Glucose-lowering effects of *Momordica charantia* in healthy rats

D M Matheka, T N Kiama, F O Alkizim, and F Bukachi

Abstract

Pharmacotherapeutic interventions for diabetes are expensive, hence the common use of alternative medicine. *Momordica charantia* (MC) is a hypoglycaemic agent used by diabetic as well as healthy people. The glycaemic effects of this plant are however not known in the latter, and we have therefore investigated the effects of MC on blood glucose level in healthy rats.

Fourteen (14), 6-month-old, healthy Sprague–Dawley rats were assigned to two equal groups of control and experimental. MC juice extract was administered (10 mL/kg) to the experimental group for 28 consecutive days. To the control group, 10 mL/kg normal saline was administered.

Fasting blood glucose (FBG) level was assessed once a week for 4 consecutive weeks. Thereafter, a 2 g/kg intraperitoneal glucose tolerance test (IPGTT) was performed on rats in both groups.-FBG level was lower in the experimental compared with the control group at day 28 (2.9±0.1 vs 3.2±0.1 mmol/L, p=0.04). Following IPGTT, there was an 84% increase in glucose level at 30 min to 7.90 ± 0.95 mmol/L which decreased by 30% at 60 min and 10% at 90 min in the experimental group. Similarly, the control group had a 142% increase in glucose level at 30 min to 10.3±0.8 mmol/L which decreased by 30% at 60 min and 16% at 90 min. In the IPGTT the BG levels were significantly lower in the experimental group compared with the controls through the 180-min period of observation (3.2±0.4 vs 3.8±0.1 p <0.01).

We conclude that MC prevents fluctuations of blood glucose level in healthy rats. Thus, it has potential therapeutic use in the prevention and treatment of type 2 diabetes.

Duncan M Matheka, T N Kiama, F O Alkizim, and F Bukachi, Department of Medical Physiology, School of Medicine, University of Nairobi, Kenya. Correspondence to Dr Frederick Bukachi, Department of Medical Physiology, University of Nairobi, PO Box 30197-00100, Nairobi, Kenya. Email: fbukachi@uonbi.ac.ke

Introduction

Diabetes mellitus is a serious chronic metabolic disorder that impacts greatly on the health, quality of life, and life expectancy of patients.[1] Pharmacotherapeutic interventions are expensive and often associated with adverse effects,[2] hence the need for alternative treatment modalities. The poor quality of life in developing countries, coupled with the huge economic burden associated with the cost of care, adverse effects of the drugs, and the high disease morbidity and mortality rate, make it imperative to keep searching for alternative interventions. The increasing use of complementary and alternative medicine (CAM) has arisen as one such intervention.[3]

Momordica charantia (MC) is one of the plants commonly used in traditional medicine for its known glucose-lowering effects.[4–10] It grows as a climber plant and belongs to the family Cucurbitaceae. Also known as bitter melon, balsam pear, or karela, it is widely cultivated in Africa, Asia, and South America both as food and for medicinal use.[11] Previously used methods of preparation of the vegetable include injectable extracts, juice extracts, and fried melon pieces.[6,7,12] The parts commonly used include the whole plant, fruit, and seeds, which are bitter due to the presence of the chemical momordicin.[13] The hypoglycaemic effect of unripe fruit juice has been reported in experimental animal models,[12] as well as in human clinical trials.[14] Active components of the fruit include charantin, vicine and polypeptide P, and an unidentified insulin-like polypeptide similar in structure to bovine insulin.[8] There is increasing use of MC in healthy people, in whom its glycaemic effects are not known.

It is established knowledge that many of the conventional drugs in current use were originally derived from medicinal plants. An example is metformin, an effective glucose-lowering drug developed from *Galega officinalis*.[15] *Momordica charantia* is widely used as food and medicine by both diabetic and healthy people. It has glucose-lowering effects in diabetic subjects[16] but its effects on healthy subjects have yet to be elucidated. The present study therefore aimed to investigate the effect of MC on the glucose profile in healthy subjects using an animal model.

Materials and methods

Study animals

Fourteen (14), 6-month-old, non-gravid healthy female Sprague–Dawley rats weighing between 200 and 250 g

were used. The animals were housed in polyacrylic cages in the animal house of the Department of Medical Physiology, University of Nairobi. A 12-hour light/dark cycle was maintained and the animals were fed on commercial pellets from a local supplier (Unga Feeds (K), Ltd). Water was provided *ad libitum*. The rats were randomly assigned to control and experimental groups of seven animals each and allowed a 15-day acclimatisation period.[17] Baseline blood glucose and body weight measurements were taken on the first day of the experiment following the acclimatisation period. Once daily, *Momordica charantia* fruit juice extract (10 mL/kg body weight)[10] was administered orally to the experimental group while an equal dose of normal saline was given to the control group for a period of 28 days.[18] All the animals were bled on days 0, 7, 14, 21 and 28 by sequential incision of the tip of the tail.[19] A commercially available glucometer (On Call® Plus, Acon Industries, Inc. 4108, San Diego, USA) was used to measure blood glucose (BG) levels.

Preparation of the extract

Fresh unripe MC fruits obtained from the local market were identified by the Herbarium of the University of Nairobi. The fruits were thoroughly washed under running water, weighed and the seeds removed.[10] Thereafter, the remaining part of the fruit was shredded into small pieces and squeezed using a domestic juice extractor. The resulting crude juice extract was administered to the animals using an oral gavage. Any leftover juice was stored in the refrigerator at 4°C for a maximum of 2 days.

Intraperitoneal glucose tolerance test (IPGTT)

At the end of the 28-day experiment, all the rats were fasted overnight (12 hours) and an IPGTT performed.[20] The experimental and control groups were fed orally with the extract and normal saline, respectively. The rats were then injected intraperitoneally with 2.0 g/kg glucose, 45 minutes after MC administration.[20] Blood samples were collected at 30-min intervals for 3 hours for glucose measurement.

Ethical considerations

The study protocol was approved by the Postgraduate Research Committee, Department of Medical Physiology, University of Nairobi. Animals were handled in accordance with the guidelines of the US National Research Council (1996) for the Care and Use of Laboratory Animals.[21]

Data and statistical analysis

Data were expressed as mean ± standard error of the mean (SEM). Student's t-test was employed to test statistical significance using SPSS version 16.0. Significance levels were set at $p<0.05$.

Results

Effect of *Momordica charantia* on glucose levels

Baseline BG levels were 3.2±0.2 and 3.2±0.1 mmol/L in the experimental (EXP) and normal control (CONT) groups respectively (see Table 1). However, after oral administration of MC juice extract for 28 consecutive days, the BG levels decreased in the EXP group (3.2±0.2 vs. 2.9±0.1 mmol/L, $p<0.05$) (see Table 1 and Figure 1). In both groups, the BG levels remained above 2.6 mmol/L – the lower glucose limit of normal rats.[22] In the CONT group, the BG levels oscillated between 3.1±0.1 mmol/L

Figure 1 Comparison of blood glucose levels in experimental (EXP) and control (CONT) groups after administration of Momordica charantia *(error bars represent ± SEM)*

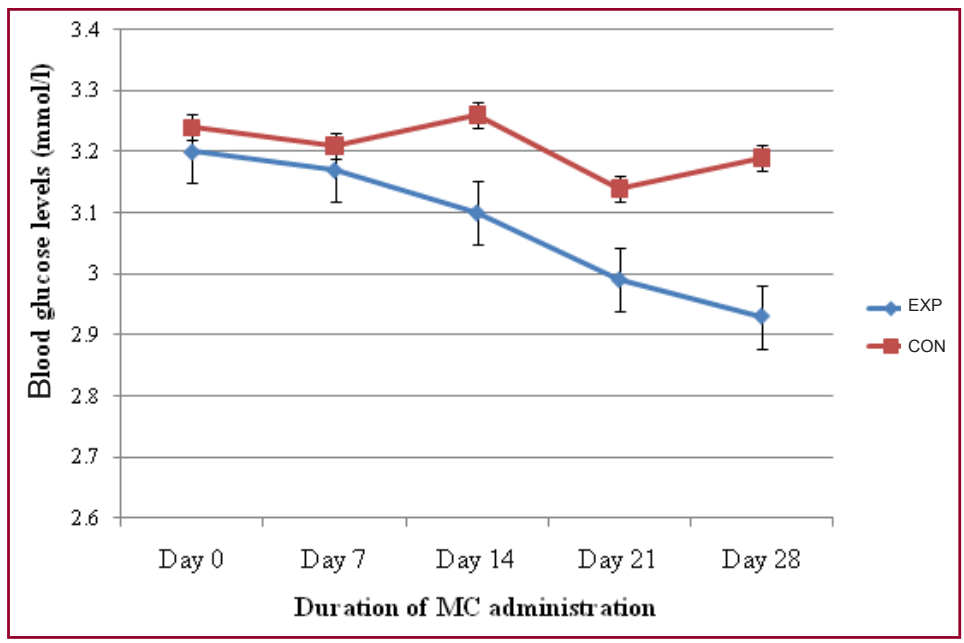

Table 1: Mean blood glucose levels and percentage change after administration of Momordica charantia

Time (day)	0	7	14	21	28
EXP (mmol/L)	3.20±0.18	3.17±0.12	3.10±0.14	2.99±0.15	2.93±0.12
EXP glucose change (%)	0.0	-0.94	-2.21	-3.55	-2.01
CONT (mmol/L)	3.24±0.07	3.21±0.05	3.26±0.06	3.14±0.05	3.19±0.03
CONT glucose change (%)	0.0	-0.93	1.56	-3.68	1.59

EXP = experimental and CONT = control groups
Values expressed as mean±SEM. p=NS. CONT v EXP in all days.

and 3.3±0.1 mmol/L (see Table 1 and Figure 1). The glucose–time curve remained consistently on a downward trend in the test group with clear separation beginning to appear at day 14 of extract administration.

Effect of IPGTT on blood glucose levels

Before the IPGTT, there were no significant differences in the baseline glucose levels between the EXP and CONT groups (4.2±0.2 in CONT vs 4.3±0.4 in EXP, (see Table 2). At a dose of 10 mL/kg of MC followed by 2 g/kg intraperitoneal glucose injection, the BG level in the EXP group increased by 84% to 7.9±0.9 mmol/L at 30 min. Thereafter, it decreased by 30% at 60 min and 10% at 90 min (see Table 2 and Figure 2). Under similar conditions the CONT group (on 10 ml/kg normal saline) had an initial sharp increase of 142% in glucose level to 10.3±0.8 mmol/L at 30 min, which progressively decreased by 30% at 60 min and 16% at 90 min. In the EXP group, which received MC, the initial glucose level at 30 min increased gradually and by a smaller margin, compared with the CONT group (7.9±0.9 vs 10.3±0.8 mmol/L, p=NS). Thereafter the BG level remained significantly lower in the EXP group at 60 min (5.6±0.6 vs 7.2±0.5 mmol/L, p=0.08) and at 90 min (5.0±0.6 vs 6.0±0.3 mmol/L, p<0.05), respectively. Overall, the glucose levels remained lower (but not significantly so) in the EXP group compared with the CONT group after 180 min (3.8±0.4 vs. 3.2±0.4 mmol/L, p=NS). The decline in glucose levels was also more gradual in the EXP group compared with the controls (see Figure 2). Overall difference in the mean glucose levels during IPGTT was significantly lower in the EXP group (4.8±0.2 vs 5.9±0.3 mmol/L, p<0.01).

Discussion

Diabetes prevalence globally is projected at 6.4% in 2010 and 7.7% by 2030.[23] Development of diabetes results from environmental factors acting on genetically predisposed individuals.[24,25] Unlike the latter, environmental factors can be modified in order to prevent the condition.

Complementary and alternative medicine (CAM) has been employed where conventional drugs are not available or in order to mitigate their adverse effects.[3] *Momordica charantia* is one of the plants commonly used in traditional medicine for its known glucose-lowering effects.[4–10] The plant is also used as a source of food and its consumption as a health product is increasing among healthy people. It is therefore imperative to investigate the potential glycaemic effects in these individuals.

The present study used an animal model to investigate the glucose profile in MC-treated rats. There was a significant decrease in the BG level in the MC-treated healthy animals as early as 2 weeks after the start of administration. This is consistent with other studies.[26,27] In addition, the glucose–time curve in the experimental rats fell gradually and consistently over the 28-day period, unlike in the healthy controls, where it remained more or less unaltered. The BG levels in both groups remained within the normal range, thus emphasising the role of MC in modulating the BG. Although the mechanism of MC action has previously been postulated,[6,28,29] contra-regulatory hormones such as glucagon may have prevented hypoglycaemia in the experimental group. Insofar as these results can be extrapolated to healthy persons, the MC

Figure 2: Effect of Momordica charantia *on the intraperitoneal glucose tolerance test (IPGTT) in healthy rats (error bars represent ±SEM; p<0.05)*

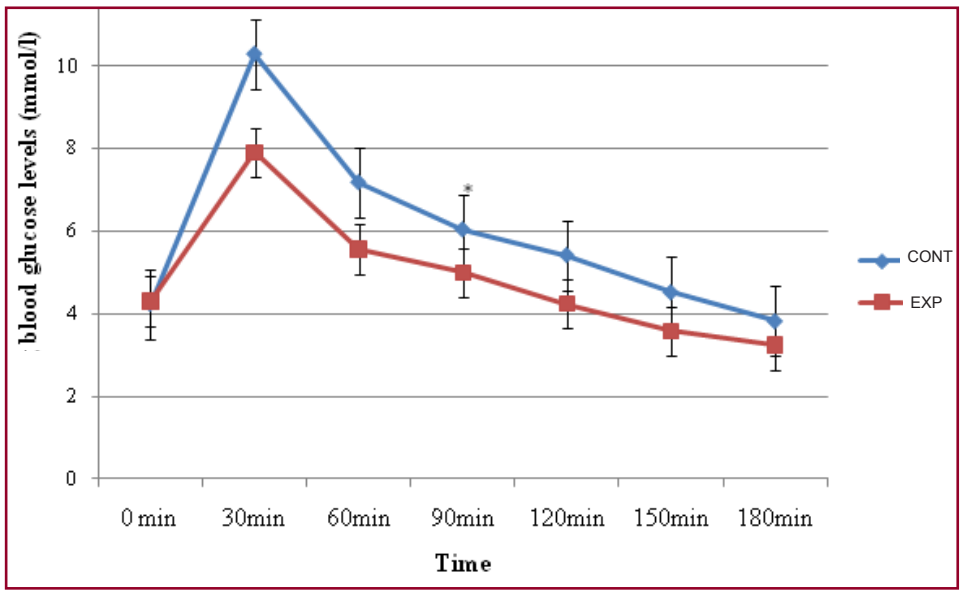

Table 2 Mean blood glucose level and percentage change during intraperitoneal glucose tolerance test (IPGTT) in healthy rats

Time (min)	0	30	60	90*	120	150	180
CONT (mmol/L)	4.24±0.23	10.28±0.79	7.18±0.51	6.04±0.34	5.42±0.27	4.52±0.22	3.82±0.14
CONT % glucose change	0.00	142.45	-30.16	-15.88	-10.26	-16.61	-15.49
EXP (mmol/L)	4.30±0.45	7.90±0.95	5.56±0.65	5.00±0.56	4.24±0.50	3.58±0.40	3.24±0.37
EXP % glucose change	0.00	83.72	-29.62	-10.07	-15.20	-15.57	-9.50

EXP = experimental and CONT = control groups.
Results expressed as means±SEM. p<0.05, CONT vs EXP.

extract consumed regularly and over a period of time, may prove useful in the prevention and/or treatment of type 2 diabetes.

In the present study, the IPGTT peak glucose levels were achieved within 30 minutes, indicating that peak glucose levels may be missed by the procedure. Thus, standardisation of the glucose tolerance curve needs to be performed for each individual species. A significant effect of MC on intraperitoneal glucose tolerance was noted. During IPGTT, the margin of glucose increase to the peak was smaller in the experimental animals compared with the controls. In addition, both the rise to the peak and the decline back to baseline were more gradual in the experimental group than in controls. Accordingly, these findings emphasise the potential role of MC in modulating glucose levels even in healthy subjects.

It is evident that MC helps the clearance of glucose from the circulation,[9] although the mode of action remains unknown. Leatherdale and colleagues (1981) showed that MC juice increased both glucose uptake by tissues *in vitro* and glycogen storage.[6] The juice can also stimulate insulin secretion by isolated beta-cells of the islets of Langerhans.[6] Further, it is postulated that MC leads to multiplication of beta-cells hence increasing insulin levels and permitting recovery of partially destroyed beta-cells or preventing their death.[28] Shubhashish et al, however, argued that MC lowers plasma glucose level partly by stimulation of glycogen synthesis in the liver and it is unlikely that it acts as an insulin secretagogue.[29] It can be concluded however that MC probably works via several mechanisms and pathways, and no single mechanism of action has so far been determined.

In the current study, MC reduced glucose levels in healthy rats. Thus, it does not seem to work solely through renewal of damaged beta-cells. The young experimental animals were healthy and presumed to have intact beta-cells. Previous studies on the effects of MC on blood glucose levels in both type 1[4] and type 2 diabetes[6,7] support the evidence that it acts via several mechanisms. Thus it is plausible that MC has a potential role in increasing secretion of insulin as expected in its action in type 1 diabetes. Moreover, in type 2 diabetes, MC enhances the peripheral utilisation of glucose or its conversion to glycogen for storage in the liver. *Momordica charantia* probably works in both healthy and diabetic animals to convert glucose to glycogen for storage in the liver as well as to increase its peripheral utilisation, both of which could result in the observed glucose-lowering effect.

Momordica charantia contains chemicals that have clinically demonstrated glucose-lowering properties or other actions of potential glucose-lowering benefit. These chemicals include a mixture of steroidal saponins known as charantins, insulin-like peptides, and alkaloids.[30] The glycaemic effect is more pronounced in the fruit, where these chemicals are found in abundance.[6]

Although some of the glucose-lowering data seen in the present study are similar to previous studies,[4–10] there were important differences. The use of healthy rats was essential to elucidate the role of MC in the management of glucose levels in health. In addition, the IPGTT was performed and confirmed clearly the role of MC in lowering glucose levels. In spite of the numerous published data available on MC, there is insufficient information on its effects in females. Female rats were used in the present study, which showed similar results to previous studies in male rats. Previous studies suggest that MC induces abortion in female rats.[31] It is, however, important to design studies with greater statistical power to elucidate the benefits of MC in preventing or treating gestational diabetes.

A considerable amount of financial resources are spent on anti-diabetic drugs and the overall management of diabetes.[32] A more simplified approach with the introduction of MC and other alternative complementary therapies may be cost effective, besides alleviating the adverse effects of conventional drugs. A limitation of the present study was the lack of proper standardization of the dose of the active ingredients, since only the volume could be kept constant. Human trials and comparison of efficacy and safety of MC with known hypoglycaemic drugs are recommended.

Acknowledgements

We wish to thank Charles Kinyungu, Charles Nzivo, Dennis Rono, Gertrude Shikote, and Jackson Mugweru for their technical assistance. The authors funded the study.

References

1. Hogan P, Dall T, Nikolov P. Economic costs of diabetes in the U.S. in 2002. *Diabetes Care* 2003; 26: 917–32.
2. Lebovitz HE. Rationale for and role of thiazolidinediones in type 2 diabetes mellitus. *Amer J Cardiol* 2002; 5; 90: 34G–41G.
3. Su D, Li L. Trends in the use of complementary and alternative medicine in the United States: 2002-2007. *J Health Care Poor Underserved*. 2011; 22: 296–310.
4. Baldwa VS, Bhandari CM, Pangaria A, Goyal RK. Clinical trial in patients with diabetes mellitus of an insulin-like compound obtained from plant sources. *Uppsala J Med Sci* 1977; 82: 39–41.
5. Akhtar MS, Athar MA, Yaqub M. Effect of *Momordica charantia* on blood glucose level of normal and alloxan-diabetic rabbits. *Planta Med* 1981; 42: 205–12.
6. Leatherdale BA, Panesar RK, Singh G, et al. Improvement in glucose tolerance due to *Momordica charantia* (karela). *Brit Med J* 1981; 282: 1823–4.
7. Shane-McWhorter L. Biological complementary therapies: a focus on botanical products in diabetes. *Diabetes Spectrum* 2001; 14: 199–208.
8. Lucy D, Anoja SA, Chu-Su Y. Alternative therapies for Type 2 diabetes. *Alternative Med Rev* 2002; 7: 45–58.
9. Chaturvedi P, George S, Milinganyo M, Tripathi YB. Effect of *Momordica charantia* on lipid profile and oral glucose tolerance in diabetic rats. *Phytotherapy Res* 2004; 18: 954–6.
10. Sridhar MG, Vinayagamoorthi R, Suyambunathan VA, et al. Bitter gourd (*Momordica charantia*) improves insulin sensitivity by increasing skeletal muscle insulin-stimulated IRS-1 tyrosine phosphorylation in high-fat-fed rats. *Brit J Nutr* 2008; 99: 806–12.
11. Ooi CP, Yassin Z, Hamid TA. *Momordica charantia* for type 2 diabetes mellitus. *Cochrane Database Syst Review* 2010; 17: CD007845.
12. Welihinda J, Karunanayake EH, Sheriff MH, Jayasinghe KS. Effect of *Momordica charantia* on the glucose tolerance in maturity onset diabetes. *JEthnopharmacol* 1986; 17: 277–82.
13. Beloin N, Gbeassor M, Akpagana K, et al. Ethnomedicinal uses of *Momordica charantia* (Cucurbitaceae) in Togo and relation to its phytochemistry and biological activity. *J Ethnopharmacol* 2005; 496: 49–55

14. Srivastava Y, Venkatakrishna BH, Verma Y, et al. Antidiabetic and adaptogenic properties of *Momordica charantia* extract. An experimental and clinical evaluation. *Phytotherapy Res* 1993; 7: 285–9.
15. Bailey CJ, Day C. Traditional plant medicines as treatments for diabetes. *Diabetes Care* 1989; 12: 553-564.
16. Leung L, Birtwhistle R, Kotecha J, et al. Anti-diabetic and hypoglycaemic effects of *Momordica charantia* (bitter melon): a mini review. *Brit J Nutr* 2009; 102: 1703–8.
17. Obernier JA, Baldwin RL. Establishing an appropriate period of acclimatization following transportation of laboratory animals. *ILAR J* 2006; 47: 364–9.
18. Eichenbaum G, Damsch S, Looszova A, et al. Impact of gavage dosing procedure and gastric content on adverse respiratory effects and mortality in rat toxicity studies. *J Appl Toxicol* 2011; 31: 342–54.
19. Fluttert M, Dalm S, Oitzl MS. A refined method for sequential blood sampling by tail incision in rats. *Laboratory Animals* 2000; 34: 372–8.
20. Jae-Jeong L, Ho-Young Y, Jae-Won Y, et al. Characterization of streptozotocin-induced diabetic rats and pharmacodynamics of insulin formulations. *Biosci Biotech & Biochem* 2003; 67: 2396–401.
21. *Guide for the Care and Use of Laboratory Animals*. Institute of Laboratory Animal Resources, Commission on Life Sciences, National Research Council. National Academy Press, Washington DC, 1996.
22. Wang Z, Yang Y, Xiang X, et al. Estimation of the normal range of blood glucose in rats. *Wei Sheng Yan Jiu* 2010; 39: 133–7, 142.
23. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabet Res & Clin Pract* 2010; 87: 4–14.
24. Tattersall R, Pyke D. Diabetes in identical twins. *Lancet* 1972; 300: 1120–5.
25. Rotter J, Rimoin D. Heterogeneity in diabetes mellitus. *Diabetes* 1978; 27: 599–608.
26. Kar A, Choudhary BK, Bandyopadhyay NG. Comparative evaluation of hypoglycaemic activity of some Indian medicinal plants in alloxan diabetic rats. *J Ethnopharmacol* 2003; 84: 105–8.
27. Reyes BAS, Bautista ND, Tanquilut NC, et al. Anti-diabetic potentials of *Momordica charantia* and *Andrographis paniculata* and their effects on estrous cyclicity of alloxan-induced diabetic rats. *J Ethnopharmacol* 2006; 105: 196–200.
28. Ahmed I, Adeghate E, Sharma AK, et al. Effects of *Momordica charantia* fruit juice on islet morphology in the pancreas of the streptozotocin-diabetic rat. *Diabet Res & Clin Pract* 1998; 40: 145–151.
29. Shubhashish S, Pranava M, Rosalind MA. Demonstration of the hypoglycemic action of *Momordica charantia* in a validated animal model of diabetes. *Pharmacol Res* 1996; 33: 1–4.
30. Ananya P, Sarmistha SR. Medicinal uses and molecular identification of two *Momordica charantia* varieties – a review. *Electron J Biol* 2010; 6: 43–51.
31. Seham A, Souad E, Osama A. Some toxicological studies of Momordica charantia L. on albino rats in normal and alloxan diabetic rats. *J Ethnopharmacol* 2006; 108: 236–42.
32. Wild S, Roglic G, Green A, et al. Global prevalence of diabetes: Estimates for the year 2000 and projections for 2030. *Diabetes Care* 2004; 27: 1047–53.