

Review Article

Anti-diabetic and hypoglycaemic effects of *Momordica charantia* (bitter melon): a mini review

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It has been estimated that up to one-third of patients with diabetes mellitus use some form of complementary and alternative medicine. *Momordica charantia* (bitter melon) is a popular fruit used for the treatment of diabetes and related conditions amongst the indigenous populations of Asia, South America, India and East Africa. Abundant pre-clinical studies have documented the anti-diabetic and hypoglycaemic effects of *M. charantia* through various postulated mechanisms. However, clinical trial data with human subjects are limited and flawed by poor study design and low statistical power. The present article reviews the clinical data regarding the anti-diabetic potentials of *M. charantia* and calls for better-designed clinical trials to further elucidate its possible therapeutic effects.

Momordica charantia: Hypoglycaemic agents: Diabetes mellitus: Complementary and alternative medicine

Diabetes mellitus is a major global health concern with a projected rise in prevalence from 171 million in 2000 to 366 million in 2030⁽¹⁾. Diabetes mellitus is characterised by chronic hyperglycaemia and postprandial hyperglycaemia, both leading to enhanced micro- and macrovascular morbidity and overall mortality^(2–3). Amongst ethnic minorities, cultural beliefs about diabetes mellitus often differ and may compromise adherence to therapy^(4–6). Complementary and alternative medicine involves the use of herbs and other dietary supplements as alternatives to mainstream Western medical treatment. A recent study has estimated that up to 30% of patients with diabetes mellitus use complementary and alternative medicine⁽⁶⁾. *Momordica charantia* (MC), also known as bitter melon, karela, balsam pear, or bitter gourd, is a popular plant used for the treating of diabetes-related conditions amongst the indigenous populations of Asia, South America, India, the Caribbean and East Africa^(7–10). MC is a tendril-bearing vine belonging to the Cucurbitaceae family. It is a climbing perennial that usually grows up to 5 m, and bears elongated fruits with a knobby surface. MC fruit has a distinguishing bitter taste, which is more pronounced as it ripens, hence the name bitter melon or bitter gourd.

Biochemical and animal model experiments have produced abundant data and hypotheses accounting for the anti-diabetic effects of MC. In comparison, clinical studies with human

subjects are sparse and low quality in design. The authors reviewed the available data regarding the hypoglycaemic effects of MC in human subjects searching the PubMed and EMBASE for articles published in English with the following key words: 'Mormodica', 'Momordica charantia', 'bitter melon', 'bitter gourd', 'hypoglycaemic', 'anti-diabetic' and 'human'.

Phytochemistry of *Momordica charantia*

Of the MC fruit, 93.2% is composed of water, while protein and lipids account for 18.02 and 0.76% of its dried weight⁽¹¹⁾. On the contrary, nearly 45% of the MC seed is composed of oils which contain 63–68% eleostearic acid and 22–27% stearic acid⁽¹²⁾. Several glycosides have been isolated from the MC stem⁽¹³⁾ and MC fruit^(14–16) and are grouped under the genera of cucurbitane-type triterpenoids. In particular, four triterpenoids have AMP-activated protein kinase activity which is a plausible hypoglycaemic mechanism of MC⁽¹⁶⁾.

Animal studies of *Momordica charantia*

Various animal studies have repeatedly shown hypoglycaemic effects of the seeds, fruit pulp, leaves and whole plant of MC in normal animals^(17–21). In particular, MC improves glucose

Abbreviations: FBS, fasting blood sugar; MC, *Momordica charantia*; PPS, postprandial sugar; T1D, type 1 diabetes; T2D, type 2 diabetes.

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tolerance⁽²²⁾ and suppresses postprandial hyperglycaemia in rats⁽²³⁾, and MC extract can enhance insulin sensitivity and lipolysis^(24,25). Some studies also claimed that the hypoglycaemic effect of MC was comparable with oral medications such as tolbutamide⁽²⁰⁾, chlorpropamide⁽²⁶⁾ and glibenclamide⁽²⁷⁾.

Abundant biochemical data have shed light upon possible mechanisms of the anti-diabetic actions of MC with the recurring theme being activation of the AMP-activated protein kinase system^(28–31). Other studies suggested a role of the α - and γ -peroxisome proliferator-activated receptors (PPAR α and PPAR γ) which are pivotal in lipid and glucose haemostasis and may mitigate insulin resistance^(32–34). Recently, a Zn-free protein bearing insulinomimetic activities was isolated from MC⁽³⁵⁾ that echoed the idea of ‘vegetable insulin’ isolated by Baldwa *et al.*⁽³⁶⁾ some 30 years ago.

Clinical studies of *Momordica charantia*

Compared with animal studies, clinical studies regarding the hypoglycaemic effects of MC have been sparse and sporadic. Lakholia, a physician, was probably the first to document the therapeutic effect of bitter melon in 1956 using himself as the subject⁽³⁷⁾. As we reviewed the studies fulfilling our search criteria, we noticed that the majority lacked proper controls or suffered from poor methodologies without baseline characterisations^(22,36,38–48), as tabulated in Table 1. Amongst those, five have been selected for further discussion as follows. Four were designed as clinical trials and the fifth study, albeit a case series, was selected due to its large sample size.

John *et al.* study

John *et al.*⁽⁴⁶⁾ randomised fifty subjects (twenty-six trials and twenty-four controls) with type 2 diabetes (T2D) to receive either dried MC fruit or riboflavin. Clear inclusion criteria based on fasting blood sugar (FBS) and postprandial sugar (PPS) levels were adopted. Sample size was calculated using a targeted reduction of sugar level by 300 mg/l (30 mg/dl) for both FBS and PPS. Baseline characteristics of all subjects were all comparable. Dried MC fruit was administered at a dose of 2 g three times per d, and riboflavin was employed as the placebo. All subjects were instructed to maintain their pre-existing oral hypoglycaemic treatment and dietary patterns. FBS and PPS levels were measured with fructosamine levels at baseline before treatment, at 2 weeks, and at 4 weeks post-treatment. Results did not show a statistically significant effect due to intervention, for which the authors ascribed to the possible use of dried MC rather than fresh fruit, or due to a suboptimal dose. In this study, there was no mention of the randomisation protocol; nor was it a double-blind design due to the non-matching placebo. Also, the authors only mentioned the lack of adverse effects, but did not account for dropouts. The Jadad score⁽⁴⁹⁾ for this randomised study is, therefore, 1 (from a score of 0 to 5).

Dans *et al.* study

Dans *et al.*⁽⁴⁸⁾ conducted a randomised double-blind placebo-controlled trial with forty subjects who were either newly diagnosed or poorly controlled T2D having HbA1c levels between 7 and 9%. Sample size was calculated using a

targeted reduction of 1% in HbA1c and estimated power of study at 0.88. Baseline characteristics of all subjects were not significantly different. A brand-name product containing a standardised dose of dried MC extract was given to the trial group at the dose of two capsules three times per d (exact amount per capsule unknown), for a period of 3 months. The control group followed the same protocol except taking a matching placebo. Baseline HbA1c and other biochemical tests were performed before initiating treatment. Subjects were then followed-up monthly for 3 months, where blood sugars were measured and compliance or adverse effects were noted. At the end of treatment, all baseline tests were repeated. Results showed a mean reduction of 0.217% in HbA1c in the trial group, which was not statistically significant ($P=0.483$) and not sufficient to reject the null hypothesis. As a conclusion, the authors suggested a repeat study with a larger sample size. Nevertheless, this study is merited for its proper design, adverse effects were clearly documented, and dropouts were individually accounted for. The Jadad score for this study is, therefore, 5.

Tongia *et al.* study

Tongia *et al.*⁽⁴⁷⁾ recruited fifteen subjects with T2D and divided them into three equal groups. Apart from diagnostic label and age, inclusion criteria were not defined. FBS and PPS levels were measured in subjects before intervention, and these data were then used as controls. The three groups then received metformin, glibenclamide, and metformin + glibenclamide, respectively, for 7 d before the FBS and PPS values were measured. In the next 7 d, subjects received oral hypoglycaemic medications at half dose, plus a standard dose of MC fruit extract twice per d (given in the dose of 200 mg twice daily) and FBS and PPS levels were measured again. Results showed reductions in both FBS and PPS levels after oral hypoglycaemics and a further reduction with MC extract. The quoted P values, although significant, have to be considered against the small sample size of fifteen subjects. Worth noting is that this study used a within-subject design and there was no clear mention of the inclusion criteria. In addition, there was no justification of the sample size and study power. As this study is not a randomised trial, it cannot be rated with a Jadad score.

Baldwa *et al.* study

Baldwa *et al.*⁽³⁶⁾ recruited fourteen diabetic subjects (type 1 diabetes (T1D) and T2D) with five healthy volunteers and investigated the effect of an insulin-like substance extracted from MC fruit that was coined the ‘vegetable insulin’. Nine diabetic subjects received subcutaneous injection of the ‘vegetable insulin’ according to a sliding scale (exact dosage not mentioned). Five other diabetic patients together with five healthy volunteers acted as controls and received a placebo injection (nature of placebo not mentioned). In the trial group, there was a 21.5% reduction in blood glucose at 30 min, 49.2% reduction at 4 h and 28% reduction at 12 h, as compared with pre-injection levels. Those who received placebo showed a 5% decrease in glucose level irrespective of whether they were diabetic or healthy controls. Despite the significant results, this study suffered methodological

Table 1. Clinical studies of *Momordica charantia* (MC)

Reference	Study design	Subjects	Form of MC administered	Treatment duration	Outcome measures	Statistical significance
Dans <i>et al.</i> ⁽⁴⁸⁾	Double-blind randomised controlled trial	Forty with T2D (twenty trial and twenty control subjects)	Commercial herbal supplement capsules	3 months	HbA1c	No
John <i>et al.</i> ⁽⁴⁶⁾	Randomised controlled trial	Fifty with T2D (twenty-six trial and twenty-four control subjects)	Tablets from dried whole fruit	4 weeks	(i) Fasting + postprandial blood glucose (ii) Fructosamine	No
Tongia <i>et al.</i> ⁽⁴⁷⁾	Controlled trial	Fifteen with T2D in three groups	Methanol extract of ground whole fruit	1 week	Fasting + postprandial blood glucose	Yes
Baldwa <i>et al.</i> ⁽³⁶⁾	Controlled trial	Trial subjects: nine DM Control subjects: five DM + five normal	Aqueous extract refined to subcutaneous injection (v. insulin)	Single treatment	Blood glucose	Yes
Ahmad <i>et al.</i> ⁽⁴⁴⁾	Case series	100 with T2D	Fresh fruit	Single treatment	(i) Fasting glucose (ii) 2 h post OGTT	Yes
Srivastava <i>et al.</i> ⁽³⁸⁾	Case series	Twelve with impaired OGTT	Arm 1: dried fruit Arm 2: aqueous extract	3–7 weeks	Arm 1: postprandial blood glucose Arm 2: postprandial blood sugar + HbA1c	Arm 1: No Arm 2: Yes
Grover & Gupta ⁽⁴³⁾	Case series	Fourteen with T2D and six with T1D	Seeds	Single treatment	Postprandial blood glucose	Yes
Welihinda <i>et al.</i> ⁽⁴²⁾ Akhtar ⁽⁴¹⁾	Case series Case series	Eighteen with DM Eight with DM	Juice from seedless fruits Powdered dried fruit	Single treatment 1 week	OGTT (i) Fasting glucose level (ii) Glycosuria (iii) OGTT	Yes Yes
Leatherdale <i>et al.</i> ⁽²²⁾	Case series	Nine T2D	Fresh fruit juice + fried fruit	Single treatment, then 7–11 weeks	(i) OGTT (ii) HbA1c	(i) Yes (with juice) No (with fried fruit) (ii) Yes (with fried fruit)
Khanna <i>et al.</i> ⁽⁴⁰⁾ Patel <i>et al.</i> ⁽³⁹⁾	Case series Case series	Nineteen with DM Fifteen with DM	'Polypeptide-p' isolated from MC Fresh fruit juice and dried powder	Single treatment 6–14 weeks	Blood glucose OGTT	Yes No

T2D, type 2 diabetes; DM, diabetes mellitus; OGTT, oral glucose tolerance test; T1D, type 1 diabetes.

limitations. There was no clear randomisation protocol; investigators and subjects were not blinded; baseline characteristics of the subjects were not uniform, either in their pathology (both T1D and T2D in the trial group), or their severity (baseline glucose levels varied from 2100 to 2950 g/l (210 to 295 mg/dl)). In addition, the control arm was also heterogeneous (both healthy and diabetic patients). Again, this is not a randomised trial and cannot be rated with a Jadad score.

Ahmad *et al.* study

Ahmad *et al.* (44) studied the effect of MC in a case series of 100 T2D subjects (fifty-eight males and forty-two females). The inclusion criteria were explicit and baseline characteristics of all subjects were statistically comparable. Subjects were instructed to stop their existing oral medications for 3 d before the trial as a washout. Fasting (s1) and postprandial blood sugar (s2) levels were measured on day 1. On day 2, fasting blood sugar was measured again (s3), and all subjects ingested a drink made from freshly blended MC fruit (dosage varied according to the body weight of subjects). Blood sugar was measured 1 h (s4) afterwards, followed by a postprandial measurement in another 2 h (s5). The control groups were s1, s2 and s3 as compared with the trial groups of s4 and s5. Results showed an 18% mean reduction both in fasting and postprandial sugar levels across 86% of all subjects. Despite the good sample size, this study used the same subjects as controls and trials. There was no mention of adverse effects or dropouts, although the authors did discuss limitations, such as lack of supervision for subjects to carry out instructions at home. Therefore, this study showed a flawed methodological design. Being a case series, it cannot be rated with the Jadad score.

It is evident that in these five studies, the forms of MC administration (from methanol extract, dried powder to fresh fruit), the actual dosage (timing and dose per kg body weight) and the outcome measures (from HbA1c, postprandial sugar levels to oral glucose tolerance test) differ widely. Therefore, it is impossible to do any meta-analysis or between-study analyses. For ease of administration, it would be best for MC to be taken in encapsulated powder; however, the available studies seemed to point to a better efficacy for MC when taken in fresh or juiced form^(38,42,44,46). Moreover, available data seem to support an acute or a single dose effect^(36,40,42–44) of MC rather than a long-term effect of longer than 4 weeks^(39,46,48). In order to evaluate the hypoglycaemic effects of MC, the authors suggest a well-designed randomised controlled clinical trial with good sample size for sufficient power. It will employ multiple arms (fresh MC juice, dried MC powder and corresponding matching placebos) with cross-over and washout, to be conducted over a period of 6–12 months with interim analysis.

Toxicity and side effects

At the time of writing the present review, there were no large-scale studies found that examined the side-effects of MC, but the years of its consumption as a dietary supplement and ethnomedicine in various countries do suggest a high level of safety. Having said, there have been isolated reports of hypoglycaemic comas in children after drinking bitter melon

tea^(50,51), and one report of death due to consumption of bitter melon fruit⁽⁵²⁾. The MC seeds contain a lectin which can inhibit protein synthesis in the intestinal walls of an animal model⁽⁵³⁾, but they produce no gastrointestinal symptoms in humans, except for a report of headache⁽⁵¹⁾. MC seeds may also induce favism in humans with glucose-6 phosphate dehydrogenase deficiency⁽⁵¹⁾, while in animals, MC fruit can lead to depressed fertility^(53–55) and induction of abortions^(56,57). In the study by Dans *et al.* (48), gastrointestinal symptoms such as abdominal discomfort and diarrhoea have been reported.

Conclusion

The concept of food as medicine is a central theme in dietetic and nutritional sciences. MC has been used as dietary supplements and ethnomedicine throughout centuries for relieving symptoms and conditions related to what we know in modern days as diabetes. Despite the abundant data from biochemical and animal studies, available clinical data as reviewed in the present article are often flawed by small sample size, lack of control and poor study designs. The present review supports the need for better-designed clinical trials with sufficient sample size and statistical power to further vindicate the acclaimed efficacy of MC as a natural nutritional treatment for diabetes mellitus. In particular, MC may be a feasible option for ethnic minorities who have a high prevalence of diabetes but prefer treatment based on natural products according to their cultural beliefs.

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