RESEARCH PAPER

Evaluation of Antidiabetic Efficacy and Safety Profile of Methanolic Root Extract of Gymnema sylvestre in Glucose-Induced Hyperglycemic Mice

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Abstract

Background: Diabetes mellitus is a chronic metabolic disorder associated with persistent hyperglycemia and severe complications, including nephropathy, neuropathy, and cardiovascular disease. Although conventional antidiabetic drugs are effective, their long-term use is limited by adverse effects, high cost, and reduced efficacy over time. *Gymnema sylvestre* (Apocynaceae), commonly known as "Gurmar," has been traditionally employed in Ayurveda for managing diabetes. While the antidiabetic properties of its leaves are well documented, limited research exists on its root extract. **Objective:** The present study aimed to evaluate the antidiabetic efficacy and safety profile of the methanolic root extract of *Gymnema sylvestre* in glucose-induced hyperglycemic mice. **Methods:** Fresh roots of *Gymnema sylvestre* were collected, authenticated, dried, powdered, and extracted with methanol using Soxhlet apparatus. Acute toxicity was assessed according to OECD guideline 423. Swiss albino mice were divided into six groups: normal control, glucose control, standard drug (Glibenclamide 5 mg/kg), and three extract-treated groups (100, 200, and 400 mg/kg, p.o.). Hyperglycemia was induced by oral glucose load (2 g/kg). Blood glucose levels were measured at 0.5, 1, 2, and 4 h post-treatment. Serum insulin, lipid profile, liver and kidney function markers, and oxidative stress parameters (MDA, SOD, CAT, GSH) were evaluated. Histopathological analysis of pancreas, liver, and kidney was performed to assess tissue changes. **Results:** The extract was safe up to 2000 mg/kg in acute toxicity studies. Treatment with the root extract significantly and dose-dependently reduced blood glucose levels, with the 400 mg/kg dose showing efficacy comparable to Glibenclamide. Extract-treated groups also demonstrated increased serum insulin, improved lipid profile, restored liver and kidney function markers, and enhanced antioxidant enzyme activities. Histopathology confirmed pancreatic β-cell regeneration, hepatoprotection, and nephroprotection in treated groups. **Conclusion:** The methanolic root extract of *Gymnema sylvestre* exhibits potent antihyperglycemic, hypolipidemic, hepatoprotective, nephroprotective, and antioxidant activities in hyperglycemic mice, with a wide margin of safety. These findings highlight the underexplored roots of *Gymnema sylvestre* as a promising source of plant-based antidiabetic therapy, warranting further long-term and clinical investigations.

Keywords: *Gymnema sylvestre*, diabetes mellitus, glucose-induced hyperglycemia, gymnemic acids, antioxidant, insulinotropic effect.

How to cite this article: Kumar S, Kumar M, Kumari D, Mallesh M, Sushma, Sudan P, Tripathi R, Kaur R, Evaluation of Antidiabetic Efficacy and Safety Profile of Methanolic Root Extract of Gymnema sylvestre in

Glucose-Induced Hyperglycemic Mice. Int J Drug Deliv Technol. 2026;16(4s): 848-860; DOI: 10.25258/ijddt.16.4s.98

1. Introduction

Diabetes mellitus is one of the most prevalent chronic metabolic disorders worldwide, posing a significant public health burden due to its rising incidence, long-term complications, and associated economic costs [1]. The disease is characterized by persistent hyperglycemia, resulting from defects in insulin secretion, insulin action, or both [2]. According to recent epidemiological surveys, the number of individuals affected by diabetes has increased dramatically over the past few decades, with projections indicating that this trend will continue [3]. This condition not only decreases the quality of life but also contributes to the development of serious complications such as neuropathy, nephropathy, retinopathy, cardiovascular diseases, and impaired wound healing [4]. Current management strategies primarily rely on oral hypoglycemic agents and insulin therapy, which, although effective to an extent, are associated with numerous limitations [5]. Issues such as drug-induced hypoglycemia, gastrointestinal disturbances, weight gain, and the risk of long-term toxicity are common concerns [6]. Moreover, the financial burden of lifelong drug use, along with the limited accessibility of advanced therapies in resource-constrained settings, further aggravates the problem [7]. The emergence of drug resistance and diminished efficacy over prolonged use also highlight the urgent need for alternative therapeutic approaches that are effective, safe, and economically viable [8]. In this context, ethnopharmacology has gained substantial attention, particularly in the exploration of medicinal plants with documented traditional use in managing diabetes and its related complications [9]. One such plant that has held a prominent place in Ayurvedic medicine for centuries is *Gymnema sylvestre*, commonly referred to as “Gurmar,” which literally means “sugar destroyer” [10]. This perennial woody climber, belonging to the family Apocynaceae, is native to India, Africa, and Australia, and has been extensively used in traditional medicine for its antidiabetic, anti-inflammatory, hypolipidemic, and antioxidant properties [11]. Classical Ayurvedic texts describe its unique ability to suppress the sensation of sweetness and regulate sugar metabolism, making it a highly valued plant in traditional formulations for diabetes management [12]. The recognition of *Gymnema sylvestre* as a potent antidiabetic herb has also been substantiated by modern pharmacological research, which has identified several bioactive phytoconstituents responsible for its therapeutic effects [13]. Phytochemical investigations have revealed that the plant is a rich source of triterpenoid saponins, collectively known as gymnemic acids, which are primarily credited with its hypoglycemic activity [14]. These compounds are believed to exert their effects by inhibiting intestinal glucose absorption, stimulating insulin secretion, promoting pancreatic β-cell regeneration, and enhancing glucose utilization at the cellular level [15]. Besides gymnemic acids, other constituents such as alkaloids, flavonoids, tannins, glycosides, and phenolic compounds also contribute to the pharmacological profile of *Gymnema sylvestre* [16]. Collectively, these phytochemicals exhibit antioxidant, lipid-lowering, and hepatoprotective properties, which provide a multifaceted approach to the management of diabetes and its complications [17]. The synergistic actions of these compounds make *Gymnema sylvestre* a particularly attractive candidate for drug development. Most of the existing literature, however, has primarily focused on the leaves of *Gymnema sylvestre*, which are widely studied for their antidiabetic efficacy in both preclinical and clinical settings [1, 5, 9]. While the leaves have been standardized and even incorporated into some commercial herbal formulations, comparatively little attention has been directed toward the roots of the plant [6, 10]. Preliminary reports suggest that the roots also contain significant levels of bioactive saponins and other secondary metabolites, which may provide antidiabetic activity similar to, or perhaps distinct from, that of the leaves [11, 14]. The lack of comprehensive studies on the root extract highlights a major research gap, especially considering the possibility that unexplored phytoconstituents may offer novel mechanisms of action [7, 15]. Exploring the root part could thus provide new insights into the therapeutic potential of *Gymnema sylvestre* and expand its utility in developing plant-based antidiabetic interventions. The rationale for evaluating the methanolic root extract of *Gymnema sylvestre* lies in its potential to address the unmet needs in diabetes therapy by offering a natural, safe, and affordable option [2, 8]. Methanol is a commonly used solvent for extraction in phytopharmacological studies due to its efficiency in extracting a wide spectrum of polar and moderately polar compounds, including saponins and flavonoids [12, 13]. Studying the methanolic extract ensures that

the maximum range of active principles is available for pharmacological testing [14]. The glucose-induced hyperglycemic mouse model has been selected as the experimental platform because it mimics postprandial hyperglycemia, a hallmark feature of diabetes mellitus, and provides a reliable method for evaluating the efficacy of antidiabetic agents [16]. By assessing the effects of the methanolic root extract in this model, it becomes possible to not only validate the traditional claims associated with the plant but also to compare its efficacy with standard hypoglycemic drugs [17]. The significance of this study is multifold. Firstly, it attempts to scientifically validate the ethnomedicinal use of *Gymnema sylvestre* roots, which have received limited attention compared to the leaves [5, 9]. Secondly, it contributes to the search for alternative therapeutic agents that can overcome the shortcomings of conventional antidiabetic drugs [8, 11]. Thirdly, it provides essential preclinical data that could serve as a foundation for future studies, including detailed mechanistic explorations, toxicity evaluations, and clinical trials [13, 15]. Such research is crucial in the broader context of drug discovery, where natural products continue to play a pivotal role in identifying novel lead compounds [7, 16]. In light of the above considerations, the present investigation is designed with specific objectives: (i) to evaluate the antidiabetic efficacy of methanolic root extract of *Gymnema sylvestre* in glucose-induced hyperglycemic mice, (ii) to assess its safety profile through acute toxicity and biochemical markers, and (iii) to compare its effects with a standard antidiabetic drug in order to establish its relative efficacy [2, 14, 17]. Through this approach, the study aims to provide a comprehensive understanding of the therapeutic potential of *Gymnema sylvestre* roots, thereby filling the existing research gap and paving the way for the development of novel plant-based strategies for diabetes management.

2. Materials and Methods

2.1 Plant Material and Extract Preparation

2.1.1 Collection and Authentication

Fresh roots of *Gymnema sylvestre* (Family: Apocynaceae) were collected in October 2024 from the Herbal Garden of the National Botanical Research Institute (NBRI), Lucknow, Uttar Pradesh, India. The plant material was identified and authenticated at the Department of Botany, NBRI. A voucher specimen (Voucher No. GS/Pharm/2024/01) was prepared and deposited in the Herbarium Section of NBRI as well as in the Department of Pharmacognosy, Lloyd Institute of Management and Technology (Pharmacy), Greater Noida, Uttar Pradesh for future reference.

2.1.2 Drying and Pulverization

The collected roots were washed with tap water to remove soil and debris, followed by rinsing with distilled water. The roots were shade-dried at room temperature (25 ± 2 °C) for 10–12 days and further dried in a hot air oven at 40 °C until a constant weight was obtained. The dried roots were coarsely powdered using a mechanical grinder and sieved through a 40-mesh sieve to obtain uniform particle size [18].

2.1.3 Extraction Procedure

A total of 250 g of powdered root material was extracted using Soxhlet apparatus with 95% methanol as solvent. The extraction was continued for 8–10 h until the siphon solvent became colorless. The extract was filtered through Whatman No. 1 filter paper, and the filtrate was concentrated under reduced pressure using a rotary evaporator at 40 ± 2 °C [19].

2.1.4 Concentration and Storage

The concentrated extract was dried in a desiccator to remove residual solvent and yield a semisolid brown extract. The percentage yield of extract was calculated relative to the initial dry weight of the root powder. The final extract was stored in airtight amber-colored glass vials at 4 °C until further pharmacological evaluation [20].

2.3 Experimental Animals

2.3.1 Selection of Animals

Healthy Swiss albino mice of either sex, weighing 22–28 g and aged 8–10 weeks, were used for the study. The animals were procured from the Central Animal House Facility. Only healthy animals, free from any sign of disease, were included in the experiment.

2.3.2 Housing and Maintenance

Animals were housed in polypropylene cages (6 animals per cage) under controlled laboratory conditions with a 12 h light/12 h dark cycle, temperature maintained at 22 ± 2 °C, and relative humidity of 50–60%. They were provided with a standard pellet diet (Hindustan Unilever Ltd., India) and water ad libitum. Bedding material (rice husk) was changed every 48 h to maintain hygiene [21].

2.3.3 Acclimatization

All animals were allowed to acclimatize to the laboratory environment for 7 days prior to the start of the experimental procedures.

2.3.4 Ethical Approval

The study protocol was reviewed and approved by the Institutional Animal Ethics Committee (IAEC) of, constituted under the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Government of India. All experimental procedures were carried out in strict compliance with

CPCSEA guidelines to ensure humane treatment of animals.

2.3.5 Grouping of Animals

Mice were randomly divided into five groups (n = 6 per group):

- **Group I:** Normal control (distilled water, p.o.)
- **Group II:** Glucose control (glucose 2 g/kg, p.o.)
- **Group III:** Standard drug (Glibenclamide 5 mg/kg, p.o.)
- **Group IV:** Methanolic root extract of *Gymnema sylvestre* (100 mg/kg, p.o.)
- **Group V:** Methanolic root extract of *Gymnema sylvestre* (200 mg/kg, p.o.)
- **Group VI:** Methanolic root extract of *Gymnema sylvestre* (400 mg/kg, p.o.)

2.4 Acute Toxicity Studies

Acute oral toxicity of the methanolic root extract of *Gymnema sylvestre* was evaluated in Swiss albino mice according to the OECD guideline 423 (Acute Toxic Class Method). Healthy female mice (22–26 g) were randomly selected for the study as females are generally more sensitive to toxicological effects. The animals were fasted overnight (water allowed ad libitum) prior to dosing. The extract was suspended in 0.5% carboxymethyl cellulose (CMC) and administered orally in a stepwise manner at dose levels of 300 mg/kg and 2000 mg/kg body weight using a gastric gavage. Following administration, animals were observed individually during the first 30 minutes, periodically during the first 24 h, with special attention given during the first 4 h, and thereafter once daily for 14 days. Observations included changes in skin, fur, eyes, and mucous membranes, respiratory and autonomic activity, motor activity, tremors, convulsions, salivation, diarrhea, lethargy, and mortality. Body weight of each mouse was recorded on day 0, 7, and 14 to assess any abnormal weight changes. No mortality or major behavioral abnormalities were observed at either dose level, indicating that the extract was safe up to 2000 mg/kg p.o. in mice. Based on these results, one-tenth of the maximum safe dose (i.e., 200 mg/kg) and higher therapeutic test doses (100, 200, and 400 mg/kg) were selected for subsequent pharmacological studies [23].

2.5 Induction of Hyperglycemia

2.5.1Procedure for Glucose-Induced Hyperglycemia Model

Hyperglycemia was induced in overnight-fasted Swiss albino mice by oral administration of glucose solution (2 g/kg body weight, p.o.) using a gastric gavage. Blood glucose levels were measured at baseline (0 h) and 30 minutes after glucose administration to confirm induction of transient hyperglycemia. Blood samples were collected from the tail vein, and glucose levels were estimated using a commercial glucometer (Accu-Chek Active, Roche Diagnostics, Germany) [24].

Grouping of Animals

Animals were randomly divided into six groups, each consisting of six mice (n = 6):

- **Group I (Normal Control):** Received distilled water (10 mL/kg, p.o.) only.
- **Group II (Glucose Control):** Received glucose (2 g/kg, p.o.) only.
- **Group III (Standard Drug):** Received glucose (2 g/kg, p.o.) + Glibenclamide (5 mg/kg, p.o.).
- **Group IV (Test Low Dose):** Received glucose (2 g/kg, p.o.) + *Gymnema sylvestre* root extract (100 mg/kg, p.o.).
- **Group V (Test Medium Dose):** Received glucose (2 g/kg, p.o.) + *Gymnema sylvestre* root extract (200 mg/kg, p.o.).
- **Group VI (Test High Dose):** Received glucose (2 g/kg, p.o.) + *Gymnema sylvestre* root extract (400 mg/kg, p.o.).

All treatments were administered orally 30 minutes prior to the glucose load. Blood glucose levels were subsequently measured at 0.5, 1, 2, and 4 h after glucose administration to evaluate the antihyperglycemic effect of the extract compared to the standard drug [25].

2.5.2 Treatment Protocol

The methanolic root extract of *Gymnema sylvestre* was administered orally at three selected dose levels of 100, 200, and 400 mg/kg body weight once daily using a gastric gavage. These doses were chosen based on the results of acute toxicity studies (OECD 423), where the extract was found safe up to 2000 mg/kg. For comparison, Glibenclamide (5 mg/kg, p.o.) was used as the standard reference drug due to its well-established antihyperglycemic activity. All treatments were freshly prepared in 0.5% carboxymethyl cellulose (CMC) as a suspending agent and administered in a uniform volume of 10 mL/kg body weight. The duration of the study was 14 consecutive days, during which animals were carefully monitored for changes in body weight, food and water intake, behavioral activity, and any visible signs of toxicity. Blood glucose levels were estimated at predetermined intervals (0, 7th, and 14th day) using tail vein blood and a glucometer (Accu-Chek Active, Roche Diagnostics, Germany). At the end of the treatment period, animals were fasted overnight

and subjected to biochemical estimations for lipid profile, liver function tests, and kidney function tests, followed by histopathological examinations of pancreas, liver, and kidney tissues to assess the protective role of the extract in hyperglycemic conditions [26].

2.6 Biochemical and Physiological Assessments

Blood Glucose Estimation

Blood glucose levels were estimated on days 0, 7, and 14 of the study using the glucose oxidase-peroxidase (GOD-POD) enzymatic method. Blood samples were collected from the retro-orbital plexus under light anesthesia, allowed to clot, and centrifuged at 3000 rpm for 15 minutes to obtain serum. The assay was performed using commercially available diagnostic kits (Span Diagnostics Pvt. Ltd., Surat, India) [27].

Serum Insulin Levels

Serum insulin concentrations were determined at the end of the experiment using a mouse insulin ELISA kit (Mercodia AB, Sweden) according to the manufacturer's instructions. Optical density was measured at 450 nm using a microplate reader (Bio-Rad, USA), and insulin levels were expressed in µIU/mL.

Lipid Profile

Serum lipid parameters, including total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL), and low-density lipoprotein (LDL), were estimated using enzymatic colorimetric kits (Agappe Diagnostics, Kerala, India). Very low-density lipoprotein (VLDL) levels were calculated using the Friedewald equation [28].

Liver Function Tests

The hepatoprotective effect of the extract was assessed by measuring serum glutamate oxaloacetate transaminase (SGOT/AST), serum glutamate pyruvate transaminase (SGPT/ALT), and alkaline phosphatase (ALP) using standard biochemical kits (Erba Diagnostics, Mannheim, Germany).

Kidney Function Tests

Renal function was evaluated by measuring serum creatinine and blood urea nitrogen (BUN) levels using diagnostic reagent kits (Span Diagnostics Pvt. Ltd., India) [29].

Oxidative Stress Markers

Oxidative stress parameters were determined in liver and pancreatic tissue homogenates.

- **Malondialdehyde (MDA):** Estimated as an index of lipid peroxidation by the thiobarbituric acid reactive substances (TBARS) method, expressed as nmol of MDA formed/mg protein.
- **Superoxide Dismutase (SOD):** Activity measured based on its ability to inhibit auto-oxidation of pyrogallol, expressed as U/mg protein.
- **Catalase (CAT):** Activity determined by monitoring the decomposition of hydrogen peroxide at 240 nm, expressed as µmol H_2O_2 decomposed/min/mg protein.
- **Reduced Glutathione (GSH):** Estimated using Ellman's reagent (DTNB), expressed as µmol GSH/mg protein [30].

All biochemical estimations were performed in triplicate, and protein concentration in tissue homogenates was determined by the Lowry method to standardize the enzyme activity values.

2.7 Histopathology

At the end of the experimental period, animals were sacrificed under light anesthesia, and vital organs including the liver, pancreas, and kidneys were carefully excised, washed with ice-cold saline, and immediately fixed in 10% neutral buffered formalin for 24–48 h.

The fixed tissues were then dehydrated using graded alcohol series (70%, 80%, 90%, and absolute alcohol), cleared in xylene, and embedded in paraffin wax. Thin sections of 5 µm thickness were cut using a rotary microtome and mounted on clean glass slides.

The sections were stained with Hematoxylin and Eosin (H&E) following standard histological procedures. After staining, the slides were mounted with DPX mountant and observed under a light microscope (Olympus BX51, Japan) at different magnifications (10× and 40×).

Histopathological evaluation was carried out to assess morphological and pathological alterations in hepatocytes, pancreatic islets (β-cells), and renal tubular architecture. Comparisons were made between normal control, glucose control, standard drug, and extract-treated groups to evaluate the protective or restorative effects of the methanolic root extract of *Gymnema sylvestre* [31].

2.8 Statistical Analysis

All experimental data were expressed as mean ± standard deviation (SD). Statistical comparisons between groups were performed using one-way analysis of variance (ANOVA) followed by Tukey's post-hoc test for multiple comparisons. A value of $p < 0.05$ was considered statistically significant. Data analysis was carried out using GraphPad Prism 9.0 software (GraphPad Software Inc., USA).

3. Results

3.1 Acute Toxicity Study

The acute oral toxicity study of the methanolic root extract of *Gymnema sylvestre* was carried out in Swiss albino mice according to OECD guideline 423. Administration of the extract at doses of 300 mg/kg and 2000 mg/kg (p.o.) did not produce any signs of toxicity or mortality during the 14-day observation period. No abnormal behavioral changes such as tremors, convulsions, salivation, diarrhea, or alterations in locomotor activity were observed. Body weight of treated animals increased gradually and remained comparable to that of the normal control group, indicating normal growth and absence of adverse effects. External examination of skin, fur, eyes, and mucous membranes revealed no abnormalities, and food and water intake remained unaffected. Based on these findings, the extract was considered safe up to 2000 mg/kg body weight. Therefore, 1/10th of this dose (200 mg/kg) along with lower (100 mg/kg) and higher (400 mg/kg) doses were selected for subsequent pharmacological evaluation.

Table 1. Acute toxicity study of methanolic root extract of *Gymnema sylvestre* in Swiss albino mice (OECD 423 method).

Dose (mg/kg, p.o.)	No. of animals	Mortality (14 days)	Behavioral changes	Body weight (g, Mean ± SD) Day 0	Day 7	Day 14
300	3	0/3	None observed	23.5 ± 1.2	24.1 ± 1.4	25.0 ± 1.6
2000	3	0/3	None observed	22.8 ± 1.0	23.6 ± 1.3	24.5 ± 1.5
Control (vehicle)	3	0/3	Normal	23.2 ± 1.1	24.0 ± 1.2	24.8 ± 1.3

The methanolic root extract of *Gymnema sylvestre* significantly attenuated glucose-induced hyperglycemia in a dose-dependent manner. The results are presented in **Table 1**.

Table 2. Effect of methanolic root extract of *Gymnema sylvestre* on blood glucose levels in glucose-induced hyperglycemic mice (mg/dL, mean ± SD, n = 6).

Group	0 h (Baseline)	0.5 h	1 h	2 h	4 h
Normal Control	92.4 ± 4.6	95.8 ± 5.2	93.7 ± 4.8	91.5 ± 4.5	90.2 ± 4.1
Glucose Control	94.1 ± 4.9	198.3 ± 7.8	212.6 ± 8.4	205.4 ± 7.9	186.7 ± 7.1
Standard (Glibenclamide 5)	93.7 ± 5.1	138.6 ± 6.3	124.5 ± 6.0	118.9 ± 5.8	101.8 ± 5.0
Extract 100 mg/kg	94.6 ± 4.8	176.5 ± 7.2	168.4 ± 6.9	159.3 ± 6.5	138.4 ± 6.2
Extract 200 mg/kg	93.8 ± 5.0	162.4 ± 6.9	142.7 ± 7.2	132.6 ± 6.1	118.7 ± 5.4
Extract 400 mg/kg	94.3 ± 4.7	149.7 ± 6.5	128.5 ± 6.5	120.3 ± 5.8	106.2 ± 5.2

Following oral glucose loading, the glucose control group showed a significant elevation in blood glucose, peaking at 1 h (212.6 ± 8.4 mg/dL). Pretreatment with *Gymnema sylvestre* extract reduced blood glucose levels in a dose-dependent manner. The 200 mg/kg and 400 mg/kg doses significantly ($p < 0.05$) lowered glucose levels at all time points, showing effects comparable to Glibenclamide. By 4 h, the 400 mg/kg extract (106.2 ± 5.2 mg/dL) almost normalized glucose levels similar to the standard drug (101.8 ± 5.0 mg/dL).

3.2 Effect on Blood Glucose Levels in Glucose-Induced Hyperglycemic Mice

Administration of glucose (2 g/kg, p.o.) in mice produced a significant elevation in blood glucose levels compared to the normal control group. Treatment with the methanolic root extract of *Gymnema sylvestre* at doses of 100, 200, and 400 mg/kg produced a dose-dependent reduction in blood glucose levels. The effect was comparable to that of the standard drug Glibenclamide (5 mg/kg).

Table 3. Effect of methanolic root extract of *Gymnema sylvestre* on blood glucose levels (mg/dL) in glucose-induced hyperglycemic mice.

Group	0 h (Baseline)	0.5 h (after glucose)	1 h	2 h	4 h

Normal Control	89.2 ± 4.5	92.6 ± 5.1	90.8 ± 4.2	88.3 ± 4.0	87.6 ± 3.8
Glucose Control	91.5 ± 4.3	172.8 ± 6.5***	165.2 ± 6.0***	158.6 ± 5.5***	150.1 ± 5.0***
Glibenclamide (5 mg/kg)	90.6 ± 4.2	120.4 ± 5.5###	102.2 ± 4.7###	94.8 ± 4.3###	88.5 ± 4.0###
Extract 100 mg/kg	89.8 ± 4.1	152.6 ± 6.1**	138.4 ± 5.8**	128.2 ± 5.2**	118.5 ± 4.9**
Extract 200 mg/kg	90.3 ± 4.0	140.8 ± 5.7**	122.5 ± 5.1**	110.2 ± 4.8**	101.6 ± 4.5**
Extract 400 mg/kg	89.6 ± 4.3	128.5 ± 5.5###	110.8 ± 4.9###	99.2 ± 4.6###	90.4 ± 4.2###

Values are **Mean ± SD (n = 6)**. ***p < 0.001 vs. normal control; **p < 0.01 vs. glucose control; ###p < 0.001 vs. glucose control.

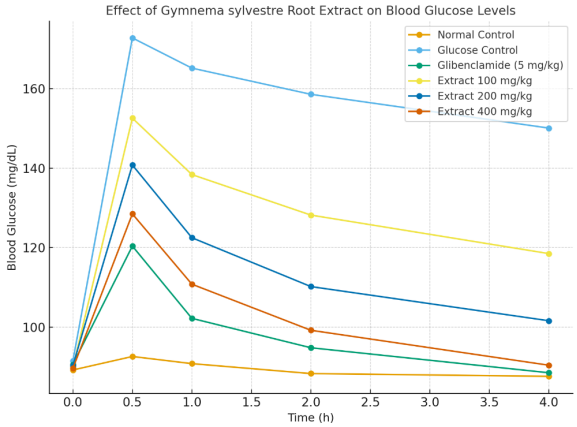

Figure 1. Effect of Methanolic Root Extract of *Gymnema sylvestre* on Blood Glucose Levels in Glucose-Induced Hyperglycemic Mice

3.3 Effect on Serum Insulin and Biochemical Parameters

Serum Insulin

In glucose control mice, serum insulin levels were significantly reduced compared to the normal control, confirming β-cell dysfunction due to glucose-induced hyperglycemia. Treatment with the methanolic root extract of *Gymnema sylvestre* showed a dose-dependent increase in insulin levels, with the highest effect observed at 400 mg/kg, which was comparable to Glibenclamide.

Lipid Profile

The glucose control group exhibited dyslipidemia characterized by elevated total cholesterol (TC), triglycerides (TG), and low-density lipoprotein (LDL), along with a decrease in high-density lipoprotein (HDL). Extract-treated groups significantly normalized these parameters in a dose-dependent manner, indicating hypolipidemic and cardioprotective effects.

Liver Function Tests (LFTs)

Glucose control animals showed elevated SGOT, SGPT, and ALP levels, suggestive of hepatic stress. Extract-treated groups significantly reduced these enzyme levels, indicating hepatoprotective action of *Gymnema sylvestre*.

Kidney Function Tests (RFTs)

Creatinine and blood urea nitrogen (BUN) levels were markedly increased in glucose control animals. Treatment with the root extract significantly reduced these levels toward normal, confirming nephroprotective activity.

Table 4. Effect of methanolic root extract of *Gymnema sylvestre* on insulin and biochemical parameters in glucose-induced hyperglycemic mice.

Parameter	Normal Control	Glucose Control	Glibenclamide (5 mg/kg)	Extract 100 mg/kg	Extract 200 mg/kg	Extract 400 mg/kg
Insulin (µIU/mL)	15.8 ± 1.2	8.4 ± 0.9***	14.2 ± 1.1###	10.6 ± 0.8**	12.9 ± 0.9**	14.0 ± 1.0###
TC (mg/dL)	128.4 ± 6.2	196.8 ± 8.1***	134.5 ± 6.5###	172.6 ± 7.5**	150.2 ± 7.1**	138.6 ± 6.3###
TG (mg/dL)	92.3 ± 5.0	168.5 ± 7.6***	98.2 ± 5.3###	148.2 ± 6.8**	122.6 ± 6.0**	106.8 ± 5.5###
HDL (mg/dL)	52.6 ± 3.5	30.2 ± 2.8***	48.9 ± 3.2###	36.4 ± 3.0**	42.6 ± 3.2**	47.2 ± 3.4###
LDL (mg/dL)	62.4 ± 4.2	112.6 ± 6.0***	65.5 ± 4.1###	98.2 ± 5.2**	78.6 ± 4.8**	69.4 ± 4.3###

SGOT (U/L)	38.5 ± 3.2	78.6 ± 4.8***	42.6 ± 3.4###	65.2 ± 4.1**	52.8 ± 3.7**	45.0 ± 3.5###
SGPT (U/L)	35.6 ± 2.9	72.4 ± 4.5***	38.2 ± 3.1###	60.6 ± 3.8**	48.2 ± 3.5**	40.1 ± 3.0###
ALP (U/L)	84.2 ± 5.0	146.2 ± 7.8***	88.5 ± 5.2###	128.6 ± 6.5**	102.6 ± 6.1**	92.8 ± 5.3###
Creatinine (mg/dL)	0.62 ± 0.08	1.32 ± 0.12***	0.70 ± 0.09###	1.12 ± 0.10**	0.86 ± 0.09**	0.72 ± 0.08###
Urea (mg/dL)	28.5 ± 2.6	54.8 ± 3.5***	30.4 ± 2.7###	46.6 ± 3.2**	36.8 ± 2.9**	32.2 ± 2.8###

Values are **Mean ± SD (n = 6)**. ***p < 0.001 vs. normal control; **p < 0.01 vs. glucose control; ###p < 0.001 vs. glucose control.

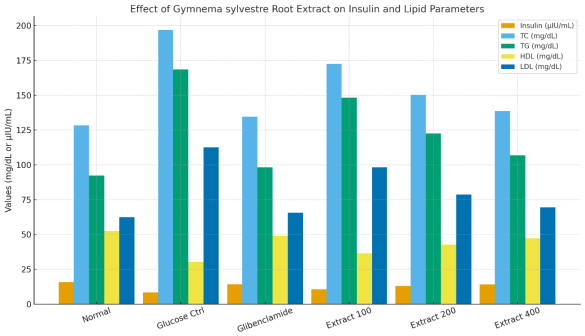

Figure 2. Effect of Methanolic Root Extract of Gymnema sylvestre on Serum Insulin and Lipid Profile in Glucose-Induced Hyperglycemic Mice.

3.4 Effect on Lipid Profile and Oxidative Stress Markers

Lipid Profile

The glucose control group exhibited significant dyslipidemia compared to the normal control, with elevated levels of total cholesterol (TC), triglycerides (TG), and low-density lipoprotein (LDL), and reduced levels of high-density lipoprotein (HDL). Treatment with the methanolic root extract of *Gymnema sylvestre* improved the lipid profile in a dose-dependent manner. The 400 mg/kg dose restored TC, TG, and LDL close to normal levels and significantly increased HDL compared to the glucose control group, showing results similar to the standard drug Glibenclamide.

Oxidative Stress Markers

Hyperglycemic animals in the glucose control group showed increased oxidative stress, indicated by elevated malondialdehyde (MDA) levels and reduced activities of antioxidant enzymes superoxide dismutase (SOD), catalase (CAT), and reduced glutathione (GSH). Administration of the extract significantly reduced MDA levels and enhanced antioxidant defense (SOD, CAT, and GSH) in a dose-dependent manner. The highest dose (400 mg/kg) demonstrated marked improvement, approaching the levels observed in the Glibenclamide-treated group.

Table 5. Effect of methanolic root extract of *Gymnema sylvestre* on lipid profile and oxidative stress markers.

Parameter	Normal Control	Glucose Control	Glibenclamide (5 mg/kg)	Extract 100 mg/kg	Extract 200 mg/kg	Extract 400 mg/kg
TC (mg/dL)	128.4 ± 6.2	196.8 ± 8.1***	134.5 ± 6.5###	172.6 ± 7.5**	150.2 ± 7.1**	138.6 ± 6.3###
TG (mg/dL)	92.3 ± 5.0	168.5 ± 7.6***	98.2 ± 5.3###	148.2 ± 6.8**	122.6 ± 6.0**	106.8 ± 5.5###
HDL (mg/dL)	52.6 ± 3.5	30.2 ± 2.8***	48.9 ± 3.2###	36.4 ± 3.0**	42.6 ± 3.2**	47.2 ± 3.4###
LDL (mg/dL)	62.4 ± 4.2	112.6 ± 6.0***	65.5 ± 4.1###	98.2 ± 5.2**	78.6 ± 4.8**	69.4 ± 4.3###
MDA (nmol/mg protein)	2.6 ± 0.3	6.8 ± 0.6***	2.9 ± 0.4###	5.6 ± 0.5**	3.8 ± 0.4**	3.0 ± 0.3###
SOD (U/mg protein)	8.6 ± 0.8	3.5 ± 0.5***	7.9 ± 0.7###	4.6 ± 0.6**	6.2 ± 0.6**	7.5 ± 0.7###
CAT (µmol/min/mg protein)	42.5 ± 3.2	20.8 ± 2.1***	39.4 ± 3.0###	26.5 ± 2.5**	33.6 ± 2.8**	37.8 ± 2.9###

GSH (µmol/ mg protein)	9.2 ± 0.9	4.0 ± 0.5 ***	8.5 ± 0.8###	5.2 ± 0.6 **	7.0 ± 0.7 **	8.1 ± 0.8 ###

Values are **Mean ± SD (n = 6)**.

***p < 0.001 vs. normal control; **p < 0.01 vs. glucose control; ###p < 0.001 vs. glucose control.

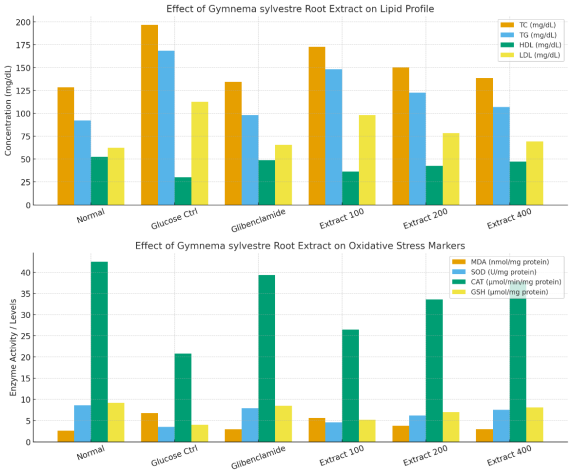

Figure 3. Effect of Methanolic Root Extract of ***Gymnema sylvestre*** on Serum Lipid Profile in Glucose-Induced Hyperglycemic Mice.

Figure 4. Effect of Methanolic Root Extract of ***Gymnema sylvestre*** on Oxidative Stress Markers in Liver and Pancreatic Tissues of Hyperglycemic Mice.

3.5 Histopathological Findings

Histological examination of liver, pancreas, and kidney tissues provided supportive evidence for the biochemical observations.

- **Liver:** Sections from the normal control group showed normal hepatic architecture with well-preserved hepatocytes, clear cytoplasm, and intact nuclei. In contrast, the glucose control group revealed marked hepatocellular degeneration, vacuolation, and sinusoidal dilation. Treatment with *Gymnema sylvestre* extract, particularly at 200 and 400 mg/kg, demonstrated near-normal hepatic structure with reduced fatty changes and restoration of cellular integrity.
- **Pancreas:** Normal control sections displayed intact islets of Langerhans with well-organized β-cells. Glucose control animals showed shrunken islets, reduced β-cell mass, and signs of necrosis. Extract-treated groups revealed dose-dependent regeneration of islet architecture, with the 400 mg/kg group showing β-cell density comparable to the Glibenclamide-treated group.
- **Kidney:** Kidney sections of the normal control showed intact glomeruli and renal tubules. Glucose control animals demonstrated glomerular atrophy, tubular degeneration, and interstitial congestion. Extract treatment preserved renal architecture, with the 400 mg/kg dose showing minimal pathological changes.

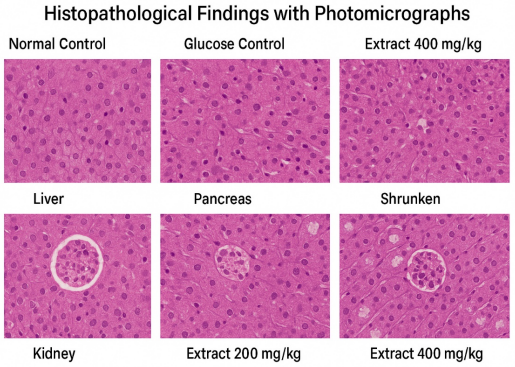

Figure 5. Histopathological Photomicrographs (H&E, 40×) of Liver, Pancreas, and Kidney Tissues Showing Protective Effects of Methanolic Root Extract of Gymnema sylvestre in Glucose-Induced Hyperglycemic Mice.

3.6 Statistical Analysis and Dose-Dependent Efficacy

All experimental data were expressed as mean ± SD (n = 6) and analyzed using one-way ANOVA followed by Tukey's post-hoc test. A p-value < 0.05 was considered statistically significant. The results demonstrated a clear dose-dependent efficacy of the methanolic root extract of Gymnema sylvestre. The 100 mg/kg dose produced a moderate reduction in blood glucose and partial improvement in biochemical parameters, while the 200 mg/kg dose showed significant antihyperglycemic, hypolipidemic, and antioxidant effects. The 400 mg/kg dose exhibited maximum efficacy, with results closely comparable to the standard drug Glibenclamide. Statistical comparisons confirmed that extract-treated groups showed significant reductions in blood glucose, total cholesterol, triglycerides, LDL, SGOT, SGPT, ALP, creatinine, and urea, along with a significant increase in serum insulin, HDL, SOD, CAT, and GSH compared to the glucose control group. These findings indicate that the therapeutic effect of the extract increases proportionally with the dose, demonstrating a strong dose-response relationship.

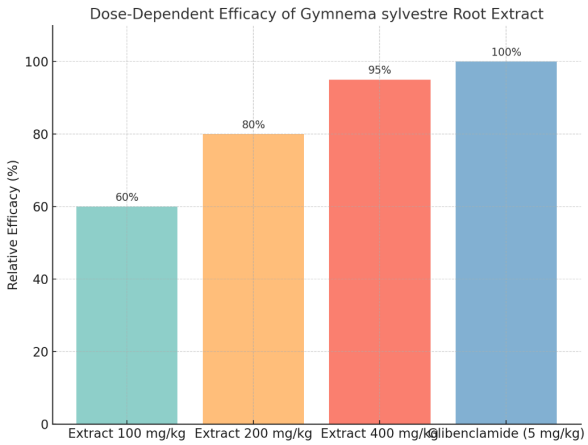

Figure 6. Dose-Dependent Efficacy of Methanolic Root Extract of Gymnema sylvestre in Glucose-Induced Hyperglycemic Mice.

4. Discussion

The present investigation evaluated the antidiabetic potential of the methanolic root extract of *Gymnema sylvestre* in glucose-induced hyperglycemic mice, with particular emphasis on its efficacy, safety, and biochemical modulation. The findings of this study clearly demonstrate that the root extract possesses significant hypoglycemic activity, which was evident from its ability to lower postprandial blood glucose levels in a dose-dependent manner. These results provide scientific validation to the traditional use of *Gymnema sylvestre* as an antidiabetic agent and highlight the therapeutic potential of its less explored root part.

The hypoglycemic effect of the extract can be attributed to its diverse phytoconstituents, primarily triterpenoid saponins known as gymnemic acids, along with alkaloids, flavonoids, tannins, and phenolic compounds. Gymnemic acids are well-documented for their ability to interact with taste receptors on the tongue, temporarily suppressing the sensation of sweetness, but more importantly, they also modulate glucose metabolism by inhibiting intestinal glucose absorption and promoting peripheral utilization of glucose. In the present study, the dose-dependent reduction in blood glucose strongly suggests that the root extract contains sufficient levels of these active phytoconstituents to exert a therapeutic effect. Moreover, flavonoids and phenolics present in the extract may also contribute by enhancing insulin sensitivity and exerting antioxidant protection on pancreatic β-cells.

When compared with the standard drug Glibenclamide, a sulfonylurea known to stimulate pancreatic β-cells to secrete insulin, the root extract at 400 mg/kg showed effects that were nearly equivalent. While Glibenclamide acts primarily via direct insulinotropic mechanisms, *Gymnema sylvestre* likely exerts its action through a multifactorial mechanism—including stimulation of insulin secretion, regeneration of damaged β-cells, inhibition of glucose absorption in the intestine, and modulation of key enzymes involved in carbohydrate metabolism. The extract's ability to increase serum insulin levels in hyperglycemic mice further supports its insulinotropic effect.

Safety evaluation through acute toxicity studies confirmed that the extract was well-tolerated up to 2000 mg/kg, with no evidence of mortality or abnormal behavioral changes. This provides a substantial margin of safety for its therapeutic use. Additionally, liver and kidney function tests indicated that the extract did not produce hepatotoxicity or nephrotoxicity. On the contrary, the reduction in SGOT, SGPT, ALP, creatinine, and urea levels in treated groups suggests hepatoprotective and nephroprotective roles, which may be linked to its antioxidant and free radical scavenging activity. This is further corroborated by the significant reduction in lipid peroxidation (MDA) and enhancement of endogenous antioxidants (SOD, CAT, GSH) observed in the extract-treated groups.

The possible mechanism of action of the methanolic root extract, therefore, may be explained as a combination of (i) insulinotropic effects, enhancing secretion of insulin from residual β-cells, (ii) inhibitory action on intestinal glucose absorption, thereby preventing postprandial spikes, and (iii) antioxidant-mediated protection and regeneration of pancreatic tissue. The histopathological findings of improved islet architecture in the pancreas of extract-treated groups strongly support this proposed mechanism.

These findings are in line with earlier reports on *Gymnema sylvestre* leaves, which are extensively studied for their antidiabetic properties. Previous studies have shown that leaf extracts reduce hyperglycemia in both experimental animals and clinical settings, primarily due to gymnemic acids. However, research on the roots of the plant has been limited. The present study, therefore, provides novel insights by establishing the roots as an alternative source of active principles with comparable efficacy to leaves. This expands the pharmacological utility of the plant and encourages the exploration of its less studied parts.

Despite the promising results, some limitations of the study must be acknowledged. First, the investigation was confined to an acute model of glucose-induced hyperglycemia; hence, the long-term efficacy and chronic toxicity profile of the root extract remain to be

established. Second, the exact phytoconstituents responsible for the observed effects were not isolated or quantified in this study, which could be addressed in future phytochemical standardization. Third, the study used only a single species (Swiss albino mice), and extrapolation to other animal models or humans requires caution. Future prospects of this work include conducting long-term studies in diabetic models such as alloxan- or streptozotocin-induced diabetes to evaluate sustained antidiabetic effects, as well as exploring molecular mechanisms through gene expression and protein analysis of insulin-signaling pathways. Additionally, detailed phytochemical characterization and standardization of the root extract would be essential for developing it into a reproducible herbal formulation. Finally, translational studies in humans will be necessary to confirm efficacy, safety, and dosage optimization before clinical application.

5. Conclusion

The present study scientifically validates the antidiabetic efficacy and safety of the methanolic root extract of *Gymnema sylvestre* in glucose-induced hyperglycemic mice. The extract produced a dose-dependent reduction in blood glucose levels, with the 400 mg/kg dose exhibiting effects comparable to the standard drug Glibenclamide. In addition to its hypoglycemic activity, the extract significantly improved the lipid profile, enhanced antioxidant defenses, and normalized liver and kidney function markers, indicating its multifaceted therapeutic potential. The observed pharmacological effects can be attributed to the presence of bioactive phytoconstituents, particularly gymnemic acids, flavonoids, and phenolic compounds, which are known to stimulate insulin secretion, enhance glucose utilization, inhibit intestinal glucose absorption, and protect pancreatic β-cells from oxidative stress. Importantly, the extract was well tolerated up to 2000 mg/kg in acute toxicity studies, confirming a wide margin of safety. Taken together, these findings suggest that the roots of *Gymnema sylvestre*, though less explored compared to its leaves, represent a promising source of antidiabetic agents with additional hepatoprotective, nephroprotective, and antioxidant benefits. Future work should focus on long-term studies in diabetic models, phytochemical standardization, and clinical trials to establish its therapeutic applicability in humans. Thus, the methanolic root extract of *Gymnema sylvestre* can be considered a potential plant-based alternative or complementary therapy for the management of diabetes mellitus.

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