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Original Research Article

Effect of *Annona muricata* L. (Soursop) on Blood Glucose Level in a Diabetic Rat Model: A Meta-Analysis

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ABSTRACT

Annona muricata L. (soursop) is a plant rich in bioactive compounds and has been extensively studied for its potential antidiabetic and antioxidant properties. However, findings across studies have been inconsistent regarding its efficacy. This meta-analysis aims to synthesize and evaluate the available scientific evidence to draw reliable conclusions about the effectiveness and underlying mechanisms of *A. muricata* in managing diabetes mellitus. Relevant studies were retrieved from three major scientific databases: PubMed, Scopus, and Web of Science. The analysis included studies that reported blood glucose levels in diabetic rodent models treated with *A. muricata* extract. Statistical analysis revealed that supplementation with *A. muricata* extract significantly reduced blood glucose levels (SMD = –7.05; 95% CI: –11.22 to –4.61; $p < 0.00001$) in diabetic rats compared to control groups. These findings indicate that *A. muricata* has a significant hypoglycemic effect and holds promise as a potential therapeutic agent for diabetes management.

Keywords: *Annona muricata* L., antidiabetic, diabetes mellitus, meta-analysis

Introduction

Diabetes mellitus is a chronic endocrine disorder characterized by persistent hyperglycemia, primarily resulting from impaired insulin production, action, or both.[1] It is commonly associated with disruptions in nutritional metabolism, increased susceptibility to infections, and vascular complications that can lead to renal, cardiovascular, and neurological impairments.[2] The global prevalence of diabetes continues to escalate, with an estimated 693 million cases projected by 2045. Furthermore, it is anticipated to become the seventh leading cause of death worldwide by 2030. [3]Despite notable advancements in pharmacotherapy, a completely effective and satisfactory treatment for diabetes mellitus remains elusive. As a result, the search for novel antidiabetic agents with high therapeutic efficacy and minimal side effects remains a critical area of research.[4,5] One promising direction is using bioactive compounds derived from medicinal plants, which are traditionally recognized for their safety, affordability, accessibility, and therapeutic potential. Numerous plant-based antioxidants have demonstrated the ability to mitigate oxidative stress and reduce the risk of chronic diseases. Given the multifactorial nature of diabetes pathogenesis, polyherbal therapy has gained attention as a favorable treatment approach.While some herbal agents may show limited efficacy individually, their combination with other plant-based compounds may produce synergistic effects, enhancing therapeutic outcomes. Consequently, the application of medicinal plants is increasingly recommended for diabetes management.[8]

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Annona muricata L. (commonly known as soursop) possesses many medicinal properties. It is native to and widely cultivated in tropical regions, including Asia, South America, and Africa.[9] Various morphological parts of the plant have been traditionally used in ethnomedicine due to their reputed bioactive properties. Rich in diverse phytochemicals, *A. muricata* has shown considerable pharmacological potential, particularly as an antidiabetic agent. [9,10]
While existing studies support the antidiabetic potential of *A. muricata*, considerable variability in research outcomes limits the ability to draw definitive conclusions.[11–13] To address these inconsistencies, we conducted a meta-analysis of published studies to evaluate the antidiabetic effects of A. muricata systematically. This approach aims to generate more robust conclusions regarding its efficacy and underlying mechanisms in managing diabetes mellitus.

Materials and Methods

Search Strategy and Eligibility Criteria
This meta-analysis was conducted following the PRISMA guidelines. Relevant research articles were identified from major scholarly databases, including Scopus, PubMed, and Web of Science (WoS). The literature search encompassed all publications available up to February 15, 2025. The search strategy utilized both MeSH and non-MeSH terms, including: (“Soursop” OR “Annona muricata”) AND (“Diabetes Mellitus” OR “Hyperglycemia” OR “Glucose Intolerance”). No restrictions were placed on publication date, but only studies published in English were included. The search results were saved as 'PubMed Set' and 'RIS' files, and subsequently imported into Mendeley for reference management and data preservation.
Study selection was conducted using a combination of AI-assisted screening via Rayyan.ai and manual review. Full-text articles were assessed according to the Population, Intervention, Comparator, Outcome, and Study Design (PICOS) criteria to exclude studies that did not meet the inclusion standards.[14]

Data Collection
Before data extraction, the included studies were evaluated for risk of bias using SYRCLE’s Risk of Bias tool.[15] The selected studies were then examined based on the following characteristics: author(s), year of

publication, country, study subjects, control groups, interventions, and outcomes. Data on post-intervention blood glucose levels were extracted and recorded as mean ± standard deviation (SD). Other quantitative data suitable for meta-analysis were also collected.

Statistical Analysis

Statistical analyses were performed using Review Manager version 5.4 (RevMan 5.4). The primary focus was on fasting blood glucose levels in the intervention and diabetic control groups. All values are reported as mean ± SD. Effect sizes were calculated as standardized mean differences (SMD) with 95% confidence intervals (CI), utilizing both fixed-effects and random-effects models to account for inter-study variability.

The I^2 statistic assessed study heterogeneity. An I^2 value greater than 50% indicated substantial heterogeneity, warranting the use of a random-effects model, while values below 50% justified the application of a fixed-effects model. Subgroup analyses were conducted to assess the dose-dependent effects of interventions on blood glucose levels. A p-value of less than 0.05 was considered statistically significant.

Results and Discussion

Figure 1 presents the selection process of relevant studies, identifying 70 articles. Following an automated screening, 20 articles were excluded due to duplication, leaving 50 articles for further assessment. These remaining articles were evaluated based on the PICOS criteria, resulting in seven eligible studies (Table 1). Ultimately, only six studies fulfilled the inclusion criteria for quantitative analysis. Table 2 summarizes the quality assessment of the included studies based on the Risk of Bias (RoB) evaluation. Overall, the studies exhibited a low risk of bias; however, one study did not report its research funding source.

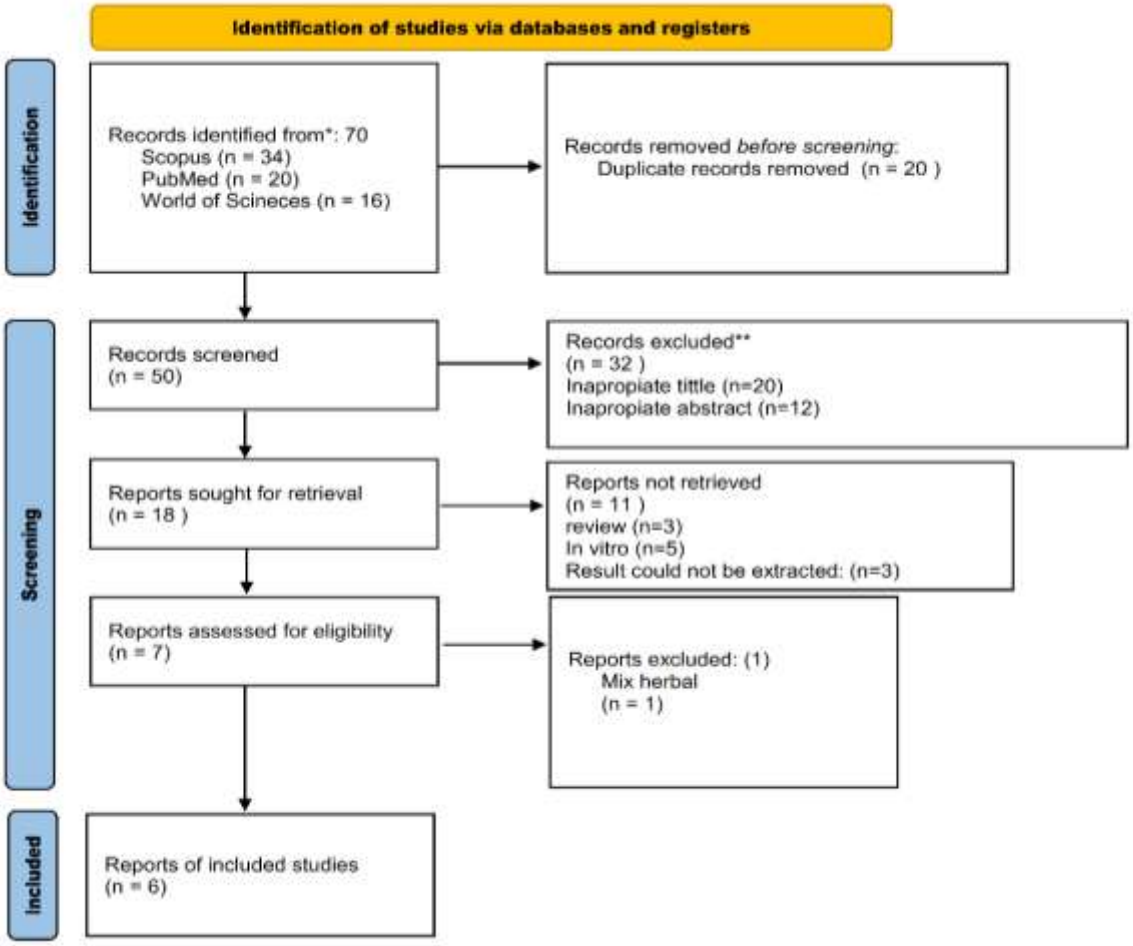

Figure 1: PRISMA flow diagram of studies search

Characteristic of the Included Studies

The studies in the quantitative analysis displayed variation in several aspects, including country of origin, extract type, extract dosage, intervention duration, and the biomarkers assessed (Table 3). These studies were conducted in various countries, including South Africa, Egypt, Nigeria, and Cameroon.

All studies employed a randomized controlled trial (RCT) approach in terms of experimental design. The animal model used across all studies was Wistar rats, with body weights ranging from approximately 140 to 250 g. One study included male and female rats,[16] whereas the other five used only male rats.[11–13,17,18] Regarding the method of diabetes induction, one study used alloxan,[17] while the others employed streptozotocin [11–13,16,18].

Most studies utilized aqueous extracts derived from different parts of *Annona muricata* L. Three studies used leaf extracts,[12,16,18] one used bark extracts [17], and two did not specify the plant part used.[11,13] The extract dosages varied considerably, ranging from approximately 6.76 mg/kg to 200 mg/kg. The duration of intervention also varied, ranging from 21 to 60 days.

Table 1: PICOS criteria for selecting

Variable	Inclusion criteria	Exclusion criteria
Population	Rat	Review article, article with no ethical clearance
Intervention	Annona muricata L.	Mix herbal
Comparator	Diabetic rat	-
Outcome	Serum blood glucose level	Δ blood glucose level
Design of experiment	RCT	-

All included studies measured serum blood glucose levels, and most also evaluated additional biomarkers. These included serum insulin, body weight, lipid profile, and oxidative stress markers in organs such as the kidney, liver, and pancreas. Some studies further assessed inflammatory parameters and sex hormone levels. Among all assessed biomarkers, only serum blood glucose levels met the criteria for quantitative analysis across all included studies.

Table 2: Risk of bias assessment using the SYRCLE's checklist tool

Studies	1	2	3	4	5	6	7	8	9	10	Conclusion
Adewole et al[16]	+	+	+	+	+	+	+	+	+	?	Low
Alsenosy et al[11]	+	+	+	+	+	+	+	+	+	+	Low
Al-syaad et al[13]	+	+	+	+	+	+	+	+	+	+	Low
Florence et al[12]	+	+	+	+	+	+	+	+	+	+	Low
Ojo et al[17]	+	+	+	+	+	+	+	+	+	+	Low
Omiyale et al[18]	+	+	+	+	+	+	+	+	+	+	Low

Meta-Analysis

Figure 2 illustrates that the administration of *Annona muricata* L. extract (AME) significantly reduced blood glucose levels in diabetic rats compared to control groups. Statistical analysis indicated a significant overall effect (SMD = -7.05; 95% CI = [-11.22, -4.61]; P < 0.00001). However, the heterogeneity index was high among the included studies (I^2 = 93%).

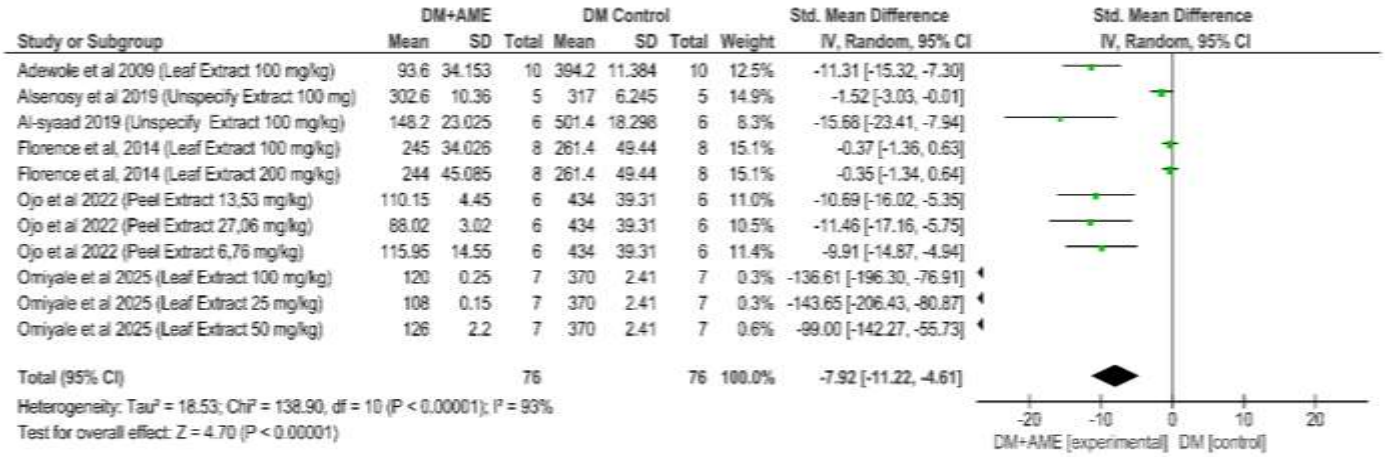

Figure 2: Forest plot for the pooled standardised mean difference (SMD) and 95% confidence interval (CI) of blood glucose level (mg/dl) in diabetic rats. D+AME: diabetic rats with *Annona muricata* L. extract; D: diabetic rats control.

Subgroup analysis revealed that AME administration at doses of 100–200 mg/kg resulted in a significant reduction in blood glucose levels (SMD = -4.29; 95% CI = [-7.25, -1.23]; P = 0.005), though the effect was inconsistent. AME at 100 mg/kg and 200 mg/kg reduced blood glucose levels in diabetic rats, but levels remained within the diabetic range.[11,12] In contrast, another study reported that a 100 mg/kg dose reduced blood glucose from the diabetic to the pre-diabetic range.[13] Interestingly, studies utilizing lower doses of AME (6.76 mg/kg to 50 mg/kg) demonstrated more consistent results (SMD = -284.17; 95% CI = [-300.26, -268.08]; P < 0.00001), with blood glucose levels declining to within the non-diabetic range.[17,18] (Figure 3).

Using plant-based products for disease treatment has long been a part of traditional practices across various cultures. Herbal medicine has played a significant role in these traditions, commonly applied as decoctions or poly herbal formulations. Scientific research has increasingly shown that synthetic drugs may cause a range of adverse effects.[19] As a result, researchers have grown interested in natural therapeutic agents due to their notable efficacy, cost-effectiveness, and relatively minimal side effects. Current reports indicate that nearly 80% of individuals in both developed and developing countries rely on herbal medicine as a primary approach to healthcare.[20]

Annona muricata L., a medicinal plant, has several parts—including its roots, stem bark, leaves, and seeds—used for therapeutic purposes.[21] These plant components are known for their diverse ethnomedicinal applications.[10,21] Recent research has highlighted its potential antidiabetic properties. This study represents the first meta-analysis to compile evidence demonstrating that *Annona muricata* L. extract (AME) can potentially lower blood glucose levels in diabetic rats. Its active polyphenolic compounds—comprising both complex and straightforward phenolics such as flavonoids—include luteolin, resorcinol, and quercetin.

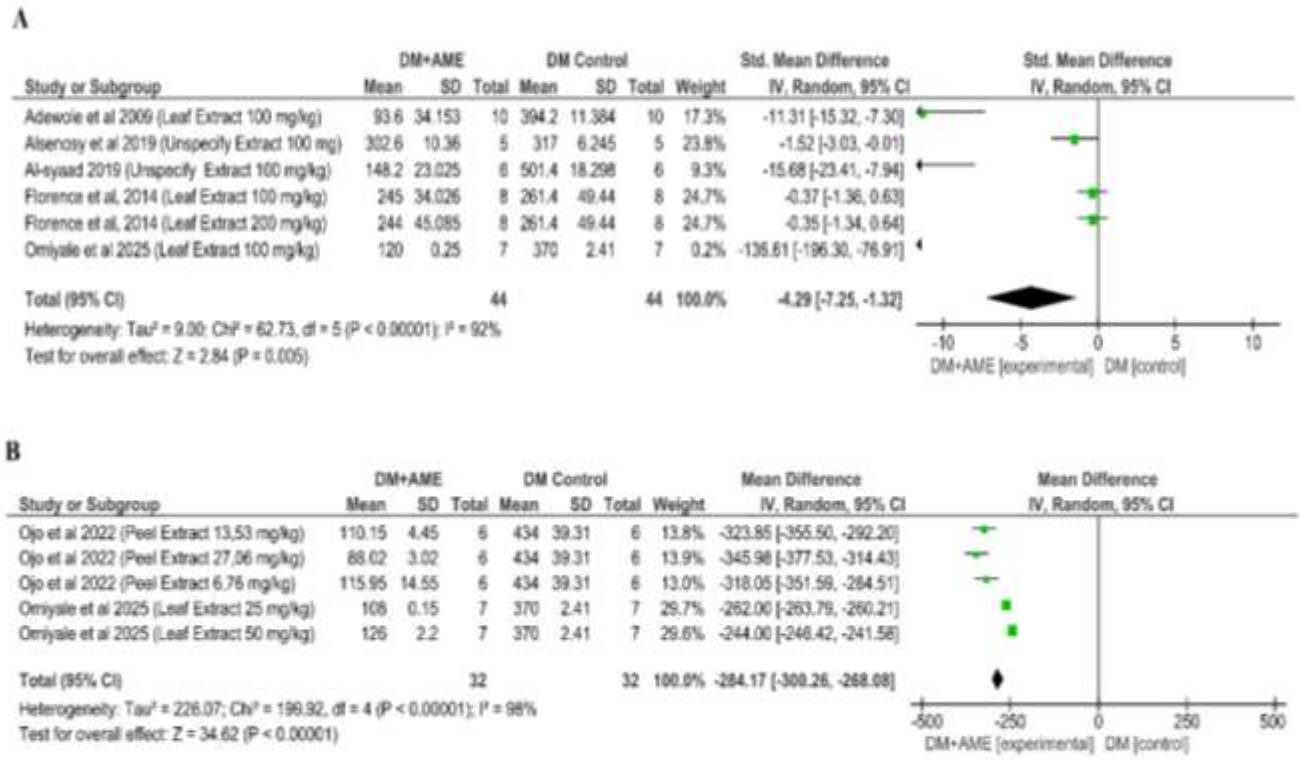

Figure 3: Forest plot for the pooled standardised mean difference (SMD) and 95% confidence interval (CI) of blood glucose level (mg/dl) in diabetic rats (A) *Annona muricata* L. extract (AME) high dose, (B) *Annona muricata* L. extract (AME) low dose. D+AME: diabetic rats with *Annona muricata* L.; D: diabetic rats control

The antidiabetic mechanism of *Annona muricata* L. is hypothesized to occur through multiple pathways. Notably, the plant has been found to inhibit the activity of α-amylase and α-glucosidase.[22] α-Amylase plays a role in breaking down polysaccharides into smaller oligosaccharides, which are subsequently hydrolyzed into monosaccharides by α-glucosidase in the intestine. Inhibiting these enzymes can delay glucose absorption into the bloodstream, reducing postprandial hyperglycemia. This mechanism may explain the observed reductions in blood glucose levels following the administration of *Annona muricata* L..[23] It has been confirmed that flavonoid compounds present in *Annona muricata* L. inhibit the activity of both enzymes.[22] In vitro experiments showed that AME inhibited α-glucosidase activity by 71.56% and α-amylase activity by 60.46%.[17]

In addition to its inhibitory effects on digestive enzymes, *Annona muricata* L. also exhibits protective and regenerative effects on pancreatic β-cells, which play a crucial role in insulin production and secretion. Reduced β-cell mass and dysfunction in insulin secretion are key contributors to the progression from hyperglycemia to diabetes. Therefore, preserving β-cell integrity represents a vital therapeutic strategy to prevent the onset and advancement of diabetes. The protective effects of *Annona muricata* L. on the pancreas have enhanced insulin secretion and function significantly, ultimately stabilizing blood glucose levels in diabetic rats.[23] *Annona muricata* L. extract (AME) administration improved pancreatic β-cell function, with enhanced insulin secretion observed following AME treatment.[12,17] These protective effects on pancreatic β-cells are believed to be attributable to polyphenolic compounds such as luteolin and quercetin.[24,25]

Strengths and Limitations

The primary strength of this meta-analysis lies in its comprehensive inclusion of diabetic mellitus (DM) rat models and its focused evaluation of AME's effects on blood glucose levels. Additionally, this study systematically assessed various potential confounding factors and publication bias.

Nevertheless, several limitations must be acknowledged. First, the meta-analysis demonstrates considerable heterogeneity, which the predefined variables could not fully explain. This high degree of heterogeneity may affect the robustness and generalizability of the findings. A key contributor to this variability may be using different plant parts of *Annona muricata* L. for extract preparation, which can result in substantial differences in bioactive compound composition. Second, environmental factors such as plant growth conditions, extraction techniques, and storage practices may also influence the concentration and efficacy of the active compounds, thereby affecting the measured biomarkers. Furthermore, the predominance of male rats in the included studies presents another limitation; future research should incorporate both sexes to assess potential sex-specific effects.

Table 3: Summary of included studies

Reference	Country	Study Design	Animal Sample	Annona Muricata Extract (AME)	Doses of AME Intervention	Duration of Intervention	Biomarker
[16]	South Africa	RCT, along with control group	Sample Size: 40 Group: 4 (10 rats each group) Sex: Male and Female Species: Wistar rats Weight: 250-300 g Diabetic Inducer: Streptozotocin	Leaf aqueous extract	100 mg/kg	60 days	Serum blood glucose, serum insulin, serum lipid profile, body weight, liver weight, hepatic CAT, hepatic SOD, hepatic ROS, hepatic GSH, hepatic GSH, hepatic GSSG, hepatic GSH-Px and hepatic MDA.
[11]	Egypt	RCT, along with control group	Species: Wistar rats Weight: 140 g Diabetic Inducer: Streptozotocin Sample Size: 40 Group: 4 (10 rats each group) Sex: Male	Unspecific part extract	100 mg/kg	28 days	Serum blood glucose, testicular testosterone, estradiol, acid phosphatase, alkaline phosphatase, GSH, MDA, NO,SOD and protein level.
[13]	Saudi Arabia	RCT, along with control group	Species:Wistar rats Weight: 150-170 g Diabetic Inducer: Streptozotocin Sample Size: 36 Group: 6 (6 rats each group) Sex: Male	Unspecific part extract	100 mg/kg	30 days	Serum blood glucose, insulin, HbA1c, SOD, CAT, GPx, GR, MDA, TNF-α, NF-κβ,
[12]	Cameroon	RCT, along with control group	Species: Wistar rats Weight: 150-250 g Diabetic Inducer: Streptozotocin Sample Size: 20 Group: 4 (5 rats each group) Sex: Male	Leaf aqueous extract	100 mg/kg 200 mg/kg	28 days	Body weight, serum blood glucose, lipid profile, liver and kidney SOD, CAT, NO and MDA.
[17]	Nigeria	RCT, along with control group	Species: Wistar rats Weight: 240 g Diabetic Inducer: Alloxan Sample Size: 36 Group: 6 (6 rats each group) Sex: Male	Peel aqueous extract	6,76 mg/kg 13,53 mg/kg 27,06 mg/kg	21 days	Serum blood gluose, body weight, organs weight (liver and pankreas), Liver and pankreas MDA, CAT, SOD, GSH and GST. Serum insulin, lipid profile, serum inflammatory marker (IL-6, TNF-α, NF-κB).
[18]	Nigeria	RCT, along with control group	Species: Wistar rats Weight: 150-200 g Diabetic Inducer: Streptozotocin Sample Size: 42 Group: (7 rats each group) Sex: Male	Leaf aqueous extract	25 mg/kg 50 mg/kg 100 mg/kg	28 days	Serum blood glucose, body weight, serum creatinine, urea, and uric acid, kidney MDA, GSH, GST, GPx, and CAT. Serum magnesium, calcium, bicarbonate and potassium. IL-6, TNF-α, KIM-1β/Actin-β.

Conclusion

Annona muricata L. extract supplementation has been shown to reduce hyperglycemia in diabetic rat models effectively. These findings provide important support for the therapeutic potential of *Annona muricata* L. in diabetes management and highlight its promise as a natural antidiabetic agent.

Conflict of Interest

The author`s declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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