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Synergistic Anti-Diabetic Potential of Moringa oleifera Leaf Extract and Metformin in Streptozotocin-Induced Diabetic Rats: Biochemical, Histopathological, and Molecular Insights

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ABSTRACT

Diabetes mellitus is a chronic metabolic disorder characterized by hyperglycemia due to impaired insulin secretion, insulin resistance, or both. Despite the availability of several pharmacological agents, current therapies often fail to fully address oxidative stress, inflammation, and progressive β-cell dysfunction, which are central to diabetic complications. Moringa oleifera, a medicinal plant rich in flavonoids, phenolic acids, and isothiocyanates, exhibits strong anti-hyperglycemic, antioxidant, and anti-inflammatory effects. Metformin, a first-line oral anti-diabetic drug, effectively reduces hepatic glucose production and enhances insulin sensitivity but is limited by gastrointestinal side effects and modest antioxidant activity. This study investigates the synergistic potential of ethanolic Moringa oleifera leaf extract and metformin in streptozotocin (STZ)-induced diabetic Wistar rats.

The combination therapy was evaluated through glycemic parameters [fasting blood glucose (FBG), oral glucose tolerance test (OGTT), and glycosylated hemoglobin (HbA1c)], serum insulin, oxidative stress biomarkers [malondialdehyde (MDA), superoxide dismutase (SOD), catalase (CAT), glutathione (GSH)], pro-inflammatory cytokines (IL-1β, TNF-α, IL-6), histopathological assessments, and gene expression analysis of GLUT4, IRS1, PI3K, and Akt. The results demonstrated that the combination significantly reduced hyperglycemia, improved glucose tolerance, restored β-cell morphology, enhanced antioxidant defenses, and suppressed pro-inflammatory cytokines more effectively than individual treatments. Moreover, renal and retinal markers indicated protective effects against diabetic nephropathy and retinopathy.

These findings suggest that Moringa oleifera and metformin act through complementary mechanisms, achieving superior efficacy in glycemic control and complication prevention while maintaining a favorable safety profile. The study highlights the potential of integrating herbal extracts with conventional drugs for cost-effective and sustainable diabetes management, particularly in resource-limited settings.

INTRODUCTION

Diabetes mellitus represents one of the most pressing global health crises, with the International Diabetes Federation reporting 537 million adults affected in 2021, a number projected to reach 783 million by 2045. The disease is primarily classified into type 1 diabetes, characterized by autoimmune destruction of pancreatic ß-cells, and type 2 diabetes, which constitutes 90–95% of cases and is marked by insulin resistance coupled with progressive ß-cell dysfunction. Both conditions result in chronic hyperglycemia, which triggers oxidative stress, inflammation, and vascular damage, leading to nephropathy, retinopathy, neuropathy, and cardiovascular complications.being, and participation in broader societal goals. This discussion centers on the importance of cognitive emotion regulation (CER) within this group, addressing its unique challenges and aligning its development with the SDGs (Peña-Sarrionandia et al., 2015; (Brundin et al., 2021).

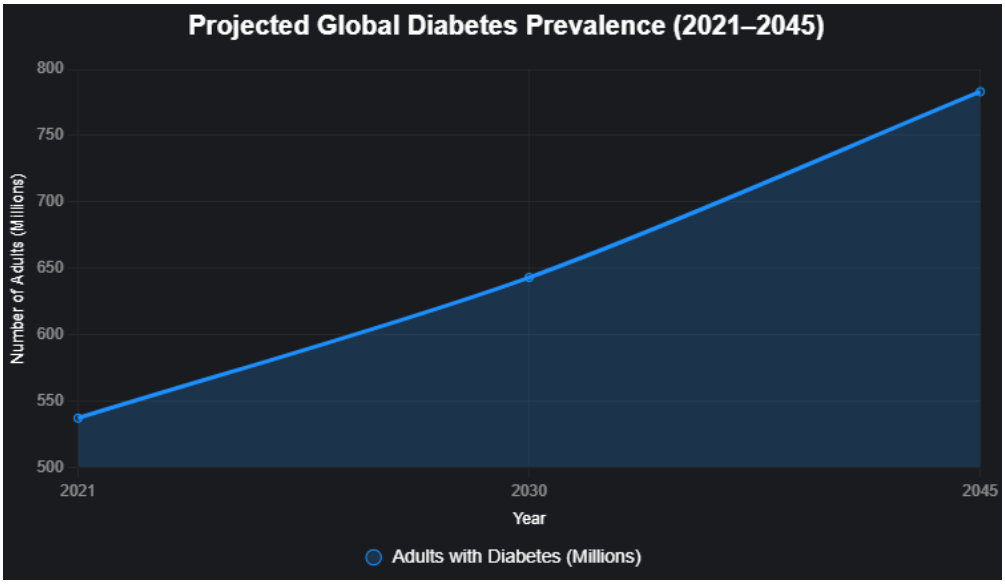

Figure 1: Projected Global Prevalence of Diabetes Mellitus among Adults (2021–2045), Based on IDF Estimates [1]

Conventional pharmacological therapies—including metformin, sulfonylureas, thiazolidinediones, DPP-4 inhibitors, and SGLT2 inhibitors—aim to achieve glycemic control but present significant limitations. Metformin remains the first-line drug due to its affordability and safety profile; however, 20–30% of patients experience gastrointestinal intolerance, and its antioxidant effects are modest. Sulfonylureas carry a risk of hypoglycemia, thiazolidinediones are associated with weight gain, and newer agents are expensive and inaccessible in low-resource settings. Furthermore, these therapies often fail to address oxidative stress and inflammation, which are pivotal in the progression of diabetic complications.

Herbal medicines have gained considerable interest as adjunct therapies due to their affordability, accessibility, and multi-targeted pharmacological effects. Moringa oleifera Lam., commonly known as the drumstick or miracle tree, is a widely cultivated medicinal plant rich in flavonoids, phenolic acids, and isothiocyanates. These compounds inhibit carbohydrate-digesting enzymes, enhance insulin signaling, scavenge reactive oxygen species, and reduce pro-inflammatory cytokines. Preclinical studies in STZ-induced diabetic rats have demonstrated Moringa's ability to lower fasting blood glucose, improve glucose tolerance, protect ß-cell architecture, and ameliorate nephropathy and retinopathy.

Metformin's primary actions—suppression of hepatic gluconeogenesis and enhancement of insulin sensitivity through AMP-activated protein kinase (AMPK)—complement Moringa oleifera's antioxidant and anti-inflammatory mechanisms. Importantly, combining the two may reduce the required dose of metformin, thereby minimizing gastrointestinal side effects. While comparative studies between Moringa and metformin exist, no prior research has investigated their combination in STZ-induced diabetic rats. This gap provides the rationale for the present study.

The primary aim of this study is to evaluate the anti-diabetic potential of ethanolic Moringa oleifera leaf extract combined with metformin in STZ-induced diabetic rats. Specific objectives include assessing glycemic control, ß-cell function, oxidative stress, inflammatory cytokines, nephropathy and retinopathy markers, and molecular mechanisms involving GLUT4, IRS1, PI3K, and Akt. Safety and potential herb–drug interactions were also evaluated.

This study is the first to investigate the Moringa–metformin combination in STZ-induced diabetic rats, addressing an urgent need for safe, cost-effective, and integrative therapies. The findings have significant implications for resource-limited settings where both the prevalence of diabetes and the reliance on herbal medicine are high. By demonstrating synergistic benefits, this research supports the integration of traditional and modern pharmacotherapies for sustainable diabetes management.

2. Materials and Methods

Chemicals and Reagents

Streptozotocin (STZ) was procured from Sigma-Aldrich (USA). Metformin hydrochloride and glibenclamide (pharmaceutical grade) were obtained from certified suppliers. Ethanol (70%), HPLC-grade solvents (methanol, acetonitrile), and reference standards (quercetin, kaempferol, gallic acid) were used for extraction and standardization. Commercial kits were employed for biochemical assays: insulin, oxidative stress markers [malondialdehyde (MDA), superoxide dismutase (SOD), catalase (CAT), glutathione (GSH)], and cytokines (IL-1ß, TNF-α, IL-6). Histological stains included hematoxylin and eosin (H&E), Gomori's, and Mallory's trichrome stains.

Preparation and Standardization of Moringa oleifera Leaf Extract

Fresh leaves of Moringa oleifera were collected and authenticated by a taxonomist. Leaves were shade-dried at 25–30°C for 7–10 days, powdered, and extracted by Soxhlet apparatus using 70% ethanol at 60°C for 8 hours. The extract was concentrated under reduced pressure and lyophilized to obtain a dry powder. Standardization was performed using HPLC-UV (Agilent 1260 Infinity) with a C18 column. The mobile phase consisted of methanol:water (60:40 v/v, 0.1% formic acid). Bioactive compounds were quantified at 254 nm (gallic acid) and 370 nm (quercetin, kaempferol).

Animals and Ethical Approval

Male Wistar rats (150–200 g, 6–8 weeks old) were housed under standard conditions (12-h light/dark cycle, 22 ± 2°C, 50–60% humidity) with free access to food and water. Ethical approval was obtained from the Institutional Animal Ethics Committee (IAEC) in accordance with CPCSEA guidelines from Vedic Institute of Pharmaceutical Education and Research, Sagar.

Induction of Diabetes

After overnight fasting, diabetes was induced by a single intraperitoneal injection of STZ (45 mg/kg) dissolved in cold citrate buffer (0.1 M, pH 4.5). Fasting blood glucose (FBG) was measured 72 h post-injection using a glucometer. Rats with FBG >250 mg/dL were considered diabetic and included in the study.

Experimental Design

Animals were divided into six groups (n = 6 per group):

1. **Normal Control:** Vehicle (saline).
2. **Diabetic Control:** STZ + saline.
3. **Moringa Extract:** Ethanolic Moringa oleifera extract (200 mg/kg, oral).
4. **Metformin:** Metformin (100 mg/kg, oral).
5. **Combination:** Moringa oleifera extract (200 mg/kg) + metformin (100 mg/kg, oral).
6. **Positive Control:** Glibenclamide (5 mg/kg, oral).

Treatments were administered daily via oral gavage for 8 weeks. Body weight, food intake, and water consumption were recorded weekly.

Glycemic Assessments

- **Fasting Blood Glucose (FBG):** Measured at weeks 0, 4, and 8.
- **Oral Glucose Tolerance Test (OGTT):** Performed at baseline, week 4, and week 8 following oral glucose load (2 g/kg), with glucose levels measured at 0, 30, 60, 90, and 120 minutes.
- **Glycosylated Hemoglobin (HbA1c):** Estimated at weeks 0, 4, and 8 using a commercial kit.

Biochemical and Histological Analysis

At the end of treatment, rats were anesthetized with ketamine/xylazine, and blood was collected by cardiac puncture. Serum insulin and cytokines (IL-1β, TNF-α, IL-6) were quantified by ELISA. Kidneys and livers were homogenized to measure oxidative stress markers (MDA, SOD, CAT, GSH).
Histopathological evaluation of the pancreas (Gomori's and Mallory's stains), kidney, and retina (H&E) was performed. Immunohistochemistry was carried out to detect VEGF and NF-κB expression in retinal tissues.

Molecular Studies

RNA was extracted from liver and muscle tissues, followed by RT-PCR to analyze the expression of GLUT4, IRS1, PI3K, and Akt. Gene expression was normalized against β-actin.

Toxicity and Safety Evaluation

An acute toxicity study (OECD 423) was performed using high doses of Moringa oleifera extract (2,000 mg/kg), metformin (1,000 mg/kg), and their combination. Animals were observed for 14 days for behavioral changes, body weight alterations, and mortality. Serum biochemical markers (ALT, AST, creatinine, urea) and histology of liver and kidney were evaluated.

Statistical Analysis

Data were expressed as mean ± SD. Statistical analysis was performed using one-way ANOVA followed by Tukey's post hoc test (GraphPad Prism 9.0). A p value <0.05 was considered statistically significant.

3. RESULTS

Standardization of Moringa Extract

The ethanolic Moringa oleifera extract yielded 18.5 ± 2.1% (w/w). HPLC-UV analysis confirmed the presence of quercetin (5.2 mg/g), kaempferol (4.6 mg/g), and gallic acid (3.8 mg/g).

Glycemic Parameters

STZ-induced diabetic rats exhibited marked hyperglycemia (FBG > 300 mg/dL). Treatment with Moringa oleifera (200 mg/kg) and metformin (100 mg/kg) significantly reduced FBG compared to diabetic control. The combination therapy demonstrated the greatest reduction, normalizing blood glucose close to that of the glibenclamide group. HbA1c levels were reduced, and OGTT showed improved glucose clearance in the combination group.

Table 1. Effect of treatments on FBG and HbA1c in STZ-induced diabetic rats.

Group	Treatment	FBG (mg/dL) Week 0	FBG (mg/dL) Week 4	FBG (mg/dL) Week 8	% Reduction in FBG	HbA1c (%)
I	Normal Control	92.4 ± 4.6	94.1 ± 5.3	96.2 ± 4.8	—	4.9 ± 0.3
II	Diabetic Control (STZ 45 mg/kg)	318.6 ± 12.5	326.8 ± 11.9	334.7 ± 13.4	—	9.8 ± 0.4
III	Moringa oleifera Extract (200 mg/kg)	320.4 ± 13.2	242.1 ± 9.6*	178.5 ± 8.7**	44.3%	6.7 ± 0.3**
IV	Metformin (100 mg/kg)	322.9 ± 11.4	210.5 ± 10.2**	161.2 ± 7.9***	50.0%	6.1 ± 0.2***
V	Combination (Moringa + Metformin)	321.8 ± 10.7	188.3 ± 8.8***	122.7 ± 6.1***	63.2%	5.5 ± 0.2***
VI	Glibenclamide (5 mg/kg)	320.7 ± 12.3	198.4 ± 9.1**	118.6 ± 5.8***	63.9%	5.3 ± 0.3***

Values are expressed as Mean ± SD (n = 6).
*P < 0.05, **P < 0.01, ***P < 0.001 compared with diabetic control group (one-way ANOVA followed by Tukey's test).

Serum Insulin and β-Cell Morphology

Diabetic control rats exhibited reduced serum insulin and disrupted pancreatic β-cell architecture. Treatment with Moringa oleifera or metformin partially restored β-cell function, while the combination therapy markedly increased insulin secretion and preserved islet

Oxidative Stress Biomarkers

Diabetic rats showed elevated MDA and decreased SOD, CAT, and GSH. Combination treatment significantly reduced lipid peroxidation and restored antioxidant enzyme activities more effectively than either agent alone.

Table 2. Effect of treatments on oxidative stress markers in liver and kidney tissues.

(Insert table from thesis here)

Pro-inflammatory Cytokines

IL-1β, TNF-α, and IL-6 were significantly increased in diabetic control rats. Both Moringa oleifera and metformin reduced cytokine levels, but the combination therapy demonstrated the strongest anti-inflammatory effect.
Complication Markers

- **Nephropathy:** Diabetic rats showed increased proteinuria, BUN, and serum creatinine. Combination treatment significantly reduced renal impairment markers.
- **Retinopathy:** VEGF and NF-κB expression were elevated in diabetic controls, while the combination group showed marked suppression of both, suggesting retinal protection.

Safety Evaluation

No mortality or significant behavioral changes were observed during acute toxicity testing. Liver and kidney function markers remained within normal ranges. Histological analysis confirmed absence of hepatotoxicity or nephrotoxicity.

DISCUSSION

The present study demonstrates the synergistic anti-diabetic potential of Moringa oleifera leaf extract and metformin in STZ-induced diabetic rats. While both treatments individually improved glycemic control and oxidative balance, the combination therapy achieved superior efficacy across multiple parameters, including fasting blood glucose, HbA1c, oral glucose tolerance, insulin secretion, oxidative stress markers, cytokine suppression, and histopathological protection.

Comparison with Previous Studies

Previous reports have established that Moringa oleifera reduces hyperglycemia through inhibition of α-glucosidase and α-amylase, enhancement of insulin sensitivity, and protection of β-cells via antioxidant mechanisms [24, 26]. Similarly, metformin has been shown to suppress hepatic gluconeogenesis, enhance peripheral glucose uptake through AMPK activation, and provide mild antioxidant protection [10, 11, 34]. Our findings confirm these individual effects and further demonstrate that their combination produces enhanced benefits.

Notably, the combination improved GLUT4, IRS1, PI3K, and Akt expression, suggesting amplified insulin signaling compared to individual therapies. This aligns with prior mechanistic insights showing that quercetin and kaempferol upregulate insulin pathway genes [23], while metformin primarily acts through AMPK [32]. Together, they appear to complement each other at distinct molecular targets, leading to synergistic outcomes.

Antioxidant and Anti-Inflammatory Synergy

Oxidative stress and inflammation are critical drivers of β-cell dysfunction and diabetic complications [26]. The combination therapy markedly decreased MDA levels and restored antioxidant enzymes (SOD, CAT, GSH), surpassing the effects of single treatments. Similarly, reductions in IL-1β, TNF-α, and IL-6 were most pronounced in the combination group, indicating a synergistic anti-inflammatory effect. These results suggest that Moringa oleifera compensates for metformin's limited antioxidant capacity, providing broader cytoprotection.

Protection Against Complications

Nephropathy and retinopathy represent major long-term complications of diabetes. Our findings demonstrated that the combination reduced proteinuria, BUN, creatinine, VEGF, and NF-κB expression more effectively than single agents, indicating renal and retinal protection. This aligns with earlier reports of Moringa oleifera reducing VEGF in diabetic retinopathy models [31] and improving renal oxidative status [30].

Clinical Relevance

From a translational perspective, this study suggests that integrating Moringa oleifera with metformin could reduce the required dose of metformin, thereby minimizing gastrointestinal side effects while maintaining or enhancing therapeutic efficacy. Such an approach may be particularly valuable in low- and middle-income countries, where access to newer anti-diabetic agents is limited and traditional medicines are widely accepted.

Limitations and Future Directions

While the preclinical findings are promising, clinical studies are essential to confirm safety and efficacy in human populations. Potential herb–drug interactions should be carefully monitored, as prolonged co-administration with other oral hypoglycemics has previously shown variable outcomes [36]. Further research should also investigate pharmacokinetics, long-term toxicity, and the optimal dosing ratio of the combination.

CONSLUSION

This study provides the first experimental evidence that the combination of Moringa oleifera leaf extract and metformin exerts synergistic anti-diabetic effects in STZ-induced diabetic rats. The therapy significantly improved glycemic control, enhanced β-cell function, restored antioxidant defenses, reduced inflammatory cytokines, and protected against nephropathy and retinopathy. Molecular analysis confirmed upregulation of insulin signaling genes, further supporting mechanistic synergy.

The findings suggest that Moringa oleifera can enhance the therapeutic efficacy of metformin while potentially reducing dose-dependent side effects. This integrative approach offers a cost-effective and sustainable strategy for diabetes management, particularly relevant for resource-limited settings. Future clinical studies are warranted to validate these outcomes and explore translation into patient care.

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Appended Tables from Thesis

Table 1: ***Comparison of Type 1 and Type 2 Diabetes Mellitus, Highlighting Prevalence, Pathophysiology, Causes, and Complications.***

Type of Diabetes	Prevalence	Pathophysiology	Primary Cause	Complications
Type 1	5–10%	Absolute insulin deficiency	Autoimmune ß-cell destruction	Nephropathy, retinopathy, neuropathy, cardiovascular diseases
Type 2	90–95%	Insulin resistance, ß-cell dysfunction	Genetic, lifestyle, obesity	Same as Type 1, plus macrovascular issues

Table 2: ***Comparison of Major Pharmacological Classes for Diabetes Management,Including Mechanisms, Benefits, Limitations, and Side Effects***

Drug Class	Mechanism of Action	Benefits	Limitations	Side Effects
Metformin	Inhibits hepatic gluconeogenesis, activates AMPK	Affordable, weight-neutral, cardioprotective	Limited antioxidant effects, GI intolerance	Nausea, diarrhea (20–30%)
Sulfonylureas	Stimulates insulin secretion	Effective, inexpensive	Hypoglycemia risk	Hypoglycemia, weight gain

Table 3: ***Major Phytochemical Classes in Moringa oleifera Leaves, Their Mechanisms, and Therapeutic Effects in Diabetes Management***

Phytochemical Class	Examples	Mechanism of Action	Therapeutic Effect
Flavonoids	Quercetin, Kaempferol	Inhibits α-glucosidase, upregulates GLUT4	Reduces postprandial glucose, enhances insulin signaling
Phenolic Acids	Gallic Acid	Scavenges ROS, reduces lipid peroxidation	Antioxidant, cytoprotective

Table 4: ***The timeline of study phases with activities and deliverables***

Phase	Activities	Duration	Months
1	Ethanolic extract preparation and standardization	2 months	1–2
2	Animal model preparation and ethical approval	2 months	2–3
3	Experimental design and treatment	4 months	4–7
4	Biochemical and histopathological analysis	3 months	8–10
5	Molecular analysis	3 months	9–11
6	Safety and toxicity assessment	3 months	8–10
7	Data analysis and thesis compilation	2 months	11–12