

ANTI-DIABETIC POTENTIAL OF *MOMORDICA CHARANTIA* LINN LEAVES EXTRACT

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ABSTRACT

The anti-diabetic potential of *Momordica charantia* Linn leaves extract was performed against Alloxan and Streptozotocin induced diabetic in rats. Two doses of hydroalcoholic extract of *M. charantia* leaves 200 mg/kg, p.o and 400 mg/kg, p.o, body weight, and standard drug glibenclamide were used against diabetic activity and parameters estimated includes estimation of biochemical parameter (serum cholesterol, TG, HDL, LDL) macroscopic evaluation and microscopic evaluation (histopathology). Both the lower (200mg/kg, p.o) and higher dose (400mg/kg, p.o) of *M charantia* leaves extract showed dose dependent significant decrease in blood glucose level and biochemical parameters such as cholesterol, triglyceride, LDL, and HDL level were increased when compared with diabetic control of both the models. Histopathology of pancreas showed regeneration of β -cells in extract treated diabetic rats. The result obtained was comparable with that of the standard drug Glibenclamide. The finding of the present study provides the evidence that, hydroalcoholic extract of *M. charantia* Linn leaves may be beneficial against Alloxan and Streptozotocin induced diabetes mellitus.

KEYWORDS: Alloxan, Anti-diabetic activity, *Momordica charantia*, Streptozotocin.

INTRODUCTION

Diabetes is a chronic metabolic disorder characterized by increased fasting and prandial blood sugar levels with disturbances of carbohydrate, fat and protein metabolism. With the progression of disease, tissue or vascular damage may occur which leads to severe diabetic complications such as neuropathy, retinopathy, cardiovascular complications and microbial complications.^[1]

It is mainly characterized by a loss of glucose homeostasis with an interruption in carbohydrate, fat and protein metabolism and defects in insulin secretion or insulin action, or both. With insulin deficiency, the body tissues, the liver, muscular and adipose tissues fall short in taking up and using glucose from the blood circulation. This results in elevation of blood glucose level, which is known as hyperglycemia.^[2]

The prevalence of diabetes has increased dramatically over the last two decades and the problem is increasing day by day.^[3] Diabetes mellitus is a serious global public health issue. The prevalence of diabetes has been shown to be approximately 2.5 % in 2000 and is projected to be

almost double by 2030. The diabetic population of the world is expected to rise from 170 million people in 2000 to approximately 365 million people by 2030.^[4] India, China and United States are the largest countries presenting more than 30 million diabetic people and the incidence is increasing day by day.^[5]

Diabetes refers to a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia is accompanied by long-term damage, dysfunction, and failure of different organs, especially the eyes, kidneys, nerves, heart, and blood vessels.^[6] Diabetes mellitus is categorized as insulin-dependent diabetes mellitus (IDDM) or type I and noninsulin-dependent diabetes mellitus (NIDDM) or type II. Type I diabetes involves cases of beta-cell degradation of the pancreatic islet and is vulnerable to ketoacidosis.^[7]

For the treatment diabetes there are alternative medicines, especially herbal medicines. Popular benefits of herbal medicinal products include efficacy, protection, affordability and acceptability. Medicinal plants and their derivatives have been widely used with less established

scientific basis of their working for the care of diabetic population around the world. Natural products from medicinal plants here fore need to be investigated for their anti-diabetic function using scientific methods.^[8] There are several drugs that are effective in lowering hyperglycaemia in patients with type 2 diabetes mellitus, however, these drugs have a high incidence of side effects such as gastrointestinal complications, thus leading to an increasing number of people seeking alternative therapy with fewer adverse effects.^[9] Prevention and control of diabetes mellitus and its complications has become one of the major issue in medical research. Conventionally, there are many herbal remedies have been used for diabetes and diabetic complications. To date, over 400 traditional herbal remedies have been reported for diabetes. However, only a small variety of those have received scientific evaluation to assess their efficacy.^[10] The interaction between herbs and drugs is often a kind of drug interaction, because the action of an herbal product is actually triggered by chemical ingredients that can be identified.^[11]

Momordica charantia is one among those herbal drugs used for diabetics from ancient times. In Guyana traditional medicine, leaf tea was used for diabetes, to expel intestinal gas, to promote menstruation, and as an antiviral for measles, hepatitis, and feverish condition. It is used topically for sores, wound, infections and internally and externally for worms and parasites.^[12] Hence, present study was conducted to evaluate the antidiabetic activity of *Momordica charantia* leaf extract in rats.

MATERIAL AND METHOD

Collection and authentication of plant material

The fresh leaves of *Momordica charantia* Linn were collected in the month of August from the local area and authenticated by Botanist. The leaves were shade dried and pulverized into coarse powder at plant mill.

Preparation of ethanolic extract of *Momordica charantia* Linn leaves:^[13]

The freshly collected leaves of *Momordica charantia* Linn. Were shade dried and then powdered to coarse size. About 150 gm of leaves powder of *Momordica charantia* Linn was subjected to cold maceration with (mixture of 50% ethanol and 50% distilled water) hydroalcoholic mixture. It was kept for 8 days. After maceration, the solvent was distilled off and the extract was concentrated on water bath.

Preliminary qualitative phytochemical analysis

The preliminary phytochemical analysis of the extract of *Momordica charantia* was performed for the detection of the active constituents present in it.

Experimental animals:^[14]

Wistar Albino rats (150 to 200g) of either sex was used for the study. They were maintained under standard

condition (temp $22 \pm 2^{\circ}$, relative humidity $60 \pm 5\%$ and 12h light/dark circle) and have free access to standard pellets diet and water *ad libitum*. The animal was house in sanitized polypropylene cages contains sterile paddy husk as bedding. The Institutional ethics committee reviewed and approved the experimental protocol (SCP/IAEC/F150/P154/2019 dated 27.12.2019).

Evaluation of Antidiabetic Activity in Rats

Preparation of stock solution of the extract for dosing

The hydroalcoholic extract of *Momordica charantia* Linn leaves was measured and suspended in 1% tween 80. Each time fresh preparation of the extract was prepared before administration. The extract was administered post orally at a constant volume of 1ml for each animal.

Alloxan Induced Diabetic Activity In Rat

Experimental design

The Wistar albino rats (150-200g) of either sex was randomly divided into five groups of six each. The different groups were assigned as follows.

Group I: Normal control (Vehicle)

Group II: Diabetic control (Alloxan 100 mg/kg, i.p.)

Group III: Alloxan (100 mg/kg, i.p.) + Standard (Glibenclamide 5mg/Kg, p.o.)

Group IV: Diabetic animals (Alloxan 100 mg/kg, i.p) + Low dose (200mg/Kg, p.o.)

Group V: Diabetic animals (Alloxan 100 mg/kg, i.p) + High dose (400mg/Kg, p.o.)

Procedure

All the animals except group I was made diabetic by a single intra peritoneal injection of Alloxan monohydrate (100mg/kg body weight) in normal saline. After two days of alloxan injection the blood glucose level was assessed using glucometer and the animals having blood sugar level >200 mg/dl will be selected for the study. Plant extract was orally administered. All the treatment was given orally once daily for entire 30 days.

On 0, 7th, 14th, 21st, day of treatment blood glucose were withdrawn under a mild anesthesia from puncture of tail vein using glucometer. Fasting blood glucose level was measured using single touch using glucose with glucometer. On 30th day of the treatment all the animals were anesthetized using anesthetic ether, blood collected by retro orbital puncture was centrifuged at 2500 rpm for 15 minutes and analyzed for various biochemical parameters like fasting glucose, Total cholesterol, triglycerides, HDL- cholesterol, LDL-Cholesterol, by using a corresponding kit from Agape diagnosis Pvt. Ltd and intensity of the colors complex formed after treating with these reagents were estimated in semi-auto analyzer. At the end of experimental period all the animals were sacrificed after the blood collection for biochemical estimation by retro orbital puncture and the pancreas was removed for histopathological studies respectively.

Histopathological studies

Pancreas was allowed to fix in 10% formalin. Washed in running water followed by dehydration with isopropyl alcohol and impregnated with paraffin wax. Section was made using microtome. After staining with eosin, the different histopathological indices were determined.

Streptozotocin induced diabetic activity in rat.^[15,16]

Experimental design

The Wistar albino rats (150-200g) of either sex was randomly divided into five groups of six each. The different groups were assigned as follows

Group I: Normal control (Vehicle)

Group II: Diabetic control (Streptozotocin 50 mg/kg, i.p)

Group III: Streptozotocin (50 mg/kg, i.p) + Standard Glibenclamide (5mg/Kg, p.o)

Group IV: Diabetic animals (Streptozotocin 50 mg/kg, i.p) + Low dose (200mg/Kg, p.o)

Group V: Diabetic animals (Streptozotocin 50mg/kg, i.p) + High dose (400mg/Kg, p.o)

Procedure

All the animals except group I was made diabetic by a single intra peritoneal injection of Streptozotocin (50mg/kg body weight) in normal saline. After two days of Streptozotocin injection the blood glucose level was assessed using glucometer and the animals having blood sugar level >200 mg/dl was selected for the study. Plant extract was orally administered. All the treatment was given orally once daily for entire 30 days.

On day 0, 7th, 14th, 21st, day of treatment blood glucose were withdrawn under a mild anesthesia from puncture of tail vein using glucometer. Fasting blood glucose level was measured using single touch using glucose with glucometer. On 30th day of the treatment all the animals were anesthetized using anesthetic ether, blood collected by retro orbital puncture was centrifuged at 2500 rpm for 15 minutes and analyzed for various biochemical parameters like fasting glucose, Total cholesterol, triglycerides, HDL- cholesterol, LDL-Cholesterol, by using a corresponding kit from agape diagnosis Pvt. Ltd and intensity of the colors complex formed after treating with these reagents were estimated in semi-auto analyzer. At the end of experimental period all the animals were sacrificed after the blood collection for

biochemical estimation by retro orbital puncture and the pancreas was removed for histopathological studies respectively.

Histopathological studies

Pancreas was allowed to fix in 10% formalin. Washed in running water followed by dehydration with isopropyl alcohol and impregnated with paraffin wax. Section was made using microtome. After staining with eosin, the different histopathological indices will be determined.

Statistical Analysis

All data were expressed as Mean ± SEM. The statistical significance between groups were compared using one way ANOVA, followed by Dennett's (multiple comparison test).

RESULT

Preliminary phytochemical screening

Preliminary phytochemical analysis was performed and the results confirm the presence of alkaloids, carbohydrates, flavonoids, cardiac glycosides, tannins, saponins, steroids, anthraquinone glycosides.

Determination of antidiabetic activity

Following are the results obtained, showing the antidiabetic effect of the hydroalcoholic extract of the leaves of *Momordica charantia*.

Alloxan Induced Antidiabetic Activity

Fasting blood glucose level (FBG) was within the range of 70-90mg/dl in all the groups a day 0. Treatment with Alloxan in normal saline (100mg/kg, ip) had increased the FBG level more than 200 mg/dl after 48 h. Changes in FBG level in different groups after repeated dose administration tabulated in Table No. 3 and represented in Fig. No.8. Diabetic control group has showed significant increase in fasting blood glucose during the study period. Glibenclamide (5mg/kg) significantly (p<0.01) reduced FBG after repeated administration as compared to diabetic control group. Whereas treatment with *Momordica charantia* at dose 200 and 400 mg/kg has significantly (p<0.01) decreased FBG as compared to diabetic control on 7th, 14th, 21st and 30th day.

Table 1: Effect of ethanol extract of leaves of *Momordica charantia* Linn leaves on blood glucose level in Alloxan induced diabetic rats.

Groups	Blood glucose level (mg/dL)				
	Initial	Day 7	Day 14	Day 21	Day 30
Normal control	71.69 ± 1.441	76.84 ± 2.204	72.16 ± 1.504	77.20± 1.465	72.31 ± 1.526
Diabetic control	322.3 ± 3.705 [#]	326.33 ± 6.305 [#]	337.2 ± 7.231 [#]	321.0± 8.002 [#]	312.6 ± 12.40 [#]
Glibenclamide (5mg/kg)	310.8 ± 3.809	283.1 ± 8.200***	227.7± 13.88***	171.3 ± 5.76***	132.6 ± 3.11**
<i>M. charantia</i> extract (200mg/kg)	317.6± 3.905	299.3 ± 6.729*	262.9 ± 4.954**	234.7 ± 10.65*	183.4 ± 5.632*

M. charantia extract (400mg/kg)	312.77 ± 3.567	289.2 ± 4.011*	233.3 ± 9.323**	188.6 ± 3.633**	148.5 ± 2.188**
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Values are expressed as mean ± S E M, n=6 in all group except in diabetic control, n=3 on 21st day and n=2 on 30th day 9 (1 animal died on 15th day, 2 died on 19th day and 1 on 23rd day) One way ANOVA followed by Dunette's t-test. *p<0.05, **p<0.01 and ***p<0.001 when compared with diabetic control rats. # p<0.001, Values are significantly different from normal with control group.

Streptozotocin Induced Diabetic Activity in Rat.

Fasting blood glucose (FBG) level was within the range of 75-90 mg/dl in all the groups at day 0. Treatment with STZ in normal saline (50mg/kg, i.p.) had increased the FBG level more than 200mg/dl after 48 h. Changes in FBG level in different groups after repeated dose of drug administration are tabulated in Table No.4 and represented in Fig No.14 Diabetic control group has

showed significant increase in fasting blood glucose during the study period. Glibenclamide (5mg/kg) significantly (p<0.01) reduced FBG after repeated administration as compared to diabetic control group. Whereas treatment with MCEE at dose of 200 and 400mg/kg has significantly (p<0.05) decreased FBG as compared to diabetic control on 7th, 14th, 21st and 30th day.

Table 2: Effect of ethanol extract of leaves of *Momordica charantia* on blood glucose level in STZ induced diabetic rats.

Groups	Blood glucose level (mg/dL)				
	Initial	Day 7	Day 14	Day 21	Day 30
Normal control	85.88 ± 0.99	85.00± 1.22	86.58 ± 1.87	86.61± 1.76	88.93 ± 1.53
Diabetic control	301.8 ± 1.56 [#]	340.2 ± 6.67 [#]	364.8 ± 2.99 [#]	327.2± 3.287 [#]	306.7 ± 5.722 [#]
Glibenclamide (5mg/kg)	294.0 ± 6.321	232.0± 5.110**	176.6 ± 10.2***	149.4 ± 3.02***	111.1 ± 4.88***
M. charantia (200mg/kg)	289.6 ± 2.99	254.8 ± 5.32*	238.5 ± 9.85*	197.8 ± 7.77**	169.3 ± 3.84*
M. charantia extract (400mg/kg)	283.9 ± 6.35	240.1 ± 4.77**	215.0 ± 1.55*	173.2 ± 5.123**	128.0 ± 1.21**

Values are expressed as mean ± S E M, n=6 in all except in diabetic control, n=4 on 21st day n=2 on 30th day (2 animals died on 17th day, 1 died on 22nd day, 1 on 23rd day) one way ANOVA followed by Dunette's test. Where, *p<0.05, **p<0.01 and ***p<0.001 when compared to diabetic control. # p<0.001, Values are significantly different from normal with control group.

Effect of *Momordica charantia* extract on serum cholesterol, triglycerides, HDL and LDL in Alloxan and STZ induced diabetic rats

Diabetic rats treated with extract showed significant (p<0.01) reduction in the elevated levels of total cholesterol and triglycerides in diabetic rats. Prolonged

treatment of extract (400 mg/kg) and glibenclamide (5mg/kg) significantly reduced the LDL-cholesterol by as compared to diabetic control group. Also, the extract significantly (p<0.01) improved the HDL-cholesterol level at 400 mg/kg.

Table 3: Effect of *M. charantia* on serum cholesterol, triglycerides, HDL. and LDL in Alloxan and STZ induced diabetic rats.

Groups	SERUM			
	Cholesterol (mg/dL)	Triglyceride (mg/dL)	HDL (mg/dL)	LDL (mg/dL)
Normal control	58.41 ± 0.21	61.07 ± 0.29	49.04 ± 1.02	32.42 ± 0.75
Diabetic control	91.87 ± 0.32 [#]	87.47 ± 2.23 [#]	20.56 ± 1.87 [#]	98.13 ± 0.65 [#]
Glibenclamide (5mg/kg)	60.89 ± 0.28**	69.54 ± 0.54**	42.57 ± 1.43***	59.38 ± 1.37***
M. charantia extract (200mg/kg)	76.58 ± 0.87*	78.59 ± 1.93*	29.61 ± 3.40*	76.89 ± 0.16**
M. charantia extract (400mg/kg)	67.29 ± 1.09**	72.52 ± 2.44*	37.37 ± 0.77**	62.39 ± 1.44**

Values are expressed as mean± S.E.M, (n=6). One way ANOVA followed by Dunnett's test. *p<0.05, **p<0.01 when compared with diabetic control group. # p<0.001, Values are significantly different from normal with control group.

Histopathological Studies

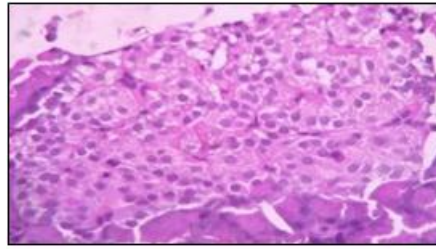


Fig1: Normal control

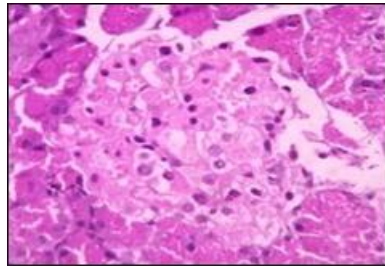


Fig. 2: Glibenclamide (alloxan)

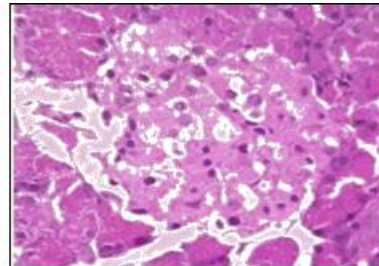


Fig. 3: Glibenclamide (STZ)

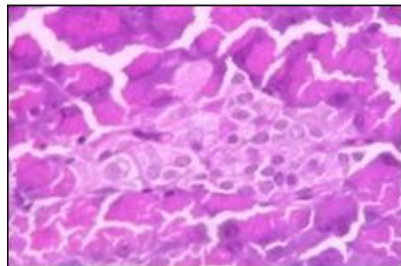


Fig. 4: TIEE 200mg/kg (Alloxan)

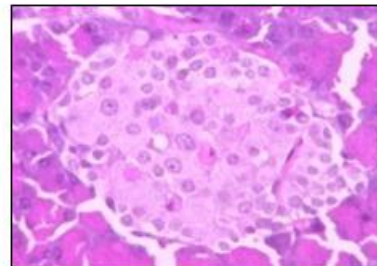


Fig. 5: TIEE 200mg/kg (STZ)

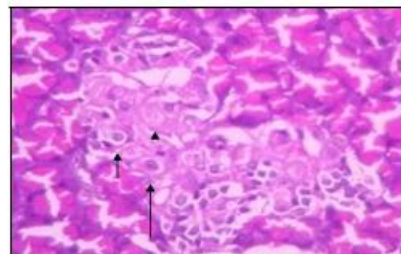


Fig.No.6: Diabetic control (Alloxan)

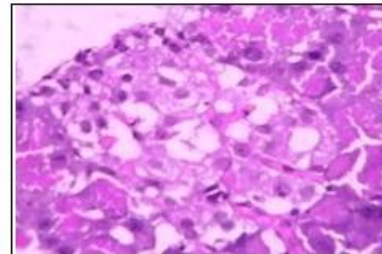


Fig.No.7: Diabetic control (STZ)

Histopathology studies of pancreas in both Alloxan and STZ induced diabetic rats:

Normal control

Normal rat showing acini and normal cellular population in islets of Langerhans and absence of both damage to islets and hyperplasia (Fig. no.1).

Standard

Diabetic rats treated with GLB 5mg/kg showing complete restoration of normal cellular population size of islets of Langerhans and absence of islet damage and presence of hyperplasia. (Fig no.2 and fig no.3) In both Alloxan and STZ model.

MCHAE treated in Alloxan induced diabetes

MCHAE 200mg/kg showing restoration of normal cellular population size of islets of Langerhans and cells are partially preserved (fig no.4).

MCHAE treated in STZ induced diabetes

It suggested less restoration of the cells of islets of Langerhans. Cells are shrunken and appear degenerated (fig no.5).

Diabetic control

It suggested extensive damage to the islets of Langerhans and reduced islets size (fig no.6 and fig no.7) in both alloxan and STZ model.

DISCUSSION

Alloxan and Streptozotocin has been used to induce diabetes mellitus in experimental rats. A Single Intraperitoneal (IP) administration of 100 mg/kg Alloxan 50 mg/Kg and Streptozotocin effectively induced diabetes mellitus in rats, which was confirmed by elevated level of fasting blood glucose obtained from the tail of the rats after 72 hours of injection.

Alloxan and Streptozotocin are widely used to induce experimental diabetes in animals. These are the most prominent diabetogenic chemicals in diabetes research. Both are cytotoxic glucose analogues. Their cytotoxicity is achieved via different pathways; their mechanisms of beta cell selective action are identical. The cytotoxic action of both these diabetogenic agents is mediated by reactive oxygen species; however, the source of their generation is different in the case of Alloxan and Streptozotocin. Due to chemical nature and greater stability, Streptozotocin is mainly used for the reproducible induction of diabetes in experimental animals. Although the animals without the insulin therapy showed marked improvement by glibenclamide which act by stimulating residual beta cells of the pancreas indicate incomplete destruction of pancreatic beta cells of the diabetic rats in this study.

Glibenclamide is often used as a standard antidiabetic drug in Alloxan and Streptozotocin induced diabetes to compare the efficacy of hydroalcoholic extract of *Momordica charantia*, it is second generation sulphonylurea derivative and found to be effective in diabetic rats that retain functioning of islet β -cells. Hence the principle mechanism of action is to stimulate the production and secretion of insulin by the β cells of pancreas. This drug may lower down the output of glucose from the liver by insulin independent mechanism.

Treatment with hydroalcoholic extract of leaves of *Momordica charantia*, showed anti-diabetic activity. Reduced blood glucose level throughout the experimental period in duration dependent manner indicating its anti-hyperglycemic activity, which were compared to standard glibenclamide.

The phytochemical screening of hydroalcoholic extract of *Momordica charantia*, has revealed the presence of triterpenes of lupane type, phenylethanoid glycosides, russetinol and russeliaoside. Leaves yielded alkaloids, flavonoids, saponins, tannins, steroids, and terpenoids. Flavonoids, sterols/triterpenoids, alkaloids, saponins and phenolics have bioactive antidiabetic principles. Flavonoids can regenerate the damaged-cells in the alloxan induced diabetic rats.

The present study showed increase in plasma triglycerides, total cholesterol and LDL cholesterol with decrease in HDL cholesterol supporting the findings of the other Potential of the extract to decrease cholesterol

and triglyceride levels researchers could be helpful in improving lipid metabolism in diabetics which in turn will help to prevent diabetic complications. LDL-cholesterol being involved in the transport of cholesterol from liver to peripheral tissues is the key factor in atherogenesis. Potential of the extract to reduce LDL-cholesterol thereby indicates its possible involvement in prevention of diabetes mellitus induced cardiovascular complications.

Histopathological studies of pancreas also supported the finding. Microscopic investigation of pancreas sections of NC rats showed exocrine acine and islets of langerhans were unevenly scattered in the pancreatic tissue and were of varying sizes in the sane lobule of pancreas and normal in appearance. The islets were extensively damaged and with size of islet are reduced in diabetic control group. Glibenclamide treated group suggest complete restoration of normal cellular size of islet of langerhans and absence of islet damage. And diabetic treated with drug extract shows partly restoration of normal cellular population size of the islets of langerhans and absence of islet damage.

CONCLUSION

Results from the present study suggest that hydroalcoholic extract of leaves of *Momordica charantia* significantly reduces elevated blood glucose level in Alloxan and Streptozotocin diabetic rats without showing any hypoglycemic effect in normal rats. Since Streptozotocin and Alloxan effectively destroys pancreatic beta cells and causes persistent hyperglycemia, the mechanism of action of *Momordica charantia* might involve actions other than pancreatic beta cells insulin release or secretion. The preliminary phytochemical screening of the hydroalcoholic extract of *Momordica charantia* leaves revealed the presence of Alkaloids, Flavonoids, Triterpenoids, alkaloids and Saponines. The antioxidant and antidiabetic effect are may be due to the presence of these phytoconstituents. The mechanism for anti-diabetic effect of the extract could be due to increased utilization of glucose by peripheral tissues, improved sensitivity of target tissues for insulin or it may be due to improved metabolic regulation of glucose. The antidiabetic activity of hydroalcoholic extract of leaves of *Momordica charantia* may be attributed to the individual or combined action of phytoconstituents present in it. Histopathological observation revealed that treatment with *Momordica charantia* extract has reversed the pancreatic damage by Alloxan and Streptozotocin.

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