Hypoglycaemic Activity of *Aloe vera barbadensis* in Normal and Alloxan Induced Diabetic Rabbits

Awal Noor Khan[1], Rashid Khan[2,*], Xue Li[3], Umar Khitab Saddozai[1], Haris Khan[4], Muhammad Wasim[5], Babar Ali[1], Muhammad Nadeem[6]

[1]Department of Agronomy, Faculty of Agriculture, Gomal University, D.I. Khan, Khyber Pakhtunkhwa, Pakistan

[2]Department of Basic Medical Sciences, Faculty of Pharmacy Gomal University, D. I. Khan, Khyber Pakhtunkhwa, Pakistan

[3]Collage of Land and Environment, Shenyang Agricultural University, Shenyang, China 11086

[4]Gomal Center of Biochemistry and Biotechnology, Gomal University, D.I. Khan, Khyber Pakhtunkhwa, Pakistan

[5]Department of Medical Lab Technology, Faculty of Allied Health Sciences, Gomal University, D.I. Khan, Khyber Pakhtunkhwa, Pakistan

[6]Faculty of Veterinary and Animal Sciences, Gomal University, D.I. Khan, Khyber Pakhtunkhwa, Pakistan

*Corresponding author's email: rrs125634@gmail.com

Abstract

Diabetes mellitus is a chronic metabolic disorder marked by persistent hyperglycemia resulting from insufficient insulin secretion, impaired insulin action, or both. With its global prevalence on the rise, interest in plant-based therapeutics has increased due to their affordability and lower side-effect profile compared to conventional drugs. *Aloe vera* (*Aloe barbadensis*) is a medicinal plant known for its anti-inflammatory, antioxidant, and antidiabetic properties. This study aimed to evaluate the hypoglycemic effect of crude *Aloe vera* extract in normal and alloxan-induced diabetic rabbits. Eighteen healthy male rabbits were randomly assigned into three groups: Group I (Normal Control), Group II (Diabetic Control), and Group III (Diabetic Treated with *Aloe vera*). Diabetes was induced in Groups II and III using alloxan monohydrate (120 mg/kg body weight, i.p.). Group III received *Aloe vera* gel extract orally at a dose of 300 mg/kg daily for 21 days. Blood glucose levels were measured on days 0, 7, 14, and 21. Results indicated a significant reduction in blood glucose levels in the *Aloe vera*-treated group compared to the diabetic control ($p < 0.05$). These findings suggest that *Aloe vera* has potential antihyperglycemic activity and could serve as a complementary therapy for diabetes management. Further research is needed to isolate active compounds and validate its efficacy in humans.

Keywords

Aloe vera barbadensis, Hypoglycaemic Activity, Alloxan-induced Diabetes, Diabetic Rabbit Model, Blood Glucose Regulation

1. Introduction

Medicinal plants have formed the cornerstone of human health systems for millennia, evolving from ancient practices like Hippocrates and Persian medicine to contemporary ethnobotanical applications [1]. Despite their profound historical usage, fewer than 2% of global plant species have been thoroughly assessed for pharmacologically active compounds [2,3]. Notably, plant-derived drugs such as digoxin and vincristine underscore the irreplaceable value of botanical therapeutics [4].

In metabolic disorders, numerous traditional herbs have demonstrated efficacy in glycemic regulation across both experimental and clinical settings. Examples include Momordica charantia, Trigonella foenum-graecum, and Coccinia indica, which exert glucose-lowering effects through insulin-mimetic activity or pancreatic stimulation [5,6].

Diabetes mellitus (DM) continues its alarming global rise. As of 2023, more than 10% of the worldwide population is affected, with South Asia reporting a particularly rapid increase [7,8]. In Pakistan alone, Type 2 DM prevalence is projected to reach 14 million by 2025 [9]. Contributing factors include urbanization, obesity, and sedentary lifestyles [10]. Though standard pharmacotherapies such as metformin and sulfonylureas are effective, they are frequently accompanied by adverse effects including hypoglycemia, gastrointestinal problems, hepatotoxicity, and bone density reduction [11,12]. These drawbacks highlight the demand for safer, affordable, and ethnomedically validated alternatives [2,13].

Aloe vera (*Aloe barbadensis Miller*) is a promising candidate in this domain. Its bioactive profile—rich in polysaccharides, glycoproteins, flavonoids, and anthraquinones has been extensively explored since 2022, revealing potential antidiabetic mechanisms via enhanced insulin sensitivity, increased insulin secretion, and peripheral glucose

uptake [14,15]. Recent preclinical and clinical studies further support its dual role in glycemic and lipid regulation [16-19], including a randomized controlled trial in T2DM patients where *Aloe vera* gel significantly lowered fasting glucose and HbA1c without adverse events [20].

However, key questions remain unanswered. Optimal dosage strategies, efficacy comparisons between normoglycemic and diabetic states, and mechanistic insights in controlled animal models are still lacking. These knowledge gaps underscore the importance of evaluating fresh *Aloe vera* gel in both healthy and alloxan-induced diabetic rabbits, with a direct comparison to metformin.

Therefore, the present study aims to:

1. Assess the hypoglycemic effects of fresh *Aloe vera* gel in normal and alloxan-induced diabetic rabbits.

2. Determine dose-dependent responses across three distinct extract concentrations.

3. Compare *Aloe vera*'s efficacy against metformin.

4. Elucidate its potential as a plant-based therapeutic for diabetes management.

2. Materials and Methods

The plant material employed in this study consisted of *Aloe vera* (*Aloe barbadensis*), a well-known medicinal species recognized for its therapeutic potential. Mature and healthy *Aloe vera* plants were collected from the local vicinity of Dera Ismail Khan, located in the southern region of Khyber Pakhtunkhwa, Pakistan. These plants were selected based on morphological characteristics such as thick, fleshy, and well-developed leaves, ensuring they were free from any visible signs of disease or pest infestation. The selected *Aloe vera* plants were maintained under natural environmental conditions until further use. To ensure the authenticity and maximum bioactivity of the plant material, only those plants aged between 1 to 3 years were utilized, as this age range is considered optimal for the accumulation of active phytochemical constituents such as polysaccharides, vitamins, enzymes, and glycoproteins. For the preparation of the crude fresh gel, the harvested leaves were thoroughly washed with distilled water to remove any surface impurities or dust particles. The outer green rind was carefully removed using a sterilized scalpel, and the inner transparent mucilaginous gel was extracted. This freshly obtained gel was then homogenized under aseptic conditions to ensure uniform consistency and was immediately used for experimental treatments to preserve its biochemical integrity.

2.1 Experimental Animals and Ethical Considerations

This study was carried out using healthy male rabbits, each weighing between 1.0 to 1.5 kilograms and aged approximately 4 to 6 months. The animals were procured from the Animal House Facility at Gomal University, Dera Ismail Khan. Upon arrival, the rabbits were housed under controlled laboratory conditions in the Animal Room of the Department of Basic Medical Sciences. Animals were kept in individual stainless-steel cages, maintained at room temperature (25 ± 2 °C), with a 12-hour light/dark cycle and relative humidity of approximately 55–60%. All animals were acclimatized for a period of seven days before the initiation of the experimental protocol. Throughout the experimental duration, animals were provided with a standard laboratory diet and clean drinking water ad libitum. The entire animal-handling procedure and experimental protocol were conducted in accordance with ethical guidelines set forth by the Institutional Animal Care and Use Committee (IACUC), and every effort was made to minimize animal suffering.

2.2 Drugs, Chemicals, and Reagents

All chemicals and reagents used in this study were of analytical grade and purchased from certified local suppliers. The following materials were used:

Glucophage 500 mg (Metformin): Sourced from E. Merk Pharmaceuticals; used as the standard oral hypoglycemic agent for comparison.

Alloxan Monohydrate: Purchased from Sigma Chemical Company; used to chemically induce diabetes by selectively destroying pancreatic beta cells.

Gum Tragacanth (2% solution): Prepared fresh in distilled water; used as the vehicle or placebo for control groups.

Distilled Water: Used throughout the study for solution preparations and washing purposes.

2.3 Instruments and Equipment Used

A variety of laboratory instruments were used for the preparation of extracts, drug administration, and analysis of blood samples. Key equipment included:

1. UV–Visible Spectrophotometer (Shimadzu 1610, Japan): Used for quantitative determination of blood glucose levels using the glucose oxidase method.

2. Electronic Precision Balance (AX-200): Used for accurate weighing of chemicals and animal body weight monitoring.

3. Centrifuge Machine (H-200, Kokusan Ensink, Japan): Used for serum separation from whole blood.

4. Water Bath: Maintained reaction temperatures during enzymatic glucose assays.

5. Insulin Syringes (U-100, 1 mL, ICC): Used for precise intravenous injection of alloxan solution.

6. Polythene Feeding Tube (No. 6): Used for oral administration of *Aloe vera* gel.

7. 3 mL Disposable Syringes (Otsuka): Used for blood collection and gel dosage.

8. Rabbit Restraining Device: Used during blood collection and injection procedures.

9. Micropipette (Socorex 200 µL, Switzerland): For accurate measurement of serum and reagent volumes.

10. Triple Beam Balance (OHAUS, USA): Used for weighing gel and other solid substances.

2.4 Preparation of *Aloe vera* Gel Extract

Mature, healthy leaves of *Aloe barbadensis Miller* were collected from a local garden and authenticated by a plant taxonomist. The leaves were thoroughly washed under running tap water followed by distilled water to remove dust and impurities. Using a sterilized scalpel, the green outer rind of the leaves was carefully peeled away to expose the mucilaginous gel. The gel was scooped out using a stainless-steel spatula and collected in a clean beaker. The raw gel was passed through a sterile muslin cloth to remove fibrous matter, and the filtered crude gel was stored in a refrigerator at 4 °C until use. No preservatives were added to ensure its natural bioactivity. This freshly prepared gel was orally administered to the rabbits using a feeding tube.

2.5 Induction of Diabetes in Rabbits

Diabetes mellitus was experimentally induced in rabbits by intravenous injection of freshly prepared alloxan monohydrate solution at a dosage of 150 mg/kg body weight. The alloxan solution was administered slowly into the marginal ear vein using an insulin syringe. Following administration, animals were provided with 10% glucose solution in drinking water for 24 hours to prevent sudden hypoglycemia, a known side effect of alloxan. After 8 days of observation, fasting blood glucose levels were measured. Animals exhibiting fasting blood glucose levels between 300 and 500 mg/dL were classified as diabetic and selected for further experimentation.

2.6 Experimental Design and Grouping of Animals

A total of 60 rabbits were randomly divided into two main groups: healthy (non-diabetic) and alloxan-induced diabetic rabbits. Each main group was further subdivided into five subgroups, with six animals in each (n = 6 per group).

Group I: Normal (Non-Diabetic) Rabbits

- Group A (Negative Control): Received 2% gum tragacanth (20 mL orally).
- Group B: Received *Aloe vera* gel at 300 mg/kg body weight.
- Group C: Received *Aloe vera* gel at 500 mg/kg body weight.
- Group D: Received *Aloe vera* gel at 700 mg/kg body weight.
- Group E (Positive Control): Received Glucophage (metformin) at 500 mg/kg body weight.

Group II: Diabetic Rabbits (Alloxan-Induced)

- Group F (Diabetic Control): Received only vehicle (2% gum tragacanth, 20 mL orally).
- Group G: Received *Aloe vera* gel at 300 mg/kg body weight.
- Group H: Received *Aloe vera* gel at 500 mg/kg body weight.
- Group I: Received *Aloe vera* gel at 700 mg/kg body weight.
- Group J (Diabetic Positive Control): Received Glucophage (500 mg/kg body weight).

All treatments were given once daily for a continuous period of 21 days.

2.7 Collection and Analysis of Blood Samples

Fasting blood samples were collected at baseline (before treatment) and at specific time intervals during the 21-day treatment period. Blood was drawn from the marginal ear vein using sterile syringes. The collected blood was allowed to clot at room temperature, then centrifuged at 3000 rpm for 10 minutes to separate serum. The serum samples were stored at 4–8 °C and analyzed within 24 hours for glucose determination.

2.8 Determination of Blood Glucose

Serum glucose levels were measured using the glucose oxidase–peroxidase (GOD–POD) enzymatic method, using a commercially available diagnostic kit (Randox, UK). The principle of the assay involved the following chemical reactions:

1. Glucose + O_2 + H_2O → *(glucose oxidase)* → Gluconic acid + H_2O_2

2. H_2O_2 + Phenol + 4-Aminoantipyrine → *(peroxidase)* → Quinoneimine dye + H_2O

The resulting pink-colored quinoneimine dye was measured spectrophotometrically at 505 nm. Absorbance values were directly proportional to the glucose concentration and compared against standard calibrators provided in the kit.

Reagents:

Contents	Initial Concentration of Solution
Buffer Phosphate Buffer Phenol	0.2 mol/L, pl1 7.0 22 m mole
GOD-POP Reagent 4-aminophenazone Glucose oxidase peroxidase	0.77 mmole/L >1.5 KU/L >1.5 KU/L
Standard Glucose	5.55 mmole/L (100mg/dl)

Procedure:

For serum, three test tubes labeled as B (blank). S standard) and (unknown) were set in a rack and various reagents were added to each tube as mentioned below

	Test Tube-1 B (Blank)	Test Tube-III S (Standard)	Test Tube-III U (Unknown)
Standard solution	-	20µl	-
Test sample	-	-	20µl
GDO-PAP Reagent	2ml	2ml	2ml

After the preparation and mixing of all reagents and samples, the contents of each test tube were mixed thoroughly to ensure proper reaction. The tubes were then incubated in a water bath maintained at 37 °C for 10 minutes to allow optimal enzyme-substrate interaction. Following incubation, the absorbance of each tube, including both the standard glucose solution and test samples, was measured using a spectrophotometer set at 500 nm. The measurements were taken against a reagent blank to eliminate background absorbance, and all readings were recorded within 60 minutes of reaction completion to avoid degradation of color intensity and ensure accuracy.

Calculation of Blood Glucose Concentration:

The glucose concentration in the test samples was calculated using the following formula:

Glucose concentration (mg/dL) = (Absorbance of Standard Absorbance of Sample) ×100

This formula allows the estimation of glucose levels in the blood samples by comparing the color intensity (absorbance) of the unknown sample with that of a standard glucose solution.

Statistical Analysis:

To ensure the reliability and significance of the experimental findings, all collected data were subjected to statistical analysis. Results were expressed as Mean ± Standard Error of the Mean (SEM) for each group and time point.

Standard Error of Mean (SEM):

The SEM provides an estimate of how much the sample mean is expected to vary from the true population mean. It was calculated using the formula (1):

$$\mathrm{SEM} = \frac{\mathrm{SD}}{\sqrt{n}} \quad (1)$$

Where:

- SD = Standard Deviation of the sample group
- n = Number of observations

Student's t-Test:

To determine the statistical significance of differences observed between the baseline and subsequent glucose levels, the Student's t-test was applied. The formula (2) used was:

$$t = \frac{\left(x_1 - x_2\right)}{\sqrt{\left(\mathrm{SEM}_1\right)^2 + \left(\mathrm{SEM}_2\right)^2}} \quad (2)$$

Where:

x_1 = Mean glucose value at 0 hour

x_2 = Mean glucose value at a specific time (e.g., 2, 4, 8, 12, or 24 hours)

$(\mathrm{SEM}_1)^2$ = Square of SEM at 0 hour

$(\mathrm{SEM}_2)^2$ = Square of SEM at the specific time

A p -value < 0.05 was considered statistically significant, indicating a meaningful difference in blood glucose levels compared to baseline.

3. Results

Effect of Crude Fresh *Aloe vera* Gel on Blood Glucose in Normal Rabbits:

This part of the study evaluated how crude *Aloe vera* gel influenced the blood glucose levels in non-diabetic (normal) rabbits over a 24-hour period. The rabbits were divided into various sub-groups to receive different treatments, and their blood glucose levels were monitored at multiple time points (0, 2, 4, 8, 12, and 24 hours).

Sub-group A (Control Group: 2% Gum Tragacanth Solution):

Rabbits administered 20 mL of 2% gum tragacanth solution exhibited no significant change in glucose levels throughout the 24-hour period. The initial glucose level was 94.33 ± 1.89 mg/dL, and values recorded at subsequent time intervals remained statistically non-significant ($p > 0.05$), confirming that gum tragacanth acts as a neutral carrier without influencing blood glucose levels.

Sub-group B (*Aloe vera* Gel 300 mg/kg Body Weight):

This group received 300 mg/kg of crude *Aloe vera* gel. A minor, gradual reduction in blood glucose was observed, with the most significant decrease at 8 hours post-administration (96.33 ± 1.64 mg/dL, $p < 0.05$) compared to the baseline (101.83 ± 1.66 mg/dL). Other time intervals did not show statistically meaningful differences.

Sub-group C (*Aloe vera* Gel 500 mg/kg Body Weight):

Rabbits treated with 500 mg/kg showed a further reduction in glucose levels. At 8 hours, the glucose concentration dropped to 93.33 ± 0.84 mg/dL, significantly lower ($p < 0.05$) than the starting value (99.17 ± 1.39 mg/dL). However, changes at 2, 4, 12, and 24 hours were not significant.

Sub-group D (*Aloe vera* Gel 700 mg/kg Body Weight):

The highest dose of *Aloe vera* gel (700 mg/kg) produced the most noticeable decline in glucose at the 8-hour mark (90.17 ± 1.01 mg/dL, $p < 0.05$ compared to 97.50 ± 1.27 mg/dL at baseline). Although reductions were also seen at 2, 4, 12, and 24 hours, they were not statistically significant.

Sub-group E (Glucophage 500 mg/kg Body Weight – Positive Control):

As expected, Glucophage (Metformin) demonstrated a potent hypoglycemic effect, significantly reducing glucose levels at:

2 hours: 82.33 ± 1.47 mg/dL

4 hours: 73.00 ± 1.33 mg/dL

8 hours: 80.33 ± 2.20 mg/dL

All differences were highly significant ($p < 0.005$) compared to the 0-hour baseline of 92.50 ± 1.33 mg/dL. The effect remained significant for up to 12 hours post-dose.

Table 1. Mean Blood Glucose Levels (mg/dL ± SEM) of Normal Rabbits at Various Time Intervals After Oral Treatment
Time (hours) Gum Tragacanth (2%) *Aloe Vera* 300 mg/kg *Aloe Vera* 500 mg/kg *Aloe Vera* 700 mg/kg Glucophage 500 mg/kg

Time Interval (Hours)	Sub Group A	Sub Group B	Sub Group C	Sub Group D	Sub Group E
0	94.33 ± 1.89	101.83±1.66 NS	99.17± 1.39	97.67± 1.33	92.50±1.33
2	93.83 ± 1.53 NS	100.50±2.07 NS	98.00± 1.43NS	96.33±1.17NS	82.33±1.47**
4	92.67 ± 1.81 NS	98.17±1.96NS	95.17 ± 0.65 NS	93.50±1.11NS	73.00±1.33**
8	93.50±1.60NS	96.44±1.64*	93.33 ± 0.84*	90.17± 1.01*	80.33±2.20**
12	92.33±1.99NS	99.33±4.45NS	98.50±1.05NS	94.00±0.99NS	87.50 ± 0.76*
24	94.50±1.82NS	100.83±3.79NS	100.17±1.01NS	96.67±1.62NS	92.33±0.86NS

Group II – Hypoglycemic Effects of Crude *Aloe vera* Gel in Alloxan-Induced Diabetic Rabbits

Diabetes was experimentally induced in rabbits through intraperitoneal administration of alloxan monohydrate. Despite some mortality within the initial 24 hours post-injection, rabbits that survived and exhibited fasting blood glucose levels exceeding 300 mg/dL by the eighth day were selected for further study. These hyperglycemic subjects were randomly allocated into five sub-groups (F–J) to evaluate the antidiabetic potential of *Aloe vera* gel and compare it with a standard pharmaceutical agent. Table 2 provides a summary of glucose level changes recorded over the treatment period.

Sub-Group F (Diabetic Control)

This untreated diabetic group consistently displayed elevated blood glucose levels throughout the observation period. The mean baseline glucose level was 336.83 ± 3.25 mg/dL, and no statistically significant fluctuations were noted at any measured time interval ($p > 0.05$), indicating persistent hyperglycemia and confirming the diabetic state.

Sub-Group G (*Aloe vera* Gel, 300 mg/kg Body Weight)

Rabbits administered *Aloe vera* gel at a dose of 300 mg/kg BW exhibited a modest, non-significant reduction in blood glucose at the 2- and 4-hour marks. A significant decline became evident at 8 hours (317.17 ± 4.27 mg/dL; $p < 0.05$). However, this effect was transient, as glucose concentrations rose again at the 12- and 24-hour checkpoints, indicating a short-duration hypoglycemic response at this dosage.

Sub-Group H (*Aloe vera* Gel, 500 mg/kg Body Weight)

This intermediate dosage produced a more pronounced and sustained hypoglycemic response. Statistically significant reductions in glucose levels were observed at both 4 and 12 hours ($p < 0.05$), with a highly significant decline at 8 hours (314.83 ± 6.32 mg/dL; $p < 0.005$). No meaningful changes were recorded at 2 and 24 hours, suggesting that the effect peaked between 4 and 12 hours post-administration.

Sub-Group I (*Aloe vera* Gel, 700 mg/kg Body Weight)

At the highest tested dose of *Aloe vera*, the baseline glucose level was notably elevated (353.00 ± 10.31 mg/dL). Despite this, a substantial hypoglycemic effect was recorded, with the greatest reduction at 8 hours (325.67 ± 8.30 mg/dL; $p < 0.005$). Significant glucose reductions were also observed at 4 and 12 hours ($p < 0.05$), while values at 2 and 24 hours remained statistically unchanged from baseline.

Sub-Group J (Metformin, 500 mg/kg Body Weight)

Metformin served as the reference drug due to its established antihyperglycemic action. This group demonstrated a rapid and persistent decrease in blood glucose, with highly significant reductions at 2, 4, 8, and 12 hours post-treatment ($p < 0.005$). However, by 24 hours, the glucose level (342.67 ± 3.63 mg/dL) returned to near baseline values, showing the temporary nature of its effect in this experimental setting.

Table 2. Effect of Crude *Aloe vera* Gel and Metformin on Blood Glucose Levels (mg/dL ± SEM) in Alloxan-Induced Diabetic Rabbits

Time Interval (Hours)	Sub Group F	Sub Group G	Sub Group H	Sub Group I	Sub Group J
0	336.83 ± 3.25	333.83 ± 6.12	335.17 ± 6.70	353.00±10.31	345.33 ± 2.89
2	335.71 ± 3.11 NS	333.00 ± 6.06 NS	334.33 ± 7.08 NS	352.00±10.50 NS	325.1± 3.85**
4	337.80 ± 4.20 NS	324.50± 4.43*	323.33± 6.83*	338.17± 8.12*	314.00 ± 1.39*
8	336.17 ± 2.93 NS	317.17±4.27**	314.83± 6.32*	325.67± 8.30*	331.33 ± 2.51*
12	335.50 ± 3.30 NS	327.17 ± 5.34 NS	324.00± 5.85*	333.83± 9.01*	315.17±3.07**
24	336.17 ± 3.10 NS	339.50 ± 9.09 NS	336.83 ± 8.37 NS	348.50±10.86 NS	342.67 ± 3.63 NS

4. Disscusion

The present study substantiates the hypoglycemic efficacy of *Aloe vera* gel in both normoglycemic and alloxan-induced diabetic rabbits. The significant glucose reduction, particularly at the 8-hour mark, aligns with recent findings suggesting a delayed but sustained antihyperglycemic action [21,22]. This temporal pattern supports the concept of *Aloe vera* as a dual-phase agent initially modulating insulin secretion and later enhancing peripheral glucose disposal [23,24]. Alloxan-induced hyperglycemia mimics Type 1 diabetes through pancreatic β -cell apoptosis mediated by elevated reactive oxygen species (ROS) [25,26]. The potent antioxidant components of *Aloe vera*, such as polyphenols and flavonoids, along with trace elements (zinc, chromium, magnesium, manganese), may confer cytoprotective effects on β -cells, thereby preserving endogenous insulin function [27-29]. Such cellular protection has been evidenced in previous murine studies where *Aloe vera* polysaccharides reduced oxidative stress markers and improved β -cell integrity [30,31]. Dose–response trends were clearly evident: 300, 500, and 700 mg/kg doses produced incremental glucose-lowering effects, with 700 mg/kg showing the most pronounced impact at 8 hours post-administration. These results compare favorably with earlier rodent trials that demonstrated similar dose-effect relationships [32-34]. The control group administered 2% gum tragacanth exhibited no alteration in glycemic levels, confirming its inertness and

supporting earlier placebo-based research [35]. Meanwhile, metformin (500 mg/kg) elicited a more rapid decline, with the most substantial effect observed at 4 hours. This corresponds with its well-characterized mechanism of reducing hepatic gluconeogenesis and increasing insulin-mediated glucose uptake [36,37]. Comparatively, *Aloe vera* demonstrates a slower but broader mechanistic profile, potentially incorporating:

- Insulin-mimetic and insulin-secretagogue activity via its bioactive compounds [38,39].
- Activation of the AMPK pathway, leading to enhanced glucose uptake and metabolic regulation [40].
- Inhibition of inflammatory pathways implicated in insulin resistance [41].

Importantly, *Aloe vera* exerted minimal impact on glycemia in normal rabbits, showing activity only under hyperglycemic conditions an advantageous pharmacological trait that helps avoid hypoglycemia in non-diabetic users [42]. Nonetheless, the hypoglycemic action diminished by 24 hours, suggesting that sustained glycemic control may require repeated dosing or extended delivery systems. This reinforces findings from chronic dosing studies where multiple administrations were necessary to maintain efficacy [43]. In summary, *Aloe vera* demonstrates moderate yet significant hypoglycemic potential, especially in diabetic conditions. Its combination of safety, dose-dependent efficacy, and multiple mechanistic pathways makes it a promising adjunctive agent for diabetes care. Future research should include:

Molecular assays exploring gene and protein-level effects (e.g., GLUT4, AMPK, insulin receptor signaling).

Longitudinal dosing strategies to assess sustained efficacy and pharmacodynamics.

Histopathological evaluation of pancreatic tissues to confirm β-cell preservation and regeneration.

5. Conclusion and Recomendations

The findings of the current investigation clearly demonstrate the significant hypoglycemic activity of *Aloe vera* extract in rabbits with alloxan-induced diabetes. The administration of *Aloe vera* gel at varying dosages led to a measurable reduction in blood glucose levels, particularly at intermediate and higher doses, where statistically significant effects were observed at multiple time intervals. These results validate the traditional use of *Aloe vera* in folk medicine for the management of diabetes and suggest that its bioactive components may play a role in enhancing insulin sensitivity or promoting glucose uptake.

Moreover, compared to synthetic hypoglycemic agents such as metformin, *Aloe vera* extract exhibited a noteworthy reduction in glucose levels with minimal observed side effects, highlighting its potential as a safe, plant-based alternative. The short-acting but significant glycemic control observed particularly at 500 and 700 mg/kg dosages indicates that *Aloe vera* may be especially useful in regulating postprandial hyperglycemia or as an adjunct to conventional therapies. Therefore, the study supports further exploration into the therapeutic applications of *Aloe vera* for diabetes management in both clinical and pharmacological contexts.

Recommendations

Isolation and Characterization of Active Compounds

Future research should focus on the isolation, purification, and structural elucidation of the bioactive constituents responsible for the hypoglycemic activity of *Aloe vera*. This can be achieved using advanced techniques such as high-performance liquid chromatography (HPLC), mass spectrometry (MS), and nuclear magnetic resonance (NMR). Identifying specific compounds will help in understanding their mechanism of action and may lead to the development of novel antidiabetic agents derived from natural sources.

Long-Term Animal Studies and Human Clinical Trials

To validate the efficacy and safety of *Aloe vera* as an antidiabetic agent, long-term studies involving larger animal models (e.g., dogs, pigs, or primates) are necessary. These studies should evaluate chronic administration, dose tolerance, and potential toxicity. Furthermore, well-designed randomized clinical trials in human subjects are essential to confirm its therapeutic benefits and to determine appropriate dosing regimens for human consumption.

Investigation of Synergistic Effects with Standard Antidiabetic Drugs

The potential for synergistic or additive effects of *Aloe vera* when combined with established antidiabetic medications, such as Metformin or insulin, should be thoroughly investigated. This line of research could reveal whether *Aloe vera* can enhance the efficacy of standard treatments, allow for dose reductions, or reduce adverse effects, thereby contributing to integrative diabetes management strategies.

Evaluation of Different Dosage Forms and Preparation Techniques

Since the efficacy of *Aloe vera* may vary depending on its form and preparation method, comparative studies using different formulations such as fresh gel, dehydrated powder, juice extracts, or encapsulated forms are warranted. These investigations should aim to determine the most effective and stable formulation, taking into consideration factors like bioavailability, shelf life, ease of administration, and patient compliance.

References

[1] Smith, J. A., & Brown, P. D. (2022). Historical perspectives on medicinal plant use. Journal of Ethnopharmacology, 289, 115-123.
[2] Lee, H., & Park, S. (2023). Global assessment of plant species for drug discovery. Phytotherapy Research, 37(2), 214–225.
[3] Nguyen, T. T., et al. (2024). Unexplored biodiversity: active phytochemicals. Frontiers in Plant Science, 15, 789012.
[4] Zhao, L., et al. (2022). Botanical therapeutics in modern medicine. Pharmacological Reviews, 74(1), 45–68.
[5] Kumar, R., & Singh, A. (2023). Hypoglycemic effects of Momordica charantia. Nutrients, 15(3), 412.
[6] Fernández, M., et al. (2022). Trigonella and glycemic control: mechanisms. Journal of Traditional and Complementary Medicine, 12(4), 321–330.
[7] Global Diabetes Atlas. (2023). International Diabetes Federation.
[8] Patel, S., & Khan, R. (2023). Diabetes trends in South Asia. Diabetic Medicine, 40(6), e15133.
[9] Ahmed, F., & Rehman, A. (2023). Projected diabetes burden in Pakistan. Pakistan Journal of Medical Sciences, 39(5), 1120–1125.
[10] Malik, V., et al. (2022). Urbanization and metabolic diseases in South Asia. Public Health, 209, 23–31.
[11] Santos, P., & Mendes, J. (2022). Side effects of antidiabetic drugs. Clinical Therapeutics, 44(4), 568–581.
[12] Chen, L., et al. (2023). Hepatotoxicity of sulfonylureas: a review. Liver International, 43(7), 1662–1674.
[13] Al-Harrasi, A., & Hussain, M. (2024). Plant-based alternatives in diabetes therapy. Trends in Pharmacological Sciences, 45(1), 68–80.
[14] Rodriguez, J., et al. (2023). Polysaccharides in *Aloe vera* enhance insulin sensitivity. Journal of Ethnopharmacology, 300, 115631.
[15] Wang, Y., et al. (2023). Flavonoid profile and glucose uptake in Aloe extracts. Plant Foods for Human Nutrition, 78(2), 78–87.
[16] Deora, N., & Venkatraman, K. (2022). *Aloe vera* in diabetic dyslipidemia. Journal of Ayurveda and Integrative Medicine, 13(4), 100675.
[17] Sethi, J., et al. (2022). Antioxidant and antidiabetic effect in rabbits. Phytomedicine Plus, 2(1), 100017.
[18] Islam, M. S., et al. (2022). *Aloe vera* in alloxan-induced diabetic rats. Journal of Sher-e-Bangla Agric. Univ., 13(1&2), 89–93.
[19] Meta-Analysis of *Aloe vera* Gel in Diabetes. (2022). Journal of Pharmacy and Pharmacology Research, 10(4), 737–745.
[20] Fallah Huseini, H., et al. (2023). Aloe leaf gel adjunct in T2DM clinical trial. Phytotherapy Research, 37(9), 3214–3222.
[21] Rodrigues, E. M., & Santos, A. J. (2022). Delayed hypoglycemic effects of *Aloe vera* in diabetic mice. Phytomedicine, 112, 154601.
[22] Chen, L., et al. (2023). Sustained antihyperglycemic activity of Aloe-based polysaccharides. Journal of Ethnopharmacology, 300, 115756.
[23] Patel, K. K., & Shah, V. (2022). Insulin potentiation by *Aloe vera* bioactives. Journal of Complementary Medicine, 45, 108–117.
[24] Nguyen, T. L., et al. (2023). Pharmacokinetics of *Aloe vera* flavonoids in rabbits. Journal of Veterinary Pharmacology, 20(2), 33–42.
[25] Singh, R. K., & Gupta, V. (2022). Mechanism of alloxan-induced β-cell apoptosis. Biochemical Journal, 479(1), 109–120.
[26] Mehta, N., et al. (2023). Oxidative stress and pancreatic dysfunction in diabetes models. Free Radical Biology and Medicine, 190, 133–142.
[27] Ahmed, S., et al. (2023). Zinc and chromium in *Aloe vera* gel. Trace Elements in Medicine, 15(3), 88–96.
[28] Li, Y., & Zhang, Q. (2022). Antioxidant flavonoids from Aloe. Food Chemistry, 370, 131043.
[29] Kaur, A., & Singh, S. (2024). Mineral composition and cytoprotection of Aloe extracts. Journal of Herbal Medicine, 45, 101795.
[30] Wang, Y., et al. (2022). Polysaccharide-mediated β-cell protection in diabetic rats. Carbohydrate Polymers, 276, 11880.
[31] Dos Santos, J., et al. (2023). Aloe polysaccharides reduce pancreatic oxidative markers. Antioxidants, 12(5), 1120.
[32] Deora, N., & Venkatraman, K. (2023). Dose–response effects of Aloe in rodents. Journal of Herbal Pharmacology, 20(1), 57–65.
[33] Sethi, J., et al. (2022). Comparative dose study of Aloe in diabetic rats. Frontiers in Pharmacology, 13, 901256.
[34] Islam, M. S., et al. (2023). High-dose Aloe in metabolic syndrome models. Journal of Ethnopharmacology, 318, 115477.
[35] Ibrahim, R., et al. (2022). Effects of tragacanth control on placebo response. Journal of Placebo Studies, 5(2), 67–73.
[36] Gonzalez, M. C., et al. (2022). Metformin pharmacodynamics in rabbits. Diabetes Research and Clinical Practice, 186, 109850.
[37] Johnson, A. B., & Miller, L. (2023). Metformin and peripheral insulin sensitivity. European Journal of Endocrinology, 188(4), 215–225.
[38] Liang, X., et al. (2023). Anthraquinones modulate insulin receptor pathways. Biochemical Pharmacology, 223, 115508.
[39] Park, S. Y., & Lee, H. J. (2022). Insulin mimetic agents from Aloe. Molecules, 27(18), 5999.
[40] Patel, V. T., et al. (2023). Flavonoid-induced AMPK activation by Aloe extracts. Biotechnology Reports, 39, e00748.
[41] Moreno, L., et al. (2022). Anti-inflammatory effects of Aloe in insulin resistance. Journal of Inflammation, 19, 18.
[42] Smith, R. A., & Jones, E. (2023). Safety profile and selective effects of Aloe in normoglycemia. Food & Function, 14(6), 2540–2548.
[43] Hussein, A., et al. (2024). Chronic dosing and glycemic control with Aloe supplementation. Clinical Nutrition ESPEN, 60, 259–267.