

International Journal of Advanced Biochemistry Research



ISSN Print: 2617-4693
ISSN Online: 2617-4707
NAAS Rating (2026): 5.29
IJABR 2026; 10(6): 390-397
www.biochemjournal.com
Received: 15-03-2026
Accepted: 18-04-2026

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Antidiabetic effect of *Gymnema sylvestre* methanolic extract in high-fat diet-fed streptozotocin-induced diabetic rats

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DOI: <https://www.doi.org/10.33545/26174693.2026.v10.i6e.8650>

Abstract

Diabetes mellitus is a chronic metabolic disorder characterised by persistent hyperglycemia and impaired pancreatic function. The present study was undertaken to evaluate the antidiabetic potential of *Gymnema sylvestre* methanolic extract in high-fat-diet-fed streptozotocin-induced diabetic rats. Experimental diabetes was induced after a high-fat diet feeding for 30 days, followed by streptozotocin administration (35 mg/kg, intraperitoneally). Animals were divided into normal control, obese, obese diabetic, metformin-treated and *Gymnema sylvestre*-treated groups. Fasting blood glucose and glycated hemoglobin levels were estimated to assess glycemic control. Histopathological examination of pancreatic tissue was performed using hematoxylin and eosin and chrom alum hematoxylin phloxine staining. Diabetic rats showed significant elevation in fasting blood glucose and HbA1c levels along with marked degeneration of pancreatic islets. Treatment with *Gymnema sylvestre* methanolic extract significantly reduced fasting blood glucose and HbA1c levels compared to diabetic control rats. Histopathological studies revealed partial restoration of pancreatic islet architecture with improved cellular integrity in treated animals.

The findings of the present study suggest that *Gymnema sylvestre* possesses significant antidiabetic activity and may provide protective effects against pancreatic damage associated with diabetes mellitus.

Keywords: Diabetes, Wistar rat, *Gymnema sylvestre*, pancreas, histopathology

Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder characterised by elevated blood glucose levels, with disturbances in insulin secretion and abnormalities in carbohydrate, lipid, and protein metabolism. It is a global health concern with a significant prevalence and associated health burdens affecting millions worldwide. According to the World Health Organisation, by 2030, diabetes mellitus will rank as the seventh most common cause of death globally [1, 2]. Diabetes can be prevented by following a healthy diet, exercising, and using medication. Pharmaceutical medications used to treat diabetes are either excessively costly or have side effects [3]. As a result, many traditional plants have been used as natural drug sources for diabetes mellitus because they are considered safe, less toxic than synthetic ones, and have potent antioxidant properties that make them more effective against diabetes [4]. Plant-based therapy is an ancient medical concept and has been followed for decades. Many chemicals, such as flavonoids, alkaloids, and polyphenols, have been shown in scientific research to have hypoglycemic and insulin-sensitising characteristics [5]. Phytotherapy utilises the healing properties of these natural chemicals, which are frequently thought to have less negative effects than synthetic medications. Medicinal plants have been extensively investigated for their therapeutic potential in the management of diabetes mellitus due to their comparatively lower adverse effects and long history of traditional use. *Gymnema sylvestre*, commonly known as Gurmar, is an important medicinal plant belonging to the family Apocynaceae [6, 7]. It has been traditionally used in Ayurvedic medicine for the treatment of diabetes mellitus. Gymnemic acids and other bioactive constituents present in the plant are reported to possess hypoglycemic activity [8, 9]. Therefore, the present study was designed to evaluate the antidiabetic effect of *Gymnema sylvestre* methanolic extract (GSME) in high-fat diet (HFD)-fed-streptozotocin-induced diabetic rats.

Materials and Methods

Plant materials

The leaves of *Gymnema sylvestre* were bought from Panchavati Herbals, Bengaluru, Karnataka. These were finely powdered in a grinder and stored for further use.

Preparation of the methanolic extract of *Gymnema sylvestre* leaves

The leaves of *Gymnema sylvestre* (Retz.) R.Br.ex.Sm, Family Apocynaceae were purchased from Panchavati Herbals, Bengaluru, Karnataka, and taxonomically identified at ICAR- National Bureau of Plant Genetic Resources, New Delhi, India (AC-14/2020, dated 04/03/2020). The extract of GM was prepared by the hot percolation method using a Soxhlet apparatus. About 30-35 g of the powdered leaves were placed in the porous thimble. The extract was then concentrated using a rotatory vacuum evaporator (Cole-Parmer, USA) under reduced pressure and low temperature (<40 °C). Thereafter, the extract was stored in air-tight containers at 4°C for further studies.

Experimental animals

Forty-eight male Wistar Albino rats weighing 150-200g were purchased from Disease Free Small Animal House, Lala Lajpat Rai University of Veterinary and Animal Sciences, Hisar, after the approval of the Institutional Animal Ethical Committee (IAEC), U.P. Pandit Deen Dayal Upadhyaya Pashu Chikitsa Vigyan Vishwavidyalaya Evam Go-Anusandhan Sansthan (DUVASU) (Project No. IAEC/24/1/36 letter No. 145 / IAEC/ 24 Dated 05-03-2024) as per guidelines of CPCSEA, Govt. of India. Rats were kept in polyacrylic cages and housed in laboratory conditions. Before the start of the experiment, animals were kept in the laboratory conditions for seven days for acclimatisation and maintained under standard management conditions with a daily 12-hour light-dark cycle along with *ad libitum* balanced pelleted feed (Ashirwad Feed Industries, Chandigarh, India).

Induction of type 2 diabetes (metabolic syndrome) in HFD-fed-Obese male Wistar rats

HFD was prepared in our laboratory with minor modifications [10]. HFD was prepared by using normal pelleted feed (365 g), lard (310 g), mixture of vanaspati ghee and coconut oil in ratio of 2:1 (50 g), soybean chunks and/or milk powder (250 g), yeast powder (1 g), sodium chloride (1 g), dl-methionine (3 g) and vitamin and mineral supplement (20 ml as syrup). The rats of each group, except the control group, were fed a high-fat diet prepared *ad libitum* for four weeks to develop an obese rat model. After four weeks of dietary manipulation with HFD, rats were injected with a single dose of Streptozotocin @ 35 mg/kg body weight dissolved in 0.1 M citrate buffer (pH 4.5) intraperitoneally after an overnight fast. Rats injected with streptozotocin were closely monitored for their behavior and any other clinical signs. The development of diabetes mellitus in the rats was confirmed by testing fasting blood glucose (FBG) levels after 72 hours of STZ injection. The rats with FBG higher than 200 mg/dL and a change in body weight of 8% of initial weight to ensure a true diabetic rat model [11]. Rats that were per the above criteria were included in the present study.

Experimental design

Rats were randomly divided into five groups (n=8), subjected to different treatments as detailed in Table 1.

Weekly body weight, feed and water intake

Body weights, weekly feed and water intake were measured weekly to determine the effect of the treatments on rats.

Hematobiochemical parameters

Fasting blood glucose levels

The effect of extracts on the fasting blood glucose levels of rats was assessed by collecting blood samples from experimental rats after overnight fasting on days 1, 3, 15, 30, 45, and 60 after induction of diabetes. Blood glucose estimation was performed using Accu-Chek Performa glucometer strips.

Serum biochemical parameters

Blood was collected in clot-activated vials from the retroorbital plexus. Total cholesterol (TC), triglycerides (TRI), low-density lipoproteins (LDL) and high-density lipoproteins (HDL) were estimated in serum samples using commercially available kits of Arkray Healthcare Pvt. Ltd. with the help of a multimode microplate reader, Spectramax i3x, after four weeks of high-fat diet and before sacrifice.

Glycated haemoglobin (HbA1c) assay

Glycated haemoglobin (HbA1c) assay was performed in whole blood samples on the 60th day, using commercially available kits of Coral Diagnostics using a multimode microplate reader, Spectramax i3x.

Histopathological examination

Pancreatic tissues isolated from rats of all the groups were fixed in 10% buffered formal-saline for 48 h, dehydrated in ascending alcohol grades, and embedded in paraffin wax. Approximately 5-6 µm-thick sections were prepared and stained with hematoxylin and eosin (H & E) for assessment of the general morphology under light microscopy [12].

Chrom alum hematoxylin phloxine (CHP) staining of pancreas

The pancreatic tissue was stained with Gomori's chrom-alum hematoxylin phloxine [13]. After deparaffinization and hydration, sections were mordanted in Bouin's solution, oxidized with potassium permanganate, and stained sequentially with chromium hematoxylin and phloxine B. The sections were then dehydrated, cleared in xylene, mounted in DPX, and examined under a Leica ICC50 microscope to assess histo-architectural changes.

Statistical analysis

Results are expressed as mean ± SEM. 'n' refers to the number of animals used in each experimental protocol. Statistical analysis of data was performed using Prism, version 8.00 (GraphPad Prism Software, San Diego, CA, USA) by One-way / Two- way ANOVA, followed by Tukey's multiple comparisons post-hoc tests. A value of $P < 0.05$ was considered statistically significant. Weekly body weight, feed intake, water intake and fasting blood glucose were analysed using two-way repeated-measures ANOVA followed by Tukey's post hoc test. Biochemical and organ weight data were analysed using one-way ANOVA followed by Tukey's multiple comparison test.

Results

Effect of high fat diet on BW, TC & TG before & after HFD

Body weight, total cholesterol and triglyceride levels were significantly ($P < 0.05$) increased in groups II-V after 30 days of high-fat diet feeding compared to group I where Group I, rats not fed a high-fat diet increase in body weight

was recorded to 218.2 ± 4 g from 157.5 ± 4.3 g, which were significantly different ($P < 0.05$) compared to groups II-V, as shown in Figure 1, where BW ranged from 255.1 ± 8.0 to 271.3 ± 12.2 g. There was a significant ($P < 0.05$) increase in serum TC and TRI in groups II-V, indicating the establishment of an obese rat model.

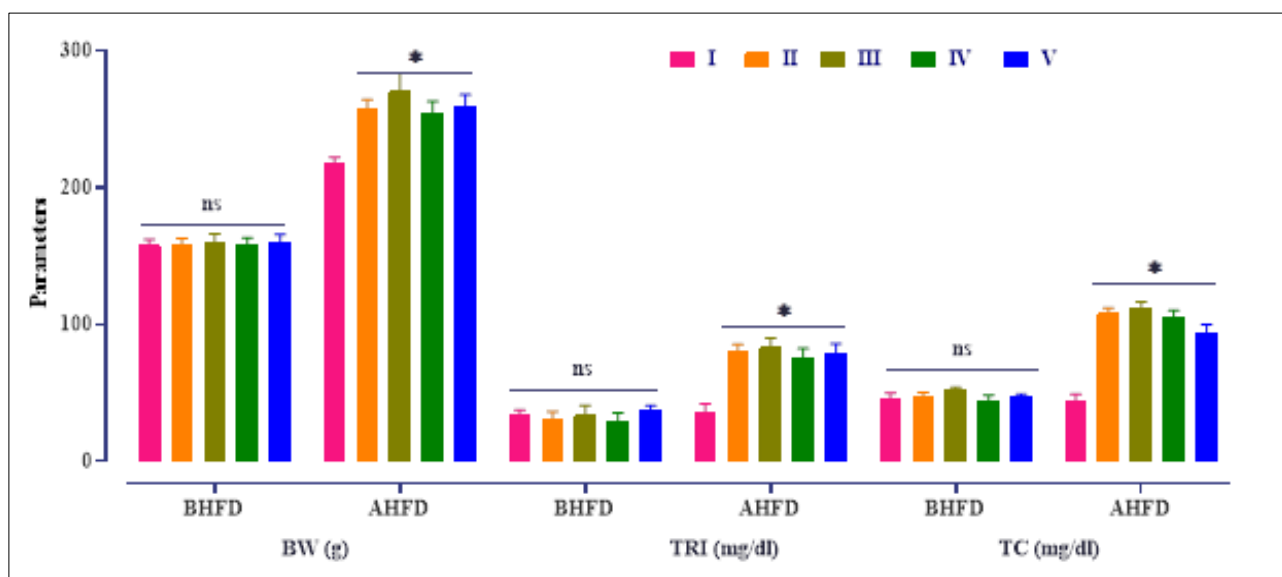


Fig 1: Effect of a high-fat diet on BW, TRI and TC. (* $P < 0.05$ vs. group I)

Effect on weekly body weight

Results showed that throughout the 8-week study period, the obese group exhibited a steady increase in body weight, rising from 252.00 ± 6.12 g at week 0 to 304.50 ± 4.21 g by week 8, reflecting a $21.12 \pm 2.01\%$ gain. In contrast, the OD group demonstrated a significant and continuous reduction

in body weight, declining from 239.75 ± 5.72 g to 179.38 ± 8.49 g, resulting in a $25.28 \pm 2.87\%$ loss (Fig. 2). The OD group showed a decrease in weight gain (-20.89%), followed by OD + GSME ($+2\%$) and OD + Met ($+3.99\%$). In contrast, the obese exhibited the highest per cent gain ($+12.1\%$) compared to the control ($+11.34\%$).

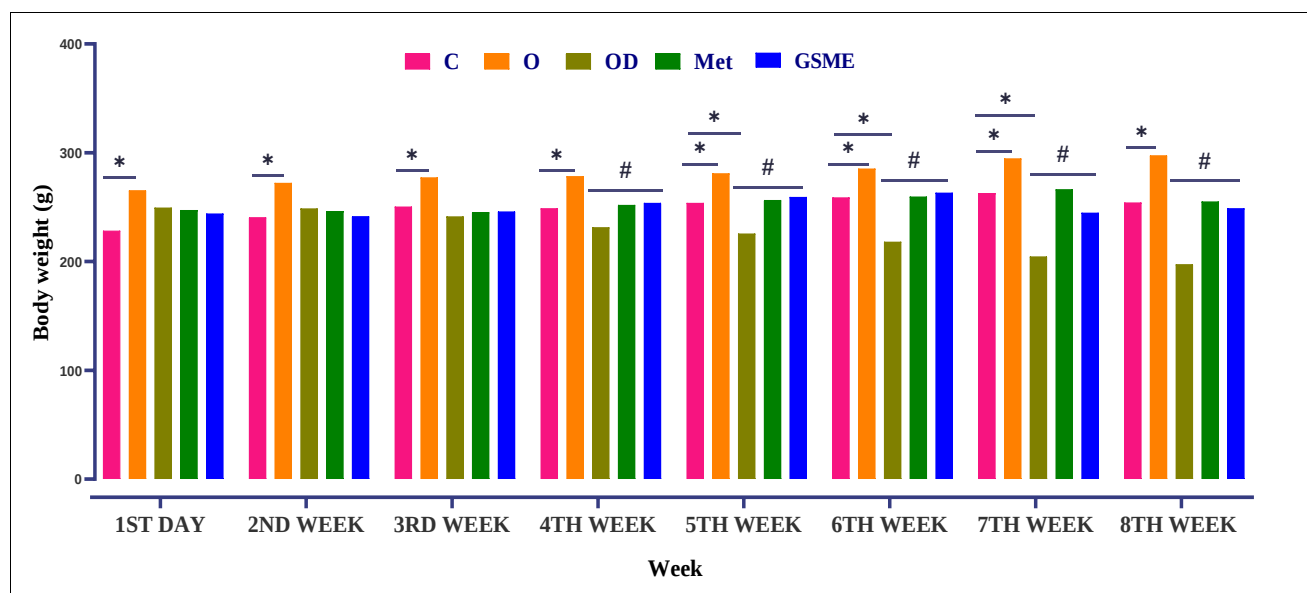


Fig 2: Weekly body weight (* $P < 0.05$ vs. Control and # $P < 0.05$ vs. Obese Diabetic)

Effect on weekly feed and water intake

Feed and water intake were measured at a weekly interval and the data were summarised in Fig 3 and 4. The OD rats

increased water (447.96 ± 0.87 ml) and feed (143.7 ± 1.3 g) intake during the experiment compared to control rats (293.41 ± 1.91 ml, $30 \pm 244.2 \pm 1.08$ g, respectively).

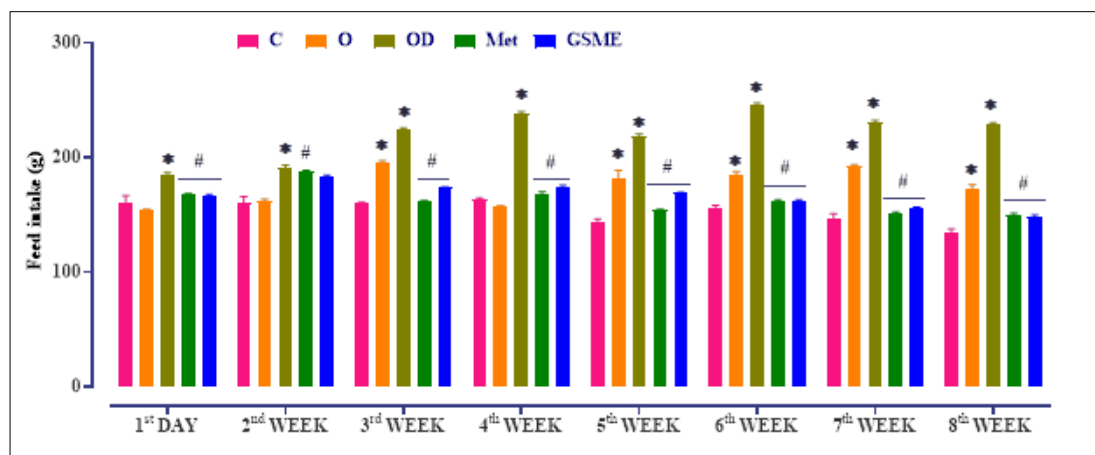


Fig 3: Weekly feed intake (* $P < 0.05$ vs. Control and # $P < 0.05$ vs. Obese Diabetic)

Whereas, OD + Met rats showed a significant ($P < 0.05$) decrease in feed intake from the 3rd week onwards and water intake from the 4th week onwards compared to the OD group. However, OD + GSME groups was almost

comparable to the control group. This group showed ($P < 0.05$) reduced feed and water intake from OD groups from the 3rd week onwards ($P < 0.05$).

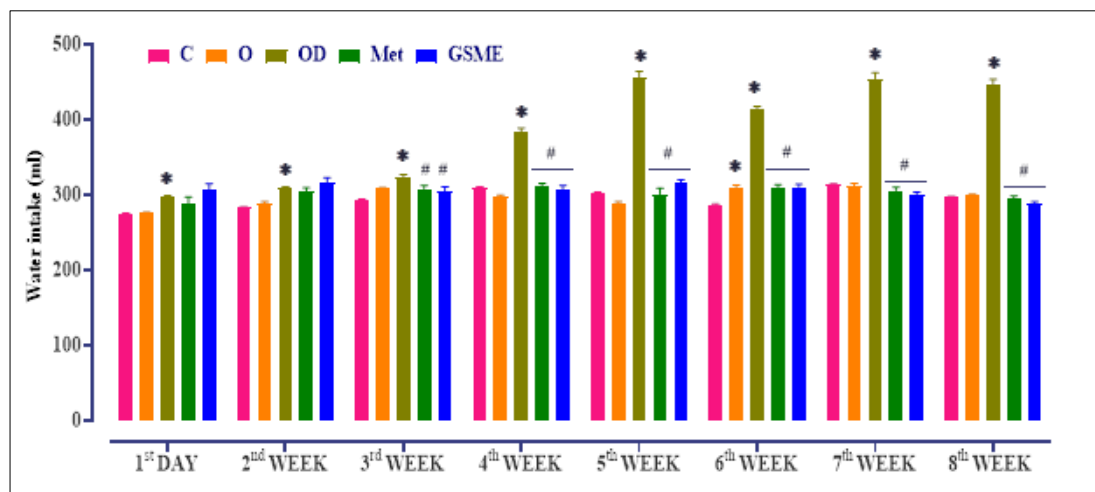


Fig 4: Weekly water intake (* $P < 0.05$ vs. Control and # $P < 0.05$ vs. Obese Diabetic)

Effect on hematobiochemical parameters

Effect on fasting blood glucose

Fasting blood glucose levels remained stable in the control group throughout the study, ranging from 99.33 ± 2.95 mg/dL on day 0 to 118.58 ± 5.32 mg/dL on day 60 (Fig. 5). The obese group showed a gradual rise, reaching

116.25 ± 6.55 mg/dL by day 60. In contrast, the OD group exhibited a sharp increase by the 3rd day (389.12 ± 33.1 mg/dL) and gradually declined to 268.81 ± 16.05 mg/dL by day 60. GSME showed marked glucose-lowering effects, with final values of 125.2 ± 13.3 mg/dL indicating their potential antidiabetic efficacy in hyperglycemic conditions.

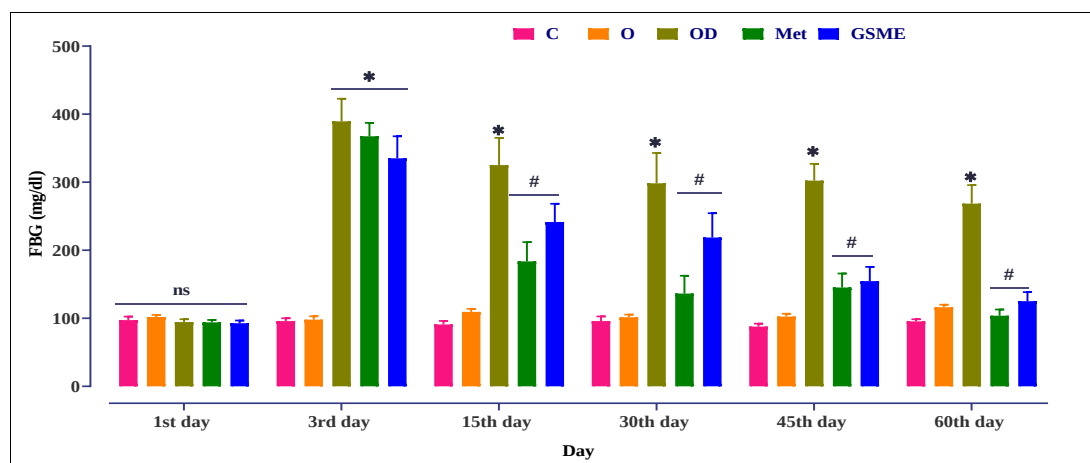


Fig 5: Fasting blood glucose (* $P < 0.05$ vs. Control and # $P < 0.05$ vs. Obese Diabetic)

Effect on serum parameters

Obese and obese diabetic rats showed a significant rise in triglycerides (TRI), total cholesterol (TC), and low-density lipoprotein (LDL), along with a marked decrease in high-density lipoprotein (HDL) compared to controls, indicating dyslipidemia. Treatment with Metformin and GSME

significantly improved lipid profiles. All the treatments lowered TRI, TC, and LDL levels while increasing HDL levels as depicted in Fig. 6. Among them, GSME showed effects comparable to Metformin, suggesting their potential in managing diabetes-associated dyslipidemia.

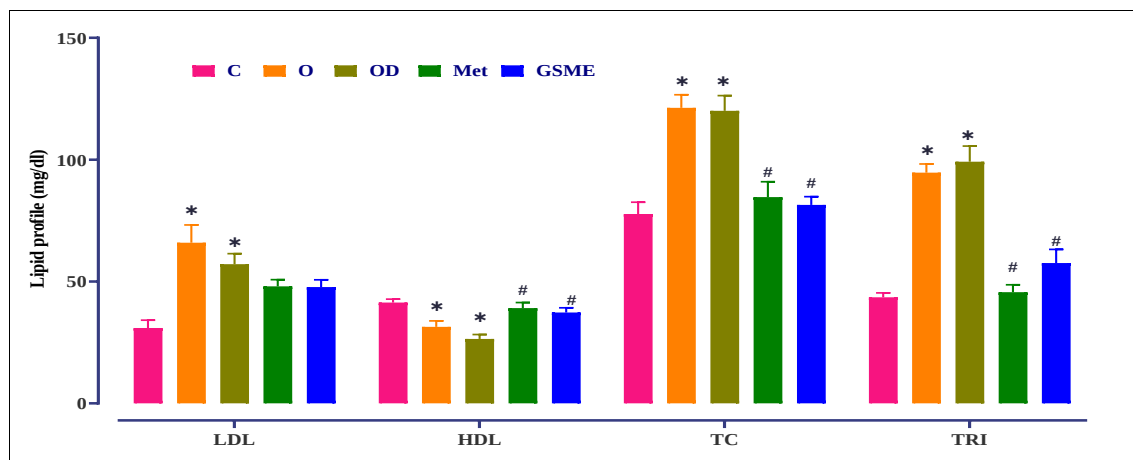


Fig 6: Lipid profile (* $P < 0.05$ vs. Control and # $P < 0.05$ vs. Obese Diabetic)

Effect on glycosylated hemoglobin

HbA1c levels were significantly elevated in the obese diabetic group (11.8%) compared to all other groups. Treatment with GSME (8.5%) significantly reduced HbA1c

levels, though not to normal levels (Fig.7). Metformin-treated rats (6.3%) showed HbA1c values similar to control (2.9%) and obese (4.1%) groups, indicating effective glycemic control.

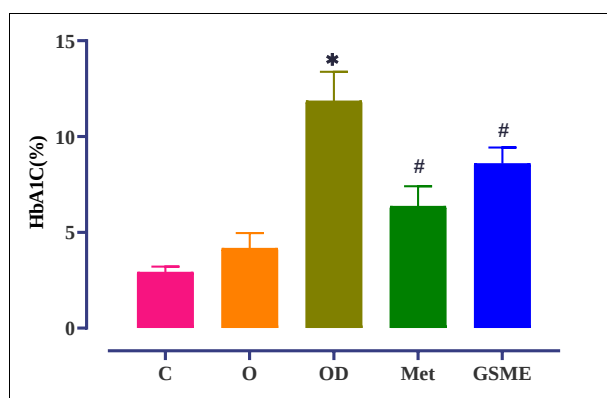


Fig 7: Glycated hemoglobin (HbA1c%) (* $P < 0.05$ vs. Control and # $P < 0.05$ vs. Obese Diabetic)

Effect on absolute and relative organ weight

A non-significant decrease in the absolute weight of these organs was recorded in the OD group compared to the control and obese group rats (Fig 8a). OD + Met group (1.08 ± 0.04) showed a significant ($P < 0.05$) increase in

pancreas weight compared to the OD group (0.69 ± 0.07). GSME have been observed to restore the absolute weights of the heart and liver towards the control value, while a nonsignificant increase in the pancreas weight compared to the OD group.

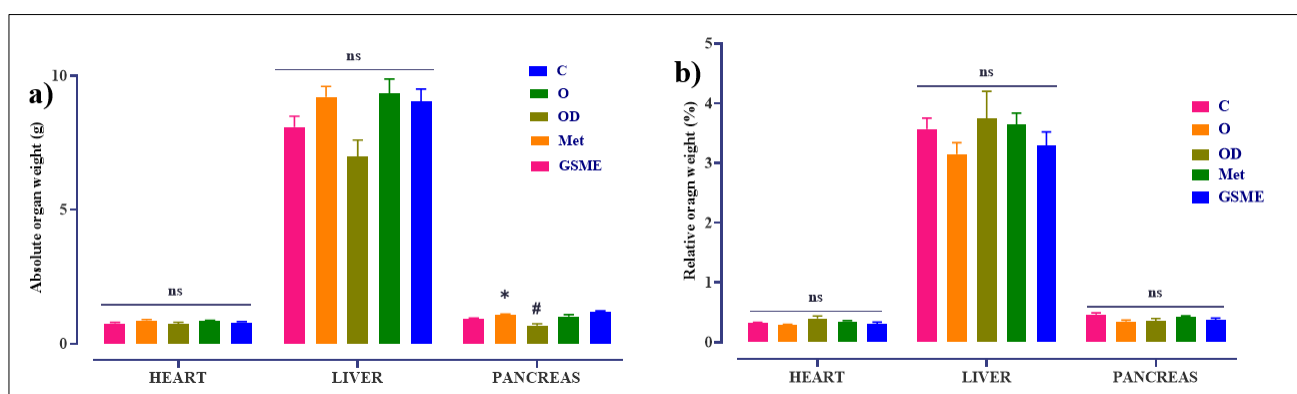


Fig 8: a) Absolute organ weights, b) Relative organ weights (* $P < 0.05$ vs. Control and # $P < 0.05$ vs. Obese Diabetic)

The relative organ weights of the OD group showed a non-significant decrease compared to the control group (Fig 8b). Perusal of the data revealed a non-significant but marked increase in relative organ weight of the liver, heart, and pancreas in OD+GSME groups compared to OD group.

Histopathology

Hematoxylin and eosin staining of pancreas

Figure 9 (A-E) depicts the histopathological changes

observed in the rat pancreas following H & E staining across different groups. Control (Fig. 9A) and obese rats (Fig. 9B) showed a normal structure of pancreatic islets with even borders. OD group showed fewer islets, constricted and showed irregular borders of the islets (Fig. 9C). Metformin and GSME showed restoration of pancreatic islets with increased size of pancreatic islets and regular borders of pancreatic islets (Fig. 9D & E).

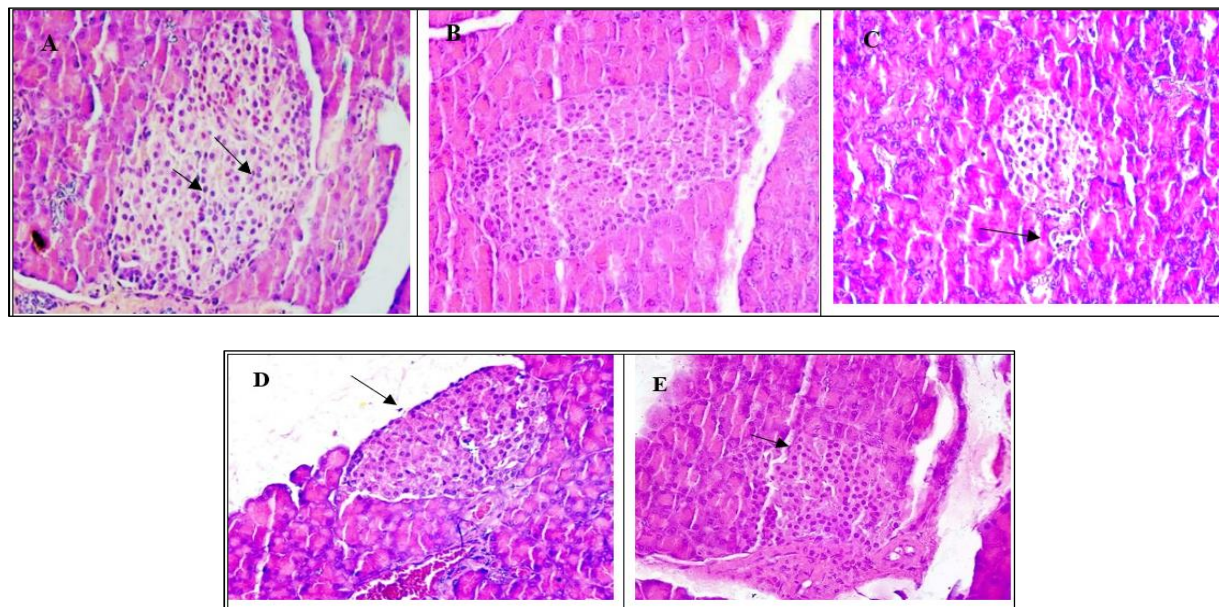


Fig 9: (A) Control: Islet cells (black arrow), normal nuclear morphology and exocrine portion, (B) Obese: normal islet nuclei and granular cytoplasm and regular outline, (C) OD: Islet with decreased number of cells, mild disorganised acini (black arrow), (D) OD + Met: Normal islet with regular outline and cells (black arrow), (E) OD + GSME: Well-defined islet with preserved outline and structure (black arrow) H & E x 400

Chrom-alum hematoxylin and eosin staining of the pancreas

Figure 10 (A-E) revealed distinct islets of Langerhans showing clear demarcation of endocrine versus exocrine regions. The chrome alum hematoxylin-phloxine staining of the pancreas of the healthy control (Fig. 10A) and obese

group (Fig. 10B) shows healthy islets with alpha and beta cells. In the OD group (Fig. 10C), shrunken islets with degeneration of beta cells were observed. Metformin (Fig. 10D), GSME (Fig. 10E) showed compact and regular margins with improved beta cell mass compared to the OD group.

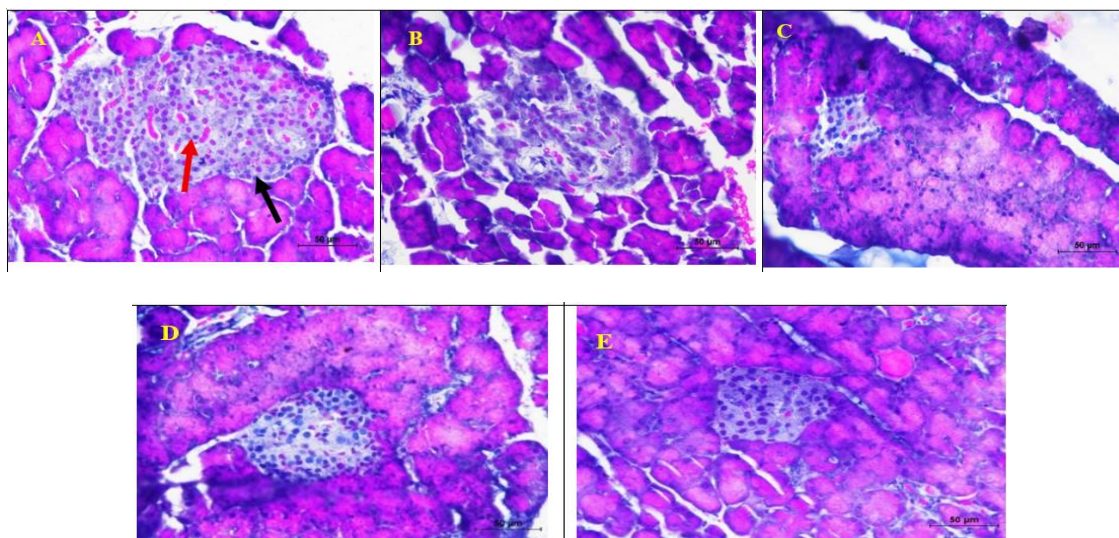


Fig 10: (A) Control: Islet with regular outline and alpha cells (red arrow) in between beta cells (black arrow), (B) Obese: Islet with regular outline and alpha, beta cells, (C) OD: Islets with damaged β cells with irregular outline and decreased number of β cells, (D) OD + Met: Islets with a partial restoration in the density of bluish-stained β -cells, (E) OD + GSME: Islet with increased beta cell compared to OD group. (CHP x 200)

Discussion

The present study demonstrated that *Gymnema sylvestre* methanolic extract exerted a significant antidiabetic effect in high-fat-diet-fed streptozotocin-induced diabetic rats. The marked reduction in fasting blood glucose observed after treatment indicates that the extract was able to improve glycemic control in a condition characterised by persistent hyperglycemia. Since the model used in this study mimics type 2 diabetes with both insulin resistance and partial beta-cell dysfunction^[14, 15], the fall in glucose levels suggests that *Gymnema sylvestre* may act through a combination of glucose-lowering and pancreatic protective effects. The improvement was not limited to a short-term change in blood glucose, because the reduction in glycated haemoglobin also showed better long-term regulation of glucose exposure^[16].

Loss of body weight is a common finding of diabetes and is primarily attributed to disruption of normal metabolic pathways. Impaired glucose utilisation for energy results in enhanced protein catabolism and reduced protein storage, ultimately leading to a decline in body weight^[17]. In the present study, diabetic rats exhibited a marked reduction in body weight and decreased percentage change in weight compared to control rats. Administration of the GSME significantly ameliorated weight loss and improved percentage weight gain in treated diabetic groups. Studies by Mishal *et al.* (2020)^[18] revealed that GSME has been shown to regulate body and visceral fat weights in obese diabetic models, supporting its role in stabilising weight through improved metabolic control. However, changes in absolute and relative organ weights were minimal and remained statistically nonsignificant except for the absolute organ weight of the pancreas in control and OD rats.

OD + GSME also produced a gradual but significant decrease in FBG. While the early glucose reduction was slower than that observed with GSME demonstrated effective glycemic management over the study period^[4, 19]. HbA1c is an important marker because it reflects average blood glucose over a prolonged period. The% HbA1c indicates partial improvement in long-term glucose homeostasis. The hypoglycemic effects of GSME are likely mediated by enhanced insulin secretion, improved insulin sensitivity, and modulation of incretin pathways, consistent with previous studies^[20]. This finding suggests that the extract did not merely cause a transient decline in glucose but also helped maintain better glycemic balance over the duration of treatment.

Diabetic rats exhibit signs of polyphagia (increased feed intake) and polydipsia (increased water intake) due to insulin deficiency, which impairs glucose utilisation. Due to insulin deficiency, cells fail to uptake glucose efficiently, leading to increased hunger and thirst. This is to compensate for energy loss and osmotic imbalance^[17].

DM is frequently associated with disturbances in lipid metabolism, leading to dyslipidemia, which plays a critical role in the development of cardiovascular complications. In the present study, obese and OD rats exhibited a significant

elevation in serum total cholesterol (TC), triglycerides (TRI) and low-density lipoprotein (LDL) levels, accompanied by a marked reduction in high-density lipoprotein (HDL) levels^[20, 21]. Treatment with GSME produced a significant normalisation of lipid profile in obese diabetic rats. These effects may be mediated through the insulinotropic and insulin-sensitising actions of *Gymnema* constituents, which enhance glucose utilisation and reduce the flux of free fatty acids to the liver. Improved glycemic control subsequently leads to better regulation of lipid metabolism. A previous study by Singh *et al.* (2017)^[22] has demonstrated that *Gymnema sylvestre* improves lipid abnormalities in high-fat diet and streptozotocin-induced diabetic rats, thereby reducing the risk of atherosclerosis and cardiovascular dysfunction.

The pancreatic histopathology further supported the biochemical findings. In untreated diabetic rats, the pancreas showed prominent structural damage, including distortion of the islets, cellular disorganisation, and degenerative changes in endocrine tissue. These changes are consistent with streptozotocin-induced pancreatic injury and with the reduction in functional beta-cell mass that occurs in experimental diabetes^[23, 24]. In contrast, rats treated with GSME showed better preservation of pancreatic architecture, improved islet integrity, and less cellular degeneration. This indicates that the extract had a protective effect on pancreatic tissue and may have helped maintain the structural basis required for insulin secretion^[24, 25].

In the obese and diabetic groups, chrom alum hematoxylin revealed distorted islet architecture, cellular disorganisation, and degenerative changes, indicating pancreatic injury caused by the diabetic state^[26]. In the metformin-treated group, the stain showed partial restoration of tissue organisation and better preservation of islet morphology compared with the untreated diabetic group. The GSME showed the most improved pancreatic histology among the herbal treatment groups, with clearer islet boundaries, reduced degeneration, and better preservation of cellular structure^[9, 18].

The preservation of pancreatic histoarchitecture is particularly significant because it suggests that the antidiabetic action of *Gymnema sylvestre* may not be limited to lowering blood glucose alone. Rather, it may also contribute to tissue repair or protection against further diabetic damage. The findings of this study also align with the traditional use of *Gymnema sylvestre* as a medicinal plant in diabetes. Overall, the present study shows that GSME improved glycemic control and protected pancreatic tissue in diabetic rats. The decrease in fasting blood glucose and HbA1c demonstrated clear antidiabetic activity, while histopathology confirmed structural improvement in the pancreas. These combined findings suggest that the extract has both functional and tissue-level benefits in experimental diabetes. The study therefore supports the potential use of *Gymnema sylvestre* as a natural antidiabetic agent with pancreatic protective properties.

Table 1: Experiment Design

Groups	Treatments
Control (C)	Normal pelleted diet
Obese (O)	High-fat diet
Obese Diabetic (OD)	High-fat diet + streptozotocin (35 mg/kg, i.p.)
OD + Metformin (Met)	High-fat diet + streptozotocin (35 mg/kg, i.p.) + metformin (50 mg/kg, p.o.)
OD + <i>Gymnema sylvestre</i> Methanolic Extract (GSME)	High-fat diet + streptozotocin (35 mg/kg, i.p.) + <i>Gymnema sylvestre</i> methanolic extract (400 mg/kg, p.o.)

Conclusion

The present study demonstrated that GSME possesses significant antidiabetic activity in high-fat diet and streptozotocin-induced diabetic rats. The extract effectively reduced fasting blood glucose and HbA1c levels and improved pancreatic histopathological alterations. These findings suggest the therapeutic potential of *Gymnema sylvestre* in the management of diabetes mellitus.

Acknowledgments

The authors are grateful to the Department of Veterinary Pharmacology and Toxicology, College of Veterinary Science and Animal Husbandry, DUVASU, Mathura, for providing the necessary facilities to conduct the research work.

Conflict of interest

The authors have no conflict of interest.

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