aglycones from bitter melon increased GLUT4 transport across membranes and activated AMPK *in vitro*. The study also reported that momordicoside modulated fatty acid oxidation and glucose disposal in insulin-sensitive and insulin-resistant mice [31].

Another possible mechanism of action was suggested by Rathi, Grover, and Vats' in 2002, where they demonstrated that bitter melon restored normal glycogen levels in insulin-dependent tissues and restored glycolytic enzyme activity levels *in vivo*. Specifically, they observed that bitter melon restored the activities of hexokinase, glucose-6-phosphatase, and phosphofructokinase [32]. In another study, Shibib, Khan, and Rahman reported that bitter melon decreased glucose-6-phosphatase and fructose-1,6-bisphophase, thereby decreasing the rate of gluconeogenesis, though this study did not include a diabetic control [33]. More work is needed to determine the exact effect on glucose metabolism.

Intra pancreatic effects

T2DM drugs focus on stimulating insulin production, and therefore many of these therapeutics act on the pancreas, where β-islet cells produce insulin at a rate dependent on blood sugar levels. Various studies have reported that bitter melon stimulates insulin production. Yibchok-Anun et al first tested this using a pancreatic perfusion assay, where rat pancreases were cannulated and infused with bitter melon extract to measure insulin and glucagon production. They reported that bitter melon significantly increased insulin production and decreased glucagon production, suggesting that bitter melon acts directly on β cells and enhances them due to its antioxidant properties [34]. In another study, an increase in islet size, total β cells, and insulin levels was observed in type-2 diabetic rats that were given bitter melon fruit pulp extract. Bitter melon may have insulin secretagogue properties which may explain in part its anti-diabetic effects [35]. In addition, the ethanol extract of bitter melon has been shown to exhibit anti-diabetic effects and improve glucose metabolism through the protein Sirtuin 1 (SIRT1). Bitter melon increases hepatic gluconeogenesis and fatty acid use via upregulation of the SIRT 1 signaling pathway and shows the favorable effects of increased insulin sensitivity [36]

Clinical trials with bitter melon and type 2 diabetes

Thirteen different clinical trials with a total of 892 participants, were reviewed which evaluated the glycemic control and hypoglycemic effect of bitter melon extract on patients with type 2 diabetes mellitus. The studies and findings are summarized in **Table 1**.

Table 1. Clinical trials with bitter melon and type 2 diabetes

Author Information	Study design	Study agent(s)	Human subjects	Results
Yang (2022) Site: Taichung City, Taiwan	Randomized, double-blind, placebo controlled. **Length:** 12 weeks	1. Two capsules Insumate® (mcIRBP-19-BGE) containing 300 mg BM each 2. Two placebo capsules containing 300 mg starch each Study agents were given once before lunch and once before dinner for three months.	41, (n=20 received Insumate® for 12 weeks, n=20 received placebo) **Inclusion criteria:** T2D patients who did not respond to pharmacological intervention	**Subgroup results:** **HbA1C (%):** Baseline: 8.0±0.7 3 months: 7.5±0.8 **FPG (mg/dl):** Baseline: 172.5±32.6 3 months: 159.4±18.3 **BMI:** Baseline: 26.0±4.5 3 months: 25.8±4.4 **Body weight (kg):** Baseline: 67.7±14.7 3 months: 66.9±14.3
Majeed (2021) Site: Madurai, India	Prospective, randomized, double-blind, active-controlled. **Length:** 120 days ± 3 days	1. GlycaCare-II ® tablets (522.5 mg) containing M. charantia extract 2. Glycirite ® (metformin) tablets, 500 mg Study agents were given twice daily, in the morning and at night, for 120 days	Arm I – **pre-diabetic** subjects: 29, (n=12 received metformin, n=17 received GlycaCare-II) Arm II – **new diabetic** subjects: 40, (n=16 received metformin, n=24 received GlycaCare-II) **Inclusion criteria:** • Age: 30-65 • HbA1C: 6.5-7.5% FBS > 125 mg/Dl	**Arm I:** **HbA1C (%):** GlycaCare-II Baseline: 6.16 ± 0.21 Metformin Baseline: 6.2 ± 0.24 **GlycaCare-II 120 days: 5.87 ± 0.15** **Metformin 120 days: 5.97 ± 0.21** **FBS:** GlycaCare-11: 15% reduction Metformin: 11% reduction **Postprandial blood sugar (mg/dL):** GlycaCare-II baseline: 169.59 ± 16.35 Metformin Baseline: 165.67 ± 14.89 GlycaCare-II 120 days: 146.0 ± 8.66 Metformin 120 days: 148 ± 8.31

Author Information	Study design	Study agent(s)	Human subjects	Results
				Arm II: **HbA1C (%):** GlycaCare-II Baseline: 6.99 ± 0.32 Metformin Baseline: 6.99 ± 0.38 for GlycaCare-II 120 days: 6.52 ± 0.19 Metformin 120 days: 6.53 ± 0.26 for **FBS:** GlycaCare-II: 11% reduction Metformin: 10% reduction **Postprandial blood sugar (mg/dL):** GlycaCare-II: absolute mean change of 32.75 mg/dl Metformin: absolute mean change of 21.06 mg/dL
Hsu (2020) Site: Pingtung City, Taiwan	Not specified **Length:** 3 months	1. Two capsules Insumate® (mcIRBP-19-BGE) containing 300 mg BM each Study agents were given once before lunch and once before dinner for three months.	142, (n=64 received Insumate®, n=78 received placebo) **Inclusion criteria:** • Age: >20 • Fasting serum glucose: ≥140 mg/dL or HbA1c: ≥7.0% • Diabetes diagnosis >1 year before the study	**FPG (mg/dL) Treatment Group:** Baseline: 136.8±63.5 3 months: 118.0±35.5 **HbA1C (%):** Baseline: 7.8±1.4 3 months: 7.4±1.1 **Insulin (mU/mL):** Baseline: 14.8±17.6 3 months: 13.3±11.5 **Triglyceride (mg/dL):** Baseline: 147.9±85.9 3 months: 114.7±64.8
Kim (2020) Site: Jinju, South Korea	Single-center, randomized, double blind, placebo-controlled. **Length:** 12 weeks	1. Capsules contained 2380 mg M. charantia extract 2. Placebo capsules contained maltodextrin and cellulose Study agents were given twice a day for 12 weeks.	• 96, (n=66 received BM 2380 mg/day for 12 weeks, n=30 received placebo)	**HbA1C (%):** Baseline: 7.0±0.5 12 weeks: 7.0±0.7 **FPG (mg/dl):** Baseline: 145.9±34.5 12 weeks: 140.5±31.9 **HOMA IR:** Baseline: 2.4 (1.3-3.5) 12 weeks: 1.8 (1.3-2.8) **Triglyceride (mg/dL):** Baseline: 137.1±83.3 12 weeks: 128.9±76.9

Author Information	Study design	Study agent(s)	Human subjects	Results
Ma T, Lee C (2019) Site: College of Health Solutions, Arizona State University, Phoenix AZ	Randomized, double-bind, placebo-controlled trial. **Length:** 1 day	1.100ml of bitter melon juice obtained from every 140g of bitter melon pulp. 2.Placebo was a sham drink that had similar color, taste, and texture as bitter melon juice.	16, (n=8 received BM 100ml juice, n=8 placebo) **Inclusion Criteria:** • >18 years old • Large waist circumference (men ≥ 102 cm, women ≥88 cm Physical inactivity (not engaged in regular recreational physical activity/ exercise)	**2-h PPG:** Significantly lower in bitter melon group as compared with control group (99.5 ± 22.3 vs 133.9 ± 36.9 mg/dL, p=0.04) **Absolute Glucose Reduction (mg/dL):** 33.4mg/dL reduction **Relative Glucose Reduction:** 26%
Kumar (2018) Site: All India Institute of Medical Sciences (AllMS) Bhubaneswar, India	Parallel randomized controlled trial. Length: 8 weeks	Group A: 1g of commercial y available Momordica charantia tablets with oral anti-diabetic agents (metformin and glibenclamide) daily for 8 weeks. Group B: 1.5g of commercially available Momordica charantia tablets with oral anti diabetic agents daily for 8 weeks Group C (control): oral anti-diabetic agents only daily for eight weeks	75, (Group A: n=25 received 1g MC with metformin and glibenclamide, Group B: n=25 received 1.5g MC with metformin and glibenclamide, and Group C: n=25 received metformin and glibenclamide) **Inclusion Criteria:** • Met the WHO diabetes diagnostic criteria for uncomplicated Type 2 DM • 40 to 60 years old • had a FBS less than 200mg/dL • had a two-hour PPG less than 300 mg/dL • had an HbA1c less than 8% abstained from alcohol, smoking, and heavy carbohydrate diet for 7 days prior to testing and until completion of the study period	**FPG (mg/dL):** **Baseline** Group A: 158.4±19.9 Group B: 144.5±18.2 Group C: 155.9±12.3 8 weeks: Group A: *142.70±9.8 Group B: *102.82±11.2 Group C: 151.60±16.2 **PPG (mg/dL):** **Baseline** Group A: 218.9±23.2 Group B: 228.9±19.9 Group C: 221.4±23.8 **8 weeks:** Group A: *196.15±15.5 Group B: *167.38±16.1 Group C: 219.95±25.65 **HbA1c (%):** **Baseline** Group A: 7.6±0.7 Group B: 7.3±0.47 Group C: 7.1±0.49 **8 weeks:** Group A: 7.42±0.5 Group B: *6.2±1.26 Group C: 7.15±0.47 **Insulin (mIU/L):** **Baseline** Group A: 40.2±4.5 Group B: 43.5±5.8 Group C: 44.8±8.1 **8 weeks:** Group A: 36.45±3.74 Group B: *29.40±5.22 Group C: 45.75±6.65 **Total Cholesterol (mg/dL)** **Baseline** Group A: 207.3±18.3 Group B: 192.6±15.6 Group C: 188.5±18.1 **8 weeks:** Group A: *188.50±19.1 Group B: *164.86±12.2 Group C: 195.90±31.7 **BMI (kg/m2)**

Author Information	Study design	Study agent(s)	Human subjects	Results
				Baseline Group A: 26.3±3.7 Group B: 27.95±3.2 Group C: 28.9±5.4 **8 weeks:** Group A: 24.3±3.75 Group B: NA Group C: 28.55±5.0 **MDA (nmol/mL)** **Baseline** Group A: 2.12±0.2 Group B: 2.1±0.2 Group C: 2.0±0.3 **8 weeks:** Group A: 2.03±0.13 Group B: *1.78±0.2 Group C: 2.2±0.61
Cortez-Navarrete (2018) Site: Guadalajara, Mexico	Randomized, double- blind, placebo- controlled. **Length:** 90 days	1. Two capsules 500 mg M. charantia fruit powder. 2. Two placebo tablets with calcined magnesia. Study agents were taken twice daily before breakfast and dinner.	24, (n=12 received M. charantia, n=12 received placebo) **Inclusion criteria:** • BMI: 25.0-34.9 kg/m2 • Fasting serum glucose: <11.6 mmol/L • A1C: 7-9% • T2DM diagnoses of > 5 years, with no pharmacological treatment for 3 months before study. • Non-smoking • Age: 35-60 • Stable body weight for at least 3 months before study	**Body Weight (kg):** Baseline: 79.4±9.2 12 weeks: 78.0±9.2 **BMI (kg/m2):** Baseline: 29.1±2.4 12 weeks: 28.3±1.9 **WC (cm):** Baseline: 106±12 12 weeks: 104±11 **2-h serum glucose (mg/dL):** Baseline: 307.8±66.6 12 weeks: 237.6±77.4 **A1C (%):** Baseline: 7.6±0.6 12 weeks: 7.1±1.1
Rahman (2015) Site: Peshawar, Pakistan	Randomized, double-blind, placebo- controlled. **Length:** 10 weeks	1000 mg capsules of bitter melon (BM) extract powder were used and charantin yield was 0.085% within extract. 1. BM 2 g/day 2. BM 4 g/day 3. Glibenclamide 2.5 mg/day	95, (n=32 received BM 2g, n=33 received BM 4g, n=30 glibenclamide 5mg) **Inclusion criteria:** • FPG: 126-240 mg/dl • Age: 30-70 years • Normal renal and liver function tests • T2DM diagnosis based on WHO criteria.	**A1C (%):** **BM 2g:** Baseline: 8.25±0.70 Week 10: 7.40±0.50 **BM 4g:** Baseline: 8.30±0.55 Week 10: 7.15±0.60 **Glibenclamide:** Baseline: 8.45±0.60 Week 10 :6.90±0.75 **FPG (mg/dL):** **BM 2g:** Baseline: 146±13.4 Week 10: 133.7±11.5 **BM 4g:** Baseline: 141.6±15.2 Week 10: 126.4±11.9 **Glibenclamide:** Baseline: 143.5±18.4 Week 10: 117±10.3

Author Information	Study design	Study agent(s)	Human subjects	Results
				2 Hour OGTT (mg/dL): **BM 2g:** Baseline: 241.3±15.6 Week 10: 235±19.5 **BM 4g:** Baseline: 247±21.9 Week 10: 240.7±25.1 **Glibenclamide:** Baseline: 255.6±26.3 Week 10: 229.4±20.8 **Plasma sialic acid (mg/dL):** **BM 2g:** Baseline: 74±8.1 Week 10: 68±6.7 **BM 4g:** Baseline: 75.30±8.2 Week 10: 63±6.7 **Glibenclamide:** Baseline: 73.9±7.2 Week 10: 75.1±5.2
Fuangchana (2011) Site: Thailand	Multicenter, randomized, double-blind, active-control trial. **Length:** 4 weeks	BM capsules contained 500 mg of dried fruit pulp powder, containing 0.04-0.05% (w/w) of charantin. 1. Metformin 1000mg 2. BM 500 mg 3. BM 1000 mg 4. BM 2000 mg Study agents were given before and after meals twice daily.	129 (n=33 received metformin 1000mg, n=33 BM 500mg/day, n=32 BM 1000 mg/day, n=31 BM 2000 mg/day) **Inclusion criteria:** • Age 35-70 years • T2DM diagnosis based on ADA criteria. • FPG: 126-180 mg/dL	**FPG (mg/dL):** **Metformin:** Baseline: 140±22.6 Week 4: 125.2±22.7 **BM 500 mg:** Baseline: 140.3±17.4 Week 4:140.9±29.4 **BM 1000 mg:** Baseline:139.5±16 Week 4: 141.6±27.4 **BM 2000 mg:** Baseline: 139.9±15.8 Week 4: 137.6±18.1 **2 Hour OGTT (mg/dL):** **Metformin:** Baseline: 262.2±73.9 Week 4: 238.8±67.7 **BM 500 mg:** Baseline: 272±44.5 Week 4: 266.6±59.6 **BM 1000 mg:** Baseline: 271.2±50.4 Week 4: 255.4±74.6 **BM 2000 mg:** Baseline:242.6±47.7 Week 4: 242.2±59.2

Author Information	Study design	Study agent(s)	Human subjects	Results
Rahman (2009) Site: Khyber Pakhtunkhwa, Pakistan	Randomized, placebo- controlled. **Length:** 6 months	BM juice was extracted from whole fruit, with a yield of 370 mL/kg. 1. Control, received placebo capsules 2. Rosiglitazone 4 mg/day, taken in two doses 3. BM juice 55 mL/day, taken in three doses	50 (n=25 received Rosiglitazone, n=25 received BM juice). **Inclusion criteria:** • Age: 30-60 years • Diagnosis with T2DM based on ADA criteria.	**Serum sialic acid (mg/dL):** Control: 57.6±5.56 Rosiglitazone: 60.2±5.8 BM: 57.9±4.9 **Serum glucose (mg/dL):** Control: 112±6.2 Rosiglitazone: 88.35±6.31 BM: 88.35±6.31
Dans (2007) Site: Manila, Philippines	Randomized, double- blind, placebo- controlled. **Length:** 3 months	1. Charantia Ampalaya Capsules © 3 g/day 2. Placebo capsules Study agents were given three times daily for three months.	40 (n=20 Charantia, n=20 placebo) **Inclusion criteria:** • Age: >18 years • T2DM diagnosis based on ADA criteria. • A1C: 7-9%	**A1C (%):** Baseline: 7.92±0.59 Charantia: 8.2±1.25 **Fasting plasma glucose (mg/dL):** Baseline: 151.4±40.4 Charantia: 143.8±13.9 **BMI (kg/m2):** Baseline: 26.4±4.8 Charantia: 26.3±4.9
Tongia (2004) Site: Indore, India	Not specified **Length:** 14 days (treatment 7 days)	1. 0.5 g Glyciphage (metformin) 2. 5 mg Daonil (glibenclamide) 3. 0.5 g Glyciphage + 5 mg Daonil Study agents were taken twice a day before meals. After seven days, each group received half doses of metformin or glibenclamide with the addition of 200 mg capsules containing methanolic extract of M. charantia for seven more days.	15 (n=5 Glyciphage + BM, n=5 Daonil + BM, n=5 Glyciphage + Daonil + BM) **Inclusion criteria:** • NIDDM (Non-insulin dependent diabetes mellitus) patients of either sex >18 years of age	**FPG (mg/dL):** **Metformin (Glyciphage) + BM:** Baseline: 122.6±2.66 After 7 days: 109.4±3.06 After 14 days: 96.4±2.36 **Glibenclamide (Daonil) + BM:** Baseline: 122.0±1.70 After 7 days: 106.8±1.07 After 14 days: 93.8±1.36 **Metformin (Glyciphage) + glibenclamide (Daonil) + BM:** Baseline: 127.0±1.52 After 7 days: 101.8±2.63 After 14 days: 85.4±1.21 **Post prandial sugar (mg/dL):** Baseline: 220.4±3.41 After 7 days: 165.4±7.22 After 14 days: 128.0±1.84 **Daonil + BM:** Baseline: 196.6±5.34 After 7 days: 156.4±4.06 After 14 days: 128.4±2.66 **Glyciphage + Daonil + BM:** Baseline: 220.8±2.46 After 7 days: 177.8±4.35 After 14 days: 133.2±2.82

Author Information	Study design	Study agent(s)	Human subjects	Results
Ahmad (1999)	Not specified **Length:** 2 days	150-200 mL freshly prepared M. charantia pulp extract from body weight in Kg * 2 = grams of pulp. Patients fasted for one day and then took M. charantia drink one time.	100 **Inclusion criteria:** • Moderate non-insulin dependent diabetic patients • free from major complications	**Fasting plasma glucose (mg/dL):** Baseline: 257.2±5.4 After M. charantia: 221.9±3.9 **Post prandial sugar (mg/dL):** Baseline: 159.6±4.1 After M. charantia: 130.5±3.7
The superscript * denotes statistical significance.				

Yang (2022)

A randomized, double-blind, placebo-controlled, parallel comparison study was conducted on 41 participants to evaluate the hypoglycemic efficacy of *Momordica charantia* insulin receptor binding peptid -19 containing bitter gourd extracts (mcIRBP-19-BGE) in subjects with type 2 diabetes who had taken antidiabetic medications but failed to achieve treatment goals [37]. Participants were randomly assigned two groups: mcIRBP-19-BGE (n=20) and the placebo group (n=20). Of the 40 subjects who completed the study, 29 participants whose HbA1c did not continuously decline at the enrollment were used for subgroup analysis. Groups received study products orally for 12 weeks of either placebo 300mg of starch, or 600mg of mcIRBP-19-BGE. The oral administration of mcIRBP-19-BGE decreased with borderline significance at fasting blood glucose (FBG; P=0.057) and HbA1c (P=0.060). The subgroup results showed that mcIRBP-19-BGE had a significant effect on reducing FBG from 172.5 ± 32.6 mg/dL to 159.4 ± 18.3 mg/dL, P = 0.041) and HbA1c (from 8.0 ± 0.7% to 7.5 ± 0.8%, p = 0.010). This study demonstrates that mcIRBP-19-BGE possesses a potential hypoglycemic effect and can reduce FBG and HbA1c when antidiabetic drugs are rendered ineffective.

Majeed (2021)

A prospective, randomized, double-blind, active-controlled clinical trial evaluating the efficacy and safety of GlycaCare-II as monotherapy in type 2 diabetes mellitus patients as compared to metformin[38]. A total of 69 subjects were enrolled, with 29 in ARM I, pre-diabetic group, and 40 in ARM II, newly diabetic group. All patients and investigators were blinded to treatment allocation. In ARM I randomization, 12 subjects were in the metformin group and 17 were in the GlycaCare-II treatment group. In ARM II randomization, 16 subjects were in the metformin group and 24 subjects in the GlycaCare-II treatment group. Groups were under each arm for a period of 120 days ± 3 days and received either 500mg of Metformin or 522.5mg of GlycaCare-II orally twice daily, morning and night, 20 minutes before food. For newly diagnosed diabetic patients, the mean change in HbA1c were not significantly different in metformin and GlycaCare-II groups, suggesting equivalent efficacy. However, a significant change was observed in the FBS level for both GlycaCare-II and metformin groups with a 11% and 10% reduction respectively. A significant change was observed in the PBS levels as well from visit three onwards for the GlycaCare-II group and the metformin group. For prediabetic patients, the mean changes in HbA1c were not significantly different in the metformin and GlycaCare-II groups, suggesting equivalent efficacy.

However, a significant change was observed in the FBS level for both GlycaCare-II and metformin group of 15% and 11% at 120 days, respectively. A significant change was observed in the PBS levels as well from visit five onwards for GlycaCare-II group and visit six onwards for the metformin group. The findings of this study demonstrated the potential of GlycaCare-II as an alternative safe and effective medication in the treatment of type 2 diabetes mellitus.

Hsu (2020)

A study conducted on a total of 142 subjects diagnosed with diabetes mellitus at least one year before the study and either a fasting blood glucose level of at least 140mg/dL or an HbA1c of at least 7.0% [39]. A total of 64 subjects were randomly assigned to the experimental group and 78 to the control group. The control group received 600mg of mcIRBP-19 with the brand name of Insumate, daily (300mg before lunch and 300mg before supper) for three months, while the control group received only education. The results showed statistically significant changes in FPG and HbA1c reduction. FPG at baseline was 136.8 ± 63.5 mg/dL and at the 3 month follow up it was 118.0 ± 35.5 mg/dL. The HbA1c at baseline was 7.8% ± 1.4% and at the 3 months follow up it was 7.4 ± 1.1%. This study provides support that taking 600mg of Insumate daily for 3 months can significantly improve the blood glucose of diabetic patients and demonstrate the therapeutic benefits of Insumate.

Kim (2020)

A randomized, placebo-controlled study was conducted on 96 patients with type 2 diabetes mellitus to assess the anti-diabetic and hypo-lipidemic effects of bitter melon over the duration of 12 weeks [40]. Participants were randomly assigned to either the control group (n=30), who received placebo capsules, or the treatment group who received bitter melon extract (n=66) twice a day for a total of 2380 mg daily. There was shown to be no statistically significant results in HbA1c levels between the control and treatment group, however the average FBG of the treatment group decreased (p=0.014) in comparison to the control group. This study demonstrated the glucose lowering benefits of bitter melon in patients with type 2 diabetes mellitus.

Ma T, Lee C (2019)

A randomized, double-bind, placebo-controlled trial at the Healthy Lifestyles Research Center in Arizona State University (ASU) was performed on 16 sedentary, abdominally obese participants [41]. Participant inclusion criteria was as follows; an age of 18 years or above, a large waist circumference (men ≥102 cm, women ≥88 cm) and physical inactivity defined as an individual not engaged in regular recreational physical activity/exercise. Exclusion criteria was diabetes or other metabolic diseases, the use of medications that can interfere with blood glucose metabolism and food allergy or medical conditions that impact normal functioning of the gastrointestinal tract, and pregnancy. The participants received 100ml bitter melon juice containing 140g of bitter melon pulp (n=8) or a placebo juice (n=8) 30 minutes prior to a 75-gram oral glucose tolerance test. Plasma glucose and serum insulin levels were measured every 30 minutes during the 2-hour postprandial period. Overall, the study showed that the intake of 100ml of bitter melon juice significantly reduced the 2-h postprandial glucose by an average of 34.4mg/dL compared with the placebo juice. The overall postprandial insulin responses were not significantly different between the two treatment groups.

Kumari (2018)

A parallel randomized controlled trial evaluated the effects of *Momordica charanita* on glycemic profile, insulin resistance, lipid profile, oxidative stress, and BMI in type-2 diabetes mellitus patients[42]. The study evaluated 75 uncomplicated type-2 diabetes mellitus patients. Group A patients were supplemented with 1g Momordica charantia tablets and anti-diabetic agents while group B was supplemented with 1.5g Momordica charantia tablets along with anti-diabetic agents daily for 8 weeks. The control group, group C, was only treated with oral anti-diabetic agents. Patients had to meet WHO diabetes diagnosis criteria for type 2 DM within the age group of 40 to 60 years, with a FBS less than 200 mg/dL and two-hour post prandial blood glucose less than 300 mg/DL with HbA1c less than 8%. Patients were excluded from the study if they had a history of hepatic failure, acute MI, or history of use of other herbal products. Group C had reductions in blood sugar levels, however they were not significant reductions. Group A, 1g of Momordica charantia along with oral anti-diabetic agents had shown significantly reduced blood sugar, HbA1c, total cholesterol, and LDL cholesterol without improving insulin sensitivity and oxidative stress. Group B, 1.5g of Momordica charantia along with oral anti-diabetic agents had shown an improved glycemic profile along with insulin resistance. A reduction in total cholesterol, LDL cholesterol and oxidative stress was shown and in increase in HDL levels. The results of this study suggest that the add on treatment of 1.5g per day of Momordica charantia can be an effective treatment option for glycemic control, lowering total cholesterol and reducing oxidative stress in type-2-diabetes mellitus patients.

Cortez-Navarrete (2018)

A randomized, double blind, placebo-controlled study evaluated the effect of bitter melon on glycemic control [43]. The study evaluated 24 patients with T2DM who were randomized to receive either 1) 500 mg capsules of dried bitter melon fruit powder (n=12) or 2) placebo tablets containing calcined magnesia and no active ingredient (n=12), twice daily before breakfast and dinner for 90 days. Patients enrolled in the study had a T2DM diagnosis based on ADA criteria, in addition to having a BMI of 25.0-34.9 kg/m^2, fasting serum glucose <209 mg/dl, and A1C between 7-9%. Patients had to be nonsmokers, between 35 to 60 years old, and have a stable body weight for 3 months prior to the study. There were significant decreases in weight, BMI, fat percentage, waist circumference (WC), A1C, and 2-h glucose in the bitter melon group. Body weight decreased from 79.4 to 78.0 kg. BMI decreased from 29.1 to 28.3 kg/m^2. Waste circumference decreased from 106 cm to 104 cm. A1C decreased from 7.6% to 7.1%. Finally, 2-hour serum glucose, measured through an oral glucose tolerance test (OGTT), decreased from 308 to 238 mg/dL. There were no significant changes observed in the placebo group. The results of this study suggest that bitter melon has a significant effect on glycemic control.

Rahman (2015)

A randomized, double blind, parallel group trial was conducted on 95 T2DM patients to evaluate the hypoglycemic effect and glycemic control of *M. charantia* (MC) [44]. Patients were randomized into three groups as follows: 1) MC low dose, 2g (n=32) 2) MC high dose, 4g (n=33) or 3) glibenclamide – an FDA approved T2DM drug, 5 mg (n=30). Each group received their respective intervention once daily for 10 weeks. Patients enrolled in the study had a T2DM diagnosis based on ADA criteria, had fasting plasma glucose (FPG) between 126-240 mg/dl, were between the ages of 30 to 70, and had normal renal and liver function. Results showed a significant reduction of A1C and FPG, compared to baseline, for all three groups. However, improvements in 2-h glucose were only significant

for group III patients. Significant improvements in A1C and FPG were seen in groups I and II, where A1C decreased from 8.25 to 7.40% and 8.30 to 7.15% and FPG decreased from 146 to 133.7 mg/dl and 141.60 to 126.40 mg/dl, respectively. Interestingly, plasma sialic acid levels significantly improved from baseline in groups I and II, while group III had no significant effect. Plasma sialic acid decreased from 74 to 68 mg/dl in group I and from 75.30 to 63 mg/dl in group II. This study favors the hypoglycemic effect of bitter melon, however, glibenclamide had a greater effect on the post-prandial glucose levels in comparison to bitter melon.

Fuangchan (2011)

A multicenter, randomized, double blind, active-control trial was conducted to assess the safety and efficacy of three doses of bitter melon as compared to metformin [45]. 129 T2DM patients were randomized to receive either 1) metformin 1000 mg/day (n=33) 2) bitter melon 500mg/day (n=33) 3) bitter melon 1000mg/day (n=32) or 4) bitter melon 2000mg/day (n=31) for four weeks. Study participants were between the ages of 35 to 70 and had a T2DM diagnosis based on ADA standards. There were significant changes in fructosamine levels observed in groups I and IV (from 3.70 to 3.58 mg/dL and from 3.49 to 3.30 mg/dL, respectively). Groups II and III did not experience any significant change. Moreover, no significant change was observed in fasting plasma glucose or 2-hour plasma glucose after OGTT for bitter melon groups (II, III, and IV), while there were significant changes observed in group I. This study found bitter melon to have very modest efficacy compared to metformin for the treatment of type 2 diabetes.

Rahman (2009)

A randomized, controlled trial evaluated the effects of bitter melon on sialic acid levels compared to versus rosiglitazone, another T2DM FDA-approved medication [46]. Fifty T2DM patients between the ages of 30 and 60 years old were divided into three groups: 1) control, 2) rosiglitazone, and 3) bitter melon treatment. Bitter melon was purchased from a local market in Pakistan, authenticated by a pharmacognosy expert, and extracted into a juice. The study was conducted from January 2008 until June 2008. Group I, the control group, did not have a specified intervention. Group II received 1 mg of Rosiglitazone twice a day. Group III received 55 mL of bitter melon juice a day total, divided into three dosages. The results showed that group II patients had an increase in serum sialic acid concentration and serum glucose concentration, whereas there was no increase in group III as compared to the control. Since sialic acid levels are typically increased in T2DM and are associated with cardiovascular mortality, this study provides evidence that bitter melon may be a safe alternative to many antidiabetic drugs because it does not increase sialic acid levels.

Dans (2007)

A randomized, double blind, placebo-controlled trial was conducted on 40 patients with T2DM to assess the change in A1C levels following bitter melon treatment [47]. Patients were divided into two groups: 1) two bitter melon tablets three times a day (n=20) or 2) placebo control with no active ingredient (n=20). Both groups received treatment for 3 months. Patients included in the study were diagnosed with T2DM, had an A1C of 7-9%, and were above 18 years of age. Investigators found a difference in mean change in A1C between the two groups to be 0.22% in favor of *M. charantia*. There was no significant change

noted on mean fasting blood sugar, total cholesterol, weight, serum creatinine, ALT, AST sodium and potassium. The investigators targeted a 1% decline in A1C with an estimated power of 88%. The observed decline of 0.24% and power of 11% was found to be a modest, statically insignificant decline in A1C levels, however investigators were unable to make a definitive conclusion on the overall effectiveness of *M. charantia.*

Tongia (2004)

A trial conducted on 15 patients with noninsulin depended diabetes mellitus (NIDDM) was performed to explore the chemical constituents in *Momordica charantia* (MC) fruit extract phytochemically and to study the influence of MC fruit extract on hypoglycemic response of metformin and glibenclamide therapy [48]. Patients were divided into 3 groups; group A (n=5) received oral metformin, 500mg twice daily before meals for 7 days, group B (n=5) received oral glibenclamide tablets, 5mg twice daily before meals for 7 days and group C (n=5) received combined oral metformin 500mg and glibenclamide 5mg twice daily before meals for 7 days. Patients in the study had NIDDM and were above the age of 18 years old. The FPG mean glucose levels (mg/dL) with Metformin and MC were 122.6±2.66 at baseline, 109.4±3.06 after 7 days of treatment and 96.4±2.36 after 14 days of treatment. Glibenclamide and MC mean blood FPG levels were 122.0±1.70 at baseline, 106.8±1.07 after 7 days and 93.8±1.36 after 14 days. For the third group, metformin, and MC plus glibenclamide and MC the mean blood FPG levels were 127.0±1.52 at baseline, 101.8±2.63 after 7 days of treatment, and 85.4±1.21 after 14 days of treatment. The PPG mean glucose levels (mg/dL) for the metformin plus MC treatment group was 220.4±3.41 at baseline, 165.4±7.22 after 7 days and 128.0±1.84 after 14 days. The PPG mean glucose levels for the glibenclamide plus MC treatment group was 196.6±5.34, after 7 days was 156.4±4.06 and after 14 days of treatment was 128.4±2.66. Finally, the PPG mean glucose levels for metformin and MC plus glibenclamide, and MC was 220.8±2.46 at baseline, was 177.8±4.35 after 7 days and was 133.2±2.82 after 14 days of treatment. Momordica charantia soft extract in addition to metformin, glibenclamide or both in combination caused hypoglycemia greater than that caused by full doses used in the study. The extract was concluded to act in synergism with oral hypoglycemics and is a potential treatment adjunct in patients with NIDDM.

Ahmad (1999)

A study conducted on 100 participants with moderate non-insulin dependent diabetes mellitus was performed at the Diabetic Association, Barisal branch to assess the effects of *Momordica charantia* on fasting and post prandial glucose levels [49]. Participants drank 150 to 200ml of *Momordica charantia* juice extract and blood samples were collected for analysis that same day and the following. Out of the 100 participants, 86 experienced a hypoglycemic effect. The study found that Momordica charantia possesses serum glucose lowering properties both in fasting and postprandial conditions.

Conclusion

The results of 13 different clinical trials are presented in **Table 1** and show that bitter melon influences glycemic control in T2DM patients. Several studies suggested that bitter melon can reduce A1C, post prandial and fasting plasma glucose levels. Of the studies that found no statistical significance in A1C reduction, a short duration of study or small sample size are possible explanations for these results. Two

studies found bitter melon to reduce BMI, weight, fat percentage, and fructosamine levels.

However, results in these two trials were not consistently convincing. One possible explanation for this variability is that different dosage forms and preparations of bitter melon were utilized along with a shorter study duration. Another weakness amongst the clinical trials is that bitter melon was not standardized to its chemical constituents. This variable is an important consideration as the phytochemical content could vary dramatically based on the products that were being studied. For example, studies used juices, or dry powder capsules. Bitter melon appears to be safe for use in humans and may have fewer side effects than other antidiabetic medications. The results from 13 clinical trials provide evidence that bitter melon may be beneficial for use of glycemic control in patients with T2DM either as an alternative treatment option to oral anti-diabetic medications or used in synergy. A study comprised of a larger cohort of participants with a duration of at least 12 weeks to fully analyze the long-term efficacy of bitter melon on T2DM regulation could be a viable future direction of study.

Acknowledgements

Johnson JJ is supported by the National Institutes of Health (R37 CA227101).

Declaration of Competing Interest

The authors declare no conflict of interest.

Abbreviations

Body mass index (BMI), diabetes mellitus (DM), fasting plasma glucose (FPG), homeostasis model assessment insulin resistance (HOMA-IR)

oral glucose tolerance test (OGTT), postprandial glucose (PPG), type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), waist circumference (WC),

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