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ANTIDIABETIC EFFECT OF BITTER MELON/KERALA (*Momordica charantia)* IN ALLOXAN INDUCED DIABETIC RAT

Rupaly Akhter[1*], Imrul Hasan Rasel[2] and Mohammad Saiful Islam[3]

[1]Department of Pharmacology and Toxicology, [2]Adjunct Faculty, and [3]Department of Anatomy, Histology and Physiology, Faculty of Animal Science and Veterinary Medicine, Sher-e-Bangla Agricultural University, Dhaka-1207, Bangladesh.

***Corresponding author:** Rupaly Akhter; E-mail: rupaly_akhter@yahoo.com

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ABSTRACT

This study aims at investigating the effect of *Momordica charantia* extract on glucose tolerance and some biochemical parameters in alloxan induced diabetes rat. A total of 150 rats (50 normal rats and 100 alloxan induced diabetic rats) were used for five trials. The rats were divided into three groups for each trial, each containing 10 individuals as follows: Group A: is the control group, Group B as diabetic control group and group C were diabetic rat received bitter melon (*Momordica charantia*). Then alloxan injection was injected at a dose rate of 150 mg/kg body weight through intra-peritoneal route to each rat to induce diabetes in groups B and C. Aqueous extract of bitter melon (*Momordica charantia*) were fed by gavage at a dose of 300 mg/kg body weight daily for 21 days in group C. On 15th day blood glucose level and the body weights, biochemical parameters were measured for the first time to ensure diabetic induction. Then all the rats of this group were kept for more 21 days for the treatment of diabetic condition. Alloxan produced a significant increase in serum glucose, triglyceride (TG), total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), Alanine aminotransaminase (ALT) and Aspartate aminotransaminase (AST) and significant decrease in body weight and high density lipoprotein cholesterol (HDLC). Bitter melon treatment reduced non-fasting and fasting glucose level ($p<0.05$). In addition, administration of bitter melon juice was associated with a reduction in the serum levels of Alanine aminotransaminase (ALT) and Aspartate aminotransaminase (AST), Triglyceride (TG), Total Cholesterol (TC) and Low Density Lipoprotein Cholesterol (LDL-C) when compared with positive diabetic control ($p<0.05$). High density lipoprotein cholesterol (HDLC) and body weight level significantly increased in bitter melon treated group C compare to Group B ($p<0.05$).

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INTRODUCTION

Diabetes mellitus is the most common endocrine disease in human. It is considered as one of the five leading causes of death in the world (Joseph et al. 2011). It can be hereditary and environmental which leads to metabolic abnormalities mainly characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both. Being a major degenerative disease, diabetes is found all over the world and it is becoming the third most lethal disease of mankind and increasing rapidly (Ogbonnia et al. 2008). *Momordica charantia* (*M. charantia*), also known as bitter melon, Kerala, Balsam Pear, or Bitter gourd, is a popular plant used for the treating of diabetes-related conditions amongst the indigenous populations of Asia, South America, India, the Caribbean and East Africa (Cousens, 2008). Bitter melon is traditionally known for its medicinal properties such as antidiabetic, anticancer, anti-inflammation, antivirus, and cholesterol lowering effects. It contains many phenolic compounds that may have the potential as antioxidant and antimutagen (Budrat et al. 2008). The fruit, stems, leaves and roots of bitter melon have all been used in traditional medicine to help treat ailments such as hyperlipidemia, digestive disorders, microbial infections and menstrual problems (Yibchok-Anun et al. 2006). Bitter melon is a powerful nutrient-dense plant composed of a complex array of beneficial compounds. Pharmacologically these include bioactive chemicals, vitamins, minerals and antioxidants which all contribute to its remarkable versatility in treating a wide range of illnesses. The fruits contain high amounts of vitamin C, vitamin A, vitamin E, vitamins B1, B2 and B3, as well as vitamin B9 (folate). The caloric values for leaf, fruit and seed were 213.26, 241.66 and 176.61 Kcal/100 g respectively (Bakare et al 2010).The fruit is also rich in minerals including potassium, calcium, zinc, magnesium, phosphorus and iron, and is a good source of dietary fiber (bitter melon “monograph”, 2008). Medicinal value of bitter melon has been attributed to its high antioxidant properties due in part to phenols, flavonoids, isoflavones, terpenes, anthroquinones, and glucosinolates, all of which confer a bitter taste (Snee et al. 2011). The main constituents of bitter melon which are responsible for the antidiabetic effects are triterpene, proteid, steroid, alkaloid, inorganic, lipid, and phenolic compounds (Budrat et al. 2008). Several glycosides have been isolated from the *M. charantia* stem and fruit and are grouped under the genera of cucurbitane-type triterpenoids particularly four triterpenoids have AMP-activated protein kinase activity which is a plausible hypoglycaemic mechanism of *M. charantia* (Tan et al. 2008). *M. charantia* fruits consist of glycosides, saponins, alkaloids, reducing sugars, resins, phenolic constituents, fixed oil and free acids (Liu et al. 2009).

Polypeptide-p or p-insulin is an insulin-like hypoglycemic protein, shown to lower blood glucose levels in gerbils, langurs and humans when injected subcutaneously (Tayyab et al. 2012). The p-insulin works by mimicking the action of human insulin in the body and thus may be used as plant-based insulin replacement in patients with Type-1 diabetes (Paul et al. 2010). The oral intake of the extract from bitter melon seeds does produce hypoglycemic effects in streptozotocin (STZ) induced type-1 diabetic rats (Wehash et al. 2012). This indicates that compounds in bitter melon seeds other than p-insulin may also be effective in the treatment of Type-1 diabetes. The objective of the present work was to evaluate the efficacy of bitter melon on lipid profile (total cholesterol, triglyceride, HDLC, LDLC), blood glucose, biochemical parameters (ALT, AST), and body weight in experimentally diabetes induced rats.

MATERIALS AND METHODS

Collection and acclimatization of rats

Total two hundred rats, long Evan’s strain (*Ratus norvegicus*) aged between 3 to 4 months and weighting between 200 to 300g was collected from International Centre of Diarrheal Disease Research, Bangladesh (ICDDR, B) or other places. For five experimental trials, all the rats were grouped into three each containing 50 rats. Each group of rats was housed at serene bottomed wire cages arranged in rows and kept in the animal house of this department. The animals were fed with pellet at a recommended dose of 100 g/kg as advised by ICDDR, B. Drinking water was supplied *ad libitum*. The rats were reared in this condition for a period of three weeks to acclimatize them prior to experimental uses.

Induction of diabetes

To induce diabetes mellitus, alloxan injection was given through intra-peritoneal route and this increased the blood glucose level ($p<0.05$) and at the same time body weight was decreased also. Single dose of alloxan administered intraperitoneally @ 150 mg/kg body weight (Belhekar et. al, 2013). In this experiment, polyuria, polydipsia and polyphagia after 24 hours of alloxan injection, it was observed. Rats with serum glucose level ranging between 150 mg/dl or above considered as hyperglycemic.

In that study, a total of 150 rats (50 normal rats and 100 alloxan induced diabetic rats) were used for five trials. The rats were divided into three groups for each trial, each containing 10 individuals as follows: Group A: is the control group and was fed standard rat chow and pure water, Group B as diabetic control group and group C were diabetic rat received bitter melon (*Momordica charantia*). After 18 hours of starvation, body weights, blood glucose, lipid profile, biochemical parameter were measured after acclimatization of rats. Then alloxan injection was injected at a dose rate of 150 mg/kg body weight through intra-peritoneal route to each rat to induce diabetes in groups B and C. All the groups of rats were reared under normal diet and water *ad libitum* from Day 1-15, on 15th day blood glucose level and the body weights gaining were measured for the first time to ensure diabetic induction. Then all the rats of this group were kept for more 21 days for the treatment of diabetic condition. During that period on Day 0, 7, 14, and 21st the body weight and blood glucose level were measured. Aqueous extract of bitter melon (*Momordica charantia*) fed by gavage at a dose of 300mg/kg body weight daily for 21 days in group C.

Preparation of freeze-dried bitter melon juice

According to the methods of Chen and Li, (2005) unripe bitter melon fresh fruit was cut open and the seeds were removed. The extracted juice from the edible portion was frozen and completely lyophilized by continuous freeze-drying operation for 72hrs. The powder was kept in airtight containers at -70C0 until used.

Biochemical analysis

Serum glucose levels and oral glucose tolerance test were performed according to the method described by Leatherdale et al. (1981), using reagent kits purchased from Bio Merieux Chemicals (France). ALT and AST activity in serum were determined according to the method of Moss DW & Henderson AR. (1996) using reagent kits purchased from Randox Company (United Kingdom). Serum triglycerides concentration was determined according to the method of Nauck et al. (1999), using reagent kits obtained from Reactivos Spinreact (Spain). Serum LDL-cholesterol concentration was determined according to Friendewald et al. (1972).

Statistical analysis

Data were analyzed using Graph Pad Instat software (version 3, ISS-Rome, Italy). Groups of data were compared with ANOVA, followed by Tukey-Kramer (TK) multiple comparisons post-test. Values of $P < 0.05$ were regarded as significant. Data were expressed as mean ± standard error (SEM).

RESULT AND DISCUSSION

Bitter melon is a popular vegetable that is widely grown in tropical areas. Documentation of its pharmacological properties back to the 16th century, although BM was found to possess antiviral, antibacterial, anti-HIV, anticancer, and immunomodulatory properties, attention has been focused on its blood glucose–lowering effect. Such an effect was demonstrated in STZ-induced diabetic, (Ahmed et al. 2004) and diet-induced obese (DIO) rats (Grover and Yadav, 2004). Table 1 show that treatment of diabetic rats with BM induced a significant increase in body weight & decrease in fasting blood glucose levels compare with diabetic untreated group.

Table 1. Effect of BME (bitter melon effect) on studied blood parameters in diabetic rats, compared to normal control (Values are expressed in Mean ± SEM, N= 10 for each group)

Parameter		Normal Control (Group A)	Diabetic Control (Group B)	Diabetic+ Bitter melon(BMD) (Group C)
Avg. Body Weight (g)	Day 0	244±5.24	271±7.18^{a*}	268±8.6
	Day 7	248.3±5.23	270.90±6.69	271.20±8.64
	Day 14	252.5±4.9	268.3±6.74	275.20±7.7
	Day 21	267.7±11..35	263.9±6.61	278±8.3
Fasting Glucose level (mg/dl)	Day 0	95.50±4.85^{c}	189.00±7.4^{a***}	92.55±3.43^{b***}
	Day 7	90.00±4.09^{c}	193.50±7.41^{a***}	95.00±3.63^{b***}
	Day 14	91.00±3.50^{c}	209.50±9.58^{a***}	94.00±4.10^{b***}
	Day 21	93.00±4.09^{c}	255±12.82^{a***}	91.00±3.65^{b***}
Non fasting Glucose level (mg/dl)	Day 0	115.35±2.45^{c}	182±7.9^{a***}	118±2.28^{b***}
	Day 7	120.35±2.45^{c}	194±9.45^{a***}	115±2.5^{b***}
	Day 14	118.8±2.28^{c}	234.50±15.8^{a***}	118.80±2.25^{b***}
	Day 21	117.9±2.53^{c}	388.70±14.03^{a***}	120.5±2.80^{b***}

a***Significantly different from control at P < 0.001, b***Significantly different from DM (Diabetic mellitus) at P < 0.001

Table 2. Effect of BME on studied blood parameters in diabetic rats, compared to normal control (Values are expressed in M±SE, N= 10 for each group)

Parameter		Normal Control (Group A)	Diabetic Control (Group B)	Diabetic+Bitter melon(BMD) (Group C)
Triglyceride (mg/dl)	Day 0	59.50±1.85^{c}	170.50±1.6^{a***}	120.55±2.43^{b***}
	Day 7	60.83±2.09^{c}	172.80±1.41^{a***}	125.00±2.63^{b***}
	Day 14	61.00±2.50^{c}	174.00±1.58^{a***}	128.20±2.10^{b***}
	Day 21	61.50±1.98^{c}	176.8±1.89^{a***}	130.50±2.65^{b***}
Cholesterol (mg/dl)	Day 0	88.50±1.05^{c}	140.00±2.4^{a***}	110.50±1.44^{b***}
	Day 7	89.00±1.23^{c}	141.50±2.01^{a***}	117.00±1.36^{b***}
	Day 14	91.00±1.58^{c}	142.58±1.58^{a***}	118.50±1.15^{b***}
	Day 21	90.00±1.69^{c}	143.05±1.82^{a***}	120.80±1.57^{b***}
HDLC (mg/dl)	Day 0	62.56 ±1.09^{c}	47.58 ±1.96 ^{a***}	59.97 ±0.57^{b***}
	Day 7	64.68 ±1.18^{c}	49.98 ±1.50 ^{a***}	60.85 ±0.76^{b***}
	Day 14	67.76 ±1.26^{c}	50.00 ±1.93^{a***}	61.00 ±0.64^{b***}
	Day 21	69.00 ±0.98^{c}	50.57 ±2.32^{a***}	61.50 ±0.89^{b***}
LDLC (mg/dl)	Day 0	10.50 ±1.88^{c}	63.43 ±1.23^{a***}	52.98 ±3.09^{b***}
	Day 7	11.00 ±1.99^{c}	64.23 ±1.43^{a***}	53.36 ±3.43^{b***}
	Day14	11.38 ±2.08^{c}	65.07 ±1.30^{a***}	54.10 ±2.89^{b***}
	Day 21	11.56 ±2.03^{c}	65.50 ±1.34^{a***}	55.00 ±3.98^{b***}

a***Significantly different from control at P < 0.001, b***Significantly different from DM (Diabetic mellitus) at P < 0.001

Triglycerides, total cholesterol and LDL-C levels were significantly increased, while HDL-C was significantly decreased by induction of diabetes, these figures were significantly ameliorated after BME treatment (Table 2).

Table 3. Effect of BME on studied biochemical parameters in diabetic rats, compared to normal control (Values are expressed in M±SE, N= 10 for each group)

Parameter		Normal Control (Group A)	Diabetic Control (Group B)	Diabetic+Bitter melon(BMD) (Group C)
		Maximum level	Maximum level	Maximum level
ALT (IU/L)	Day 0	35.33±1.21^{c}	53.45±0.60^{a***}	36.75±0.76^{b***}
	Day 7	37.45±1.53^{c}	64.54±0.76^{a***}	35.50±1.06^{b***}
	Day 14	38.50±1.23^{c}	67.68±0.53^{a***}	37.75±0.86^{b***}
	Day 21	36.85±0.95^{c}	69.78±0.85^{a***}	34.35±1.45^{b***}
AST (IU/L)	Day 0	137.00±2.24^{c}	180.25±1.10^{a***}	139.75±1.24^{b***}
	Day 7	135.55±2.50^{c}	210.37±1.45^{a***}	137.83±1.53^{b***}
	Day 14	139.85±2.83^{c}	225.50±1.68^{a***}	136.69±1.87^{b***}
	Day 21	140.95±1.93^{c}	228.86±1.85^{a***}	138.86±1.76^{b***}

This table indicate significant increase in the activity of both transaminases (ALT & AST) in diabetic control group, compare to normal control.

Treatment of diabetic rats with bitter melon induced a significant increase in body weight as compared to diabetic control rats. These results are in agreement with the findings of Fernandes et al. (2007) and Yuan et al. (2008), but disagree with Dans et al. (2007). Regarding serum glucose level (OGTT), treatment of diabetic rats with bitter melon caused significant decreases in fasting and post- prandial serum glucose levels as compared to the diabetic untreated group. These results are in accordance with the findings of Jayasuriyaet al. (2000), Fernandes et al. (2007) Yuan et al. (2008) and Chatuvedi et al. (2004). The present finding disagrees with the finding of Dans et al. (2007) who reported that bitter melon had no significant hypoglycemic effect in alloxan diabetic rats. Regarding liver enzymes, the present study revealed a significant decrease in the activities of both alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in diabetic rats treated with bitter melon as compared to the diabetic untreated group. These findings are in agreement with studies of Garau et al. (2003). Results of Dans et al. (2007) on diabetic rats treated with alloxan showed no effect on serum ALT and AST. The present results elucidated a significant increase of total cholesterol, triglycerides and LDL cholesterol concentrations in the serum of diabetic control rats as compared to normal control group. These results are in agreement with Newairy et al. (2002). On the other hand, HDL-cholesterol level was significantly decreased in serum of diabetic control rats in the present study as compared to the normal control group. This finding parallels that of Nakura et al. (1997), and disagrees with Wasan et al. (1998) who reported a significant increase of HDL-cholesterol in alloxan diabetic rats.

CONCLUSION

In conclusion, the present study calls attention to the therapeutic use of bitter melon in diabetes mellitus. The results of the current study demonstrated that bitter melon has numerous anti-diabetic effects such as, decreasing serum glucose concentration, decrease in the activities of both alanine aminotransferase (ALT) and aspartate aminotransferase (AST), total cholesterol, triglycerides and LDL cholesterol in diabetic rats treated with bitter melon &significant increase of HDLC in bitter melon treated rats. In addition, it showed hypolipidemic and thus cardiac protective effects. It was shown in this study that bitter melon did not cause hypoglycemia when given for normal rats, this indicates that it is safe if utilized by normoglycemic persons for its other beneficial effects.

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CONFLICT OF INTEREST

Statement none of the authors has any financial or personal relationship**.**

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