THE ANTIDIABETIC, ANTIOXIDANTS AND ANTIOBESITY PROPERTIES OF ORAL ADMINISTRATION OF AQUEOUS LEAF EXTRACT OF *Momordica charantia* IN ADULT MALE WISTAR RATS

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Abstract: This study was conducted to investigate the antidiabetic, antibody as well as antioxidant properties of aqueous leaves extract of *Momordica charantia* (MC) in male Wistar rats. Twenty-four male Wistar rats weighing between 150 – 200 g were divided into four groups of six rats each: Group A (High dose), Group B (Medium dose), Group C (Low dose) and Group D (control). 400 mg/kg body weight (High), 200 mg/kg body weight (medium), and 100 mg/kg body weight (low) doses of aqueous leaves extract of MC were administered orally to three groups of rats while the control group received distilled water only. The result of LD_{50} showed that administration of the extract caused 50 and 83.33% mortality at the doses of 500 and 2000 mg/kg bwt, respectively. The aqueous leaves of MC caused significant (*$p<0.05$) and dose-dependent decrease in blood glucose level and BMI of male Wistar rats when compared to the control group while there was a non-significant increase ($p > 0.05$) in the GSH and SOD activities in Wistar rats administered with 100 mg/kg but significant increase ($p < 0.05$) in 200 and 400 mg/kg body weight (bwt) of aqueous leaf extract of MC when compared to control. There was significant increase ($p < 0.05$) in the CAT activity in Wistar rats administered with the various doses of aqueous leaf extract of MC when compared to control. The CAT activity of the 100 mg/kg dose group was 26.65 ± 1.43, 200 mg/kg dose was 27.28 ± 1.84, 400 mg/kg dose was 29.84 ± 2.01 and control group was 23.85 ±1.21. The findings in this study suggest that aqueous leaves of MC possess hypoglycaemic as well as anti-obesity properties and it also has anti-oxidant activities and can be used to control obesity.

Keywords: Blood glucose, anti-diabetic, anti-obesity, antioxidants, male Wistar rats

Introduction

Momordica charantia (MC) popularly known as bitter melon is a tropical and sub-tropical vine of the Cucurbitaceous family (Joseph and Jini, 2013; Mardani *et al*., 2016) its name was derived from a Latin word Momordica, meaning 'to bite' referring to the jagged edges of the leaves which appear as if they have been bitten. It is widely believed that *Momordica charantia* originated in India and it was carried to China in the 14th century (Bagchi, 2005). This plant has been traditionally used in folk medicine due to its many nutritive and pharmacological properties against many diseases such as diabetic, ulcer, inflammatory and cancer (Basch *et al*., 2003; Grover and Yadav, 2004).

It has twice the potassium of bananas and it is very rich in Vitamin A and Vitamin C as well. It is also rich in phosphorus. It purifies blood, activates the spleen and liver. It is also rich in iron, potassium, beta carotene and other nutrients (Torres, 1996). MC has been extensively used as a therapy against diabetes mellitus which is characterized by persistent increased blood glucose level (Vamshi *et al*., 2010). Previous studies indicated that fruit contains many bioactive constituents like cucurbitane-type triterpenoids (Lin *et al*., 2011), saponins (Keller *et al*., 2011), flavonoids (Shan *et al*., 2012). Literature has revealed that triterpenoids from *Momordica charantia* fruit are associated with their antioxidant activity (Lin *et al*., 2012). Of late phytochemical investigations revealed that cucurbitane-type triterpenoids from *Momodica charantia* fruits (Zhao *et al*., 2014) had the same structural characteristics with those from its leaves (Zhang *et al*., 2012).

According to experimental evidence, whole plant-aqueous extract contains hypoglycaemic principle, which is an insulin-like peptide (polypeptide p-insulin) or an alkaloid, variously called foetidin, momordicin, or charantin (Mardani *et al*., 2016). It is hypothesized that this plant extracts mimics or improves insulin action at the cellular level, and may even have an extra-pancreatic mode of action (Ojewole *et al*., 2006). Theoretical mechanisms have also been proposed and these include increased insulin secretion, tissue glucose uptake, liver and muscle glycogen synthesis, glucose oxidation, and decreased hepatic gluconeogenesis.

In numerous studies, at least three different groups of constituents of aqueous leaves extract of MC have been chemically demonstrated to possess hypoglycaemic or other actions of potential benefits in diabetes mellitus (Ali *et al*., 1993). The hypoglycaemic activity is enhanced by charantin (a mixture of steroidal saponins, insulin-like peptides and alkaloids (Welhinda *et al*., 1986; Shih *et al*., 2014).

MC increases glucose utilization by liver (Sarkar *et al*., 1996), decreases gluconeogenises via inhibition of two key enzymes: glucose -6- phosphatase and fructose -1, 6 bi-phosphatase and improve glucose oxidation through the shunt pathway by activating glucose -6-phasphate dehydrogenase (Shibib *et al*., 1993; Ahmed *et al*., 1998; Mardani *et al*., 2016).

MC has been found to increase insulin sensitivity (Sridhar *et al*., 2008; Mardani *et al*., 2016). It also contains lectin which has insulin-like activity due to its non-protein specific linking together to insulin receptors. This lectin lowers blood glucose concentration by acting on peripheral tissues similar insulin effects in the brain, suppresses appetite. This lectin is likely to be a major contributor to the hypoglycaemic effects that develops after eating bitter melon (Ng *et al*., 1986). Antidiabetic properties of MC have been researched upon by many scientists and one of these was done by Xu *et al*. (2015). In the study, anti-diabetic properties of polysaccharide from the fruits of MC in alloxan induced diabetic mice was examined and the results suggested that water soluble polysaccharide has significant anti-diabetic activity on alloxan induced diabetic mice (Xu *et al*., 2015).

A number of large epidemiologic studies have proved that mortality increases with obesity (Haslam and James, 2005). Obese individuals are prone to many cardiovascular risks factors. Type 2 diabetes mellitus is strongly associated with overweight and obesity (Chan *et al*., 1984; Sheen, 2000). The prevalence of these risk factors substantially increases with increasing BMI.

MC has been experimentally proven as a therapy for diabetes and also an effective herb for the management of body weight. Hypoglycaemic agents in bitter melon promote efficient oxidation of glucose into fuel and conversion to starch. During glucose shortages, fats/fatty acids are used as fuel and demand for energy in the absence or shortage of glucose causes fat cells to release their fat content to maintain energy balance and this increased in fatty acid oxidation will eventually lead to weight loss (Umesh *et al*., 2005).

Due to the fact that both diabetics and non-diabetic individuals use MC for prophylactics purpose for long duration, it becomes imperative to investigate the possible effects of aqueous leaf extract of MC on blood glucose level, anti-oxidants activities and body mass index (BMI). Hence this study was designed to study the possible effects of MC in male Wistar rats.

Materials and Methods

Materials

Cotton wool, Accu check Glucometer, test strip, Syringes**,** Pins**,** Table scale**,** Oral cannula, Disposable gloves**,** *Momordica charantia* leaves**,** twenty-four male Wistar albino rats**,** Markers**,** Bowl for feeding rats**,** Rat cages**,** and Paper tapes.

Methods

Animal housing

Twenty-four (24) healthy adult male Wistar rats weighing between 150 – 200 g were used for this study. The rats were purchased at a reputable animal house located at Ilisan, Ogun state, Nigeria. Animals were housed in separate wooden and wire gauzed cages for proper ventilation to prevent the build-up of ammonia and carbon dioxide. The room was maintained at a constant room temperature of 23 - 27ºC, wood shavings were used as beddings to keep each compartment dry. Animals were kept in a 12 h light-dark cycle and provided with water and food ad libitum. The rat feed was obtained from Topmost feed, Sagamu depot.

Collection of plant materials

Herbs: Fresh leaves of *Momordica charantia* were collected from an open grass land in Ayepe - Ijebu, Ogun State, Nigeria. The plant was then identified and authenticated by Forest Research Institute Ibadan where the leaf was assigned voucher no: FHI 109921. A voucher specimen was deposited in the Forest Herbarium, Ibadan.

Fig 1: A picture of *Momordica charantia* as confirmed by Forest Research Institute Ibadan where the leaf was assigned voucher No: FHI 109921

Determination of LD_{50}

LD50 was determined by giving one of the following fixed doses: Five (5 mg/kg bwt), 50, 500, and 2000 mg/kg bwt at a time to six male Wistar rats each. The extract caused fifty percent (50%) mortality at the dose of 500 mg/kg bwt and 83.33 percent mortality at the dose of 2000 mg/kg bwt (Table 4).

Preparation of aqueous extract of MC

The plant materials were sorted out to eliminate all extraneous materials and the seeds. The freshly collected leaves were air dried under shade at room temperature until a constant weight of the plant was reached. The dried leaves material was grounded into powdered form and weighed. The method of Akueshi *et al*. (2002) and Oben *et al*. (2006) was modified for the aqueous extraction. One hundred gram (100 g) of the powdered leaves was soaked in one thousand ml (1000 ml) distilled water for 3 days under refrigeration. The resultant liquid was filtered; the obtained residue was poured into beakers of known weights and was dried in an oven at 40ºC for 3 days. The percentage yield was 45.9%. Stock solution of the extract that contained 800 mg/ml was prepared. Other concentrations were made as required from the stock solution and the solutions were stored in the refrigeration until they are needed.

Animal grouping and experimental design

The male Wistar rats were divided into four groups namely:

High dose group: This group consists of six male Wistar rats; each rat was treated orally with 400 mg/kg body weight of the aqueous leaf extract of *Momordica charantia* for thirty days.

Medium dose group: This group consists of six male rats; each rat was treated orally with 200 mg/kg body weight of the aqueous leaf extract of the *Momordica charantia* for thirty days.

Low dose group: This group consists of six rats; each rat was treated orally with 100 mg/kg body weight of the aqueous leaf extract of *Momordica charantia* for thirty days.

Control dose group: This group also consists of six rats; none of the rats in this group was treated with the aqueous leaf extract of *Momodica charantia* in the course of this experiment, rather they were only fed with the normal feed and water.

Determination of blood glucose with Accu check glucometer

The test was conducted after thirty days of administration of aqueous leaves extract of *Momordica charantia* with the aid of Accu Check glucometer. Values obtained using the glucometer have been shown to correlate excellently with those from the use of standard biochemical methods (Ajala *et al*., 2003). A day before the test day, the rats were fasted overnight. Using aseptic precaution, blood was collected from the capillary bed of their tail tip by pricking method and blood glucose level was measured by putting drops of blood on the test strip which was inserted in the glucometer. The values of blood glucose for the experiment were recorded in mg/dL.

Determination of body mass index

This was carried out with the aid of a table scale and a measuring tape. The weights and lengths of all the rats administered with the various doses of the extract and the control were taken on the final day of the experiment in order to know if there will be variations in the body mass index (BMI).

Determination of anti-oxidants activities

Determination of SOD activity: The level of SOD activity in plasma was determined by the method of Misra and Fridovich (1972).

Determination of catalase activity: Catalase activity was determined according to the method of Sinha (1972). This method is based on the fact that dichromate in acetic acid is reduced to chromic acetate when heated in the presence of H_2O_2 with the formation of perchromic acid as an unstable intermediate. The chromic acetate that was produced was measured colorimetrically at 570 – 620 nm.

Determination of glutathione – S-transferase activity

Glutathione –S- transferase activity was determined by the method according to Habig *et al*. (1974).

Principle: This is based on the fact that all known glutathione –S- transferase demonstrate a relatively high activity with 1-

Chloro – 2, 4 – dinitrobenzene (CDNB) as the second substrate. Consequently, the conventional assay for glutathione – S- transferase activity utilizes 1 – Chloro – 2, 4 – dinitrobenzene as substrate. When this substrate was conjugated with reduced glutathione (GSH), its absorption maximum shifted to a longer wavelength. The absorption increased at the wavelength of 340 nm which provides a direct measurement of the enzymatic reaction.

Statistical analysis

The values are expressed as mean ± SD (Standard deviation from mean). The means of the group were compared using one-way ANOVA (Analysis of variance) and the level of significance was done using least significant difference (LSD) and Duncan Multiple range test (DMRT) at P < 0.05 (Norusis, 1998).

Animal ethics and ethical clearance

All procedures involving animals in this study conformed to the guiding principles for research involving animals as recommended by the Declaration of Helsinki and the Guiding Principles in the Use of Animals (American Physiological Society, 2002). Ethical clearance was obtained from the departmental ethical committee.

Results and Discussion

Blood Glucose level:

The Table 1 below showed the results of the effect of aqueous leaf extract of MC on blood glucose level. The test showed that there was a significant decrease ($p < 0.05$) in blood glucose level when compared to the control value and these reductions were dose dependent.

Table 1: Blood glucose level after administration of aqueous leaf extract of MC on male Wistar rats

Groups	Blood glucose (mg/dL) Mean± SD
Control	107.60±7.01
Low dose	90.40±3.51*
Medium dose	81.41±5.09*
High dose	66.80±4.82*

*Significant ($p < 0.05$) compared with control

Table 2: Body mass index after administration of aqueous leaf extract of MC on male Wistar rats

Groups	BMI (kg/m²) Mean± SD
Control	0.17 ± 0.02
Low dose	0.13 ± 0.01*
Medium dose	0.10 ± 0.02*
High dose	0.08 ± 0.02*

*Significant ($p < 0.05$) compared with control

BMI: The Table 2 below showed the results of the effect of aqueous leaf extract of MC on body mass index (BMI). The test showed that there was a significant decrease ($p < 0.05$) in body mass index when compared to the control value and these reductions were dose dependent.

Activities of anti-oxidants

Activity of GSH

As shown in the results in Table 3, there was a non-significant increase ($p > 0.05$) in the GSH activity in Wistar rats administered with 100 mg/kg but significant increase ($p < 0.05$) in 200 and 400 mg/kg body weight (bwt) of aqueous leaf extract of MC when compared to control. The GSH activity of the 100 mg/kg bwt group was 0.37 ± 0.09, 200 mg/kg bwt was 0.44 ± 0.08, 400 mg/kg bwt was 0.55 ± 0.06 and control group was 0.26 ± 0.06.

Activity of SOD

There was a non-significant increase ($p > 0.05$) in SOD activity in the rats administered with 100 mg/kg bwt of aqueous extract of MC but there was significant increase ($p < 0.05$) in the SOD activity in Wistar rats administered with 200 and 400 mg/kg bwt of aqueous leaf extract of MC when compared to control. The SOD activity of the 100 mg/kg bwt group was 2.76 ± 0.17, 200 mg/kg bwt was 3.38 ± 0.37, 400 mg/kg bwt was 3.97 ± 0.54 and control group was 2.41 ± 0.29. (Table 3)

Table 3: Effect of Aqueous leaf extract of MC on activity of anti-oxidants

Groups	GSH (Mean ± SD) (Umol/mg protein)	SOD (Mean±SD (Umol/mg protein)	CAT (Mean± SD) (Umol/mg protein)
Control	0.26 ± 0.06	2.41 ± 0.29	23.85±1.21
Low dose	0.37 ± 0.09	2.76 ± 0.17	26.65 ± 1.43*
Medium dose	0.44 ± 0.08*	3.38 ± 0.37*	27.28 ± 1.84*
High dose	0.55 + 0.06*	3.97 + 0.53*	29.84 + 2.01*

*Significant ($p < 0.05$) compared with control

Table 4: Determination of LD_{50} of Aqueous leaf extract of MC on male Wistar rats

Number of male Wistar rats/group	Dose (mg/kg bwt)	Number of dead male Wistar rats	Percentage Mortality (%)
6	5	0	0
6	50	0	0
6	500	3	50
6	2000	5	83.33

Activity of CAT

As shown in Table 3, there was significant increase ($p < 0.05$) in the CAT activity in Wistar rats administered with the various doses of aqueous leaf extract of MC when compared to control. The CAT activity of the 100 mg/kg dose group was 26.65 ± 1.43, 200 mg/kg dose was 27.28 ± 1.84, 400 mg/kg dose was 29.84 ± 2.01 and control group was 23.85 ±1.21. MC is a plant widely grown in Asia, Africa and the Caribbean and it is widely known for its edible fruit (Okabe *et al*., 1982). In this experiment we found that aqueous leaf extract of MC significantly decreased blood glucose level, body mass index as well as anti-oxidants under investigation in dose dependent manner.

According to experimental evidence, whole plant-aqueous extract contains a hypoglycemic principle, which is an insulin-like peptide (polypeptide p-insulin) or an alkaloid, variously called foetidin, momordicin, or charantin. The hypoglycemic potential of MC was investigated in normal and diabetic rats (Srivastava *et al*., 1993; Xu *et al*., 2015) and in patients with type 2 diabetes (Srivastava *et al*., 1993; Li *et al*., 1997; Xu *et al*., 2015). It is hypothesized that this plant extract mimics or improves insulin action at the cellular level, and may even have an extra-pancreatic mode of action (Ojewole *et al*., 2006; Abas *et al*., 2015). Theoretical mechanisms have also been proposed and these include increased insulin secretion, tissue glucose uptake, liver muscle glycogen synthesis, glucose oxidation, and decreased hepatic gluconeogenesis via inhibition of two key enzyme glucose -6-phasphat and fructose -1,6 bisphosphatase and, improve glucose oxidation through the shunt pathway by activating glucose -6-phasphate dehydrogenase (Shibib *et al*., 1993; Abas *et al*., 2015). In addition, amelioration of insulin resistance and dyslipidemia by MC was observed (Abas *et al*., 2015).

Bitter melon has been found to increase insulin sensitivity (Sridhar *et al*., 2008). It also contains lectin which has insulin-like activity due to its non-protein specific linking together to insulin receptors. This lectin lowers blood glucose

concentration by acting on peripheral tissues, similar insulin effects in the brain suppresses appetite which will ultimately lead to decrease in body weight. This lectin is likely to be a major contributor to the hypoglycaemic effects that develops after eating bitter melon (Ng *et al*., 1986).

The present study also demonstrated that MC decreased significantly the body mass index which implies that the extract reduced weight gain and body fat. Fat synthesis is considered to be a key step in the process of obesity hence regulating this step would effectively control obesity progression (Rosen and Spiegelman, 2006). Data from Shobha *et al*. (2017) showed that 50% ethanolic extract of MC is a potent inhibitor of lipogenesis and stimulator of lipolysis in 3T3-L1 pre-adipocytes (Shobha *et al*., 2017). Weight gain may involve transition of undifferentiated fibroblastic pre-adipocytes into mature adipocytes and also involves differential regulation of adipogenic genes and lipid accumulation. (Rayalama *et al*., 2008) hence reduction in weight loss and consequently body mass index will involve inhibition of adipogenic process and lipid accumulation due to dedifferentiation and lipid mobilization. The inhibition of fat synthesis and promotion of glucose utilization of MC is associated to adiponectin, leptin, GLUT-4 and by promoting their regulation it enhances fatty acid oxidation and inhibits adipocyte differentiation in order to achieve anti-obesity effect (Zhu *et al*., 2012). Adipocytokines like leptin and adiponectin that are involved in food intake, energy metabolism and weight gain have been shown to be regulated by MC in cell culture and mammals' studies (Shih *et al*., 2008).

In the present study, Wistar rats treated with various doses of aqueous leaves extract of MC decreased significantly various anti-oxidants under investigation in dose dependent manner. MC aqueous leaves extract possesses potent anti-oxidants and free radical scavenging activities. These anti-oxidant activities might have contributed in part to the effect of MC aqueous leaves extract on suppressing lipid peroxidation (Wu and Ng, 2008).

In conclusion, the study demonstrated that aqueous leaves extract of MC has potent in-vitro anti-diabetic, anti-obesity and anti-oxidants activities.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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