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Antidiabetic Potential Of An Insulin-Like Molecule From The Seeds Of *Momordica Charantia* Linn. In Experimental Diabetes

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Abstract
Background: *The current study evaluates antidiabetic potential of a novel hypoglycemic active principle (insulin-like molecule) MCK_3P_8 obtained from a fraction of the ethanolic extract MCK_3 from the seeds of Momordica charantia Linn in experimental diabetes. Since time immemorial Momordica charantia, commonly known as "Karella" (family: Cucurbitaceae), has been known for its antidiabetic potential. It is one of the most common plants for the treatment of diabetes mellitus and its late complications. Momordica charantia whole fruit, fruit pulp, flower, leaves and the seeds are reported for having hypoglycemic activity in diabetic animals. The seeds are the most prevalent part of the plant used medicinally, as it contains steroidal saponins, vicin and other active hypoglycemic principle(s).*
Materials and Methods: *A hypoglycemic active principle (MCK_3P_8) obtained from a fraction of the acid-ethanolic fraction MCK_3 of the seed extract of Momordica charantia seeds (14 ml containing 196 mg of proteins) by gel fitration CC. This hypoglycemic active principle and the Protamine Zinc Insulin were given by intraperitonial injection to alloxan-induced male wistar diabetic rats at a dose of 15 mg/kg body weight of experimental animals. Hypoglycemic activities studied in control, insulin, MCK_3, MCK_3P_8 and Proteinase-K treated alloxan-induced diabetic rat by measuring the blood glucose level enzymatically by drawing blood from the tail vein during the study period.*
Results: *The present study reports purification of a novel hypoglycemic active principle MCK_3P_8 (insulin-like molecule) from Momordica charantia seeds. The insulin-like molecule was able bring down the blood glucose level significantly ($P<0.001$) by 3 hours after administration. The hypoglycemic activity brought about by MCK_3P_8 was comparable to that observed with insulin treatment of the diabetic rats. Loss of hypoglycemic activity of MCK_3P_8 upon proteinase-K treatment indicates the proteinceous nature of the hypoglycemic insulin-like molecule.*
Conclusion: *Based on the results of this study, we conclude that MCK_3P_8 the hypoglycemic active principle (insulin-like molecule) of Momordica charantia Linn. seeds when given intraperitoneally at a dose of 15 mg/kg b.wt. possesses significant hypoglycemic activity in experimental diabetes, and it is proteinaceous in nature. MCK_3P_8 the insulin-like molecule (a novel hypoglycemic active principle) may find application in treatment of diabetes mellitus without evident toxic effects.*
Key Word: *Momordica charantia, Antidiabetic potential, Insulin-like molecule, Experimental diabetes.*

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I. Introduction

Ayurveda and other traditional system of medicine for the treatment of diabetes describe numerous plants used as herbal medicines. Because of low side effects and low cost they play an important role as an alternative drug. The alternative complementary medicinal system is now gaining momentum with the knowledge of active principles identified from plant and plant extracts as an alternative to mainstream western medical treatment. Since ancient times *Momordica charantia* Linn. Commonly known as "Karella" in Hindi, Bittergourd / Bittermelon / Balsam pear in English has drawn considerable attention from scientists as a monoherbal medicine for the treatment of diabetes mellitus. *Momordica charantia* is one of the most used plants used in traditional medicine for the treatment of diabetes and some of its late complex abnormalities including hepatotoxicity, nephropathy, neuropathy, electrolytic imbalance and retinopathy etc. Bittergourd whole fruit, fruit pulp, seeds in diabetes mellitus [1-5], roots as an abortifacient [6] and the leaves for hypoglycemic activity in diabetic animals [7]. The presence of hypoglycemic principle(s) in its fruits and seeds capable of eliciting hypoglycemia in experimental animals as well as diabetic patients are known. However, medicines made from the seeds showed maximum hypoglycemic response. Previously isolated constituents

from *Momordica charantia* include sterols, charantin, momordicine [8-10], cardenolides [11], and polypeptide-P [12].

II. Material And Methods

Plant Material: *Momordica charantia* Linn. (Cucurbitaceae), seeds purchased from sales counter of Indian Agriculture Research Institute (IARI), Pusa road, New Delhi in August 2010, in large quantity to maintain the consistency of the stock for extract preparation and were authenticated by the Taxonomist of the University Department of Botany, Aryabhatt Knowledge University, Bihar, India. A voucher specimen is deposited in the Department of Biochemistry, Shyamlal Chandrasekhar Medical College, Khagaria-851205, Bihar, India.

Chemical: All the chemicals were of analytical grade and were procured from Sigma Aldrich Chemical Co., USA or Boehringer Mannhiem, Germany, unless otherwise stated. Protamine Zinc Insulin was procured from Boots Pharmaceuticals Ltd India.

Animal: Randomly bred male wistar rats, 175-200 g (12-14 weeks), were housed in standard laboratory conditions, in the small animal facility of Department of Biochemistry of the Patna University, Patna. The animals were provided with rat feed (Hindustan Liver Ltd, India) and water ad libitum.

Induction of Diabetes: The male wistar rats were made diabetic by using alloxan. Briefly, alloxan was administered i.p. after starving the animals for 36 hrs. at a dose of 150 mg/kg b.wt. Animals were stabilized for 3 days by insulin administration, 1-2 units per day for 2 days. Only those animals having blood glucose level more than 300 mg/100 ml. blood were selected for further analysis.

Tested Material: In the present study, *Momordica charantia* seeds were used for the consistency of the stock for extract preparation in order to identify the hypoglycemic principle(s). From decorticated seeds, fraction MCK_3 was obtained from ice cold ethanol extract (75% C_2H_5OH 1 mM PMSF. 0.2 N HCI), centrifuged and concentrated in speed vac at 4^0C. The supernatant was neutralized with $(NH_4)_2CO_3$ to pH 7.2 and centrifuged with liquid ammonia. The supernatant, fraction MCK_3 was further subjected to differential precipitation with $(NH_4)_2SO_4$ containing 0.25% TCA which resulted in precipitation of all protein. The hypoglycemic $MCK3P_8$ was obtained from the fraction MCK_3 (14 ml containing 196 mg of proteins) by gel filtration CC with Sephacryl S100 eluting with 0.2 M NH_4HCO_3 (pH 7.2-7.4). Bioactivity of the fractions was measured at each step of purification.

Statistical Analysis: All the results were analyzed statistically using student's paired t-test for paired data of different levels of significance. All the results were expressed as mean ± S.E. P values less than 0.05 were considered significant. N represents number of experimental animals.

Ethical clearance: The use of animals was duly approved by the Institutional Animal Ethics Committee of the Aryabhatt Knowledge University (AKU), Bihar, India and the guidelines prescribed by the Institutional Animal Ethics Committee, AKU, were followed while handling animals.

III. Results

The present study reports purification of an insulin-like hypoglycemic active principle from *(Momordica charantia)* seeds. Hypoglycemic activities studied in control, insulin, fraction MCK_3, MCK_3P_8, Proteinase-K plus MCK_3P_8 treated alloxan-induced diabetic rat by measuring the blood glucose level enzymatically [13] by drawing blood from the tale vein during the study period. The hypoglycemic active principle MCK_3P8 given by intraperitoneal injection to alloxan- induced diabetic rats at a dose of 15 mg/kg b.wt. showed significant hypoglycemic activity. Results are reported in Table 1.

Table 1: Hypoglycemic activity of fraction MCK_3, insulin-like hypoglycemic active principle MCK_3P_8 and Proteinase-K treated MCK_3P_8 of *Momordica charantia* seeds

Treatment i.p	Blood glucose level (mg/dl)	
	0 hour	3 hours
Normal control + saline (0.5 ml)	90 ± 10.0	85 ± 9.1
Control Diabetic+ saline (0.5 ml)	347 ± 44.92	355.4 ± 28.20
Diabetic insulin (5U / kg b. wt)	351 ± 18.0	205 ± 16.0[a]
Diabetic fraction MCK_3 (15mg / kg b.wt)	399.70 ± 38.50	344.76 ± 43.88
Diabetic MCK_3P_8 (15 mg / kg b.wt)	385.04 ± 47.86	252.90 ± 20.24[a]
Diabetic Proteinase-K treated MCK_3P_8	414.3 ± 92.4	378.16 ± 46.95

Values are mean ± S .E, N (number of experimental animals) = 5

[a] P 0.001 (Student's t-test) vs control diabetic +saline (0.5 ml).

IV. Discussion

Far from being a mere pointer of affluence and physical inactivity until recent past, diabetes of late, has been growing steadily on prevalence scale among all sections of society as the world's largest endocrine disease resulting in post-prandial and fasting hyperglycemia and hyper-insulinemia [14-15]. Control of hyperglycemia is the main aim in the management of diabetes mellitus which is usually achieved by dietary modifications, oral hypoglycemic agents and insulin therapy. Oral hypoglycemic agents, the insulin secretogogues, though in frequent use, have their own limitations and have also certain undesirable side effects [16]. Insulin, on the other hand, in spite of highest purity grade available, is not thought to be ideal therapy by subcutaneous administration (subcutaneous insulin absorption is normally too slow to mimic the normal rapid increments of insulin in blood in response to nutrient intake). Moreover, insulin therapy carries a positive risk of certain undesirable side effects. Therefore, newer and better approaches for treatment of diabetes were urgently sought. Plants have long been a source of traditional anti-diabetic medicines. The evaluation of medicinal plants, herbs and especially, of their active principle(s) is a logical way of searching for new drugs to treat this disease. A recent study has estimated that up to 30% of pateints with diabetes mellitus use complementary and alternative medicine. [17]. *Momordica charantia* (MC) has been used in indigenous and modern system of medicine since long. Some phytochemical studies have revealed that this fruit-vegetable is sufficiently rich in proteins [18]. It is believed that both fruits and seeds of MC contain hypoglycemic components that may include alkaloid, orally active insulin-like or insulinomimetic compound(s) [19]. In the present study a novel insulin-like hypoglycemic active principle MCK_3P_8 was purified from a fraction MCK_3 obtained from the ethanolic seeds extract of *Momordica charantia* Linn. MCK_3P_8 was able to bring down the blood glucose level significantly by 3 hours after administration in alloxan-induced diabetic rats. The hypoglycemic activity brought about by MCK_3P_8 was comparable to that observed with insulin treatment of the diabetic rats. Upon proteinase-K treatment the hypoglycemic activity of the insulin-like molecule was found to be lost that indicates that MCK_3P_8 is proteinceous in nature.

V. Conclusion

Based on the results of this study, we conclude that a novel hypoglycemic active principle MCK_3P_8 (insulin-like molecule) obtained from *Momordica charantia* seeds when given intraperitoneally at a dose 15mg/kg b.wt. brings about significant hypoglycemic activity in alloxan-induced diabetic rats by 3 hours after administration. Loss of hypoglycemic activity of MCK_3P_8 upon proteinase-K treatment indicates its proteinceous nature. The insulin-like novel hypoglycemic active principle may find application in treatment of diabetes mellitus without evident toxic effects.

Conflict of interests

There are no conflicts of interest pertaining to the publishing of this research, according to the authors.

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