In vivo hypoglycemic effect of methanolic fruit extract of *Momordica charantia L*

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Abstract

Background: *Momordica charantia L.* is a medicinal plant commonly used in the management of diabetes mellitus.

Objectives: We investigated the blood glucose lowering effect of the methanolic fruit extract of the Ugandan variety of *M. charantia L.* in alloxan-induced diabetic albino rats.

Methods: 500g of *M. charantia* powder were macerated in methanol and the extract administered to two groups of alloxan-induced diabetic rats. The first group received 125mg/kg, the second 375mg/kg and a third group 7mg/ kg of metformin. A fourth group received 1ml normal saline. Fasting blood glucose (FBG) levels were measured at 0.5,1,2,3,5,8 and 12 hours and compared using one-way ANOVA.

Results: There was an initial rise in FBG for 1 hour after administration of extracts followed by steep reductions. Significant reduction in FBG occurred at 2 hours for 125mg/kg of extract (-3.2%, 313±25.9 to 303±25.0mg/dL, p = 0.049), 375mg/kg of extract (-3.9%, 356±19.7 to 342±20.3mg/dL, p = 0.001), and metformin (-2.6%, 344±21.7 to 335±21.1mg/dL, p = 0.003) when compared to normal saline. The maximum percentage reduction in FBG by both extracts occurred between 3 and 12 hours post dose.

Conclusions: The methanolic fruit extract of *M. charantia* exhibits dose dependent hypoglycaemic activity *in vivo*.

Key words: *Momordica charantia*, methanolic extract, Diabetes Mellitus, hypoglycaemic effect, in vivo

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Introduction

Diabetes Mellitus (DM) is a leading cause of illness and death in developed countries and is epidemic in many developing and newly industrialized countries. Its macrovascular and microvascular complications are debilitating. The prevalence of diabetes in the world at all ages was estimated to be 2.8% in 2000, and it is expected to approximate 4.4% in the year 2030.The estimated global number of people of all ages and sex with diabetes in 2000 was 171 million. This is projected to increase to 366 million by 2030, with about 4 million deaths every year attributed to its complications[1,2].

The estimated number of people with diabetes in sub-Saharan Africa was 10.8 million in 2006, and this could rise to 18.7 million by 2025. Major risk factors are similar to those of other regions of the world such as urbanization, obesity, physical inactivity, or others that are not quite mutable such as increasing age and ethnicity. Most African countries still face a number of problems related to the management and treatment of the disease, such as critical shortage of diabetes medicine, the rising cost of drugs and treatment, competition for resources by HIV/AIDs, tuberculosis, and malaria. The general lack of equipment to diagnose the disease has hampered efforts to manage and control diabetes mellitus[3,2] . In Uganda, there is a new surge of non-communicable diseases, among them diabetes and this is partly due to changing lifestyle. Many urbanites neither exercise nor do physical work. The number of people with diabetes is now thought to have passed a million, with 560,000 registered patients and it is thought an equal number unknowingly have undiagnosed disease[4,5].

Anti-diabetic treatments or interventions are grouped into three major categories; diet and exercise which form part of first line treatment of diabetes, insulin and oral hypoglycaemic agents. However, the latter are often expensive and inaccessible to many

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low-income generating individuals in Uganda, given their high cost and the sometimes long distance that has to be travelled to the hospitals and health facilities that avail them. Also, these drugs are not without side effects and yet the treatment is life-long, due to the chronic nature of disease. Because of this, some patients use affordable and cost effective alternative therapy for management of diabetes in the form of traditional medicines, which are both locally available and cheap[2, 4].

Several herbal remedies used in the management of diabetes have been reported to possess hypoglycemic effects[6-11]. Among these is *Momordica charantia* L Fam. Cucurbitaceae (African cucumber, bitter gourd, bitter melon) a medicinal plant used traditionally as an antidiabetic, an emetic, a laxative, a tonic, and to treat anaemia, arthritis, colds, fever, gout, infertility, kidney stones, peptic ulcers, stomach ache and intestinal helminthes[12] . It is also used as an antimalarial, together with related species, and as an abortifacient[13-15]. Some pharmacological and safety studies of this herb have been carried out[16,17]. In addition to hypoglycaemic activity, *M.*charantia has been shown to have antioxidant[18-20], anti-tumour[21-25], neuroprotective[26], anti-inflammatory[27-29] and antimicrobial activity[30,31]. It has a resistance modifying effect for aminoglycosides against methicillin-resistant *Staphylococcus aureus*[32]. The plant is a source of urease for urea determination[33]. Wan et al[34] have also found that *M. charantia* peroxidase can be used for biotransformation of piceatannol into antihyperglycaemic oligomeric stilbenes.

This study aimed at investigating the effects of the Ugandan variety of *M. charantia* L. methanolic fruit extract on blood glucose levels in alloxan-induced diabetic rats.

Methods

Plant collection and extraction

M. charantia ripe fruits were obtained from Kabanyolo farm at the beginning of the dry season (December 2011 to February 2012).The herbarium specimen was prepared and verified at the Department of Botany, Makerere University. Studies have shown that hybridization occurs between cultivated and wild varieties and that there is transfer of genetic material between species[35,36]. The fresh fruits were washed with tap water to remove dust and other foreign material. They were then air dried in the laboratory. The dry fruits were blended into a powder form using a mortar and pestle. The powder was weighed using a digital weighing machine and weighed 138.6g.The powder was put in a clean empty bottle and methanol added until it covered the powder, with vigorous shaking to mix the content. Methanol was added to make 2 litres. The bottle was then corked and kept for 3 days with occasional shaking to facilitate extraction of the active component from the powder. A 2 litre measuring cylinder and funnel and round bottomed flask were cleaned and dried. The cotton was placed in the neck of the funnel and placed on top of the cylinder. The macerating mixture was poured into the funnel to filter off the large size marc. The process was repeated on the filtrate using Whartman filter paper and the filtrate collected in a round bottomed flask. The dry extract was obtained using a rotary evaporator. The percentage yield was 17 percent. The extract was stored in a vial in a cupboard.

Methanol was used because it is a polar solvent and so hopefully would extract active principles, which otherwise would have been extracted using water. Also, it is easier to evaporate compared to water.

Preparation of the extract and metformin

5g of extract were suspended in 25ml of normal saline solution to form a 200mg/ml suspension. One tablet of metformin (500mg) obtained from a pharmacy was powdered and the powder dissolved in 50ml of normal saline to form a 10mg/ml suspension.

Animal preparation

Twenty four male albino rats weighing between 150 and 180g were chosen in order to provide uniform results and minimize error that occurs due to variation in species, sex and weight. The animals were obtained from the School of Veterinary Medicine and Animal Resources, Makerere University and habituated at the Department of Pharmacology, College of Health Sciences, in cages for 3 days under normal laboratory conditions of; temperature, humidity and light (12 hours day, 12 hours night).They were fed on standard animal feed and water ad libitum.

Induction of Diabetes Mellitus in animals

The animals were made to fast for 18 hours receiving only water. They were weighed and the Fasting Blood Glucose (FBG) of each animal measured by bleeding the diethyl ether anesthetized animal on the tail and recording the glucose level using a glucometer. 1.5g of alloxan powder, purchased from BDH

laboratories, was dissolved in 25ml of 0.9% normal saline to form a 60mg/ml solution. This was put in a vial, autoclaved at 121^{0}C for 3 hours and cooled. Specific volumes of the solution were taken off and injected into the tail veins of diethyl ethyl anesthetized animals such that each animal got 65mg/kg body weight[37]. The animals were then monitored for 5 days and elevation of FBG confirmed after 18 hours. Only animals with FBG above 200mg/dL were used in the study.

Administration of test substances

Twenty four animals were randomly assigned to 4 groups of 6 each namely I, II, III and IV, and fasted for 18 hours. Using a syringe and endogastric tube, suspensions of the extract were administered by gavage to restrained animals such that group IV received 1ml normal saline, group III 7mg/kg body weight of metformin suspension, and groups I and II 125mg/kg and 375mg/kg body weight of M. charantia respectively.

Measurement of Fasting Blood Glucose

Blood drops were obtained by piercing the tip of diethyl ether anesthetized tails of the rats and FBG measured using a glucometer. The fasting blood glucose levels were measured at 0, 0.5,1,2,3,5,8 and 12 hours after administration of the substances.

Statistical analysis

The means of fasting blood glucose levels for the test and control groups were compared at different times by one-way analysis of variance (ANOVA) using SPSS 11 software. A p value <0.05 was considered statistically significant.

Ethical considerations

This study was approved by the Institutional Review Committee of the School of Medicine, College of Health Sciences, Makerere University. All experiments were conducted in accordance with internationally accepted principles for animal use and care.

Results

There was an initial increase in the FBG when the extract was administered, which lasted the first 1 hour. The rise was greater with 125mg/kg (13.0%) than 375mg/kg (8.9%) of the extract. Thereafter, there was a significant reduction in FBG at 2 hours for 125mg/kg of extract (-3.2%, 313±25.9 to 303±25.0mg/dL, p = 0.049), 375mg/kg of extract (-3.9%, 356±19.7 to 342±20.3mg/dL, p = 0.001), and metformin (-2.6%, 344±21.7 to 335±21.1mg/dL, p = 0.003) when compared to normal saline (figure 1). The maximum percentage reduction in FBG by both extracts occurred between 3 and 12 hours post dose (table 1).

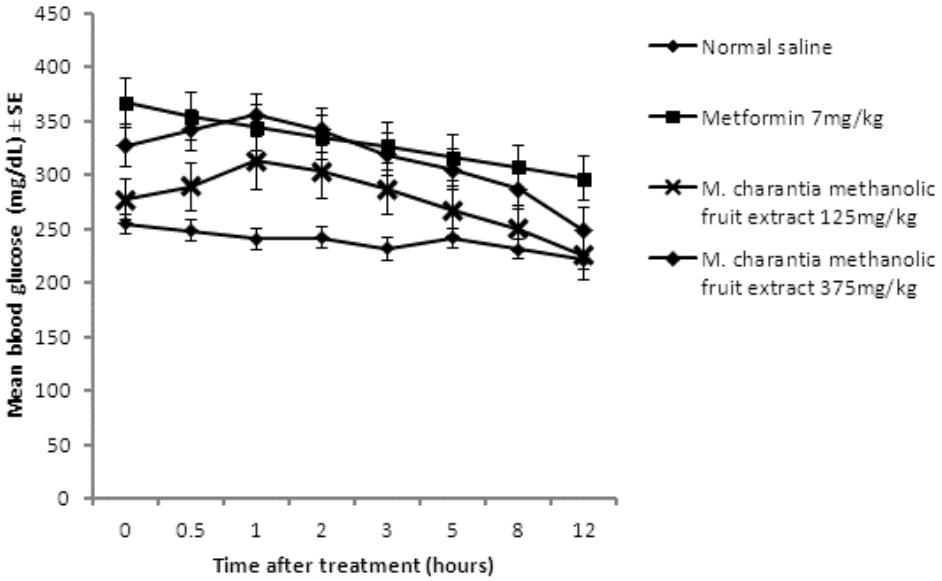

Figure 1: Mean blood glucose (mg/dL) after administration of methanolic fruit extract of *Momordica charantia* and metformin in alloxan-induced diabetic rats (n=6)

SE = standard error of mean

Table 1: Percentage glycaemic change after administration of methanolic fruit extract of *Momordica charantia L.* in alloxan-induced diabetic rats (n=6)

Treatment	Percent glycaemic change*							
	Time (Hours)							
	0	0.5	1	2	3	5	8	12
Normal saline 1ml	0	-2.7	-2.8	0.4	-4.1	4.3	-4.5	-4.3
Metformin 7mg/kg	0	-3.5	-2.8	-2.6	-2.4	-3.4	-2.8	-3.3
M. charantia extract 125mg/kg	0	4.3	8.3	-3.2	-5.3	-6.9	-6.2	-10.0
M. charantia extract 375mg/kg	0	4.6	4.1	-3.9	-6.7	-4.4	-5.9	-13.6

*Negative values indicate reductions

The subsequent FBG reductions 2 hours after administration of extract remained significant up to 12 hours for 375mg/kg, while that of 125mg/kg of extract was significant after the third hour. The percentage reductions for both concentrations of the extract were greater than those of metformin between 8 and 12 hours (14% and 10% as compared to 3% respectively). The effect on FBG of 375mg/kg of the methanolic extract was comparable to that of metformin ($p > 0.05$ between 2 and 12 hours).

Discussion

The antidiabetic effect of *M. charantia* was investigated and the results show that at 2 hours, both concentrations of the methanolic fruit extract exhibited declines in blood glucose, with 375mg/kg of extract having a greater effect than 125mg/kg of extract. The onset of glucose lowering was not as rapid as with metformin, yet the trajectory appeared superior. Both the extract and metformin lowered blood glucose levels without inducing hypoglycaemia. The initial rise in blood glucose could be attributed to the carbohydrate content of the plant or as a result of a physiological phenomenon[38]. This was not observed in mice administered normal saline. This initial rise in FBG seems to offset the early anti-hyperglycaemic effect of the crude extract.

Kolawole et al[39] showed that the methanolic fruit extract of *M. charantia* decreased blood glucose in both normal and diabetic animals, comparable to 10mg/kg of chlorpropramide in doses of 400 to 600mg/kg. Mamun[40] also found a significant decrease in blood glucose and increase in serum insulin when powdered fruits of the plant were administered to diabetic rats, while Rathnaker et al [41] have demonstrated the hypoglycaemic effect of a polyherbal product containing *M. charantia*. In another study, a different species, *Momordica cymbalaria* was found to produce a time-dependent decrease in fasting blood glucose levels[42]. However, a systematic review of four Randomized Controlled Trials of *M. charantia* for type 2 DM by Ooi et al[43] showed no difference with placebo, metformin or glibenclamide indicating the need for further clinical studies, standardization and quality control of preparations.

In this study, the anti-hyperglycaemic effects of metformin (7mg/kg) and 375mg/kg extract were more or less similar. While metformin lowers FBG concentrations by decreasing hepatic gluconeogenesis and increasing insulin-stimulated glucose uptake by skeletal muscle and adipose tissues, *M. charantia* appears to act by repairing damaged Beta-cells, increasing insulin secretion, enhancing insulin sensitivity in peripheral tissue by promoting glucose uptake, inhibition of hepatic gluconeogenesis, decreasing glucose absorption by inhibiting glucosidase and disaccharidases in the intestine, and enhancing the activity of AMP-activated protein kinase[44] . Indeed some of the constituents of the extract like oleanolic acid 3-O-glucuronide and momordin exert their anti-hyperglycemic effect by inhibiting glucose transport at the brush border of the small intestine. The aqueous extract of the unripe fruit of *M. charantia* has been shown to partially stimulate insulin release from isolated Beta-cells of the pancreas in rats, while the fruit juice significantly increased the number of Beta-cells[6]. *M. charantia* has also been reported to inhibit 11Beta-hydroxysteroid dehydrogenase, a potential anti-diabetes target[45].

Major active principles in *M. charantia* are sterols, triterpenes, glycosides notably momordin Ic, charantin, goyaglycosides, momordicosides and other cucurbitane glycosides, goyasaponins, the alkaloid momordicin, phenolic compounds, tannins, flavonoids, carotenoids and bioactive proteins like polypeptide p and alpha-momorcharin[12,44,46-50]. The

oleanane-glycoside momordin Ic and cucurbitane-type triterpenoid glycosides especially charantin and polypeptide p have been shown to have hypoglycaemic activity[44,51-54]. While Harazika et al[55] have demonstrated that momordicilin a triterpene, is a potent inhibitor of glycogen synthase kinase-3, an enzyme involved in glucose homeostasis and potential target for anti-diabetic compounds.

These findings provide further evidence for hypoglycemic activity of *M. charantia* similar to that seen in other members of the Cucurbitaceae Family.

Limitations

It is noteworthy that initial blood glucose levels were slightly different for extract, metformin and saline groups at baseline. This was difficult to control. However, we determined the rate and extent of decrease in blood glucose, which was greater for the metformin and extract groups compared to normal saline.

Conclusion

The study revealed that the methanolic fruit extract of *M. charantia* exhibited anti-hyperglycaemic effects comparable to those of metformin, in appropriate doses, in alloxan-induced diabetic rats, but the initial effect appears to be offset by the carbohydrate content of the extract. The anti-hyperglycaemic activity increased with an increase in dose of extract.

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