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RESEARCH ARTICLE

Momordica charantia improves biochemical indices in alloxan-induced diabetic rat model

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ABSTRACT

Background: Diabetes mellitus is a serious disorder of carbohydrate, protein, and fat metabolism researchers on alternative medications in the management of diabetes with low costly and little or no side effect over long-term use still continue. **Aim and Objective:** This study evaluated how *Momordica charantia* (MC) improved biochemical indices in alloxan-induced diabetic rats. **Materials and Methods:** Twenty-five male rats whose weights were between 150 and 200 g used for this study were divided into five groups with five rats per group. Group A received water, Groups B, C, D, and E were all diabetic but received water, aqueous leaf extract of MC, aqueous leaf extract of MC, and anti-diabetic drug and anti-diabetic drug only, respectively. Treatments were carried out for 21 days; from the blood sample, liver enzymes, lipid profile, blood electrolytes, and glucose were determined using standard methods. **Results:** Observation from results showed that blood glucose, liver enzymes, lipid profile, and blood electrolytes in diabetic groups treated with MC when compared with diabetic group reduced significantly ($P < 0.05$). **Conclusion:** The management of diabetes induced with alloxan in rats treated with aqueous leaf extract of MC reduced the chance of chronic renal failure, hyperlipidemia, liver disease, and excessive gain in body weight.

KEY WORDS: Diabetes; Management; *Momordica charantia*; Biochemical Indices

INTRODUCTION

Diabetes mellitus is a serious carbohydrate, proteins, and fat metabolic disorder. In 1500 BC., a Greek physician describes diabetes as a condition where flesh and bones run together and are siphoned into urine.[1,2] Diabetes mellitus arises from decreased insulin production and or the inability of target cells to respond to insulin. These situations lead to increase blood glucose (hyperglycemia) after any type of meal. However, in abnormal conditions, hyperglycemia may persist for long, resulting in damage and failure of target organ as well as death if not properly controlled or managed.[1-4] The WHO report on diabetes showed that the number diabetic adult increased by four folds in the past 40 years. Records also have it that globally 2.8% of the population suffer from diabetes mellitus, and there is possibility that it will increase more than 5.4% by 2025.[5]

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We have many glucose-reducing drugs, which promote anti-diabetic effects through different mechanisms which include secretion of insulin (meglitinides and sulfonylurea drugs), increase peripheral absorption of glucose (biguanides and thiazolidinediones),[6] delay absorption of carbohydrates from the intestine (alpha-glucosidase), and reduce hepatic

gluconeogenesis (biguanides).[7] Despite the significant progress made in the treatment of diabetes, result obtained from patients fall below expectation. Results from the studies shown that these treatments have some disadvantages, which are: Reduced efficiency, side effects, toxicity, and damage of internal organ over time. For instance, sulfonylureas lose their potency after use for over a period of 6 year in about 44% of patients. Glucose-lowering drugs are not able to control hyperlipidemia.[8] Use of synthetic drugs led to side effects with persistence hyperglycemic conditions. Usage over long period led to serious complications and damage to the heart, blood vessels, eyes, kidney, and nerves, as well as increase in the risk of heart diseases and stroke.[9] Progressive reduction in β-cell functions made it difficult to maintain glycemic control in diabetic patients.[10] The setback in glycemic control coupled with high incidence with variable pathogenesis and diabetic complications demand the urgent need for effective treatment. Many researches are on-going for alternative use to anti-diabetic drugs, which will be less costly with little or no side effects over long-term use and the ability to perform better than any anti diabetic drug. Treatments with medicinal plants are now recommended,[11] because they contain phytochemicals (carotenoids, flavonoids, terpenoids, alkaloids, and glycosides) with anti-diabetic effects.[12] Some plants with considerable anti-diabetic activity include *Momordica charantia* (MC), *Acacia arabica* bark, *Achyranthes aspera* leaves, *Acosmium panamense*, *Allium sativum*, *Aloe barbadensis* miller, *Andrographis paniculata*, and so on. Their ability to improve the function of pancreatic tissue, by increasing insulin secretions or reduction of the intestinal absorption of glucose. However, this study is designed to evaluate the efficacy of MC in the management (improve biochemical parameters) of alloxan-induced diabetes in experimental rats.

MATERIALS AND METHODS

Collection of MC Leaf

MC leaves were harvested fresh, from a farm located in Ikenne close to Sagamu axis in Ogun state, Nigeria. Dr. Oyesiku of the Department of Botany, Olabisi Onabanjo University, Ogun state, Nigeria, confirmed and authenticated the leaf. Forestry Research Institute of Nigeria located in Ibadan confirmed it with herbarium number 109921.

Extract Preparation

The collected plant material was carefully selected to gather only the leaf materials of MC. They were dried to a constant weight and grounded into powdered form. Aqueous leaf extraction was prepared with modified methods of Mandal *et al*.[13] and Oben *et al*.[14] The leaves were soaked in distilled water for 3 days under refrigeration. One thousand gram of the powdered leaf was soaked in 5000 ml of water for 3 days inside a refrigerator. A funnel plugged with glass wool was used to filter the resultant liquid. Further extraction was done with 5000 ml of distilled 2–3 times until there was no more extractable material from the leaf, judging from the obtained water color. Filtrate aliquot was poured into beakers of known weight and dried in an oven. Four thousand milligram of the crude leaf extract was dissolved in 100 ml of distilled water to obtained 400 mg/kg dosage. One milliliter of the solution containing 40 mg extract was given to 100 g rat. One thousand mg of the crude leaf extract was dissolved in 100 ml of distilled water to obtained 100 mg/kg dosage. One milliliter of the solution containing 10 mg extract was given to 100 g rat. They were stored in the refrigerator until they were needed.

Animals and Grouping

The 25 male Wistar rats used for this study were obtained from a reputable animal house in Ibadan, Oyo State. They weighed between 150 and 200 g. They were housed in standard plastic cages under normal atmospheric condition in the department of physiology animal house, Olabisi Onabanjo University, Ogun state. They acclimatized for 2 weeks before the commencement of the study and were fed on available commercial rat feed. They were supplied with water *ad libitum* and were randomly distributed into five groups (n = 5). Group A (normal rats), Group B (diabetic rat administered with normal saline), Group C (diabetic rats administered with aqueous leaf extract of MC only), Group D (diabetic rats administered with aqueous leaf extract of MC and antidiabetic drug), and Group E (diabetic rats administered with antidiabetic drug only). The administration was done orally and treatment lasted for 21 days. International, national, and institutional rules and guidelines with the use and care of laboratory animals were followed during the study. The ethics committee of the department gave approval for the study.

Preparation and Administration of Alloxan, Drug, and Glucose

Alloxan was prepared at a concentration of 3 g/100 ml in normal saline and was administered intra peritoneal to rat at 150 mg/kg weight. The anti-diabetic drug (PerglimM-2) was purchased from a reputable pharmaceutical store in Ogun state Nigeria. Five hundred milligram of drug dissolved in 125 ml of normal saline was orally administered at 1.43 mg/100 g rat weight. 20 g and 5 g of glucose were dissolved in 100 ml of distilled water to get 20% and 5% glucose solution, respectively.

Diabetes Induction in Rats

A single dose of freshly prepared alloxan monohydrate solution (150 mg/kg) was injected intraperitoneally into rats fasted for

about 16 h over the night. Alloxan is capable of producing fatal hypoglycemia due to increase pancreatic insulin release. Therefore, 20% glucose solution was administered orally after 6 h. Further hypoglycemic condition was prevented by oral administration of 5% glucose solution through their water bottle. Commercially available blood glucose monitoring system (Accu-Chek Active Meter) was used to determine the rats' glucose level. Rats that showed hyperglycemia with blood glucose greater than 200 mg/dl, 48 h after alloxan monohydrate injection were selected for the study.

Fasting Blood Glucose Determination

Blood samples of overnight fasted rats were collected by cutting the tail-tip of the rats. Blood samples were collected before alloxan treatments, 48 h after alloxan treatment and at interval after confirmation of diabetes using commercially available kit (Accu-Chek Active Test Meter).

Collection of Blood Samples

Sodium pentobarbitone (60 mg/kg body weight) injected intraperitoneally was used to anesthetized the animals. An incision was made in the thoracic region to expose the heart. Blood samples were collected with a syringe from the heart into plain bottles. Lipid profile and other biochemical parameters were estimated from the blood.

Blood Glucose and Biochemical Parameters Determination

The blood glucose of the rats was evaluated before and 48 h after treatment with alloxan and days; 5, 10, 15, and 21 after induction of diabetes with Accu-Chek Active Test Meter glucometer. Biochemical parameter determined were serum albumin, blood urea nitrogen, bilirubin, creatinine, and liver enzyme such as aspartate aminotransferase (AST) and alanine aminotransferase (ALT). The method of Lowry *et al*.[15] was used to determine protein content, using bovine serum albumin as a standard. Doumas[16] method was used to determine serum albumin concentration. Randox Laboratory kit reagents were used to determined serum total cholesterol and high-density lipoprotein and triglyceride. Low-density lipoprotein cholesterol was calculated using the formula TG/2.2 mmol/L. Bilirubin concentration of the sample was determined with the method described by Evelyn and Malloy.[17] Serum creatinine concentration was determined by the method described by Tietz *et al*.[18] while serum urea was determined by the procedure of Kaplan.[19] Liver enzymes (ALT and AST) activities were evaluated by the procedure described by Kind and King.[20] Spectrophotometer (ultraviolet-visible spectrophotometer model) was used to monitor the absorbance of all tests. Colorimetric method described by Tietz *et al*.[18] was used to determine phosphate ion concentration and flame photometer was used to determine sodium and potassium ion level.

Statistical Analysis

Obtained results were analyzed by one-way analysis of variance with the use of SPSS software version 16.0. Results expressed as mean ± standard error of mean (SEM). Duncan multiple range test was used to compare the differences between animal groups. Significant level was taken at a probability level of <5% ($P < 0.05$).

RESULTS

Table 1 showed weight changes in diabetic rats treated with both synthetic drug (PerglimM-2) and MC extract. Observation from the results when compared within Group A showed significant ($P < 0.05$) weight loss in Group B. Groups C, D, and E also lost weight but not significant in Group E. There was a percentage weight loss of 14.33% in Group C, 1.04% in Group D, and 2.65% in Group E.

Blood glucose level in alloxan-induced diabetic rats was expressed in Table 2 after 21 days treatment. Results clearly showed that the rats became hyperglycemic after 24 h of alloxan administration with blood glucose level of 446.2 ± 4.68, 440.6 ± 1.86, 430.6 ± 3.67, and 449.2 ± 4.95 mg/dl, respectively, in Groups B to E. On the 21 day, blood glucose level in Group D was 55.0 ± 4.14 mg/dl which reduced significantly in comparison with Groups A and B. Blood glucose in Group E (63.0 ± 3.39 mg/dl) reduced significantly in comparison with Groups A and B. Blood glucose level in Group C rats (89.6 ± 7.02 mg/dl) was not significantly different when compared with Group A even though it was higher but when compared with Group B (529.8 ± 8.38 mg/dl), there was a significant reduction.

Table 3 showed lipid profile and some blood electrolytes in diabetic rats, when administered with aqueous leaf extract of MC and anti-diabetic drugs. Observation showed decrease in the level of triglyceride in Groups C and D in comparison with Groups A and B independently. Group D triglyceride decreased significantly when compared with

Table 1: Weight changes in diabetics rats upon administration with aqueous leaf extract MC and anti-diabetics drugs

Groups	Weight (g)		% weight change
	Day 0	Day 21	
Group A (control)	178.2±6.74	204±4.57	14.48%
Group B (diabetes control)	189.6±6.98	142±10.2	−25.11%[a]
Group C (diabetes+MCE)	182.8±7.04	209±5.97	14.33%[b]
Group D (diabetes+MCE+drug)	193.0±4.36	191±7.24	−1.04%[b]
Group E (diabetes+drug)	189.0±6.41	184±6.12	−2.65%[b]

Values are expressed as mean±SE (n=5) in each group. [a]Values considered significant at P<0.05 when compared with Group A. [b]Values considered significant at P<0.05 when compared with Group B. MC: *Momordica charantia*

Group B. Cholesterol level in Groups C, D, and E decreased significantly when compared with Groups A and B, while cholesterol in Group E showed no significant difference when compared with Group A. High-density lipoproteins (HDL) level increased significantly in Groups C, D, and E when compared with Groups A and B. Likewise in Group B, the HDL level increased significantly when compared with Group A. Low-density lipoproteins (LDL) level decrease significantly in Groups C and D when compared with Group B, likewise Groups D and E deceases significantly when compared with Group A. Sodium ions of Groups C, D, and E increased when compared with Group B, but a significant decrease was observed in Group B when compared with Group A. Potassium ion in Groups C, D, and E decreased but were not significant when compared with Group B. However, Group C decreased significantly when compared with Group B. The urea level in Group E decreased significantly when compared with Group B but Groups B, C, and D urea level increased significantly when compared with Group A. The level of creatinine in Groups C, D, and E increased significantly when compared with Group B and it was also significant when compared with Group A.

Table 4 expressed the changes in liver enzymes of alloxan-induced diabetic rats treated with MC and anti-diabetic drug. In all the liver enzymes, comparing Group B with Group A showed significant increase. Groups C, D, and E were compared with Group B for all the enzymes and observation showed significant ($P < 0.05$) decreases.

DISCUSSION

Results from these findings showed clearly that the use of MC aqueous leaf extract has improved biochemical indices in diabetes management. Researchers continues to work on new therapy involving plant products to combat diabetes.[21] Combination therapies were also reported to ease the cumbersome burden of injectable and oral agents. These encouraged abilities of patients to stay with treatments to achieve and maintain normal range of

Table 2: Blood glucose level in alloxan-induced diabetic rats administered with aqueous leaf extract of MC and anti-diabetic drug

Groups	Fasting blood glucose level (mg/dl)						Percentage change in glucose level (%)	
	Initial glucose reading	48 h after alloxan	5 days after diabetes	10 days after diabetes	15 days after diabetes	21 days after diabetes	After alloxan administn.	After 21 days
Group A (control)	80.2±2.59	80.2±3.22	77.8±3.51	84.2±2.61	84.2±4.15	82.2±2.33	Nil	2.49
Group B (diabetes control)	62.6±1.29	446.2±4.68	462.5±6.42	482.6±13.89	497.0±12.22	529.0±8.38[a]	612.78	745.05
Group C (diabetes+MCE)	63.4±1.12	440.6±1.86	382.6±29.67	311.2±54.08	151.2±24.7	89.6±7.02[b]	794.95	41.32
Group D (diabetes+ MCE+drug)	70.0±4.53	430.6±3.67	250±12.26	153.6±16.4	74.0±1.95	55.0±4.14[a,b]	515.14	−21.43
Group E (diabetes+drug)	88.6±4.83	449.2±4.95	337.4±46.5	248±62.45	83.8±4.33	63.0±3.59[a,b]	406.99	−28.89

Value are expressed as Mean±SEM (n=5) in each group. [a]Values considered significant at P<0.05 when compared with Group A. [b]Values considered significant at P<0.05 when compared with Group B. MC: *Momordica charantia*

Table 3: Biochemical parameters in alloxan-induced diabetic rats administered with aqueous leaf extract of MC and anti-diabetic drug

Groups	Triglyceride (mg/dl)	Cholesterol (mg/dl)	HDL (mg/dl)	LDL (mg/dl)	Sodium ion (mmol/L)	Potassium ion (mmol/L)	Urea (mg/dl)	Creatinine (mg/dl)
Group A (control)	32.8±2.48	78.96±0.48	59.6±0.51	128.0±0.29	124.0±1.36	4.14±0.18	33.4±5.59	0.20±0.00
Group B (diabetes control)	38.4±2.75	92.3±3.41	27.0±2.57[a]	57.7±4.95[a]	116.0±0.00[a]	4.99±0.65[a]	99.1±10.2[a]	0.80±0.34[a]
Group C (diabetes+ MCE)	27.4±1.63	59.2±2.46[a,b]	40.4±2.64[a,b]	33.32±0.34[b]	130.4±2.86[a,b]	3.88±0.18[b]	74.0±14.2[a]	0.52±0.37[a,b]
Group D (diabetes+ MCE+ Drug)	25.8±3.35[b]	41.0±2.24[a,b]	36.0±1.34[a,b]	30.16±3.27[b]	128.0±0.45[b]	4.25±0.16[b]	99.0±5.37[a]	0.60±0.44[a,b]
Group E (diabetes +Drug)	42.8±7.00	78.24±10.78	34.0±0.84[a,b]	35.6±10.55[a,b]	128.0±2.04[b]	4.44±0.09[b]	46.4±9.45[b]	0.70±0.32[a,b]

Values are expressed as Mean±SEM (n=5) in each group. [a]Values considered significant at P=0.05 when compared with Group A. [b]Values considered significant at P<0.05 when compared with Group B. MC: *Momordica charantia*. HDL: High-density lipoproteins, LDL: Low-density lipoproteins

Table 4: Liver enzymes in alloxan-induced diabetic rats administered with aqueous leaf extract of MC

Group	Albumin (g/dl)	Bilirubin (mg/dl)	AST (u/L)	ALT (u/L)
Group A (control)	3.02±0.08	0.20±0.03	4.50±0.22	22.00±1.80
Group B (diabetes control)	5.50±0.46[a]	1.01±0.09[a]	115.0±38.22[a]	117.60±23.50[a]
Group C (diabetes+MCE)	2.90±0.13[b]	0.40±0.14[b]	9.80±3.63[b]	25.60±5.16[b]
Group D (diabetes+MCE+drug)	2.50±0.09[b]	0.20±0.05[b]	4.00±0.00[b]	31.40±8.30[b]
Group E (diabetes+Drug)	2.90±0.15[b]	0.20±0.04[b]	4.00±0.00[b]	14.00±2.77[b]

Value are expressed as Mean±SEM (n=5) in each group. [a]Value considered significant at P<0.05 when compared with Group A. [b]Value considered significant at P<0.05 when compared with Group B. MC: *Momordica charantia*

blood glucose and eliminate or reduced microvascular complication risks.[21-25]

Diabetes mellitus is identified by heterogeneous disorder, manifesting as hyperglycemia and glucose intolerance resulting from insulin deficiency, or/and ineffective action of insulin.[26] Difficult emanated from regulatory system abnormal performance to store metabolic fuel movement, which includes metabolism of food substances (carbohydrate, protein, and fat) that result from insulin secretion abnormalities and or its actions.[27,28] Diabetes management or therapy aimed to reduce blood glucose, lipid level, and blood electrolytes and prevent weight loss. In addition, life style management and modification, pharmacotherapy, oral hypoglycemic, and plant-derived medication have been documented by researchers to reduced blood glucose.[29-31] These have prevented complications (retinopathy, nephropathy, neuropathy, and cardiovascular risk) that may result from hyperglycemic condition as recorded in Group D [Table 1]. Diabetes was considered to be sugar related disease because sugar tasted in the urine and not lipid.[32]

However, the devastating effects or complications of fat material deposition on the inner wall of blood vessels were more dangerous than those caused by the effect of glucose.[33,34] Studies were unable to completely remove diseases that resulted from cardiovascular related activities when sugar level was managed,[35,36] but cholesterol-lowering treatment was demonstrated to have major impact in the diabetes treatment.[37,38] Glucose metabolism switches to fat metabolism during abstinence from food. Lack of insulin resulted into high serum glucose together with increase serum triglycerides level from lipoprotein in form of triglyceride, cholesterol, high-density lipoprotein, and low lipid lipoprotein. Fasting hyper-triglyceride has a lot to do with cardiovascular activities which can cause death;[39] same as postprandial triglycerides.[40,41] Bariatric surgery and lack of food have intense influence on serum lipids[42,43] and insulin regulatory pathway (cholesterol absorption and synthesize). Homeostasis of cholesterol is controlled through bile acid cholesterol pathway.[44]

Dysfunction in glucose homeostasis impacts acid-base regulation.[45] The dilute extracellular sodium levels lead to lower plasma sodium levels causing hyponatremia (Groups C, D, and E). The treated group with increase sodium level was probably due to the hypoglycemic properties of MC and anti-diabetic drug in the glucose concentration leading to a decrease in the osmotic force that draws water to the extracellular space.[45] Potassium level, increase significantly in the diabetic rat (Group B), with high plasma glucose level concentration leads to efflux to the extracellular space causing hyperkalemia in diabetic patient.[45] Decreased pattern of change in the treated groups according to this study gives credibility to the use of MC and the anti-diabetic drug. Electrolyte imbalance characterized patients suffering from diabetes mellitus although may be multi-factorial, but usually result from insulin deficiency in diabetic ketoacidosis and hyperglycemia.[46] Urea and creatinine level in control diabetic Group B is probably due to some bio-makers found in the blood (urea and serum creatinine), which rise with hyperglycemia especially in an uncontrolled diabetes causing severe kidney damage and dysfunction.[47-49] Diabetes mellitus caused kidney failure through diabetic nephropathy and it is also linked with elevated cholesterol (fats), abnormal high blood pressure, and fat storage within abdominal cavity which increase the incidence of contacting chronic kidney disease and cardiovascular diseases.[50-56] This is characterized by abnormal levels of albumin (macroalbuminuria) and abnormal renal function (blood urea and creatinine abnormality).[57,58] The rise in the diabetic control group of ALT and AST is clear indicators of hepatocellular injury. Increased activity of these makers is linked with resistance to insulin, metabolic syndrome, and insufficient insulin secretion or production. However, the treated Groups C, D, and E their biochemical parameters showed a reduction that is significant in comparison with the control Group B, emphasizing the positive influence of MC in diabetes management.

CONCLUSION

Diabetes mellitus, a known chronic metabolic syndrome of multiple etiology, it breaks down the blood vessels and body lipid, damaging millions of nephrons and decreasing the function of liver enzymes was controlled or treated in this study with a medicinal plant (MC) and PerglimM-2 an anti-diabetic drug. However, medicinal plants such as MC, reported to be cheap, readily available less, or non-toxic are proved in this study not only for its hypoglycemic functions

but also have the properties to balance most biochemical parameters. MC has shown its functionalities in the reduction of urea level, creatinine level, albumin level, bilirubin level, AST level, ALT level, and balance body electrolyte which is one of the major causes of chronic renal failure in diabetic patient.

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