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Antidiabetic activity of mango peel extract and mangiferin in alloxan-induced diabetic rats

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Abstract

Background In diabetic animals, there is a significant increase in plasma glucose, serum total cholesterol, triglyceride, and low-density lipoprotein levels, and decreased body weight, liver and muscle glycogen, and high-density lipoprotein. Effective treatment of diabetes mellitus is not yet known, even though the management of diabetes mellitus is considered a global concern. Plants and herbs have played an important role in the healthcare of many societies throughout history. Today's researchers are investigating the potential for using these nonpharmaceutical approaches to treat and control diabetes, either in conjunction with standard treatments or as an alternative to them. Herbal formulations are favored because to lower cost and fewer side effects compared to other methods for alleviating diabetes and its consequences. In ethnomedicinal practices, different parts of *Mangifera indica* are used to treatment of diabetes. The present investigation was undertaken to evaluate the antidiabetic activity of an ethanolic extract of *Mangifera indica* and mangiferin in alloxan-induced diabetic rats. This experiment was conducted in a set of two with four groups of animals namely control (Tc), treatment alloxan (Ta), treatment extract (Tae), and treatment mangiferin (Tam). To develop diabetes, Wistar rats treated with 150 mg/kg b.w. of alloxan monohydrate were injected intraperitoneally. Tae and Tam's groups received a freshly prepared single dose of extract and mangiferin in distilled water via the oral route. All experimental groups received laboratory pallet feed diet and drinking water ad libitum. Diabetic rats were treated for 21 days with an ethanolic extract of mango peel and pure mangiferin orally daily at rates of 200 mg/kg b.w. and 20 mg/kg b.w.

Results An alloxan-induced diabetic rat treated with mango peel extract and mangiferin significantly improved the overhead impact due to diabetes. There was a significant ($p < 0.05$) body weight loss in the alloxan-induced diabetic rats (Ta), whereas animals given mango peel extract and mangiferin showed a significant increase in body weight from 2 weeks onwards in comparison with control. Alloxan-induced rats (Ta) group have higher blood glucose levels and are significantly different ($p < 0.01$) from the control group. Mango peel extract and mangiferin significantly reduced the levels of fasting glucose after 21 days of treatment in comparison with diabetic animals. Mango peel extract and mangiferin influence the glycogen synthesis pathway in diabetes groups by increasing glycogen levels in muscle and liver. mango peel extract and mangiferin were found to have a nonsignificant impact on plasma cholesterol and HDL levels compared with the control group. Mango peel extract was found to have a significant difference ($p < 0.05$) in LDL levels compared with the control group. Mangiferin was found to have a significant difference ($p < 0.05$) in triglyceride and VLDL levels when compared with the control group. Histopathological examination of the pancreas in rats with type I diabetes caused by alloxan found that therapy with an ethanolic extract of mango peel and mangiferin restored beta cell function as well as rejuvenation of Islets of Langerhans.

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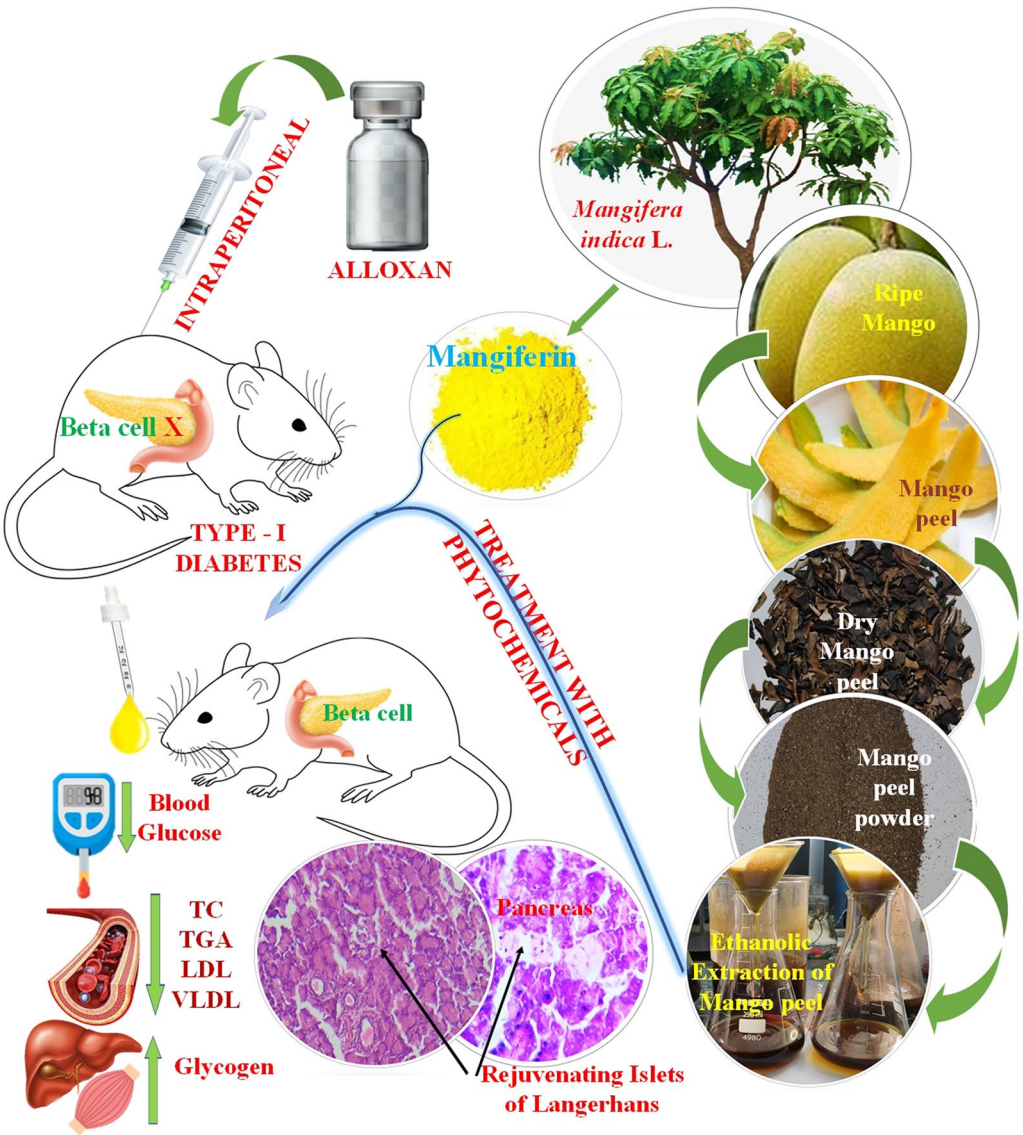
Conclusions Mango peel extract and mangiferin have antidiabetic, glycogenesis, and hypolipidemic properties when administered to alloxan-induced diabetic rats.

Keywords Diabetes, Alloxan, *Mangifera indica*, Mangiferin, Mango peel, Ethanolic extract, Beta cell

Graphical abstract



Background

Diabetes mellitus is a metabolic illness with several etiologies defined by elevated blood glucose levels and disruptions of the metabolism of proteins, lipids, and carbohydrates as a result of inadequate insulin production. More than one hundred million people all over the world are affected by diabetes mellitus, making it the most prevalent endocrine illness. In the year 2000, it affected approximately 171 million individuals across the world, and projections indicate that number might rise to at least 366 million by the year 2030 [1–3]. In India, the incidence of diabetes increased from 7.1% in 2009 to 8.9% in 2019. India is second to China in diabetes prevalence, with 77 million diabetics. There are 12.1 million of them who are under 65 and that number is expected to rise to 27.5 million by the year 2045 [4]. Diabetes that is

not treated can, over time, cause substantial damage to a number of different physiological systems. Diabetes can be prevented by maintaining a healthy diet and a healthy weight. The effective treatment of diabetes mellitus is not yet known, despite the fact that management is considered a global concern. This condition is brought on by a subsequent reduction in the action of insulin and/or a moderate to a severe shortfall in the amount of insulin that is secreted, both of which can lead to a lack of insulin [5]. Therefore, the collection of symptoms associated with diabetes mellitus is distinguished by chronic hyperglycemia accompanied by glucosuria and a predisposition to developing ketoacidosis. [6]. In the pancreas, alloxan is a noxious glucose analog that kills insulin-producing beta cells. Rodents and other animal species can develop insulin-dependent diabetes that is similar to type 1 diabetes in humans when it is administered. The GLUT2 glucose transporter is used to transfer alloxan into pancreatic beta cells. When thiols are present intracellularly with alloxan, ROS (reactive oxygen species) are generated in a cyclic reaction with the reduction of dialuric acid that occurs. In this redox process, free radicals are the ones that make alloxan toxic to beta cell. [7]. The most significant drawbacks of oral diabetes medications are the nasty side effects they cause and the high expense of the treatment. It is common knowledge that medicines derived from plants are both safer and less expensive than synthetic or contemporary medications. Simple accessibility, consumption in its natural state, and preparations derived from plants continue to lead the peak among all types of sources due to their low cost, low risk of adverse effects, and high efficiency [8]. *Mangifera indica L.*, which belongs to the family Anacardiaceae, is a significant tropical plant that may be found all throughout India, both in rural and in semi-urban areas [9]. Because of the high quality of the fruit that it bears, it is cultivated extensively across numerous regions of Asia and Africa [9]. The bark, roots, and leaves of *M. indica* are all utilized in conventional medical practices in various sections of the planet. Patients suffering from illnesses such as asthma, cough, leucorrhoea, jaundice, diarrhea, dysentery, aches, and diabetes are candidates for treatment with *Mangifera indica L.* [10, 11]. Phytochemical analysis of various parts of the *M. indica* plant has demonstrated the existence of phenolic constituents, phytosterol, polyphenols, triterpenes, and flavonoids [12–16]. Mangiferin is a C-glucoside xanthone glucoside found in *Mangifera indica* L. This species is thought to have a wide variety of therapeutic applications, such as analgesic, anti-inflammatory [17], immunostimulant [18], antioxidant [19], antidiarrhea [20], antihyperlipidemic [21, 22], antidiabetic [22–24], antiamebic [25], anthelminthic [26], antiallergic [26] and antibacterial [27] uses. In spite of the fact that *M. indica* has been examined for its wide range of therapeutic characteristics, in-depth investigations into its ability to treat diabetes have not yet been conducted. In light of the aforementioned [21–24], the present investigation was performed to reveal the hypoglycemic and hypolipidemic effects of mango peel as well as the mango peel's active component, mangiferin on alloxan-induced diabetic albino rats.

Methods

Preparation of plant extractions

Fresh ripe mango was collected from the mango orchard of the University of Kalyani campus. The identification and authentication of *Mangifera indica* Linn. plants were done by Partha Loadh, Assistant Professor of the Department of Botany, Government General Degree College at Kaliganj, and the voucher specimens numbered 260 were placed and preserved in the Herbarium of the Department of Botany, Government General Degree College at Kaliganj. Mango peels were collected from freshly ripe mango of *Mangifera indica*, and peels were washed and sun-dried for 2 weeks. Peels were ground to powder (500 g) and homogenized with 70% ethanol (1000 ml). The powder was solubilized and mixed well with intermittent stirring for 3 days continually. A layer of Whatman filter paper (No. 1) was used to filter the plant-solvent combination after it had been created. In order to evaporate the acquired solvent, Petri dishes were placed in an oven heated to 45–50° Celsius and left there for four to five days. The resulting extracts were collected and preserved in a refrigerator for future usage.

Acute toxicity study of mango peel extract and mangiferin:

In 2001, the OECD (Organization for Economic Cooperation and Development) published an international guideline on acute oral toxicity and fixed-dose procedures [28]. To execute the acute oral toxicity and fixed-dose procedure test of mango peel extract and mangiferin on albino Wistar rats, a separate experiment was performed for each phytochemical. 8–12-week-old male and female Wistar albino rats weighing about 100–150 g in a 3:2 ratio were divided into 4 groups of 5 animals each and were administered a single dose of ethanolic extract of mango peel (2000 mg/kg b.w.) and mangiferin (300 mg/kg b.w.) orally, prepared in distilled water. All the experiments were performed after getting permission from the institutional animal ethical committee. After administration, animals were observed with special attention for the first 24 h. Thereafter, observation was continued periodically for a total of 14 days. The precise time when toxicity symptoms appeared or the appropriate time of death was recorded. Throughout this acute toxicity test, no animal

deaths were recorded. No apparent signs of toxicity were observed throughout the study. The animals did not show any increase or decrease in body weight. The skin, fur, and eyes were found to be normal. No abnormal changes in behavior were observed during this study. They were taking their food and water as usual. From this study, it can be concluded that the estimated LD_{50} of mango peel extract is above 2000 mg/kg b.w. and the LD_{50} of mangiferin is 300 mg/kg b.w. when given orally. As a result, at maximum doses of 2000 mg/kg b.w. and 300 mg/kg b.w., this extract and mangiferin can be considered safe and nontoxic.

Animals

Before starting the experiments, all the animals will be adapted for an interval of 7–10 days to the usual laboratory environments with 12:12 h day and night cycle for each 24-h period with ambient room temperature (25 ± 2 °C) and relative humidity 55–60%. For the present antihyperglycaemic study, adult male and female Albino Wistar rats ranged between the weight of 100–150 g were considered in 2:1 ratio. Sterile polypropylene cages were used to uphold the rats in the animal house. The animals were provided with a standard diet of rat pellets and were given access to clean water on an unlimited basis. Every experiment involving animals was carried out with the approval of the Institute Animal Ethical Committee (IAEC), University of Kalyani, as well as in compliance with the standards for the appropriate use of animals in the laboratory.

Experimental design

This experiment was conducted in a set of two. Four groups of animals (three in each group) received treatment. Tae and Tam's groups received freshly prepared mango peel extract and mangiferin in a single dose with distilled water via the oral route. After 21 days, all the animals were killed by mild ether anesthesia. Blood was collected and centrifuged for serum separation. Organs were collected and preserved for histological investigation.

Groups	Group symbol	Drugs used	Dose (mg/kg/b.w.)
Control	C	–	–
Alloxan	Ta	Alloxan	150 mg/kg b.w. (single)
Alloxan + extract	Tae	Alloxan + extract	200 mg/kg b.w. (21 days)
Alloxan + mangiferin	Tam	Alloxan + mangiferin	20 mg/kg b.w. (21 days)

Induction of diabetes by alloxan in Wistar rat

Individually identifiable animals will be chosen, weighed, and marked. To develop diabetes in fasting Wistar rats weighing 100–50 g, 150 mg/kg b.w. of alloxan monohydrate in saline (0.9 percent NaCl) was injected intraperitoneally (IP) into the animals [29]. After one hour of alloxan administration, to combat the early hypoglycemia shock, a solution of dextrose with a concentration of 5% will be administered by feeding bottle for one full day. After a period of 72 h, animals whose blood glucose concentrations are above 250 mg/dl will be classified as diabetic and deemed appropriate for the study.

Instruments and reagents

All the biochemical tests of blood and others were done using a semi-automated biochemistry analyzer 'Prietest easy lab' made by Robonik India Pvt. Ltd., A-374, TTC Industrial Area, Mahape, Navi Mumbai-400710, India. Pure mangiferin extracted from *Mangifera indica* and Alloxan was purchased from Sigma-Aldrich Chemicals Private Limited, India. Test kits were purchased from Robonik India Pvt. Ltd., and all other reagents used were of analytical grade.

Collection of blood

On day twenty-two, blood was drawn from the rat's heart via a cardiac puncture under a light ether anesthetic following an overnight fast. The blood was then allowed to clot at room temperature for ten minutes. The blood samples were centrifuged for ten minutes at a speed of 3000 rpm. After the serum was separated, it was kept at a temperature of − 20° Celsius until the biochemical measurements could be made.

Estimation of blood glucose

Fasting plasma glucose levels were assayed by the enzymatic (GOD/POD), photometric, trinder reaction, and endpoint methods [30]. The assay kit was supplied by Robonik India Pvt. Ltd., A-374, TTC Industrial Area, Mahape, Navi Mumbai-400710, India. To estimate the level of glucose at regular intervals, withdrawn from the tail vein of an animal.

Estimation of liver and muscle glycogen

Rats from each of the groups had to be killed so that their livers and skeletal muscles could be collected. The 100 mg of the liver and muscle tissues were homogenized in five volumes of an ice-cold 30% (w/v) KOH solution and dissolved in a boiling water bath (100° C) for 30 min. With the use of ethanol, the glycogen was precipitated; it was then washed and resoluble in distilled water. The anthrone-reagent approach was then used to determine

the glycogen content in the muscle and liver tissues [31]. Using a spectrophotometer, the absorbance was determined to be 620 nm. The amount of glycogen was represented as mg per gram of tissue.

Estimation of serum lipid parameters

Lipid profiles were performed within one week for each group of samples, following the procedures provided with kits, after running the controls for confirmation of the accuracy of each test. The blood total cholesterol level was assayed by the "CHOD-PAP," an enzymatic photometric test, trinder, endpoint [32]. A photometric test was used to measure blood triglyceride levels using the enzymatic GPO, trinder, and endpoint method [33]. HDL-C level was assayed by the precipitation, phosphotungstic acid method [34]. Measurement of serum creatinine was performed by the kinetic-spectrophotometric alkaline picrate method [35]. The assay kit was supplied by Robonik India Pvt. Ltd., A-374, TTC Industrial Area, Mahape, Navi Mumbai-400710, India. LDL cholesterol (low-density lipoproteins) in the blood is as follows: It is computed using Friedewald's equation [36].

$$\begin{aligned}\mathrm{LDL}-C\left(\mathrm{mg/dl\ or\ mmol}/l\right) &= \text{Total cholesterol}\\ &\quad -\text{HDL cholesterol}\\ &\quad -\frac{\text{Triglycerides}}{5}\end{aligned}$$

$$\begin{aligned}&\mathrm{VLDL}-C \text{ can be determined from serum triglyceride}\\ &\text{using the following formula} - \mathrm{VLDL}\\ &-C\left(\mathrm{mg/dl\ or\ mmol}/l\right)=\frac{\text{Triglycerides}}{5}\end{aligned}$$

Histological assessment

The rat's pancreas was promptly removed and treated in Bouin's solution. Tissues were then dehydrated in graduated alcohol concentrations before being embedded in paraffin. Four–six micrometer tissue sections were stained by hematoxylin and eosin (H & E). For each animal, six H & E-stained slides were investigated for histological alterations [37].

Statistical analysis

The data are presented as (SEM). Students t-tests were used to statistically analyze all the data at the 1% and 5% levels of significance. Using the SPSS 12.0 edition and Microsoft Excel software, mean, standard deviation (SD),

Table 1 Effect of mango peel extract and mangiferin on body weight in the alloxan-induced type I diabetic rat

Days	Tc (g)	Ta (g)	Tae (g)	Tam (g)
0 Day	134.66 ± 2.10	138.83 ± 2.83	126.66 ± 1.49	139.83 ± 1.74
7 Day	135.16 ± 2.27	136.50 ± 2.47	129.16 ± 1.55	141.33 ± 1.89
15 Day	138.33 ± 2.10	131.50 ± 1.82	134.16 ± 1.35	143.16 ± 2.77
21 Day	138.83 ± 2.28	128.66 ± 3.29*	137.83 ± 1.66#	144.5 ± 1.56#

Values are mean ± SEM ($n = 6$); *Significant at 5% level, **Significant at 1% level and #Not significant

The fluctuations in body weight in different groups are stated in Table 1. There was a significant ($p < 0.05$) decline in body weight in all alloxan-induced type I diabetic rats compared to the control group within 21 days

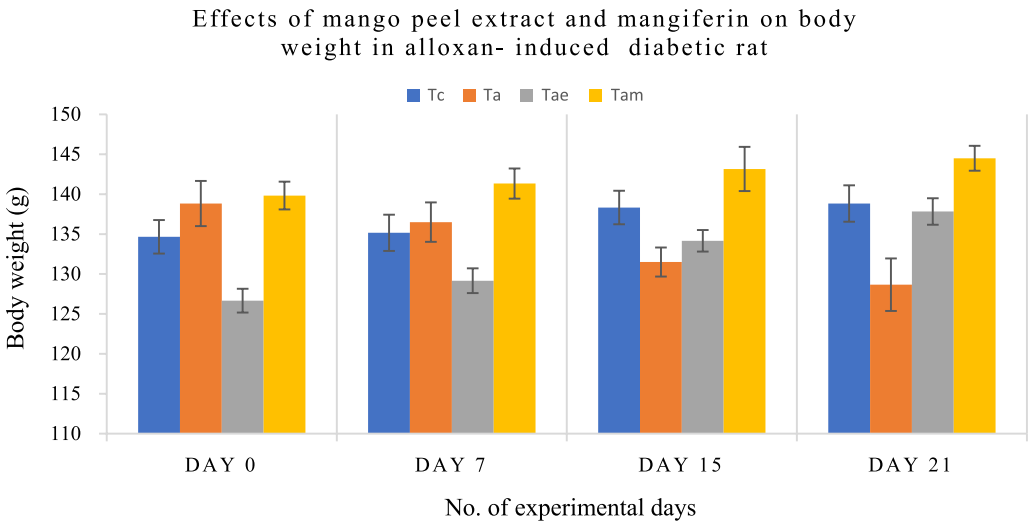


Fig. 1 Effect of mango peel extract and mangiferin on body weight in the alloxan-induced type I diabetic rat. There was a significant decline in body weight in all alloxan-induced type I diabetic rats compared to the control group within 21 days. Tc, Tae and Tam were shown to increase in body weight with regular interval of days

Table 2 Effect of mango peel extract and mangiferin on fasting plasma glucose level in the alloxan-induced type I diabetic rat

Days	Control (Tc) (mg/dl)	Alloxan (Ta) (mg/dl)	Alloxan + extract (Tae) (mg/dl)	Alloxan + mangiferin (Tam) (mg/dl)
0	87.16 ± 1.22	285 ± 6.13	312.83 ± 11.02	314.83 ± 10.83
7	86.33 ± 1.08	286.83 ± 6.77	233 ± 10.89	221 ± 7.67
15	83.5 ± 1.28	310.5 ± 4.16	137.83 ± 4.16	136.33 ± 2.66
21	85.83 ± 1.19	308.83 ± 6.09**	88.5 ± 1.80#	91.16 ± 2.54#

Values are mean ± SEM ($n = 6$); *Significant at 5% level, **Significant at 1% level and #Not significant

The fluctuations in body weight in different groups are stated in Table 2. Ta group has higher blood glucose levels and is significantly different ($p < 0.01$) than the control group (Tc). Plasma glucose levels are similar in the other groups as they are in the control group, and there was no significant difference

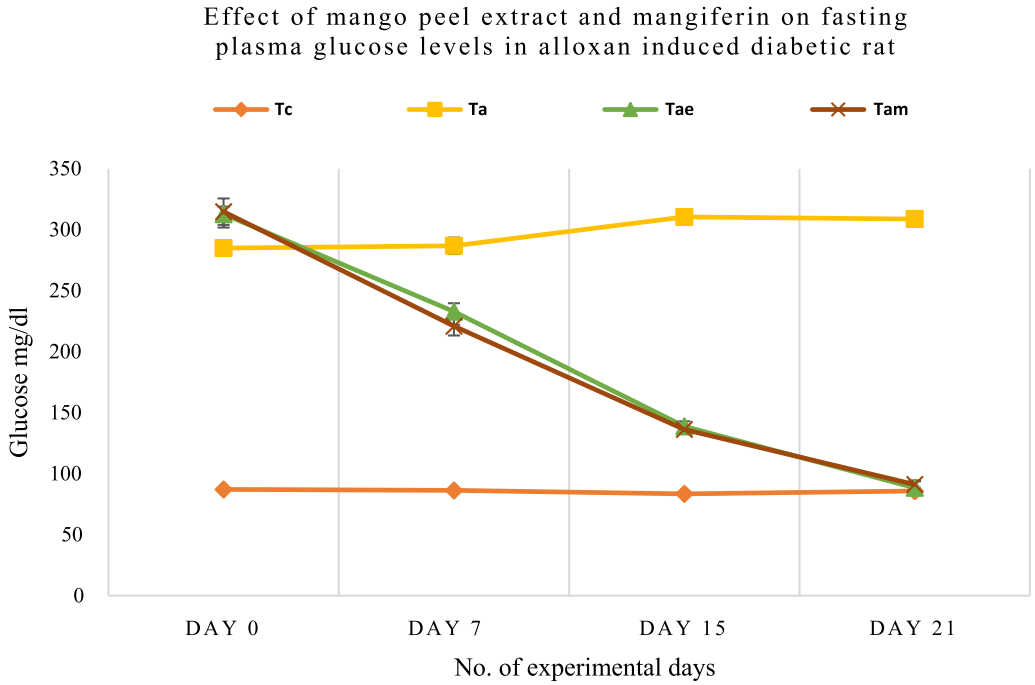


Fig. 2 Effect of mango peel extract and mangiferin on fasting plasma glucose levels in the alloxan-induced type I diabetic rat. In this figure shows that the Ta group has higher plasma glucose levels than the Tc group, Tae and Tam show a significant decrease in plasma glucose levels with the duration of days of treatment

standard error of the mean (SEM), and other statistical computations were performed [38, 39].

Result

Effects of mango peel extract and mangiferin on body weight in the alloxan-induced type I diabetic rats

There was a significant body weight loss (7.32% loss of weight in the 0–21-day interval) in the alloxan-induced type I diabetic rats (Ta), whereas animals given mango peel extract (Tae) and mangiferin (Tam) at 200 mg/kg b.w. and 20 mg/kg b.w. orally once daily showed a significant increase in body weight from 2 weeks onwards. The fluctuations in body weight are stated in Table 1 and Fig. 1. In the Tae group, there was an 8.81% increase in the 0 to 21-day interval; in the Tam group, there was a 3.33% increase in the 0 to 21-day interval; and in the control group, there was a 3.09% increase in the 0–21-day interval.

Effects of mango peel extract and mangiferin on plasma glucose levels in the alloxan-induced type I diabetic rat:

The rise in fasting plasma glucose levels in alloxan-treated rats peaked between the fifth and seventh days. According to the findings of this study, the plasma glucose level in Ta is significantly higher ($p < 0.01$) and statistically significant. It is the same in the other groups as it is in the control group. The fluctuations in plasma glucose levels in different groups are

Table 3 Effect of mango peel extract and mangiferin on Liver and Muscle glycogen level in the alloxan-induced type I diabetic rat

Group	Liver glycogen (mg/g)	Muscle glycogen (mg/g)
Control (Tc)	18.31 ± 0.26	9.05 ± 0.38
Alloxan (Ta)	10.35 ± 0.42**	5.98 ± 0.53**
Alloxan + extract (Tae)	19.31 ± 0.41$^{\#}$	9.6 ± 0.24$^{\#}$
Alloxan + mangiferin (Tam)	15.57 ± 1.09$^{\#}$	8.29. ± 1.72$^{\#}$

Values are mean ± SEM ($n = 6$); *Significant at 5% level, **Significant at 1% level and $^{\#}$Not significant

The fluctuations of stored glycogen in liver and muscle levels in different groups are stated in Table 3. The difference between the diabetic groups (Ta) and control (Tc) was statistically significant ($p < 0.01$). In mangiferin-treated group (Tam) and mango peel extract group (Tae), there was no statistically significant disparity with the control group (Tc)

stated in Table 2 and Fig. 2. *Mango peel extract* (200 mg/kg) significantly reduced the levels of glucose in the fasting condition after 21 days of treatment. Mango peel extract-treated group (Tae) with 200 mg/kg and the plasma glucose levels were 137.83 ± 4.16 mg/dl on the 15th day and 88.5 ± 1.80 mg/dl on the 21st day, in comparison with the fasting plasma glucose levels of 310.5 ± 4.16 mg/dl on the 15th day and 308.83 ± 6.09 mg/dl on the 21st day in the alloxan-induced diabetic group (Ta). Mangiferin (20 mg/kg) significantly decreases the levels of glucose in the fasting condition. In the mangiferin-treated group (Tam), with 20 mg/kg mangiferin, the levels of fasting glucose were 136.33 ± 2.66 mg/dl on the 15th day and 91.16 ± 2.54 mg/dl on the 21st day, in comparison with a fasting plasma glucose level of 310.5 ± 4.16 mg/dl on the 15th day and 308.33 ± 6.09 mg/dl on the 21st day in the alloxan-induced diabetic group (Ta).

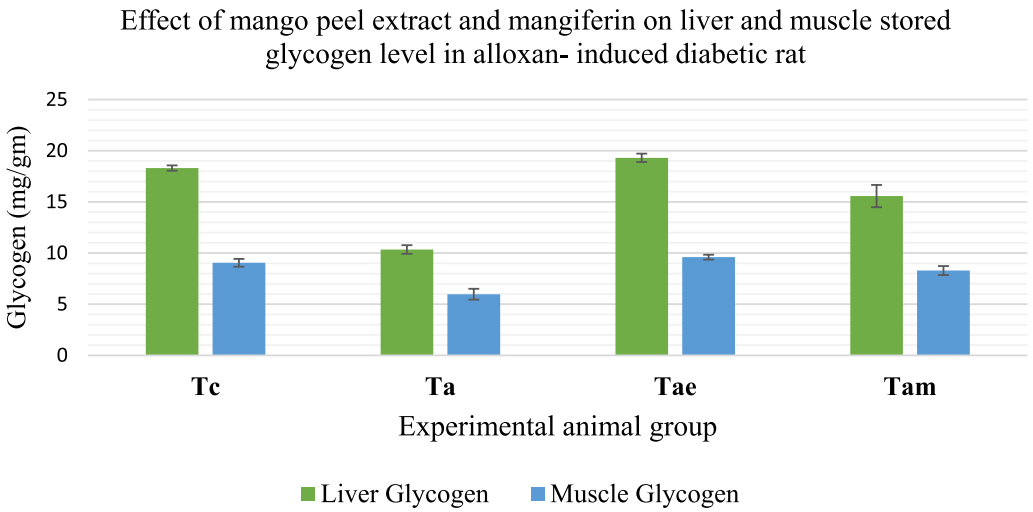


Fig. 3 Effect of mango peel extract and mangiferin on Liver and Muscle glycogen levels in the alloxan-induced type I diabetic rat. Liver and muscle glycogen levels are decreased in Ta group compared to Tc group. In Tam and Tae there was an increase in glycogen content in liver and muscle with the control group (Tc)

Table 4 Effect of mango peel extract and mangiferin on serum lipid profile in the alloxan-induced type I diabetic rat

Group	Total Cholesterol (TC) (mg/dl)	Triglyceride (TGA) (mg/dl)	HDL (mg/dl)	LDL (mg/dl)	VLDL (mg/dl)
Control (Tc)	74.85 ± 0.95	123.49 ± 1.31	26.07 ± 0.89	24.08 ± 1.35	24.69 ± 0.26
Alloxan (Ta)	88.64 ± 1.28**	135.16 ± 1.28**	22.46 ± 0.53**	38.18 ± 1.34**	27.03 ± 0.25**
Alloxan + Extract (Tae)	72.24 ± 1.08$^{\#}$	126.04 ± 1.40$^{\#}$	28.79 ± .1.10$^{\#}$	18.24 ± 1.94*	25.20 ± 0.28$^{\#}$
Alloxan + Mangiferin (Tam)	77.5 ± 1.05$^{\#}$	127.38 ± 1.15*	28.16 ± 1.16$^{\#}$	23.85 ± 1.48$^{\#}$	25.47 ± 0.23*

Values are mean ± SEM ($n = 6$); *Significant at 5% level, **Significant at 1% level and $^{\#}$Not significant

The fluctuations of serum total cholesterol, triglyceride, HDL, LDL, and VLDL levels in different groups are stated in Table 4. Ta group has higher serum cholesterol, triglyceride, HDL, LDL, and VLDL levels, and they are significantly different ($p < 0.01$) than the Tc group. Tae group had a significant difference ($p < 0.05$) in LDL levels compared with the control group. Tam group had a significant difference ($p < 0.05$) in triglyceride and VLDL levels when compared with the control group

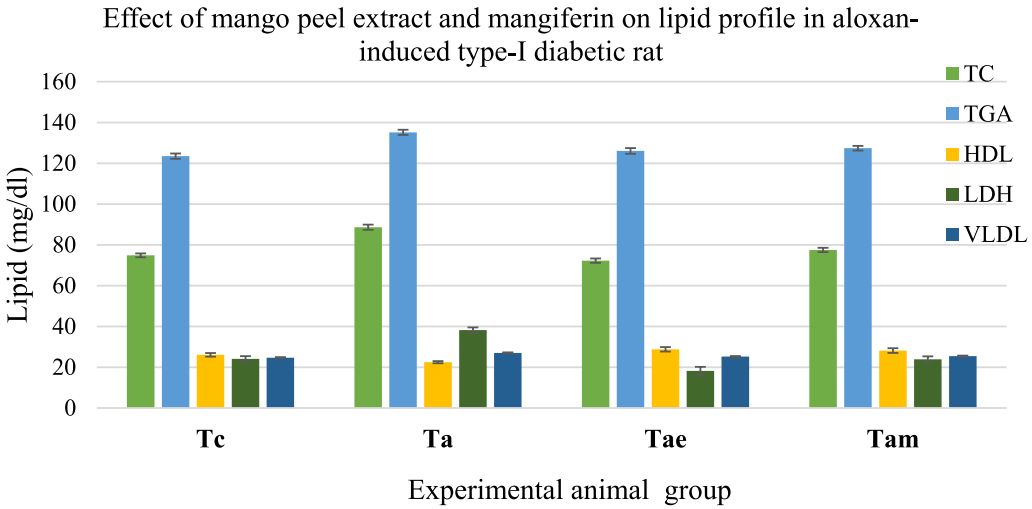


Fig. 4 Effect of mango peel extract and mangiferin on serum lipid profile in the alloxan-induced type I diabetic rat. The fluctuations of serum cholesterol, triglyceride, HDL, LDL, and VLDL levels in different groups are stated in this figure. Ta group has higher serum cholesterol, triglyceride, HDL, LDL, and VLDL levels than the Tc. Tae and Tam groups have lower cholesterol levels compared to the diabetic group (Tc)

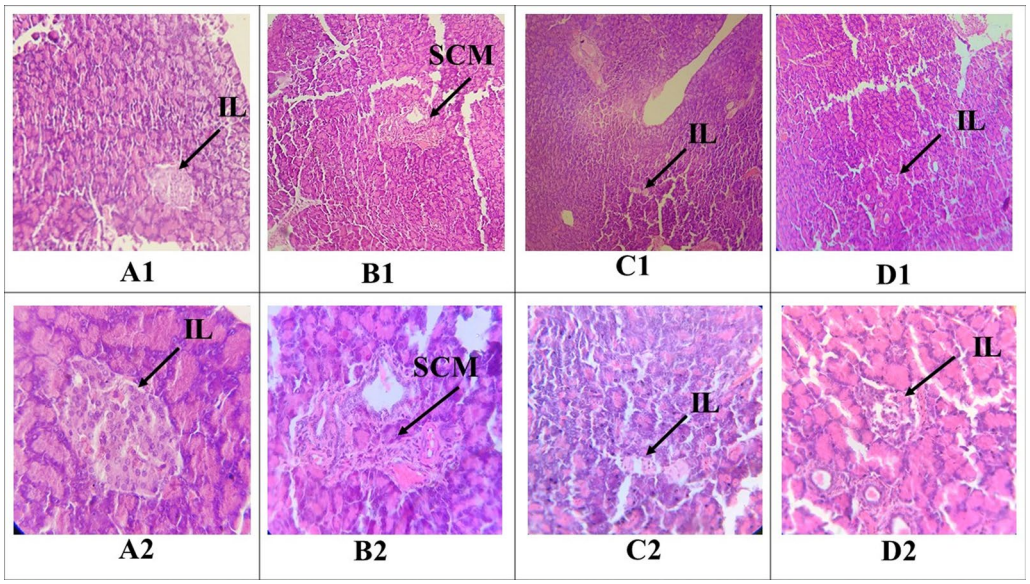


Fig. 5 Histopathological changes of the Pancreas of the control and various experimental groups of rats. IL indicates the Pancreatic Islets of Langerhans and SCM indicates the shrinking cell mass (A1 and A2—Tc group at 100× and 400× magnification, B1 and B2—Ta group at 100× and 400× magnification, C1 and C2—Tae group at 100× and 400× magnification, D1 and D2—Tam group at 100× and 400× magnification)

The effect of mango peel extract and mangiferin on liver and muscle glycogen levels in the alloxan-induced type I diabetic rat

Liver glycogen and tissue glycogen were assessed in different groups after the study period of 21 days. In diabetic rats (Ta), there was a considerable decrease in hepatic glycogen, as seen in Table 3 and Fig. 3. Glycogen content in the liver is 18.31 ± 0.26 mg/g in the control (Tc) group and 10.35 ± 0.42 mg/g in the alloxan (Ta) group. The difference between the control and diabetic groups (Ta) was statistically significant ($p < 0.01$). Mango peel extract and mangiferin had a direct influence on glycogen synthesis in diabetes groups by increasing glycogen levels. Glycogen content in the liver is 19.31 ± 0.41 mg/g in the extract (Tae) group and 15.57 ± 1.09 mg/g in the mangiferin (Tam) group. When the mangiferin-treated group (Tam) and mango peel extract group (Tae) were assessed with the control

group (Tc), there was no statistically significant disparity in liver and muscle glycogen levels. The glycogen content of muscles follows the same pattern as the glycogen content of the liver.

The effect of mango peel extract and mangiferin on serum lipid profile level in the alloxan-induced type I diabetic rat

The mean serum total cholesterol (TC), triglyceride (TAG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and very high-density lipoprotein (VLDL) levels of the control rat group (Tc), diabetic group (Ta), mango peel extract group (Tae), and mangiferin group (Tam) are shown in Table 4 and Fig. 4. Alloxan-induced rats (Ta group) have higher serum cholesterol, triglyceride, HDL, LDL, and VLDL levels, and they are significantly different ($p < 0.01$) than the control group (Tc). Mango peel extract and mangiferin were found to have a nonsignificant impact on serum cholesterol and HDL levels compared with the control group. Mango peel extract was found to have a significant difference ($p < 0.05$) in LDL levels compared with the control group. Mangiferin was found to have a significant difference ($p < 0.05$) in triglyceride and VLDL levels when compared with the control group.

Histological study of the pancreas

The histopathological study of pancreatic structure at 100X and 400X magnification is shown in Fig. 5. Histopathological analysis of the control group (Tc) revealed that the pancreas had a normal structure, and the islets of Langerhans (IL) were of significant size. In the group of rats that were treated with alloxan (Ta), the pancreas had shrunken cell mass (SCM) along with damaged or even destroyed pancreatic lobules, acini, and cells. The pancreas of the animals treated with ethanolic extract of mango peel group (Tae) and mangiferin-treated group (Tam) showed an appearance that was more or less comparable to that of the control (Tc) group in terms of pancreatic lobules, acini, and cells. There were no Islets of Langerhans present in the alloxan (Ta) group. When the alloxan (Ta) group was treated with mango peel extract and mangiferin regeneration of the Islets of Langerhans was seen.

Discussion

Effects of mango peel extract and mangiferin on body weight in the alloxan-induced type I diabetic rat

The fluctuations in body weight are stated in Table 1 and Fig. 1. There was a significant ($p < 0.05$) decline in body weight in all alloxan-induced type I diabetic rats compared to the control group within 21 days. The ethanolic extract of mango peel and mangiferin increased body weight in the same way that the control group did. A nonsignificant disparity was observed between the Tae and Tam groups in comparison with the Tc (control) group. The findings of Saleem et al. [40] confirm the present study and show that body weight is directly correlated with the time period. As a result of the activity of lipid regulatory systems, body weight also increased in the later weeks, according to the findings of Barik et al. [41].

Effects of mango peel extract and mangiferin on plasma glucose levels in the alloxan-induced type I diabetic rat

When compared to the rats used as a control, the induction of alloxan resulted in a huge increase in the amount of glucose, which may be responsible for the cytotoxic impact that alloxan has on beta cells. Due to the fact that alloxan preferentially accumulates in insulin-producing pancreatic beta cells after being taken up by the glucose transporter GLUT2, alloxan poses a moderate threat to the beta cells of the pancreas [42]. This harmful activity is mediated by reactive oxygen species (ROS), and dialuric acid, which is a reduction product of alloxan, is the source of ROS formation. These free radicals eventually transform into hydrogen oxide (H_2O_2). The activity of ROS, along with a significant increase in the concentration of cytosolic calcium at the same time, causes the rapid demise of beta cells [41]. This results in a decrease in the amount of insulin secretion, which in turn leads to an increase in the levels of fasting blood glucose. The findings of other researchers [43–46] are consistent with the results that were obtained. According to a study by Muruganandan et al. (2005) [47], prolonged intraperitoneal injection of mangiferin, isolated from *M. indica*, at doses of 10 and 20 mg/kg once daily for 28 days, shows an antihyperglycemic effect by significantly lowering the levels of fasting blood glucose in STZ- (Streptozotocin) induced diabetic rats. In our study, ethanol extract of mango peel and mangiferin of *M. indica* were also effective in type 1 diabetic rats, and there were no significant differences in fasting plasma glucose levels. Mango peel extract and mangiferin promote or have regeneration ability to regenerate the pancreatic beta cells (Fig. 5) and enhance the secretion of insulin hormone or improve insulin action. As Patel et al. [48] pointed out, potentiation of insulin secretion in the Islets of Langerhans cells, together with its release, has been postulated as a mechanism by which these plants' antidiabetic potentials work. After seven days of treatment, M. Saleem et al. [38] discovered that administering a hydro-alcoholic extract of the *M. indica* plant to alloxan-induced diabetes mice led to a reduction in the postprandial blood glucose concentration. They found that the extracts helped to defend the blood

glucose levels from going up, the body weight from going down, and the beta cell mass from going down. Table 2 and Fig. 2 show that alloxan-induced rats (Ta group) have higher blood glucose levels and are significantly different ($p < 0.01$) than the control group (Tc), which explains the cytotoxic effects of alloxan. Mango peel extract was found to have a significant effect on the changed sugar level. In type 1 diabetic rats, daily oral treatment with 200 mg/kg body weight of mango peel extract for 21 days results in a powerful and significant hypoglycemic impact. In alloxan-induced diabetic rats, oral administration of mangiferin, which is a xanthone glucoside that was isolated from *M. indica*, at a dose of 20 mg/kg once daily for 21 days showed antidiabetic activity.

Effects of mango peel extract and mangiferin on liver and muscle glycogen level in the alloxan-induced type I diabetic rat

In addition to its role in the production of glycogen, the liver plays a buffering role in the body's blood sugar levels after meals. In diabetes, insulin deficiency affects the liver's ability to synthesize glycogen. Increased glycogenolysis happens when glycogen synthase levels deteriorate, and glycogen phosphorylase levels rise. This raises blood glucose levels. This makes the diabetes problem even worse. Hepatic glycogen synthesis is a very important part of keeping glucose levels stable. After a mixed meal, the liver takes glucose from the portal vein and the rest of the body and stores it temporarily as glycogen. [49]. Poorly controlled type 1 diabetic animal have trouble with high blood glucose management after a meal [50] and less glycogen synthesis in the liver [51]. Liver's process of glycogenesis, which is accelerate when food is taken, can be stimulated by mango peel extracts (Creutzfeldt et al.) [52]. This effect was supported by Perpetuo et al. in 2003 [53], who demonstrated that there was a 66% decline in fasting blood glucose levels in type I diabetic rats, compared to control after feeding mango flour for 90 days. Additionally, it was shown that glycogen content in the liver of the control rat was 64% higher than in the diabetic group. According to the author, the rise in glycogen levels in these animals may have helped lower their blood glucose levels. In our study, mangiferin and mango peel extract both worked well to reduce blood sugar levels. They achieve this by increasing the production of glycogen in the liver and skeletal muscle. Glycogenesis capacity of these tissues are consistent with the findings of Perpetuo and Salgado's study as of 2003 [53].

Effects of mango peel extract and mangiferin on serum lipid profile in the alloxan-induced type I diabetic rat

Our studies confirmed that the treatment with mango peel extract and mangiferin has optimized lipid profile values, such as a decrease in serum total cholesterol (TC) levels and triglyceride (TGA) levels (Table 4). Villas Boas et al. [54] found that long-term treatment with *Mangifera indica* aqueous extract was beneficial in lowering blood glucose levels and bringing other biochemical parameters back to normal in diabetic rats. Additionally, they verified that, when compared to diabetic controls, oral treatment of *Mangifera indica* seed kernel extracts decreased total cholesterol and triglyceride levels in diabetic rats. The level of HDL increased and was consistent with Elango's et al. findings [55]. HDL cholesterol plays a beneficial role by helping to transfer cholesterol from peripheral tissues to the liver. When mango peel extract and mangiferin were administered to alloxan-induced diabetic rats, HDL cholesterol levels increased. This suggests that mango peel extract and mangiferin may assist in transporting cholesterol from peripheral tissues to the liver, reducing blood cholesterol levels. The dyslipidemia seen in alloxan-induced diabetic rats is consistent with the studies of Howard and Shan et al. [56, 57]. Diabetes-induced hyperlipidemia may be caused by the excessive mobilization of fat from adipose tissue due to insufficient glucose utilization [58]. The ability of mango peel extract and mangiferin to resist lipid peroxidation may explain their hypolipidemic effect [59, 60]. The improvement in serum lipid profile following mango peel extract and mangiferin treatment suggested that it could be used as a lipid-lowering agent. It has long been established that diabetic dyslipidemia and coronary heart disease (CHD) are strongly correlated. The most serious and potentially fatal complication of diabetes is CHD, and having diabetes doubles or triples one's risk of developing it [61]. Increased TGA and TC levels and lower HDL cholesterol levels are indicative of an abnormal lipid profile known as an atherogenic profile, which contributes to the development of CHD. Following treatment with Mango peel extract and mangiferin, an improvement in lipid profile was found, indicating that the extract may aid in preventing the advancement of cardiovascular illnesses.

Histological study of the pancreas

Histopathological analysis of the control group (Tc) revealed that the pancreas had a normal structure, and the islets of Langerhans (IL) were of significant size. In the group of rats that were treated with alloxan (Ta), the pancreas had shrunken cell mass (SCM) along with damaged or even destroyed pancreatic lobules, acini, and cells. There were no Islets of Langerhans present in the Alloxan (Ta) group. After treatment with mango peel extract and mangiferin, the alloxan (Ta) group experienced beta cell and Islets of Langerhans regeneration. This observation is similar to the study of Wang et al. [62], where mice treated with mangiferin exhibited

significant improvements in glycemia and glucose tolerance, greater beta cell hyperplasia, increased beta cell proliferation, and reduced beta cell death. Mangiferin therapy thus significantly increases beta cell proliferation and islet regeneration, most likely by regulating key genes involved in the cell cycle and islet regeneration processes.

Conclusion

According to the findings of our research, the ethanolic extracts of mango peel and mangiferin appear to have antidiabetic, glycogenis and antihyperlipidemic actions on diabetic rats produced by alloxan. The results of the study confirm the effectiveness of mango peel extract and mangiferin in the treatment of diabetes in animal models.

Abbreviations

µm	Micrometer
°C	Degree celsius
CHOD	Cholesterol oxidase
G	Gram
GLUT2	Glucose transporter 2
GOD	Glucose oxidase
GPO	Glycerophosphate oxidase
H & E	Hematoxylin and eosin
HDL-C	High-density lipoprotein cholesterol
IL	Islets of Langerhans
IP	Intraperitoneally
LD50	Lethal dose, 50%
LDL-C	Low-density lipoprotein cholesterol
mg/dl	Milligram/deciliter
mg/g	Milligram/gram
mg/kg b.w.	Milligram/kilogram/body weight
mg/kg	Milligram/kilogram
min	Minute
ml	Milliliter
mmol/l	Millimole/liter
NaCl	Sodium chloride
Nm	Nanometer
PAP	Phenol 4-amino antipyrine peroxidase
POD	Peroxidase
ROS	Reactive oxygen species
rpm	Revolutions per minute
SCM	Shrunken cell mass
SD	Standard deviation
SEM	Standard error of the mean
Ta	Treatment alloxan
Tae	Treatment alloxan extract
TAG	Triglyceride
Tam	Treatment alloxan mangiferin
TC	Total cholesterol
Tc	Treatment control
VLDL	Very-low-density lipoprotein

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Author contributions

JM, SS, and SB carried out the experiment. MB supervised the whole experimental process and investigation. All authors discussed the results and contributed to the final manuscript.

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Availability of data and materials

My manuscript has associated data in a data repository. Follow the link below for experimental data. Body weight—https://zenodo.org/record/7294365. Glucose levels—https://zenodo.org/record/7294376. Glycogen content-https://zenodo.org/record/7294396
Lipid content—https://zenodo.org/record/7294394. Histology of Pancreas—https://zenodo.org/record/7274832

Declarations

Ethics approval and consent to participate

This study was performed in accordance with the guidelines for the care and purpose of laboratory animals. All the experiments were carried out in accordance with the recommendations of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), India (No. 892/GO/Re/S/o1/CPCSEA), with the approval of the Institute Animal Ethical Committee (IAEC), University of Kalyani.

Consent for publication

All authors hereby consent to the publication of this work in the Future Journal of Pharmaceutical Sciences.

Competing interests

All authors declare that they have no competing interests.

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