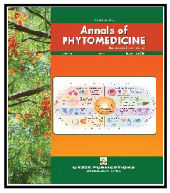
Annals of Phytomedicine 15(1): 727-735, 2026

DOI: http://dx.doi.org/10.54085/ap.2026.15.1.65

Annals of Phytomedicine: An International Journal
http://www.ukaazpublications.com/publications/index.php

Print ISSN : 2278-9839 Online ISSN : 2393-9885



Original Article : Open Access

Antidiabetic activity and pancreatic histopathological analysis of *Rabdosia rugosa* (Wall. Ex Benth.) H. Hara leaf extract on streptozotocin-induced diabetes in Wistar rats

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Article Info

Article history
Received 23 April 2026
Revised 26 May 2026
Accepted 27 May 2026
Published Online 30 June 2026

Keywords
Rabdosia rugosa (Wall. Ex. Benth.) H. Hara
CERR
Streptozotocin
Diabetes
Histopathology

Abstract

Diabetes mellitus (DM) is a chronic disorder featured by persistent hyperglycaemia due to defective insulin secretion and/or action, along with metabolic complications. Treatment of diabetes in the far-flung area is difficult and costly, with adverse effects. The "Sulae" aka *Rabdosia rugosa* (Wall. Ex. Benth.) H. Hara is a medicinal plant found in the Himalayan region, and traditionally, its leaves are used by local communities to manage diabetes; to validate its antidiabetic potential, the study was planned. Chloroform extract of *R. rugosa* leaf (CERR) was assessed for its antihyperglycemic activity in STZ-induced diabetic female rats. The study employed female Wistar rats, which were randomly assigned to 3 Groups (n=6). Group 1 served as the negative control, while non-diabetic rats in Groups 2 and 3 received CERR at @ 50 mg/kg and 300 mg/kg, respectively. Diabetes was induced in Wistar rats using streptozotocin (55 mg/kg BW), and those that crossed the 250 mg/dl of blood glucose in 7 days were assigned randomly into 4 Groups (n=6 each). Group 4 served as the diabetic control; Groups 5 and 6 received CERR @ of 50 and 300 mg/kg orally, respectively; and Group 7 received glibenclamide @ 5 mg/kg BW for 4 weeks. Blood glucose, body weight and histopathological changes in the pancreas were evaluated using standard methods. Administration of CERR produced an outstanding, dose-dependent drop in blood glucose and a concomitant increase in mean body weight among diabetic rats in Groups 5 and 6. Histopathology of the pancreas revealed dose-dependent restoration of normal pancreatic microanatomy, with reduced cellular deterioration. The mean blood glucose in Groups 2 and 3 and the pancreatic histopathology, were as good as in the normal non-diabetic Group 1, indicating that the extract is safe and does not induce hypoglycaemia in non-diabetic animals. To conclude, the chloroform extract of *R. rugosa* leaf at the dose rates of 50 and 300 mg/kg BW can help reduce hyperglycaemia in diabetic animals and regenerate and restore pancreatic acini and islet cells damaged by the cytotoxic effect of streptozotocin. The same extract remained safe for nondiabetics, thereby supporting its traditional medicinal use.

1. Introduction

Diabetes mellitus (DM) is a chronic disorder featured by persistent hyperglycaemia due to defective insulin secretion and/or action (American Diabetes Association, 2014). It is a non-communicable ailment, prevalent worldwide, that leads to severe complications that include neuropathy, nephropathy, retinopathy and cardiovascular conditions (Forbes and Cooper, 2013). The incidence of DM is increasing at an alarming rate. According to the IDF, approximately 382 million people were affected by diabetes worldwide in 2013, with a projection of about 592 million by 2035 (IDF, 2013). In addition, diabetes is projected to be the 7th top cause of death worldwide by the year 2030 (WHO, 2016). Type 1 DM is an insulin-dependent condition caused by insufficient insulin production due to damage or dysfunction of pancreatic β-cells. In contrast, type 2 DM is a non-insulin-dependent disorder characterised by insulin resistance and/or reduced insulin secretion. Notably, nearly 95% of diabetic cases are attributed to type 2 DM (Kharroubi and Darwish, 2015).

The modern antidiabetic remedies do accompany adverse effects, *i.e.,* hypoglycaemia, fluid retention, osteoporosis and cardiovascular difficulties, which often limit their protracted use (Inzucchi *et al*., 2012). These concerns prompt the researcher to seek safer, yet effective therapeutic agents to deal with diabetes. Despite the quiver being relatively full of various modern antidiabetic drugs, which are used for a protracted duration, often life-long, they are associated with adverse effects, limited efficacy and high cost. These have led to increased traction for medicinal plant-based alternative therapies that are easily accessible, culturally acceptable, and relatively safe and cost-effective (Modak *et al*., 2007). Traditional medicine systems most often advocate plant-based remedies for managing various ailments, including diabetes. The Himalayan range has diverse agroclimatic conditions and therefore harbours numerous medicinal herbs that local communities have used for generations (Zahoor *et al*., 2024).

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R. rugosa (syn. *Isodon rugosus*) is an herb from the family Lamiaceae. It is dispersed in the Himalayan range and has ethnomedicinal value (Singh *et al*., 2019). It has multiple local-language names, such as "Maldah" and "Sulae" in Jammu and Kashmir, and "Chichiri" in Kinnaur. "Sulae" commonly flourish on dry mountain slopes at altitudes of almost 5000 to 10000 ft and are scattered across India, Nepal, Pakistan, Afghanistan, Southwest China and Southeast Arab. It is an aromatic, profusely branched shrub with quadrangular stems, ovate-elliptical leaves and white to light purple flowers arranged in terminal panicles. Various parts of the "Sulae" plant contain a range of phytochemicals, including phenolics, flavonoids, terpenoids and others, which have substantial biochemical and pharmacological activities (Singh *et al*., 2019).

Oral hypoglycaemic agents, such as metformin (biguanides), are used in modern medicine to manage type 2 diabetes, facilitate glucose uptake, and suppress glucose output from the liver (Lorenzati *et al*., 2010). glibenclamide (sulfonylureas) kindles insulin secretion from islet β-cells (Rena *et al*., 2017). Liraglutide (a glucagon-like peptide-1 receptor agonist) improves glycaemic control, with additional slimming benefits and cardiovascular safety (Davies *et al*., 2018). Although, the pharmacological quiver has multiple options, managing diabetes remains a challenge. The high treatment costs and adverse effects continue to drive people to seek safer, more effective, and more economical remedies (American Diabetes Association, 2023; Davies *et al*., 2018). The flora and fauna around do harbour medicinal plants which have been used as remedies since ancient times and remain important in managing diseases such as diabetes. This prompted us to study and evaluate the antidiabetic potential of the leaves of *R. rugosa*, using qualitative and quantitative phytochemical analysis, antioxidant assays, biochemical estimations and histopathological examination in STZ-induced diabetic rats. The study aims to provide scientific evidence supporting the traditional use of this plant in diabetes management.

2. Materials and Methods

The plants of *R. rugosa* (as depicted in Figure 1), the leaves of which were collected from Bhaderwah (Doda), located as shown in Figure 2. The plant specimen was submitted for authentication to the Department of Botany, University of Jammu, under Accession No. HBJU-18101. The collected leaves were washed thoroughly, made lint-free, shade-dried, crushed and ground into a fine powder, then extracted in a Soxhlet apparatus using HPLC-grade chloroform as solvent, concentrated and stored in a suitable airtight jar for further use. Before oral gavage to the rats, the extract was homogenised in 0.1% carboxymethyl cellulose (CMC) to obtain the desired concentration.

Figure 1: The plant of *Rabdosia rugosa* (Wall. Ex. Benth.) H. Hara *in situ*.

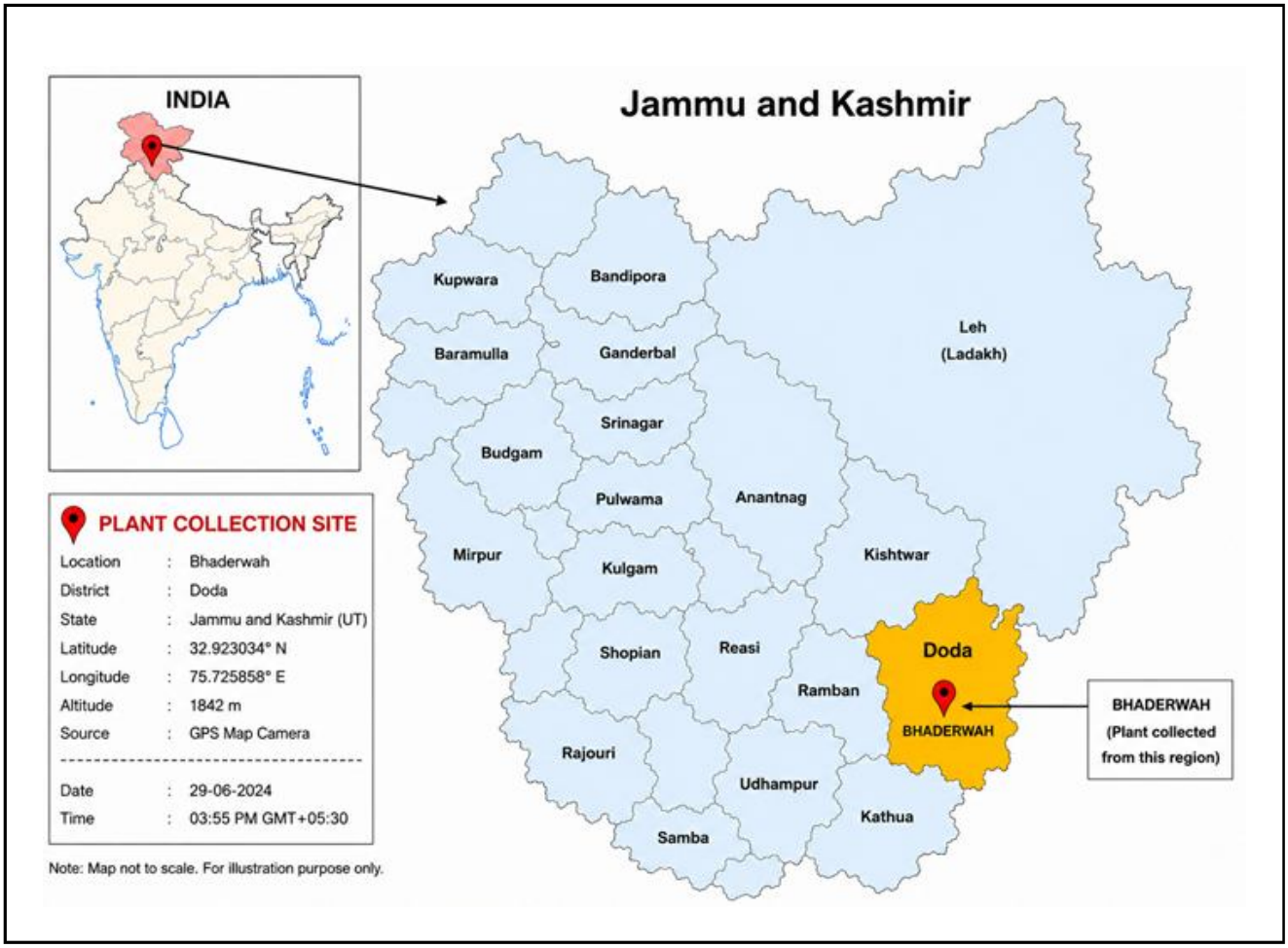

Figure 2: The location of the collection of the *Rabdosia rugosa* (Wall. Ex. Benth.) H. Hara leaf.

Analytical- and/or HPLC-grade chemicals were used throughout the course of study. A total of 42 female Wistar rats were procured from the IIIM, Jammu, Jammu and Kashmir (UT), India. The Wistar rats were allowed to acclimatise for three weeks before the experiment commenced. The Wistar rats were placed in the ambience at 25°C, 50-60% relative humidity and an even light/dark cycle under optimal standard laboratory conditions and were provided with a standard pelleted ration and water *ad lib.* The animals were under continuous observation throughout the study span, and the experimental procedures were conducted in accordance with the NIH guidelines for laboratory animals (NIH No. 85-23, revised 1996). The experimental protocol of the study was preapproved vide IAEC approval no. 1/IAEC/24/2025.

2.1 Determination of extraction yield

The extractability percentage is calculated by the formula mentioned:

$$\text{Percent extractability} = \frac{\text{Weight of the extract}}{\text{Weight of the plant material taken for extraction}} \times 100$$

2.2 Phytochemical studies

The *R. rugosa* leaf, chloroform extracts (abbreviated as CERR) was subjected to qualitative and quantitative phytochemical analysis, to determine the presence of bioactive constituents.

2.2.1 Qualitative analysis

The extract of *R. rugosa* leaf (CERR) was analysed for the detection of various phytochemicals, *viz.,* alkaloids, glycosides, tannins, saponins, phenols, flavonoids and sterols. Qualitative phytochemical screening of the CERR was carried out using standard procedures. Mayer's, Wagner's, and Dragendorff's tests for the detection of alkaloids (Evans, 1997; Wagner, 1993; Waldi, 1965), Legal's test for glycosides (Evans, 1997), saponins test by Kokate (1999), tannins detected using the atropine sulphate and lead acetate tests (Harborne, 1983; Hymete, 1986). Flavonoids were detected by the Lead acetate test (Mace, 1963), reducing sugars by Benedict's test, as mentioned by Ramakrishnan *et al.* (1994), the ferric chloride test was employed to identify phenol (Savitree *et al*., 2004) and Liberman-Burchard's test, as mentioned by Finar (1986) was used for the detection of phytosterols. The presence of phytoconstituents was confirmed based on characteristic colour changes or precipitate formation.

2.2.2 Quantitative estimation

The CERR was analysed to quantify the major phytochemical constituents. The Folin-Ciocalteu method was used to estimate total phenols (Ranalli *et al*., 2006) and total flavonoids were estimated

using the method mentioned by Zhishen *et al*. (1999). Tannin and non-tannin contents were estimated using the method as mentioned by Velioglu *et al*. (1998). The method mentioned by Mohan *et al*. (2012) was employed to estimate β-carotene and lycopene content. Chlorophyll a and b were estimated according to Butnariu and Coradini (2012). All assessments were performed in triplicate, and outcomes were expressed as the mean ± standard error.

2.3 Toxicity test

The acute oral toxicity study was accomplished in harmony with OECD guideline 420 (OECD, 2001). Different doses of the extract, *i.e.,* 5, 50, 300 and 2000 mg/kg BW, were administered orally *via* gavage. The animals were continuously monitored for the first 72 h for any signs of toxicity and behavioural abnormalities, including restlessness, convulsions, diarrhoea, altered sleep patterns, touch sensitivity and mortality.

2.4 Experimental design

The plant leaf extract was freshly homogenised in a 0.1% CMC suspension daily to a final volume of 1 ml for oral administration over the 4-week study period. The normal, non-diabetic Wistar rats were randomly assigned to three Groups (n=6). Wistar rats of Group 1 received CMC (1ml, 0.1%), whereas Groups 2 and 3 received CERR at 50 and 300 mg/kg BW, respectively, in one ml (0.1% CMC). A diabetic model was created using STZ (Pandit *et al.,* 2010). Briefly, a single i/p injection of freshly prepared STZ in 0.1 M cold citrate buffer (pH 4.5) @ 55 mg/kg body weight. After seven days of STZ administration, pre-prandial blood glucose levels were assessed, and rats with blood glucose levels over 250 mg/dl were allocated (n=6) randomly as Groups 4, 5, 6, and 7. Group 4 served as the diabetic control and received 1 ml of 0.1% CMC, while the diabetic rats in Groups 5 and 6 were administered CERR at 50 and 300 mg/kg body weight, respectively, in 0.1% CMC. Group 7 diabetic rats received glibenclamide (5 mg/kg) in 0.1% CMC as the standard antidiabetic treatment as depicted in Table 1.

Blood samples were collected suitably from the retro-orbital sinus, and blood glucose levels were estimated immediately using a glucometer (Dr Morepen, Bayer Pharmaceuticals Private Ltd., India). On the 28th day, the pancreatic tissue was collected, fixed in formalin and subjected to histopathological examination as described by Drury and Wallington (1980).

Table 1: Experimental design

S. No.	Groups (n=6)	Oral gavaging
1.	Normal control rats	CMC (0.1%) 1ml/day, PO
2.	Normal rats	CERR @ 50 mg/kg/day, PO
3.	Normal rats	CERR @ 300 mg/kg/day, PO
4.	Diabetic control rats	CMC (0.1%) 1ml/day, PO
5.	Diabetic rats	CERR @ 50 mg/kg/day, PO
6.	Diabetic rats	CERR @ 300 mg/kg/day, PO
7.	Diabetic rats	Glibenclamide @ 5 mg/kg BW PO

2.5 Statistical analysis

One-way ANOVA was employed to analyse biochemical and oxidative stress parameters in a completely randomised design (CRD), along with Duncan's Test of significance at the 5% level. The values are presented in mean ± standard error.

3. Results

3.1 Extractability and qualitative analysis of plant extracts

The extractability percentage and physical properties of CERR are presented in Table 2. The CERR extracts were subjected to qualitative analysis for the presence of various phytochemicals using spot tests, and the findings are expressed in Table 3.

Table 2: Extractability percentage and physical properties of CERR

Properties	Chloroform extract of the leaf of *R. rugosa* (CERR)
Extractability (%)	12.62%
Colour	Light green
Consistency	Hard and solid

Table 3: Qualitative phytochemical analysis of CERR

Active principles	Test	Chloroform extract
Reducing sugars	Benedict's test	-
Glycosides	Legal's test	++
Tannins	Lead acetate (2%)	++
	Atropine sulphate (0.1%)	++
Alkaloids	Mayer's test, Wagner's test and Dragendorff's test	++
Flavonoids	Lead acetate test (10%)	++
Saponins	Foam test	-
Phenols	Ferric chloride test	++
Sterols	Liberman-Burchard's test	++

3.2 Quantitative analysis of plant extract

Quantitative analysis of phytochemical ingredients was performed to assess flavonoid, total phenolic, lycopene, â-carotene, tannin, non-tannin, and chlorophyll contents as determined in different extracts of selected plants, and the obtained results are presented in Table 4.

Table 4: Quantitative analysis of major phytochemical constituents present in CERR

Parameters	Units	Chloroform extract
Total phenolic content	(mg of GAE/g extract)	7.32 ± 0.60
Total flavonoid content	(mg quercetin/g extract)	60.10 ± 3.90
Non-tannin content	(mg of GAE/g extract)	5.20 ± 0.50
Tannin content	(mg of GAE/g extract)	0.42 ± 0.08
β-carotene	(mg/g of extract)	3.45 ± 0.40
Lycopene	(mg/g extract)	2.90 ± 0.30
Chlorophyll a	(µg/g extract)	10.80 ± 0.95
Chlorophyll b	(µg/g extract)	8.45 ± 0.80

Values are expressed as the mean of three replicates ± SE.

3.3 Effect of CERR on mean blood glucose level

Mean blood glucose (MBG) in normal control rats hovered around 123.0 ± 2.30 mg/dl on day 0, to 133.66 ± 2.53 mg/dl on day 28 (Figure 3). The non-diabetic rats in Groups 2nd and 3rd were administered CERR at doses of 50 and 300 mg/kg BW, respectively, which did not produce any significant changes, with values remaining comparable to those of the normal control (Group 1). Induction of diabetes using STZ in Group 4 led to a significant elevation of MBG beyond 400 mg/dl during the study span, confirming successful induction of diabetes. Oral administration of CERR once daily in diabetic rats led to a significant dose-dependent decline in MBG, decreasing from 424.50 ± 12.03 mg/dl to 252.16 ± 5.62 mg/dl at 50 mg/kg and from 420.66 ± 16.16 mg/dl to 208.50 ± 6.21 mg/dl at 300 mg/kg dose/day by 28th day, exhibiting significantly effective and dose-dependent glycaemic control of the treatment by CERR. Standard treatment with glibenclamide also showed a significant reduction in MBG, from 421.16 ± 14.54 mg/dl (day 0) to 189.0 ± 3.53 mg/dl (day 28), indicating effective glycaemic control (Figure 3).

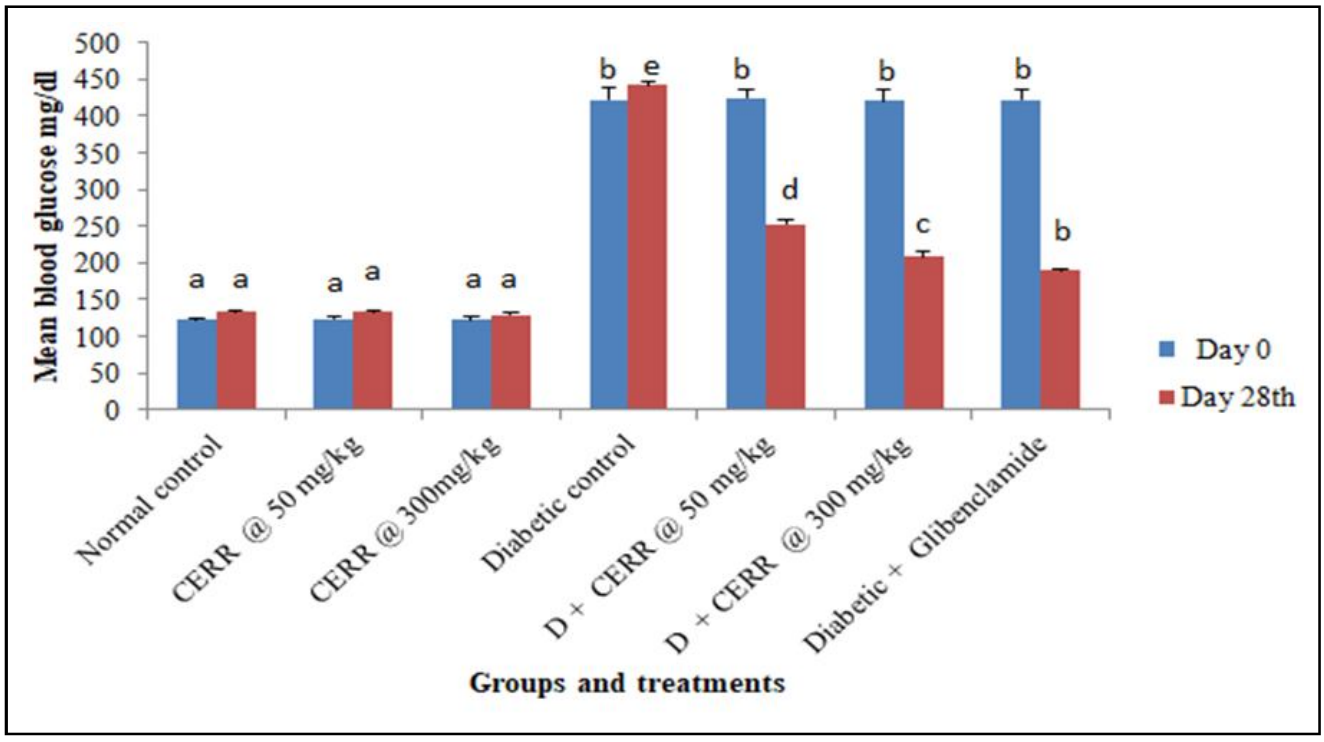

Figure 3: Mean blood glucose (mg/dl) on day zero and 28th in rats.

3.4 Effect of extract on body weight

The data on body weight in different Groups are presented in Figure 4. Body weight in normal control rats of Group 1 was 154.0 ± 4.34 g on day 0, which increased to 195.50 ± 2.26 g on day 28. Treatment Groups 2 and 3, which were administered CERR at dose rates of 50 and 300 mg/kg BW, did not show any significant alteration in the body weight profile and remained comparable to the normal control Group on both day 0 and day 28. The STZ-exposed diabetic rats exhibited an average loss of weight by 15 gm within 7 days before allocation into the designated Group, which exhibited an additional significant ($p<0.05$) decline in body weight, *i.e.*, from 136.0 ± 2.40 g

(day 0) to 99.16 ± 1.60 g on day 28 (Figure 4). The diabetic rats of Groups 5 and 6 subjected to daily oral administration of CERR showed a substantial dose-dependent improvement in body weight, which surged from 133.66 ± 1.94 g to 189.0 ± 4.00 g at a 50 mg/kg dose and from 135.33 ± 1.72 g to 204.33 ± 3.12 g at a 300 mg/kg dose by day 28, as depicted in Figure 4. glibenclamide, @ 5 mg/kg BW, also showed a significant increase in body weight, from 133.50 ± 1.78 g to 192.16 ± 2.59 g.

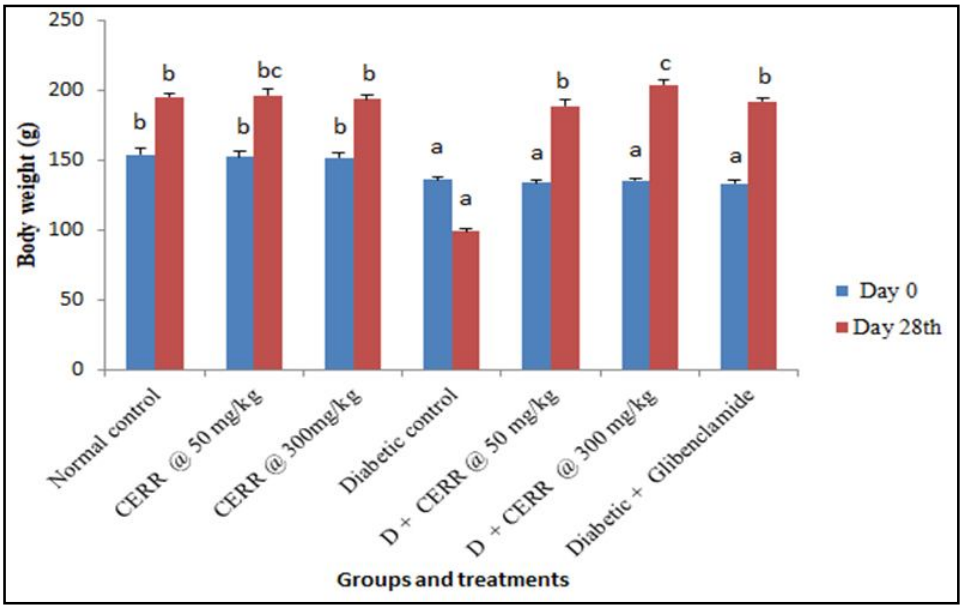

Figure 4: Body weight (g) on day zero and 28th in rats.

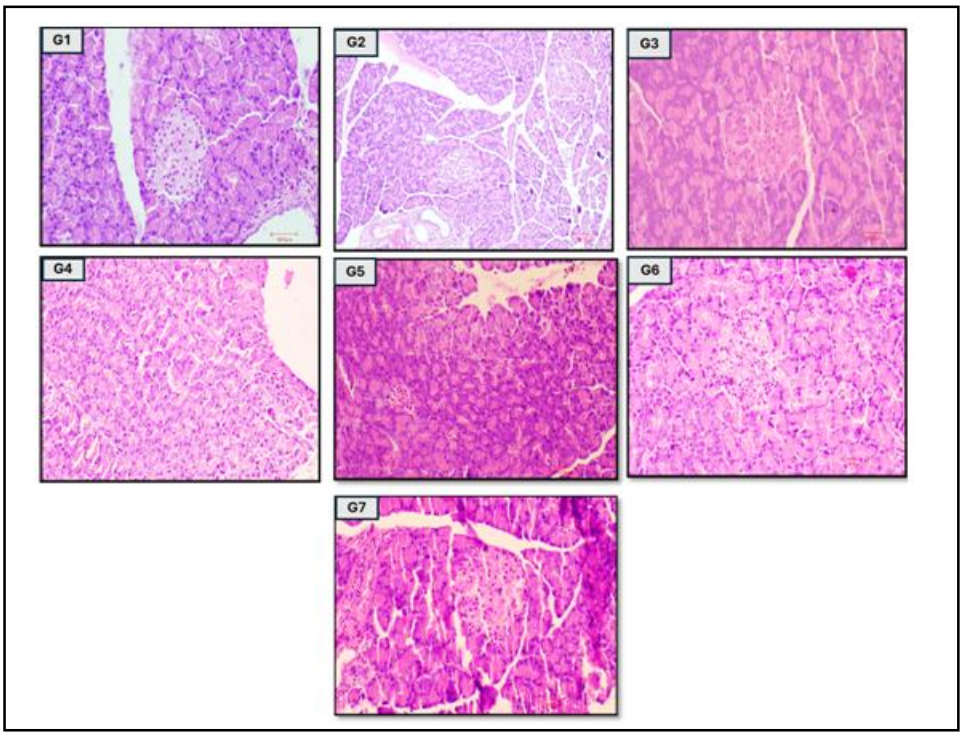

Figure 5: Histomorphology of the pancreatic tissue of the rat. Hematoxylin and Eosin Stain 200X: G1: Normal islet architecture, intact β-cells; G2 and G3: Normal histological appearance of islet, well-preserved and densely packed acini; G4: Marked degeneration of pancreatic acini and islets of Langerhans cells, poorly defined hypocellular islets along with cytoplasmic vacuolation and necrosis. G5: Architectural regeneration of islet cells and acini, lighter-staining clusters. G6: Better organisation of histological architecture and regeneration of the islet beta cells. G7: Notable regeneration of islets and acini, similar to the animals of G6.

3.5 Histopathology

3.5.1 Pancreas

Histological evaluation of pancreatic tissue from rats was performed using Hematoxylin and Eosin staining (200X) for all groups. Normal islet architecture, intact β-cells were observed in the control Group 1 (G1). The normal acini were closely associated with pyramidal-shaped structures. The Group 2 (G2) and 3 (G3) rat pancreases treated with the respective doses of CERR also maintain a normal histological appearance of islets and well-preserved, densely packed acini, without any visible degeneration, vacuolation, or necrosis. The diabetic control rats of Group 4 (G4) showed marked degeneration of pancreatic acini and islets of Langerhans, characterised by poorly defined, hypocellular islets with cytoplasmic vacuolation and necrosis. The STZ diabetic rat treated with the respective doses of CERR in Groups 5 (G5) and 6 (G6) showed architectural regeneration of islet cells and acini. The islets of Langerhans were better-preserved, and the rounded, lighter-staining clusters (islets) are more visible and defined. This suggests partial regeneration of β-cells, which indicates restoration of cellular architecture Figure 5(G5). The exocrine acini appear more organised and compact, closer to the normal pancreatic structure observed in Figure 5(G6). This implies a dose-dependent improvement in the restoration of histological architecture and the regeneration of islet beta cells, as observed in Figures 5(G5) and 5(G6). The Group 7 (G7) rats treated with STZ and glibenclamide also demonstrated notable regeneration of islets and acini, similar to that observed in G6 animals. The tissue microstructure is closer to normal pancreatic morphology and shows less evidence of necrosis or vacuolation compared to the positive control.

4. Discussion

The present study indicated significant anti-hyperglycaemic effects of the CERR in STZ-induced diabetic Wistar rats. STZ is selectively cytotoxic to pancreatic β-cells by generating reactive oxygen species-mediated oxidative stress, leading to persistent hyperglycaemia and metabolic disturbances (Szkudelski, 2001). In the present study, STZ induced significant hyperglycaemia along with a simultaneous significant loss of body weight, confirming successful induction of diabetes. Treatment with CERR significantly reduced blood glucose levels and restored body weight in a dose-dependent pattern. The anti-hyperglycaemic and pancreas-protecting activities of the CERR have been recorded in the present study. A few reports indicate similar findings connected to *Isodon rugosus* syn. *R. rugosa* (Mehta *et al*., 2023; Yadav *et al*., 2010). The gain in body weight observed in CERR-treated diabetic rats may be attributed to improved glycaemic control and anabolism of structural proteins and fats. Similar restoration of body weight has previously been reported following treatment with the ethanolic extract of *R. rugosa* in diabetic rats (Mehta *et al*., 2023). The histopathological evidence of islet cell regeneration in the pancreas (Figure 5 G5 and G6) led to improved insulin secretion, which might have contributed to the antihyperglycemic effect observed in the present study and further improved peripheral glucose utilisation (Aybar *et al*., 2001). Simultaneously, the phytochemicals, such as total flavonoids and phenolics, have been reported to protect pancreatic β-cells against STZ-mediated oxidative injury (Lee *et al*., 2020).

Earlier reports on *I. rugosus* indicated strong antioxidant activity due to the availability of phenolics and flavonoids (Abbasi *et al.*, 2019; Janbaz *et al*., 2014). Earlier phytochemical studies on the chloroform fractions of *I. rugosus* also reported the presence of terpenoids, sterols and flavonoids with significant pharmacological potential (Zeb *et al.*, 2014). In addition, Alqahtani *et al*. (2021) reported significant α-glucosidase inhibitory activity of bioactive compounds isolated from *I. rugosus*, supporting its antihyperglycemic activity. The phytochemicals may boost insulin secretion, augment glucose metabolism, impede carbohydrate-digesting enzymes, regenerate and shield the β-cells of the islets from oxidative damage. The regeneration of the organs further reinforced the biochemical observations. There were serious degenerative changes in the organs of diabetic control rats, evidenced by pathological alterations in microphotographs of the pancreas. The CERR-treated diabetic rats displayed rebuilding of normal tissue microarchitecture and reduced cellular deterioration. The microanatomical genesis and restoration of pancreatic tissues observed in the present study may therefore be attributed to the antioxidant and cytoprotective properties of the phytochemicals present in the CERR, acting in concert. Mehta *et al.* (2023) have reported similar regeneration and organ protection in diabetic models using extracts of *R. rugosa*. Overall, the findings of the present study provide scientific validation of the traditional use of *R. rugosa* in diabetes management. The availability of various antidiabetic phytochemicals reported by workers (Abbasi *et al.*, 2019; Janbaz *et al*., 2014) may act in tandem to synchronise their anti-hyperglycaemic activities; however, at the present stage of the study, the actual mechanism underlying these antidiabetic activities cannot be ascertained. glibenclamide also exhibited regeneration and restoration of the microarchitecture of the pancreatic acini and islet β-cells, similar to the CERR as depicted in Figure 5 (G6).

5. Conclusion

The chloroform extract of *R. rugosa* (CERR) has antidiabetic activities in diabetic Wistar rats. The CERR reduced the mean blood glucose level and helped restore body weight lost to diabetes. The CERR also restored altered protection against diabetes-related pancreatic damage. Analysis of microphotographs of tissues confirmed the regeneration and restoration of pancreatic islets and acini in diabetic rats. The therapeutic effects of CERR may be attributed to bioactive phytochemicals such as flavonoids, phenolics, sterols, tannins and terpenoids, which restore pancreatic acini and islet cells, thereby improving insulin secretion and regulating glucose metabolism. The findings validate the traditional use of *R. rugosa* by locals in Jammu and Kashmir (UT), as a remedy for diabetes. This study also highlights *R. rugosa* as a natural, multiorgan-protective antidiabetic agent. The isolation, purification, and characterisation of the specific bioactive compounds responsible for its antidiabetic need to be undertaken in the future and the mechanism of action of the phytochemicals needs to be deciphered using molecular techniques.

Acknowledgements

The authors acknowledge the facilities and research project extended by the University Authority of SKUAST-Jammu for carrying out the present study.

Contributors

Lenesha Manhas conducted the study and prepared the manuscript; **Nrip Kishore Pankaj** conceptualised, guided, and corrected the manuscript; **Neelesh Sharma** conceptualised and corrected the manuscript; **Pankaj Goswami** performed the histopathology; **Pawan Kr. Verma** helped execute the study and the manuscript; **Minakshi Rani and Priyanka Sharma** helped **Lenesha Manhas** during the study.

Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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Citation **Lenesha Manhas, Nrip Kishore Pankaj, Neelesh Sharma, Pawan Kr. Verma, Pankaj Goswami, Minakshi Rani and Priyanka Sharma (2026). Antidiabetic activity and pancreatic histopathological analysis of *Rabdosia rugosa* (Wall. Ex Benth.) H. Hara leaf extract on streptozotocin-induced diabetes in Wistar rats. Ann. Phytomed., 15(1):727-735, http://dx.doi.org/10.54085/ap.2026.15.1.65.**