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Unlocking the potential of corosolic acid in *Ziziphus jujuba* leaf: *in vitro* & *in vivo* exploration for diabetes management

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Ziziphus jujuba, commonly known as jujube or Chinese date, is valued in traditional medicine for its diverse therapeutic properties. This study investigates its importance in diabetes management, with emphasis on corosolic acid, a compound known for its antidiabetic effects. The study aims to comprehensively evaluate the antidiabetic potential of *Ziziphus jujuba*, specifically evaluating corosolic acid concentration, antioxidant activity, and alpha-amylase inhibition, as well as its efficacy on diabetic rat models. The study employs a combination of qualitative and quantitative analyses, *in vitro* assays, and *in vivo* experiments to assess the antidiabetic potential of *Ziziphus jujuba* leaf extract. Fresh leaf samples of *Ziziphus jujuba* were collected and subjected to corosolic acid analysis. *In vitro* antioxidant and antidiabetic activities were analyzed using DPPH and alpha-amylase inhibition assays, respectively. *In vivo* studies involved treating diabetic rat models with the leaf extract and assessing various parameters including blood glucose levels, lipid profiles, and pancreatic histopathology. The study revealed a significant concentration of corosolic acid in the leaf extract of *Ziziphus jujuba*, showed potent antioxidant activity and notable inhibition of alpha-amylase in *in vitro* assays. Treatment with the plant extract on diabetic rat models resulted in significant reductions in blood glucose levels, improvements in lipid profiles, and regeneration of pancreatic islet cells. Our study line up with previous experiments on antidiabetic effects of corosolic acid and further indicated the role of *Ziziphus jujuba* in diabetes management, providing a plant based substitute for glycemic control.

Keywords: Antidiabetic, Alpha-amylase inhibition, Corosolic acid, *In vitro, In vivo*, *Ziziphus jujuba*

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The utilization of plants in traditional medicine has persisted across civilizations, evolving alongside advancements in science and technology. Traditional medicinal practices, deeply rooted in cultural heritage and indigenous knowledge systems, continue to play a significant role in healthcare, offering natural alternatives to synthetic pharmaceuticals. This enduring trust on traditional remedies is underscored by the fact that over 80% of the global population incorporates traditional medicines into their healthcare practices[1]. Despite remarkable advancements in medical science, the burden of chronic diseases continues to escalate worldwide, necessitating innovative approaches to disease management and prevention. Among the myriad chronic ailments afflicting humanity, diabetes mellitus stands out as a burgeoning global health crisis. Characterized by deregulated blood glucose levels resulting from inadequate insulin production or utilization, diabetes poses significant challenges to public health systems and individual well-being. Type 2 diabetes mellitus, in particular, accounts for approximately 90% of diabetes cases globally, reflecting the influence of lifestyle factors such as sedentary behavior, unhealthy dietary patterns, and escalating rates of obesity[2].

The epidemiological landscape of diabetes is alarming with projections indicating a substantial rise in the prevalence of the disease in the coming decades. Estimates suggest that the global diabetic population, which numbered 537 million in 2021, is poised to surpass 578 million by 2030 and a staggering 700 million by 2045[3]. This trajectory underscores the urgent need for effective strategies to manage and mitigate the impact of diabetes on individuals and societies.

Current therapeutic approaches to diabetes management typically involve a combination of lifestyle modifications, pharmacological interventions, and, in severe cases, insulin therapy. However, the costs associated with conventional treatments and their adverse side effects highlight the need for exploring alternative approach of diabetes management. In this

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context, traditional medicinal plants emerge as promising candidates in the treatment of diabetes.

Ziziphus jujuba, commonly known as jujube or Chinese date. This species, belonging to the Rhamnaceae family, has a long-standing history of use in traditional medicine systems across various cultures, including Traditional Chinese Medicine (TCM) and Ayurveda. *Ziziphus jujuba* is revered for its versatile pharmacological properties, encompassing antiulcer, antidiabetic, antioxidant, and antimicrobial activities, among other[4]. Its bioactive constituents, including flavonoids, triterpenoids, and polysaccharides, contribute to the diverse therapeutic effects and have garnered considerable attention from researchers exploring natural remedies for chronic diseases[5].

Of particular interest in the context of diabetes management is corosolic acid, a pentacyclic triterpenoid- known as 2-alpha-hydroxyursolic acid, exhibits notable antidiabetic properties, including enhanced insulin sensitivity, inhibition of carbohydrate-digesting enzymes, and modulation of glucose metabolism[6]. These pharmacological actions position corosolic acid as a promising natural alternative for blood glucose control.

In the realm of traditional medicine, *Ziziphus jujuba* has been employed for its purported therapeutic properties, including its potential to alleviate symptoms associated with diabetes[7]. Traditional healers across cultures have utilized different parts of the jujube plant, including the fruit, leaves, and seeds, to manage various health conditions, including diabetes[8].

Despite the extensive research elucidating the antidiabetic potential of *Ziziphus jujuba* and its bioactive constituents, significant gaps remain in our understanding of its mechanisms of action, pharmacokinetics, and clinical efficacy. Furthermore, the exploration of unexplored plant resources, particularly, those endemic to regions with rich biodiversity like Himachal Pradesh, India, presents exciting opportunities for discovering novel therapeutics for diabetes and other chronic diseases.

Based on these considerations, this study aims to investigate the therapeutic benefits of *Ziziphus jujuba* leaf in diabetes management, with a specific focus on its corosolic acid content. Through a multidisciplinary approach encompassing qualitative and quantitative analyses, *in vitro* assays, and *in vivo* studies, we seek to comprehensively evaluate the antidiabetic properties of *Ziziphus jujuba* leaf extract and contribute to the growing body of evidence supporting the therapeutic potential of natural remedies in addressing the global burden of diabetes.

Methodology

Location of survey area

The survey was conducted in District Hamirpur, Himachal Pradesh, India. This location was selected due to its diverse flora and accessibility for sample collection.

Source and nature of material

Fresh leaf samples of *Ziziphus jujuba* were gathered from District Hamirpur. The botanical identity of the plant was confirmed as *Ziziphus jujuba* Mill. through taxonomic authentication. Voucher specimen PAN Number: 22676 was deposited at the PAN Herbarium, Panjab University, Chandigarh, India.

Experimental design

The experimental design involved both *in vitro* and *in vivo* investigations to assess the pharmacological properties of *Ziziphus jujuba* leaf extract. *In vitro* studies included antioxidant and antidiabetic assays, while *in vivo* studies were conducted on Wistar rats to evaluate antidiabetic potential of leaf extract.

Material and Methods

Chemical compounds

Corosolic acid pure standard (>98%) was procured from Wuhan ChemFaces Biochemical Co., Ltd, Wuhan, China. Porcine pancreatic alpha-amylase, DPPH, Acarbose, and Alloxan monohydrate (98%) were obtained from Sigma-Aldrich.

Plant sample collection and identification

Fresh leaf samples of *Ziziphus jujuba* were collected from District- Hamirpur, Himachal Pradesh, India, in July 2021 Figure 1.

Official name: *Ziziphus jujuba* Mill.

Local name: Indian jujube.

English name: Jujube or Chinese date.

PAN Number: 22676, deposited at the PAN Herbarium, Panjab University, Chandigarh, India

The plant name has been checked with http://www.theplantlist.org.(accessed April 15, 2024). Full publication details for this name can be found in IPNI: http://ipni.org/urn:lsid:ipni.org:names:7192131.

Fig. 1 — *Ziziphus jujuba* leaves and fruits

Standard solution preparation

A stock solution of corosolic acid (1000 µg/mL) was prepared by dissolving 10 mg of pure corosolic acid in 1 mL of methanol. From this stock solution, a working solution was prepared by diluting 0.01 mL of the stock to 1 mL with methanol. The working solution was then filtered through a 0.22 µm membrane filter, and 20 µL was injected into the HPLC system for analysis.

Extraction of plant sample

The collected *Ziziphus jujuba* leaves were cleaned, shade-dried, and finely powdered. A total of 20 mg of leaf powder was extracted with 2 mL of methanol using an orbital shaker assisted with an ultrasonic bath. The resulting extract was filtered, and 0.1 mL of the filtrate was diluted to 1 mL with methanol. The diluted extract was then filtered through a 0.22 µm membrane filter, and 20 µL was injected into the HPLC system for analysis and for *in vivo* study the methanolic leaf extract was vacuum-dried using a rotary evaporator under reduced pressure and at controlled temperature to ensure complete removal of any residual methanol. The dried extract was then stored in a desiccator until further use.

Analysis of corosolic acid

Reverse-phase high-performance liquid chromatography (RP-HPLC) was employed to analyze the concentration of corosolic acid in the leaf extract. The HPLC system consisted of an auto-sampler, a nucleodur C18 column (250×4.6 mm) maintained at 30°C, LC solution software, and a photodiode array (PDA) detector. The mobile phase consisted of acetonitrile and 0.1% orthophosphoric acid (75:25 v/v), and the detection wavelength was set at 210 nm[9].

***In vitro* antioxidant activity**

DPPH assay

A 0.1 millimolar solution of 2, 2-diphenyl-1-picrylhydrazyl (DPPH) was prepared in methanol. Various concentrations (50 - 250 µg/mL) of the *Ziziphus jujuba* leaf extract were dissolved in dimethyl sulfoxide (DMSO), and each concentration was subjected to the DPPH inhibition assay in triplicates (n=3). The absorbance of the reaction mixture was measured at 517 nm using a spectrophotometer after incubating for 30 min, and the percentage inhibition of DPPH was calculated[10].

***In vitro* antidiabetic activity**

Alpha-smylase inhibition assay

The alpha-amylase inhibitory activity of the leaf extract was determined following the developed method[11]. Different concentrations (50-250 µg/mL) of the plant extract were tested in triplicates for their ability to inhibit alpha-amylase activity. The absorbance was measured at 540 nm, and the percentage inhibition of alpha-amylase was calculated.

Plan of *in vivo* antidiabetic study

Healthy male Wistar rats weighing between 180 g – 400 g were procured from the Central Animal House at Panjab University, Chandigarh. The animal study was conducted following internationally accepted principles for laboratory animal use and care, as well as institutional guidelines. The Institutional Animal Ethics Committee (IAEC) of the Central Animal House, Panjab University, Chandigarh, has approved the research proposal under approval number PU/45/99/CPCSEA/IAEC/ 2021/506.

Treatment groups

Animals were acclimatized for 5-7 days before the commencement of the study.

The rats were divided into four groups (n=5 each) as follows:

Normal control

Untreated with standard feed and water ad libitum.

Diabetic control

Administered alloxan (150 mg/kg) to induce diabetes.

Plant dosed

Pretreated with alloxan and fed with *Ziziphus jujuba* extract (100 mg/kg).

Glibenclamide dosed

Pretreated with alloxan and administered glibenclamide (5 mg/kg).

Diabetes induction

Experimental diabetes was induced in the rats by administering alloxan monohydrate at a dose of 150 mg/kg. The induction of diabetes was confirmed by monitoring blood glucose levels, with levels ≥ 200 mg/dL indicating successful induction. Alloxan, at higher concentrations is usually used to induce type 1 diabetes by β-cell cytotoxicity, however under our experimental conditions and at the provided dose, alloxan mimics type 2 diabetes mellitus, which is characterized by partial β-cell dysfunction and prolonged hyperglycemia.

Blood sampling and histopathological study

Blood samples were collected from the rats on days 1, 7, and 14 of the experimental periods. On the 14th day, retro-orbital plexus blood was collected for the analysis of lipid profiles. After blood collection, the rats were euthanized, and histopathological analysis of the pancreatic tissues was performed. Pancreatic sections were stained with hematoxylin and eosin for microscopic examination of any anatomical changes[12].

Results

As previously mentioned, corosolic acid, a phytocompound recognized for its medicinal potential, particularly as an antidiabetic agent, was investigated for its presence and efficacy in *Ziziphus jujube* Figure 1. The confirmation of its presence in leaves of *Ziziphus jujuba* and its commendable efficacy in diabetes treatment is a significant finding.

Quali-quantitative analysis of corosolic acid

The chromatogram of the standard corosolic acid exhibited a peak with a retention time of 9.052 min (Fig. 2 a). *Ziziphus jujuba* leaf sample also displayed a peak at 9.11 min (Fig. 2 b). For quantitative analysis, five different concentrations of corosolic acid (10-30 µg/mL) were examined, and a standard calibration curve was established through linear regression based on peak areas. Microsoft Excel was employed for calibration data plotting and corosolic acid concentration quantification. Methanolic leaf extracts of *Ziziphus jujuba* revealed a substantial concentration of corosolic acid, *i.e.,* 56.87 µg/20 mg

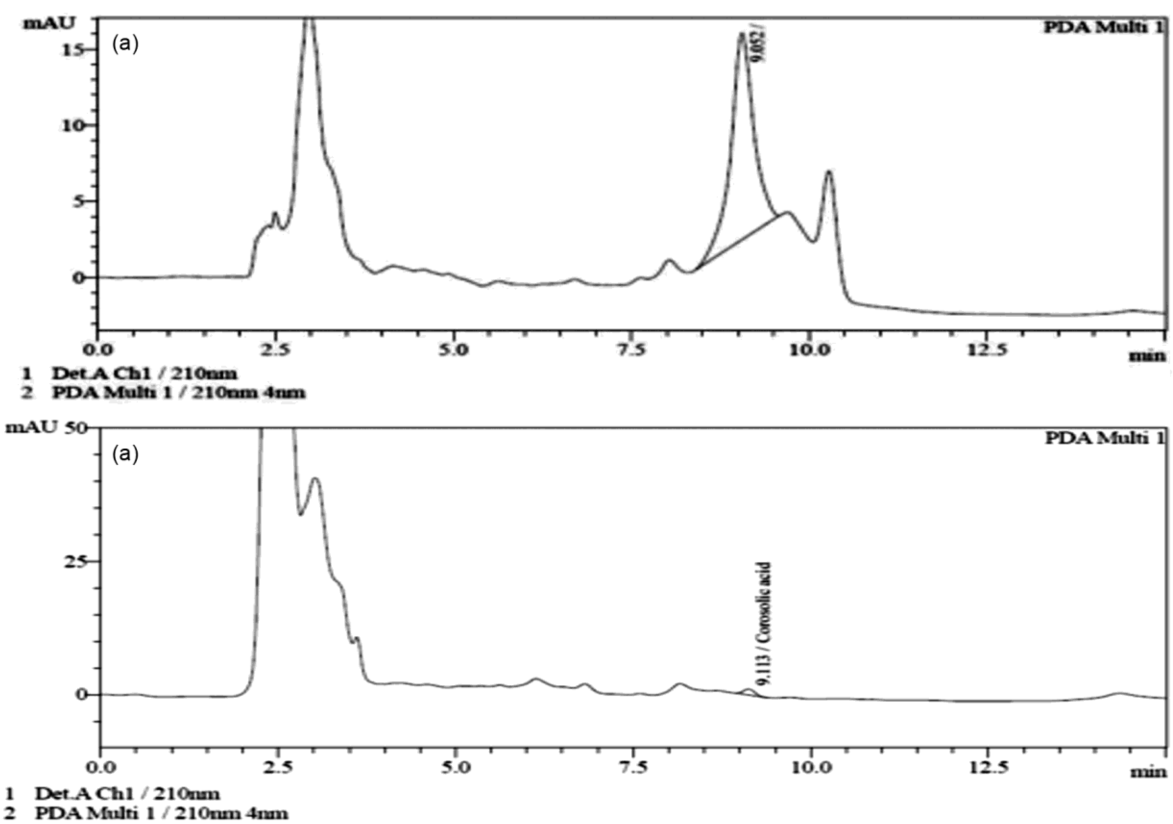

Fig. 2 — (a-b) HPLC Chromatogram of standard corosolic acid & *Ziziphus jujuba*

dry weight. Calibration equation: $Y = 1498.2x + 7838.8$, $R^2 = 0.9978$

In vitro antioxidant activity (DPPH Assay)

Free radicals are highly unstable oxygen containing molecules with unpaired electrons that reacts with other molecules causing damage to cell membranes, organs, DNA and leads to various diseases. Medicinal plants bio-synthesizes antioxidants and can counteract free radicals thus preventing the damage.

Ziziphus jujuba: With an IC50 value of 80.3±1.026 µg/mL, plant extract was shown to have 97% efficiency in inhibiting DPPH at 250 µg/mL, but standard ascorbic acid only had 82.3% efficiency at the same dose. *Ziziphus jujuba* leaf extract has a lower IC 50 value, which indicates that it is a powerful antioxidant (Table 1).

In vitro antidiabetic activity (alpha amylase inhibition)

The inhibition of alpha amylase by the methanolic leaf extract of *Ziziphus jujuba* revealed its antidiabetic potential owing to the presence of corosolic acid which has been proclaimed to be an excellent antidiabetic phytocompound. Acarbose was used as a reference standard which was found to have higher IC50 value than the tested plant extract (Table 2). Percentage inhibition of alpha amylase by methanolic leaf extract of *Ziziphus jujuba* at 250 µg/mL was 80.5% with an IC 50 value of 132.83±1.967 µg/mL (Table 3). Lower IC50 value of *Ziziphus jujuba* leaf extract depicts its excellent antidiabetic potential without any side effects in comparison to acarbose.

Table 1 — % inhibition of DPPH by *Ziziphus jujuba* and Ascorbic acid

Concentration (µg/mL)	% Inhibition *Ziziphus jujuba*	IC50 (µg/mL)	% Inhibition Ascorbic acid	IC50 (µg/mL)
50	90.5±0.87		42.63±0.78	
100	91.7±0.70		54.09±0.15	
150	92.4±0.36	80.3±1.026	67.29±0.36	117.1±1.03
200	94.9±0.98		73.80±0.62	
250	97.0±0.75		82.39±0.58	

Table 2 — Percentage inhibition of Alpha amylase by Acarbose

Concentration (µg/mL)	% Inhibition *Ziziphus jujuba*	IC50 (µg/mL)
50	26.49±1.123	
100	45.54±1.181	
150	56.55±0.929	132.83±1.967
200	62.35±1.364	
250	80.51±0.258	

In vivo antidiabetic activity

Alloxan monohydrate induction successfully produced diabetes in rats, confirmed 48 hours post-injection with observed symptoms like increased thirst and frequent urination. *Ziziphus jujuba*, rich in corosolic acid, was selected for diabetic rat treatment, with glibenclamide chosen as a positive control. Treatment extended for 14 days, monitoring changes in body weight and blood sugar levels on days 1, 7, and 14.

Effects on body weight

The normal control group displayed a 6.18% increase in body weight, while diabetic rats exhibited a sudden 7.26% decrease. Diabetic rats treated with the plant extract showed a significant 4.31% increase, and the glibenclamide-treated group exhibited a 3.43% increase in body weight (Table 4).

Effect on blood glucose level

Administration of the methanolic extract showed no abnormal behavioral or clinical symptoms in the experimental animals. The animals remained healthy and active throughout the experimental period, indicating that the extract was well-tolerated at the administered dose. The methanolic leaf extract of

Table 3 — Percentage inhibition of Alpha amylase by *Ziziphus jujuba*

Concentration (µg/mL)	% Inhibition Acarbose	IC50 (µg/mL)
50	13.69±0.929	
100	17.26±1.123	
150	40.92±0.682	193.62±0.634
200	55.51±0.515	
250	62.95±0.446	

Table 4 — Effects of plant extract and drug treatment on body weight of diabetic rats

	Change in body weight (g)			
Treatment period	Normal control	Diabetic (Alloxan alone)	Diabetic (Alloxan+ MetPE (100 mg/kg bw) of Z. *jujuba*)	Diabetic (Alloxan+ Glibenclamide) (5 mg/kg bw)
1st Day	372±2.14	289±2.75[a]	278±1.65[b,c]	262±1.23[a,c]
7th Day	380±1.65	276±1.56[a]	283±3.19[a,c]	265±2.67[b,c]
14th Day	395±2.34	268±2.94[a]	290±1.54[a,c]	271±1.93[b,c]
Percent change of body weight	6.18%	- 7.26%	4.31%	3.43%

Bw- Body weight; MetPE- Methanolic plant extract.
Values are expressed as mean ± SEM; each group contains 5 rats (n = 5). Values are statistically significant at [a] $p \leq 0.05$ and [b] $p \leq 0.01$ (when values are compared with normal control) and [c] $p \leq 0.05$ (when values are compared with diabetic control); Analyzed by one- way ANOVA followed by Dunnett post hoc test.

Ziziphus jujuba demonstrated a notable glucose-lowering effect on diabetic rats, attributed to corosolic acid. In the diabetic control group, blood glucose levels increased by 47.4%. Diabetic rats treated with the plant extract showed a consistent reduction in acute hyperglycemia, up to 61.5% decrease, while the glibenclamide-treated group showed a 59.1% reduction in blood sugar levels (Table 5).

Effect on lipid profile and creatinine levels

Diabetes induces lipid abnormalities, termed diabetic dyslipidemia, characterized by elevated triglycerides, VLDL-cholesterol, LDL-cholesterol, and reduced HDL-cholesterol. The methanolic leaf extract of *Ziziphus jujuba* effectively rectified these lipid abnormalities. Diabetic rats treated with the plant extract and glibenclamide exhibited a significant decrease in elevated creatinine levels, triglycerides, total cholesterol-LDL, VLDL, and an increase in HDL-cholesterol compared to the diabetic control group, which displayed decreased HDL-cholesterol and elevated VLDL, LDL cholesterol, triglycerides, and creatinine levels (Table 6).

Histopathological study of pancreas

Pancreas dissection revealed normal histological structure in the non-diabetic control group, with intact islet cells surrounded by acinar cells. The diabetic group displayed pathological changes in endocrine and exocrine components, with shrunken or nearly lost islet cells and lymphocytic infiltrations. The group treated with the plant extract exhibited complete regeneration of islet cells, returning to a normal state within the exocrine portion of the pancreas. Similar results were observed in the group treated with glibenclamide, except some degeneration of beta cells.

a). Normal control- Showed usual structure of pancreatic islets of Langerhans, with properly organized and intact cells.

b). Diabetic control- Showed degeneration and vacuolization of islet cells.

c). Plant extract treated- Showed normal histological structure except some alteration in shape of islet cells.

d). Glibenclamide treated - Islet cells returned to normal structure except some degeneration (Fig. 3).

Discussion

Antioxidant activity and corosolic acid content

Our study emphasized the antioxidant potential of *Ziziphus jujuba* leaf extract, due to its rich content of corosolic acid-a bioactive compound known for its free radical scavenging properties[13,14].

By neutralizing reactive oxygen species (ROS) and inhibiting lipid peroxidation, corosolic acid produce protective effects on pancreatic beta cells, preserving

Table 5 — Effect of plant extract and drug treatment on blood glucose levels of diabetic rats

Lipid panel	Normal control	Diabetic (Alloxan alone)	Alloxan + plant extract (Z. *jujuba*)	Alloxan + glibenclamide
TC (mg/dL)	77.32±1.65	111.9±1.27[b]	83±3.42[a,c]	91.9±0.65[b,c]
TG (mg/dL)	87.6±2.34	147.4±2.86[a]	89.3±1.75[b,c]	91.4±1.74[b,c]
HDL (mg/dL)	28.12±0.48	17.6±1.75[a]	26.9±1.98[a,c]	32.6±0.19[b,c]
VLDL (mg/dL)	15.9±1.12	26.4±1.64[a]	17.8±1.22[a,c]	19.6±1.29[a,c]
LDL (mg/dL)	34.11±3.65	67.9±2.64[a]	38.3±0.63[b,c]	39.7±1.09[a,c]
Creatinine (mg/dL)	0.11±2.41	1.11±0.55[b]	0.21±2.23[a,c]	0.34±0.87[b,c]

Values are expressed as mean ± SEM; each group contains 5 rats (n = 5). Values are statistically significant at [a] $p \leq 0.05$ and [b] $p \leq 0.01$ (when values are compared with normal control) and [c] $p \leq 0.05$ (when values are compared with diabetic control); Analyzed by one- way ANOVA followed by Dunnett post hoc test.

Table 6 — Effect of Diabetes treatment on Lpid profile and creatinine levels

Treatment period	Change in blood glucose level (mg/dL)			
	Normal control	Diabetic (Alloxan alone)	Diabetic (Alloxan+ MetPE (100 mg/kg bw) of *Z. jujuba*)	Diabetic (Alloxan+ Glibenclamide) (5 mg/kg bw)
1st Day	90.3±1.48	407.19±1.57[b]	452±3.25[b,c]	445±3.65[b,c]
7th Day	88±2.65	584.6±2.68[a]	324±2.16[a,c]	336±1.89[b,c]
14th Day	89.9±1.29	600±1.49[a]	174±1.34[b,c]	182±2.64[a,c]
Percent change of blood glucose	0.44%↓	47.4%	61.5%↓	59.1%↓

Bw- Body weight; MetPE- Methanolic plant extract. Values are expressed as mean ± SEM; each group contains 5 rats (n = 5). Values are statistically significant at [a] $p \leq 0.05$ and [b] $p \leq 0.01$ (when values are compared with normal control) and [c] $p \leq 0.05$ (when values are compared with diabetic control); Analyzed by one- way ANOVA followed by Dunnett post hoc test.

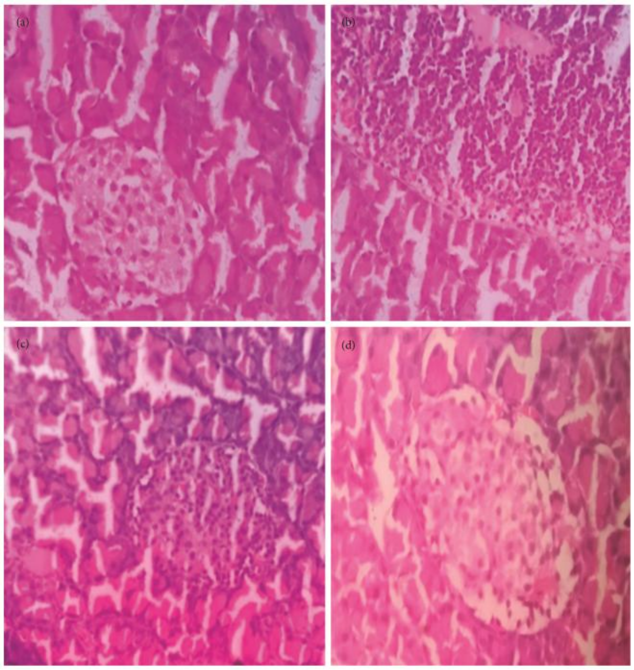

Fig. 3 — Microscopic observations of isolated pancreas

their function and viability[14]. Our study, correspond with previous research highlighting the antioxidant potential of *Ziziphus jujuba* and underscore the role of corosolic acid in directing its pharmacological effects[15].

Antidiabetic mechanism of action

Inhibition of alpha-amylase by *Ziziphus jujuba* leaf extract presents an effective treatment option for postprandial hyperglycemia, a defining characteristic of diabetes mellitus.

Alpha-amylase inhibitors reduce the rise in blood glucose levels after meals by blocking the conversion of complex carbohydrates into glucose. Similar to the common drug acarbose, our work shows how effectively the extract inhibits alpha-amylase activity, indicating that it may be a natural substitute for glycemic control[13]. Dual function of plant extract as an alpha-amylase inhibitor and antioxidant highlights its diverse therapeutic potential in the treatment of diabetes[14]. In our *in vivo* investigation, upon administration of leaf extract, the diabetic rats showed significant improvement in fasting blood glucose, serum insulin, lipid profile, and oxidative stress markers. Basically, alloxan is used to induce Type 1 diabetes through selective β-cell cytotoxicity, the dosage used in our study, produces partial β-cell dysfunction and moderate hyperglycemia, thereby showing features of Type 2 diabetes mellitus (T2DM). This experimental model is suitable for evaluating the effect of antidiabetic plants like *Ziziphus jujuba*, which are traditionally used for managing Type 2 diabetes by improving insulin sensitivity and preserving β-cell function[16]. The capacity of plant extract to improve insulin sensitivity, promote peripheral tissues' absorption of glucose, and reduce hepatic glucose production is responsible for these beneficial metabolic effects[14]. Histopathological data showing tissue regeneration and maintenance of beta-cell mass further supports the protective actions of plant extract on pancreatic beta cells[17].

Clinical implications and future directions

The findings of our study hold promising clinical implications for the management of diabetes mellitus and its associated complications. *Ziziphus jujuba* leaf extract emerges as a potent therapeutic agent for improving hyperglycemia and oxidative stress, thereby mitigating the risk of diabetic complications. Its natural origin, coupled with its varied pharmacological effects, positions it as a promising adjunctive therapy alongside conventional antidiabetic agents[13,14]. Notably, previous research has shown that certain plant extracts not only improve blood glucose levels but also prevent secondary complications such as diabetic osteopathy. For instance, *Cissus quadrangularis* stem and *Trigonella foenum-graecum* seed extracts were reported to significantly prevent bone degeneration in diabetic rats, as confirmed by μCT analysis[18]. Looking forward, additional investigation must be conducted to fully understand the molecular processes that produce the medicinal benefits of *Ziziphus jujuba* leaf extract. The subsequent research might focus on determining how it affects important signalling pathways related to insulin secretion, glucose homeostasis, and pancreatic beta-cell function. Additionally, to confirm the extract's safety, effectiveness, and ideal dosage schedules in diabetes patients, carefully planned clinical trials are essential. To determine its clinical relevance and therapeutic potential, long-term metabolic parameter monitoring and a thorough evaluation of its impact on diabetic complications are essential. Moreover, aqueous leaf extract of *Ziziphus jujuba* has been reported to be safe up to the levels of 5000 mg/kg in wistar rats[19].

Conclusion

This investigation highlights the remarkable therapeutic potential of *Ziziphus jujuba* leaf extract in the management of diabetes mellitus. Through a combination of *in vitro* and *in vivo* studies, we have demonstrated the extract's robust antioxidant activity, potent antidiabetic effects, and favorable metabolic outcomes. The presence of corosolic acid, a bioactive compound renowned for its antidiabetic properties, underscores the pharmacological relevance of *Ziziphus jujuba* in mitigating hyperglycemia and oxidative stress. Our findings hold significant clinical implications, offering a natural and cost-effective alternative for glycemic control and diabetes management. The extract's multifaceted pharmacological effects, including its ability to enhance insulin sensitivity, inhibit alpha-amylase activity, and preserve pancreatic beta-cell function, position it as a promising adjunctive therapy alongside conventional antidiabetic agents. In summary, our study provides compelling evidence supporting the use of *Ziziphus jujuba* leaf extract as a natural and potent remedy for diabetes mellitus. By harnessing the medicinal properties of this botanical resource, we can pave the way for innovative strategies in diabetes management, offering hope for improved outcomes and enhanced quality of life for diabetic patients worldwide.

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Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author Contribution

SK- conceived the study, conducted the experiments, analyzed the data, and wrote the manuscript. RP- provided guidance throughout the study, contributed to the experimental design, and critically revised the manuscript for important intellectual content. Both authors have read and approved the final manuscript.

Ethics Approval

All experimental procedures involving animals were conducted in compliance with the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Government of India. The study was approved by the Institutional Animal Ethics Committee (IAEC) of Panjab University, Chandigarh with approval number PU/45/99/CPCSEA/IAEC/2021/506.

Informed Consent

Not applicable, this study did not involve human participants.

Data Availability

The data generated or analyzed during the current study are available from the corresponding author on reasonable request.

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