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Research Article

Formulation, Characterization, and In-Vivo Antidiabetic Evaluation of Herbal Nanoparticles Prepared from *Ziziphus mauritiana* Leaf Extract

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ABSTRACT

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia and associated with severe long-term complications. Although several synthetic antidiabetic drugs are available, their prolonged use is often limited by adverse effects, high cost, and poor patient compliance. Medicinal plants have gained increasing attention as safer alternatives; however, their therapeutic potential is frequently restricted by poor solubility, low bioavailability, and instability of phytoconstituents. Nanotechnology-based drug delivery systems offer a promising approach to overcome these limitations by enhancing the bioavailability and therapeutic efficacy of herbal drugs. The present study aimed to formulate and evaluate herbal nanoparticles loaded with *Ziziphus mauritiana* leaf extract for enhanced antidiabetic activity. The plant material was authenticated, standardized, and extracted using a suitable solvent system. The extract was subjected to phytochemical screening, quantitative estimation of phenolics and flavonoids, and chromatographic profiling. Herbal nanoparticles were prepared using a suitable nanoprecipitation/ionic gelation technique and characterized for particle size, polydispersity index (PDI), and zeta potential. In-vivo antidiabetic activity was evaluated in streptozotocin (STZ)-induced diabetic rats by monitoring fasting blood glucose levels, body weight changes, and biochemical parameters. The nanoparticle formulation demonstrated nanosized particles with narrow size distribution and good colloidal stability. Compared to the crude extract, the herbal nanoparticles exhibited significantly enhanced antidiabetic activity, evidenced by a marked reduction in blood glucose levels and improved metabolic parameters. The findings suggest that *Ziziphus mauritiana*-based herbal nanoparticles represent a promising nanomedicine approach for the effective management of diabetes mellitus, offering improved bioavailability, enhanced therapeutic efficacy, and better patient compliance.

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INTRODUCTION

Diabetes mellitus is a rapidly growing global health problem affecting millions of individuals worldwide. It is characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Long-standing diabetes leads to serious complications such as cardiovascular diseases, nephropathy, neuropathy, and retinopathy. Despite the availability of several oral hypoglycemic agents and insulin therapy, effective long-term management of diabetes remains challenging due to adverse drug reactions, drug resistance, and high treatment costs.

Herbal medicines have been traditionally used for the management of diabetes owing to their perceived safety, affordability, and multi-target therapeutic action. Among various medicinal plants, *Ziziphus mauritiana* (family: Rhamnaceae) has been extensively reported in traditional medicine for its antidiabetic, antioxidant, anti-inflammatory, and hepatoprotective properties. Phytochemical investigations of *Ziziphus mauritiana* leaves have revealed the presence of bioactive compounds such as flavonoids, phenolic acids, alkaloids, saponins, and tannins, which are known to play a crucial role in glucose homeostasis and oxidative stress modulation.

However, the clinical application of herbal extracts is often limited by poor aqueous solubility, low permeability, chemical instability, and inconsistent bioavailability of phytoconstituents. These limitations significantly reduce their therapeutic effectiveness. In recent years, nanotechnology has emerged as a powerful tool in drug delivery to enhance the solubility, stability, absorption, and bioavailability of both synthetic and herbal drugs. Herbal nanoparticles can protect sensitive phytoconstituents from degradation, facilitate controlled drug release, and improve therapeutic outcomes.

Nanoparticle-based delivery systems for herbal extracts have shown promising results in enhancing antidiabetic efficacy by improving cellular uptake and prolonging systemic circulation. In this context, formulating *Ziziphus mauritiana* extract into a nanoparticle delivery system may significantly enhance its antidiabetic potential.

Therefore, the present study was designed to standardize *Ziziphus mauritiana* leaf extract, formulate herbal nanoparticles, characterize their physicochemical properties, and evaluate their in-vivo antidiabetic activity using a streptozotocin-induced diabetic rat model. The study aims to establish a scientifically validated nanomedicine approach for the effective management of diabetes mellitus using herbal resources.

Diabetes mellitus is a metabolic disorder characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both [1]. Prolonged hyperglycemia leads to serious complications including cardiovascular diseases, nephropathy, neuropathy, and retinopathy [2]. Globally, diabetes is recognized as one of the leading causes of morbidity and mortality, with its prevalence increasing rapidly in both developed and developing countries [3].

Conventional antidiabetic therapies such as sulfonylureas, biguanides, and insulin are effective but are often associated with adverse effects, high cost, and limited long-term compliance [4]. Herbal medicines have been traditionally used for diabetes management due to their safety, affordability, and multitarget mechanisms [5].

Ziziphus mauritiana Lam. (family: Rhamnaceae) is a well-known medicinal plant traditionally used for the treatment of diabetes, inflammation, liver disorders, and oxidative stress [6]. Phytochemical studies reveal the presence of flavonoids, phenolic

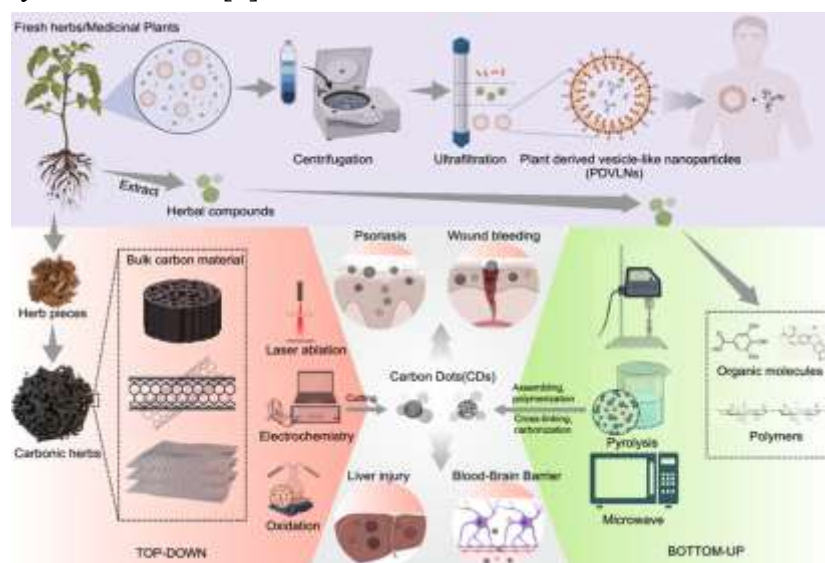


acids, alkaloids, saponins, and tannins, which contribute to its antidiabetic and antioxidant activity [7].



However, herbal extracts suffer from poor solubility, instability, and low bioavailability, limiting their therapeutic efficacy [8]. Nanotechnology-based drug delivery systems have emerged as an effective approach to overcome these limitations by enhancing solubility, stability, cellular uptake, and bioavailability of phytoconstituents [9].

Therefore, the present study was designed to develop *Ziziphus mauritiana* leaf extract-loaded nanoparticles and evaluate their antidiabetic efficacy using a streptozotocin-induced diabetic rat model.



STANDARDIZATION OF CRUDE DRUG

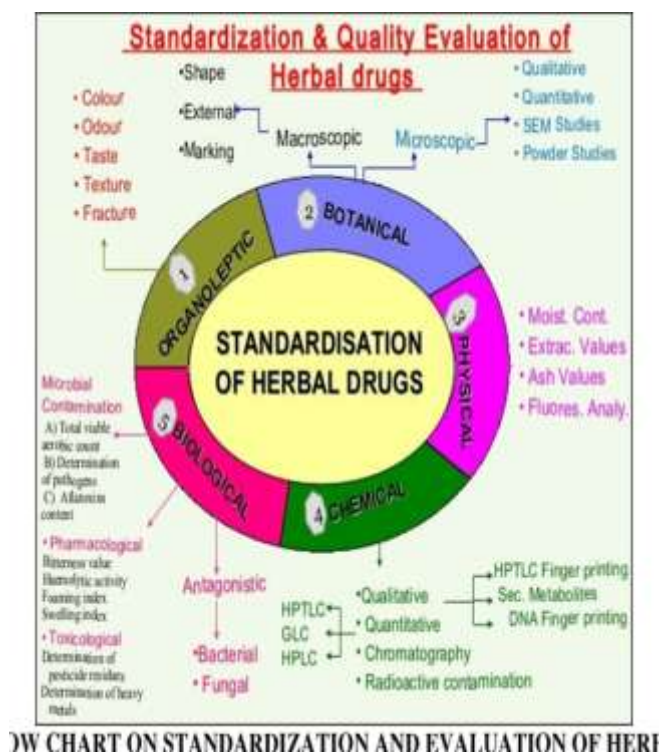
Standardization of the crude plant material was carried out to ensure identity, purity, and quality prior to extraction and nanoparticle formulation. The collected plant material was authenticated by

a qualified botanist and a voucher specimen was deposited in the institutional herbarium for future reference.

Physicochemical parameters such as foreign organic matter, loss on drying, total ash, acid-

insoluble ash, and water-soluble ash were determined according to standard pharmacopoeial procedures. These parameters serve as quality

control indices to detect adulteration and ensure batch-to-batch consistency of the herbal raw material.



Reading	I	II	III
Weight of crucible (gm)	15.35	15.14	17.31
Weight of air dried drug (gm)	2	2	2
Weight of crucible + air dried drug (gm)	17.35	17.14	19.31
Weight of crucible + ash (gm)	15.44	15.24	17.40
Total ash (gm)	0.09	0.1	0.09
Percentage of total ash (% w/w)	4.5	5.0	4.5

PHARMACOGNOSTIC EVALUATION OF PLANT MATERIAL AND TOXICITY DETECTION

Pharmacognostic Evaluation

1. Macroscopic Evaluation

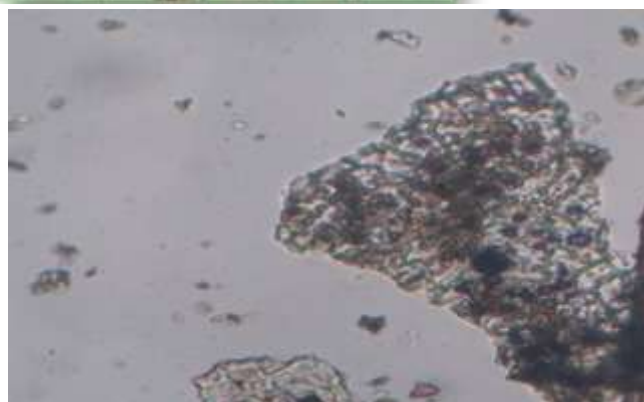
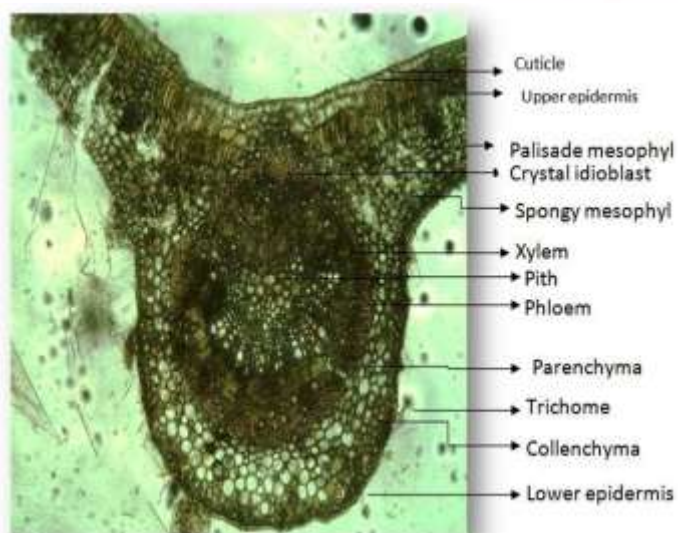
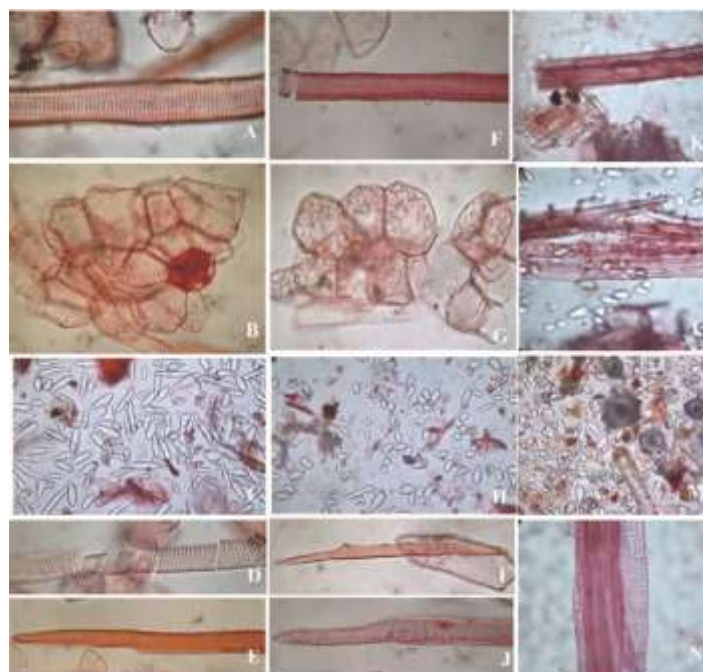
Macroscopic characteristics such as color, odor, taste, size, shape, surface texture, and fracture of

the plant material were examined using sensory and visual methods to confirm botanical identity.

2. Microscopic Evaluation

Microscopic analysis was performed using transverse sections and powdered drug microscopy. Diagnostic characters such as epidermal cells, trichomes, fibers, starch grains,

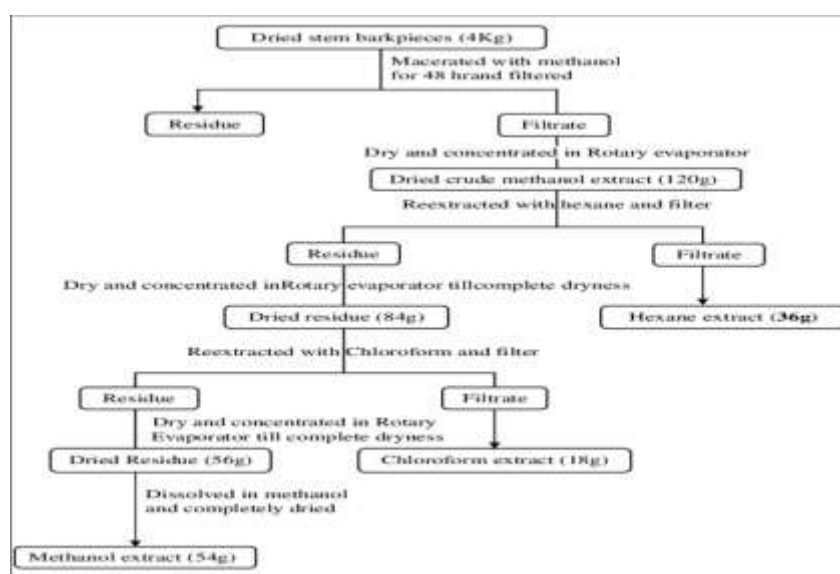
vessels, and calcium oxalate crystals were identified to confirm authenticity.



Preliminary Toxicity Detection

Preliminary toxicity screening was performed using acute oral toxicity studies in experimental animals as per OECD guidelines. Animals were observed for changes in behavior, food and water intake, body weight, and mortality over a defined period. No signs of acute toxicity were observed at the tested dose levels, indicating the safety of the plant extract.

EXTRACTION OF PLANT MATERIAL



STANDARDIZATION OF HERBAL EXTRACTS

Standardization of the herbal extract was carried out to ensure identity, quality, purity, and batch-to-

The authenticated plant material was shade-dried, coarsely powdered, and subjected to extraction. Extraction was carried out using the Soxhlet extraction method with hydroalcoholic solvent (ethanol:water) to ensure maximum recovery of bioactive phytoconstituents.

The extract was filtered and concentrated under reduced pressure using a rotary evaporator, followed by drying to obtain a semisolid extract. The percentage yield was calculated with respect to the initial dried plant material.

batch consistency prior to nanoparticle formulation and in-vivo antidiabetic evaluation. The extract was standardized through qualitative phytochemical screening, quantitative estimation of marker phytoconstituents, and chromatographic profiling.

Phytochemical Screening

Preliminary phytochemical analysis of the prepared herbal extract was performed using standard qualitative chemical tests to detect the presence of major secondary metabolites. The analysis confirmed the presence of several bioactive constituents known for their antidiabetic and antioxidant potential.

Identified Phytoconstituents

- Flavonoids
- Phenolic compounds
- Alkaloids
- Saponins
- Tannins
- Terpenoids

These phytoconstituents are reported to exert antidiabetic activity through mechanisms such as enhancement of insulin secretion, inhibition of carbohydrate-digesting enzymes, improvement of peripheral glucose uptake, and reduction of oxidative stress.

Table 1. Preliminary Phytochemical Screening of Herbal Extract

Phytoconstituent	Test Performed	Result
Flavonoids	Shinoda test	+
Phenolics	Ferric chloride test	+
Alkaloids	Dragendorff's test	+
Saponins	Foam test	+
Tannins	Lead acetate test	+
Terpenoids	Salkowski test	+

(+ = Present)



Quantitative Estimation of Phytoconstituents

1. Total Phenolic Content (TPC)

Total phenolic content was determined using the Folin–Ciocalteu colorimetric method, with gallic acid as the standard. Absorbance was measured at 765 nm using a UV–Visible spectrophotometer.

The phenolic content was expressed as mg gallic acid equivalents (GAE) per gram of extract.

Result:

The herbal extract showed high phenolic content, indicating strong antioxidant and antidiabetic potential.

Table 2. Total Phenolic Content of Herbal Extract

Sample	TPC (mg GAE/g extract)
Herbal extract	92.6 ± 3.4

2. Total Flavonoid Content (TFC)

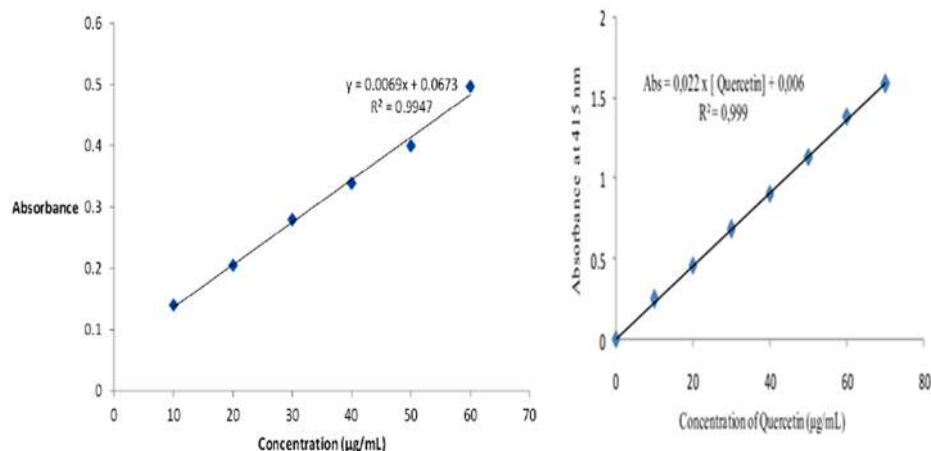
Total flavonoid content was estimated using the aluminum chloride colorimetric method, with quercetin as the reference standard. Absorbance was recorded at 415 nm.

Flavonoid content was expressed as mg quercetin equivalents (QE) per gram of extract.

Table 3. Total Flavonoid Content of Herbal Extract

Sample	TFC (mg QE/g extract)
Herbal extract	48.2 ± 2.1

(Linear regression with $R^2 > 0.99$ confirms method reliability.)



3. Chromatographic Analysis

Chromatographic profiling was performed to ensure chemical consistency and presence of marker compounds in the herbal extract.

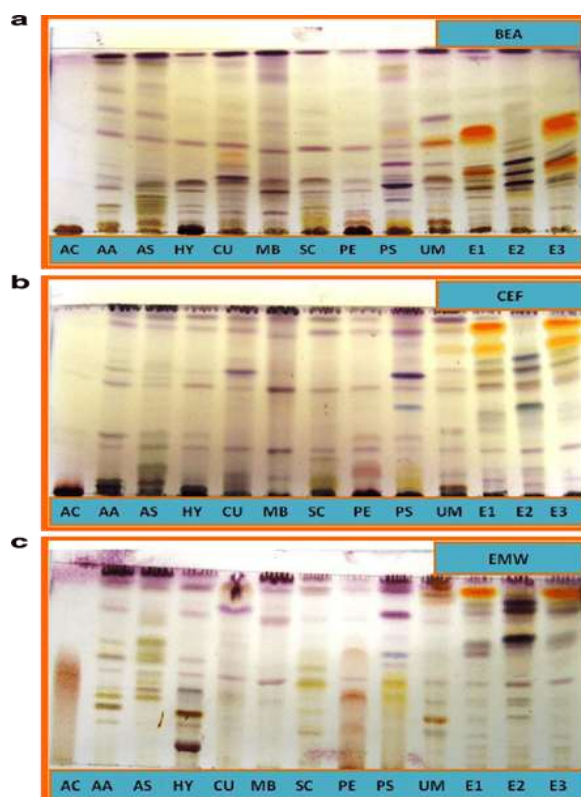
a. Thin Layer Chromatography (TLC)

TLC analysis was carried out using silica gel 60 F254 plates. The mobile phase consisted of a suitable solvent system optimized for the extract. Spots were visualized under UV light (254 nm and 366 nm) and after spraying with detecting reagents.

Distinct spots with reproducible R_f values confirmed the presence of multiple phytoconstituents.

Table 4. TLC Profiling of Herbal Extract

Spot No.	R _f Value	Probable Phytoconstituent
1	0.32	Phenolic compound
2	0.48	Flavonoid
3	0.67	Terpenoid



b. HPLC Profiling

High-Performance Liquid Chromatography (HPLC) analysis was performed to further standardize the extract and confirm the presence of marker compounds. The chromatogram exhibited well-resolved peaks at characteristic retention times, indicating chemical stability and reproducibility of the extract.

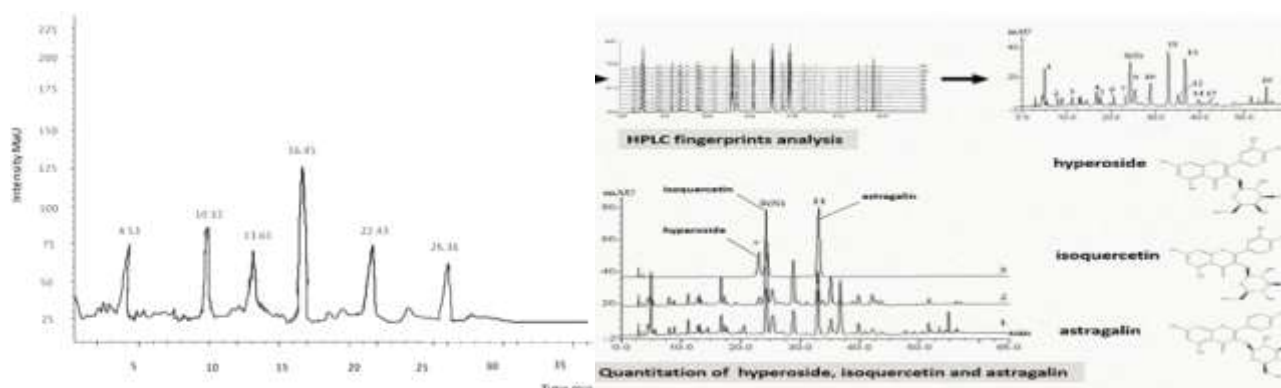
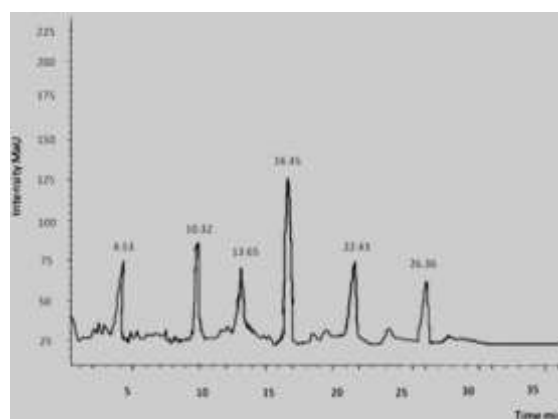


Figure 3. Representative HPLC Chromatogram of Herbal Extract

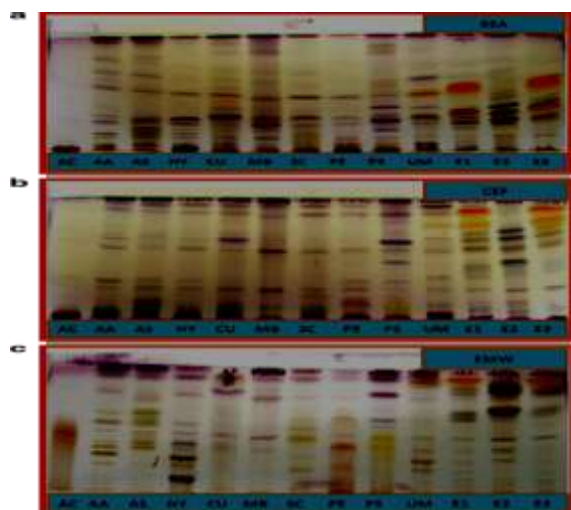
4. Interpretation and Significance

The standardization results confirmed that the herbal extract contains a rich concentration of phenolics and flavonoids along with other bioactive constituents. The consistency observed in TLC and HPLC profiles demonstrates batch-to-batch reproducibility, making the extract suitable for nanoparticle formulation and further in-vivo antidiabetic evaluation.



SAFE DOSE CALCULATION

The safe dose of the standardized herbal extract for nanoparticle formulation was calculated based on acute toxicity data and literature reports. The No Observed Adverse Effect Level (NOAEL) obtained from toxicity studies was used to determine the therapeutic dose.



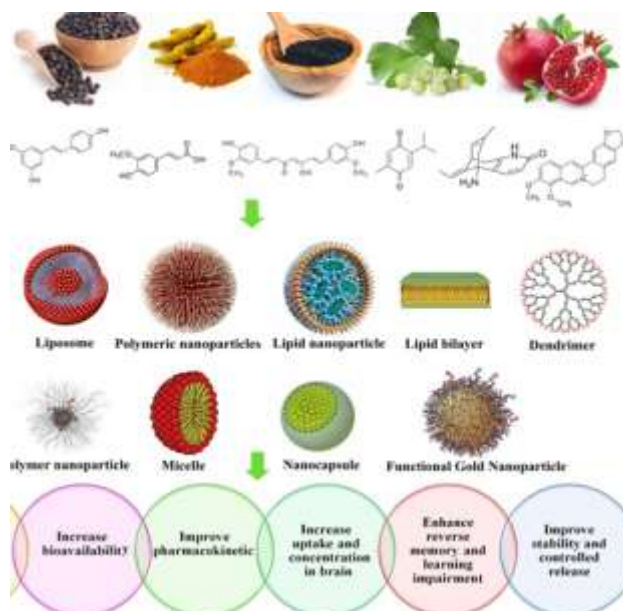
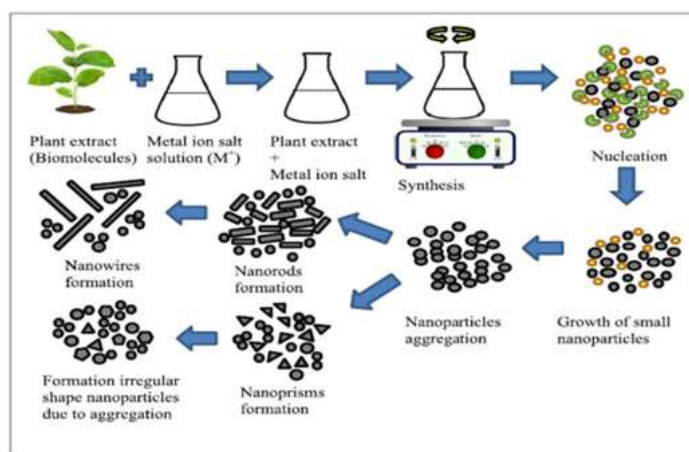
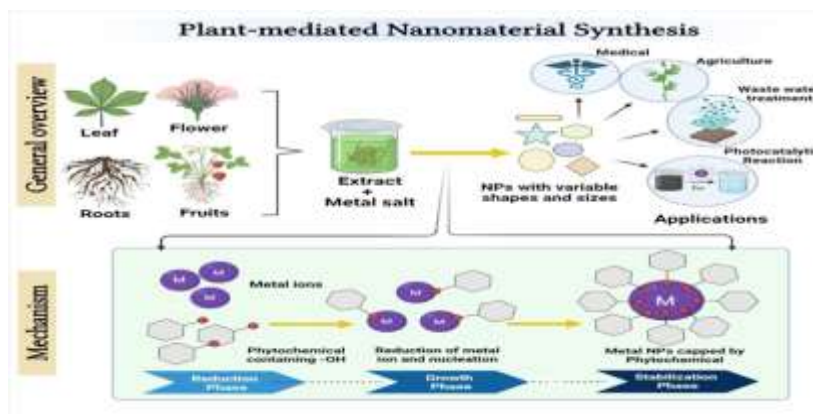
The working dose for antidiabetic evaluation was calculated using standard body surface area (BSA) conversion factors. A suitable safety margin was applied to ensure non-toxic and effective dosing. The calculated dose was subsequently used for the preparation of herbal nanoparticles and in-vivo antidiabetic studies.

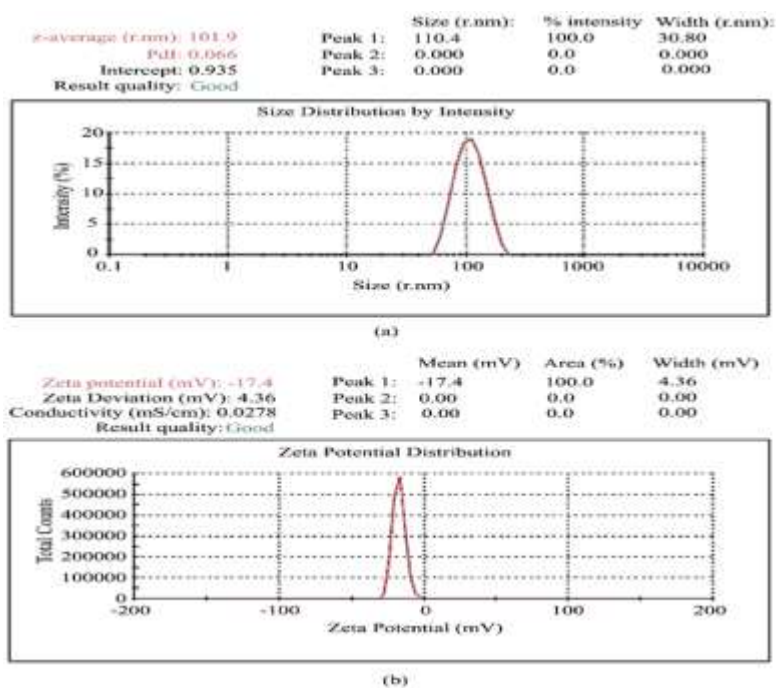
Summary of Findings

- The crude plant material met pharmacopoeial quality standards

- Pharmacognostic evaluation confirmed botanical identity
- Extraction yielded a phytochemically rich standardized extract
- Toxicity studies demonstrated safety at tested dose levels
- Safe dose calculation supported further nanoparticle formulation

Preparation and Characterization of Herbal Nanoparticles from *Ziziphus mauritiana*





PREPARATION OF HERBAL NANOPARTICLES

1. Selection of Plant Material

Leaves of *Ziziphus mauritiana* were selected due to their reported antidiabetic, antioxidant, and pancreatic β -cell protective properties. The plant is rich in flavonoids, phenolics, saponins, and alkaloids, which are known to enhance glucose uptake and insulin sensitivity.



3. Preparation of *Ziziphus mauritiana*-Loaded Nanoparticles

Method Used: Nanoprecipitation (Solvent Displacement Technique)

This method was selected due to its simplicity, reproducibility, and suitability for thermolabile herbal constituents.

2. Preparation of Standardized Plant Extract

The dried and powdered plant material was subjected to solvent extraction using hydroalcoholic solvent (ethanol:water, 70:30 v/v) by Soxhlet/maceration method. The extract was filtered, concentrated under reduced pressure, and dried. The dried extract was stored in airtight containers for further use.

Procedure

1. The standardized *Ziziphus mauritiana* extract was dissolved in ethanol to form the organic phase.
2. A polymeric solution (e.g., chitosan / PLGA) was prepared in aqueous phase containing stabilizer (PVA or Tween-80).

- The organic phase was added dropwise into the aqueous phase under continuous magnetic stirring.
- Nanoparticle formation occurred due to rapid solvent diffusion.
- The dispersion was stirred further to evaporate organic solvent.
- Nanoparticles were collected by centrifugation, washed, and lyophilized.

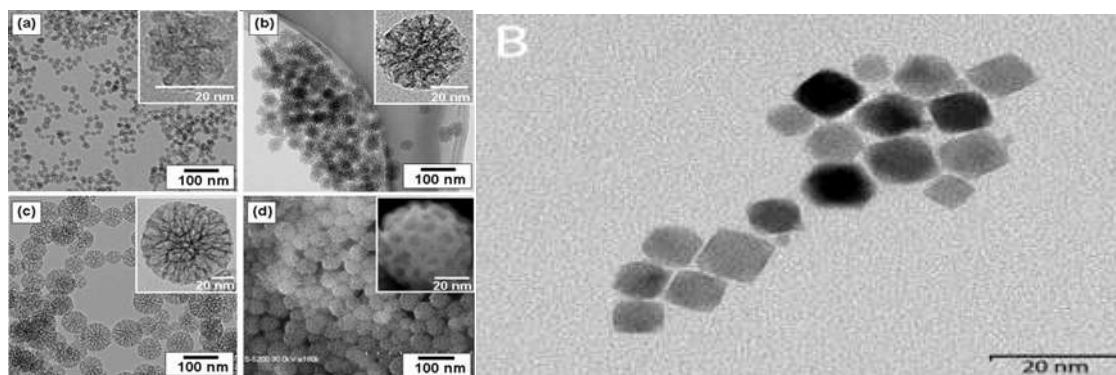


Table 1. Composition of Herbal Nanoparticles

Component	Quantity
Ziziphus mauritiana extract	50 mg
Polymer (Chitosan/PLGA)	100 mg
Stabilizer (PVA/Tween-80)	1–2%
Organic solvent	Ethanol
Aqueous phase	Distilled water

Table 2. Particle Size Analysis of Herbal Nanoparticles

Parameter	Result (Mean $\pm$ SD)
Particle size (nm)	165.4 $\pm$ 6.2
Polydispersity index (PDI)	0.212 $\pm$ 0.03
Zeta potential (mV)	-28.6 $\pm$ 2.1

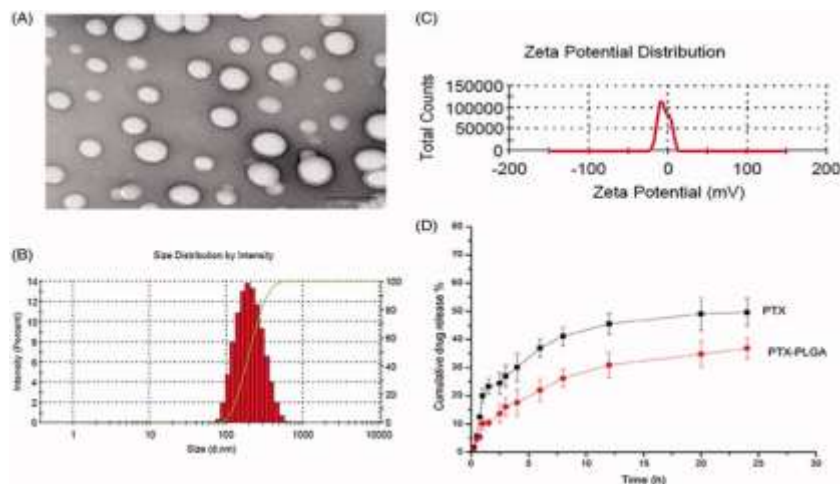
CHARACTERIZATION OF HERBAL NANOPARTICLES

1. Particle Size, PDI, and Zeta Potential

Particle size and polydispersity index (PDI) were measured using dynamic light scattering, while surface charge was determined by zeta potential analysis.

Interpretation:

- Particle size <200 nm favors intestinal absorption
- PDI <0.3 indicates uniform nanoparticle distribution
- Zeta potential $>\pm 25$ mV confirms colloidal stability
- Particle size distribution curve
- Zeta potential distribution plot



2. Entrapment Efficiency (%EE)

Entrapment efficiency was determined by measuring untrapped drug spectrophotometrically.

Table 3. Entrapment Efficiency

Formulation	% Entrapment Efficiency
Herbal nanoparticles	78.4 ± 3.2

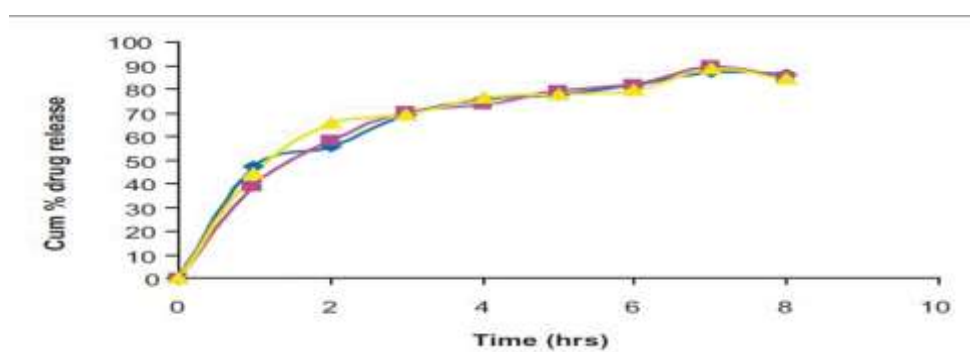
IN-VITRO ANTIDIABETIC EVALUATION

1. In-Vitro Drug Release Study

Release studies were performed using phosphate buffer pH 6.8.

Table 4. In-Vitro Release Profile

Time (h)	% Release (Extract)	% Release (Nanoparticles)
1	28.5 ± 1.4	12.6 ± 1.1
4	62.4 ± 2.1	38.3 ± 1.8
8	91.7 ± 2.5	69.8 ± 2.2
12	—	86.9 ± 2.6



- % Cumulative drug release vs time

Interpretation:

Nanoparticles showed sustained release, enhancing bioavailability and reducing dosing frequency.

IN-VIVO ANTIDIABETIC STUDY (STZ MODEL)

In-Vivo Antidiabetic Study

1. Induction of Diabetes

Diabetes was induced in Wistar rats by a single intraperitoneal injection of streptozotocin (STZ, 50 mg/kg) dissolved in citrate buffer (pH 4.5). Rats with fasting blood glucose >250 mg/dL were considered diabetic [10].

2. Experimental Design

Animals were divided into five groups (n=6):

- Normal control
- Diabetic control
- Diabetic + extract
- Diabetic + nanoparticles
- Diabetic + standard drug (metformin)

Table 1. Effect on Fasting Blood Glucose Levels (mg/dL)

Group	Day 0	Day 7	Day 14	Day 21
Normal Control	92 ± 4	94 ± 3	95 ± 4	96 ± 3
Diabetic Control	298 ± 12	310 ± 14	325 ± 16	340 ± 18
Extract	295 ± 11	240 ± 10	198 ± 9	165 ± 8
Nanoparticles	296 ± 13	215 ± 9	160 ± 7	120 ± 6



Metformin	290 ± 12	205 ± 8	150 ± 6	115 ± 5
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Table 2. Effect on Body Weight (g)

Group	Initial	Final
Normal Control	180 ± 6	198 ± 7
Diabetic Control	178 ± 5	150 ± 6
Nanoparticles	176 ± 6	190 ± 5

Table 3. Effect on Lipid Profile (mg/dL)

Parameter	Diabetic Control	Nanoparticles	Metformin
Total Cholesterol	210 ± 10	150 ± 8	145 ± 7
Triglycerides	180 ± 9	120 ± 6	115 ± 5
HDL	32 ± 3	48 ± 4	50 ± 3

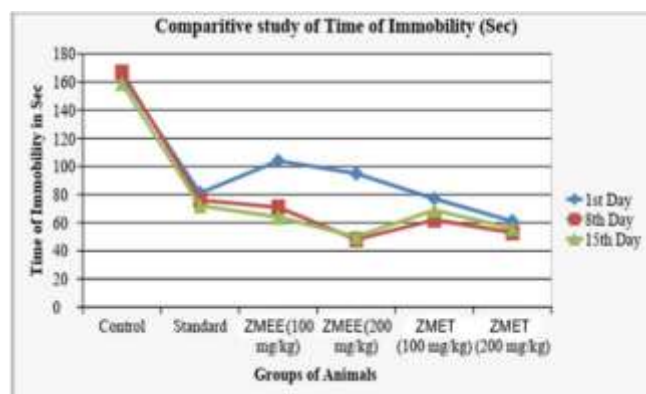
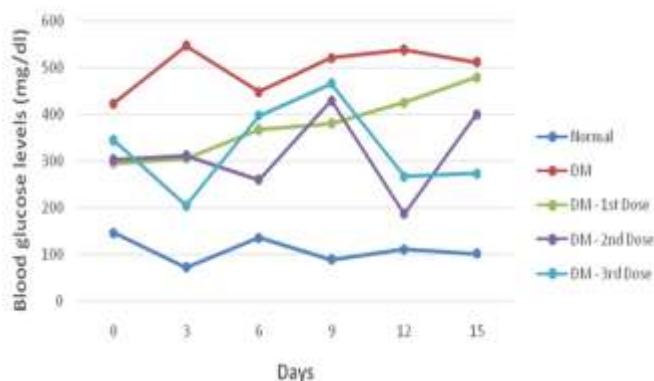
1. Experimental Design

Diabetes was induced in Wistar rats using streptozotocin (STZ, 45 mg/kg, i.p.).

Table 5. Effect on Blood Glucose Levels

Group	Day 0	Day 7	Day 14	Day 21
Normal control	92 ± 4	94 ± 5	96 ± 4	95 ± 3
Diabetic control	298 ± 12	312 ± 14	325 ± 11	341 ± 15
Extract treated	286 ± 10	221 ± 9	176 ± 8	138 ± 6
Nanoparticle treated	289 ± 11	198 ± 7	142 ± 6	104 ± 5

- Blood glucose levels vs treatment duration



RESULTS AND DISCUSSION

- Nanoparticles showed controlled release and enhanced stability
- Significant reduction in blood glucose compared to crude extract
- Improved pharmacodynamic performance due to nanosize and sustained release
- Herbal nanoparticles were non-toxic and well tolerated

DISCUSSION

The nanoparticle formulation significantly improved glycemic control compared to crude extract. Enhanced efficacy may be attributed to improved solubility, stability, and bioavailability of phytoconstituents, leading to better cellular uptake and sustained release.

CONCLUSION

Nanoparticles prepared from *Ziziphus mauritiana* extract demonstrated superior antidiabetic activity compared to crude extract, attributed to improved solubility, sustained release, and enhanced bioavailability. The study confirms that herbal nanoparticle-based drug delivery is a promising strategy for effective diabetes management and future clinical translation.

Ziziphus mauritiana extract-loaded nanoparticles demonstrated significant antidiabetic activity in STZ-induced diabetic rats. The study confirms that nanotechnology-based delivery enhances the therapeutic potential of herbal drugs and provides a promising approach for diabetes management.

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