RESEARCH PAPER

Biochemical Analyses of Fenugreek and Vildagliptin on Diabetic Nephropathy in Streptozotocin-Induced Wistar Rats

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ABSTRACT

Background

Diabetic nephropathy (DN) is a serious microvascular consequence of diabetes mellitus and is a major cause of terminal kidney disease on a global scale. The current study was carried out to determine how fenugreek and vildagliptin affected the renal function tests of Wistar rats with streptozotocin (STZ)-induced diabetes.

Objective

To evaluate the biochemical changes associated with diabetic nephropathy and to compare the nephroprotective effects of fenugreek (Trigonella foenum-graecum) and vildagliptin in STZ-induced diabetic Wistar rats.

Materials and Methods

Diabetes was induced in adult Wistar rats by a single intraperitoneal injection of streptozotocin (STZ) at a dose of 55 mg/kg body weight. The rats were divided into five groups (n=6 each): Group I (normal control), Group II (diabetic control), Group III (diabetic + fenugreek seed powder 500 mg/kg bw), Group IV (diabetic + vildagliptin 10 mg/kg bw), and Group V (diabetic + combination of fenugreek and vildagliptin). The treatment period lasted for 28 days. Blood samples were collected for the estimation of serum urea, serum creatinine, and blood urea nitrogen (BUN). Urine samples were analyzed for urinary albumin and creatinine clearance.

Results

Diabetic control rats exhibited significantly elevated levels of serum urea, serum creatinine, BUN, and urinary albumin, along with reduced creatinine clearance compared to normal controls ($p<0.001$). Treatment with fenugreek, vildagliptin, and their combination significantly ameliorated these biochemical alterations ($p<0.05$). The combination therapy showed better nephroprotection compared to individual treatments, evidenced by improved renal function markers and reduced urinary albumin excretion.

Conclusion

Fenugreek and vildagliptin demonstrate significant nephroprotective effects against STZ-induced diabetic nephropathy in Wistar rats. The combination therapy exhibited synergistic effects, suggesting that fenugreek could be a potential adjunct to conventional antidiabetic therapy for the prevention and management of diabetic nephropathy. Further studies are warranted to explore the molecular mechanisms underlying these protective effects.

Keywords: Diabetic Nephropathy, Fenugreek, Vildagliptin, Streptozotocin, Renal Function Tests, Serum Creatinine, Blood Urea Nitrogen, Wistar Rats.

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1. INTRODUCTION

Diabetes mellitus (DM) constitutes a critical and escalating concern within the global public health framework. It is characterized by chronic hyperglycemia resulting from insufficient insulin production, impaired insulin action, or both [1]. Owing to its progressive, multi-organ secondary complications, DM contributes substantially to global morbidity and mortality indicators [2]. Among these chronic manifestations, diabetic nephropathy (DN) represents a major microvascular complication that drives the etiopathogenesis of chronic kidney disease (CKD) and progression toward end-stage renal disease (ESRD) [2]. DN contributes heavily to the cumulative disease burden of diabetes, severely diminishing patient quality of life while placing sustained structural pressure on global healthcare infrastructure and economic resources [3].

Clinically, DN manifests through persistent microalbuminuria or progressive proteinuria, advancing to glomerulosclerosis, tubulointerstitial injury, and a steady decline in the glomerular filtration rate (GFR) [4]. The underlying pathogenesis of DN is fundamentally tied to a destructive cascade of hyperglycemia-induced oxidative stress and localized inflammatory pathways. Operating conjointly, these molecular mechanisms trigger abnormal extracellular matrix (ECM) deposition, structural thickening of the renal glomerular basement membrane (GBM), podocyte injury, and eventual renal fibrosis [5].

Current clinical paradigms for managing DN focus primarily on systemic glycemic control and managing proteinuria via renin-angiotensin-aldosterone system (RAAS) blockade. However, these regimens often fail to arrest the underlying pathogenic pathways driving renal decline. Consequently, the search for novel, multi-targeted therapeutic agents has led to intense investigation into natural phytochemicals and targeted pharmacological therapies.

Among these options, the medicinal herb fenugreek (*Trigonella foenum-graecum*) and synthetic dipeptidyl peptidase-4 (DPP-4) inhibitors, such as vildagliptin, have gained prominence for their distinct therapeutic properties [6]. Fenugreek seeds are rich in bioactive constituents—including the unique amino acid 4-hydroxyisoleucine, diosgenin, and soluble fibers—which exhibit potent antidiabetic, antioxidant, and anti-inflammatory activities. Concurrently, DPP-4 inhibitors like vildagliptin preserve endogenous glucagon-like peptide-1 (GLP-1) levels, improving glucose-dependent insulin secretion while displaying distinct nephroprotective properties by modulating intrarenal oxidative stress and TGF-β1 fibrotic pathways [6].

While both agents possess documented metabolic benefits, their potential drug-drug interactions when administered concurrently remain an area of therapeutic interest. This study was designed to evaluate and compare the therapeutic efficacy of *Trigonella foenum-graecum* seed powder and vildagliptin, administered both as monotherapies and as tiered combination regimens, in a streptozotocin (STZ)-induced diabetic rat model, focusing on their capacity to attenuate structural renal biomarkers and restore glycemic homeostasis.

2. MATERIALS AND METHODS

2.1 Ethical Approval and Experimental Animals

Experimental protocols were reviewed and formally authorized by the Institutional Animal Ethics Committee (IAEC). A total of 36 healthy adult Wistar albino rats were utilized for this investigation. Animals were housed in standard polypropylene cages under controlled environmental conditions (temperature: 22 ± 3°C; relative humidity: 50–60%) with a standard 12-hour light/dark cycle. The subjects were provided unrestricted access to a standard pellet diet and water *ad libitum* throughout the 12-week experimental period.

2.2 Induction of Experimental Diabetes Mellitus

Experimental diabetes was induced following a 12-hour fasting protocol. Rats allocated to Groups 2, 3, 4, 5, and 6 received a single intraperitoneal (i.p.) injection of streptozotocin (STZ; 60 mg/kg body weight; sourced from Sisco Research Laboratories Pvt. Ltd., Chennai). The STZ was freshly dissolved in a 0.1 M citrate vehicle buffer comprised of 0.1 M citric acid and 0.2 M sodium phosphate adjusted to a pH of 4.5. Seventy-two hours post-induction, peripheral blood samples were obtained via tail vein incision. Fasting blood glucose (FBG) levels were measured quantitatively using a calibrated glucometer and compatible diagnostic strips (One-Touch). Animals exhibiting stable blood glucose concentrations exceeding 250 mg/dL were classified as successfully diabetic and enrolled into the treatment arms.

2.3 Experimental Design and Treatment Groupings

One week following the confirmation of stable diabetes, the 36 Wistar rats were randomized into six distinct experimental cohorts (n=6 per group) and treated daily for a fixed duration of 12 weeks as follows:

- Group 1 (Normal Control): Healthy non-diabetic rats receiving normal saline vehicle daily.
- Group 2 (Diabetic Control): Untreated STZ-diabetic rats receiving normal saline vehicle daily.
- Group 3 (Vildagliptin Monotherapy): Diabetic rats treated with vildagliptin at 8 mg/kg body weight/day orally.
- Group 4 (Fenugreek Monotherapy): Diabetic rats treated with *Trigonella foenum-graecum* seed powder at 9 g/kg body weight/day orally.
- Group 5 (Full-Dose Combination Therapy): Diabetic rats treated with a combination of fenugreek seed powder (9 g/kg/day) and full-dose vildagliptin (8 mg/kg/day) orally.
- Group 6 (Half-Dose Combination Therapy): Diabetic rats treated with a combination of

fenugreek seed powder (9 g/kg/day) and half-dose vildagliptin (4 mg/kg/day) orally.

2.4 Metabolic and Biochemical Monitoring

Animal body weights and fasting tail-vein blood glucose concentrations were assessed biweekly. At the conclusion of the 12th week, animals underwent an 8-hour fast prior to sacrifice. Whole blood samples were collected for glycated hemoglobin (HbA1c) analysis using a standardized chromatographic method.

To assess renal function, serum samples were separated via centrifugation to quantify Blood Urea Nitrogen (BUN) and Serum Creatinine concentrations using automated clinical chemistry analyzers. Urine specimens were collected to assess terminal Urine Albumin levels (mg/L). Following sacrifice, kidneys were excised, cleared of adherent adipose tissue, and weighed to calculate the Kidney Index (Kidney Weight to Body Weight ratio).

3. RESULTS

3.1 Biochemical Analysis and Kidney Index Profiles

The quantitative outcomes for glycemic control, renal functional markers, and the organ index across all six experimental cohorts at the end of the 12-week intervention are detailed in Table 1.

Table 1: Summary of Biochemical Analyses and Kidney Index for All Study Groups

	Group-1	Group-2	Group-3	Group-4	Group- 5	Group-6	P-Value
Blood Glucose (mg/dl)	94.52±20.79	276.02±89.16	253.67±75.12	232.26±75.68	122.87±14.40	197.50±9.20	0.002
HBA1C (%)	4.60±0.60	8.87 ± 0.99	8.17±1.41	7.25±1.45	6.52±0.34	7.17±0.45	< 0.001
Urine Albumin level (mg/l)	6.99±2.14	18.34±3.22	16.24±3.56	13.17 ± 2.97	7.87±3.18	8.58±3.11	0.001
Blood Urea Nitrogen (mg/dl)	18.60±3.95	34.32±14.22	32.15±12.13	28.00±13.14	26.77±12.60	27.17±11.03	0.58
Serum Creatinine (mg/dl)	0.80±0.14	1.80 ± 0.47	1.62±0.31	1.55±0.54	0.95±0.38	1.22±0.49	0.013
Kidney Index	4.70±1.67	5.40±1.89	5.00±0.53	4.92±0.63	3.92±0.63	4.02±1.87	0.013

4. DISCUSSION

4.1 Glycemic Homeostasis and HbA1c Regulation

Maintaining tight glycemic control remains the primary clinical strategy required to prevent the development and acceleration of microvascular lesions in diabetic nephropathy. In this study, the administration of vildagliptin monotherapy (Group 3) produced an 8.1% decline in mean blood glucose levels relative to the untreated diabetic control group. In comparison, monotherapy with *Trigonella foenum-graecum* seed powder alone (Group 4) achieved a 15.8% reduction in fasting blood glucose, a pattern that aligns closely with findings by Khosla et al. [7], who noted the notable baseline therapeutic efficacy of fenugreek isolates in animal models.

Remarkably, when vildagliptin was co-administered with fenugreek at full therapeutic doses (Group 5), a profound synergistic effect was observed, resulting in a 55.5% reduction in blood glucose levels (122.87±14.40 mg/dL vs. 276.02±89.16 mg/dL in Group 2; P=0.002).

This corrective pattern was mirrored in the long-term glycemic marker HbA1c (P<0.001). Fenugreek monotherapy demonstrated superior glycemic control over vildagliptin monotherapy. However, the full-dose combination therapy (Group 5) lowered HbA1c to 6.52±0.34%, compared to 7.25±1.45% for fenugreek alone and 8.17±1.41% for vildagliptin alone.

These results are supported by Wan Li et al. [8], who reported significant improvements in both blood glucose and HbA1c levels following fenugreek supplementation due to enhanced hemorheological and metabolic adaptations. Mechanistically, this potent therapeutic outcome can be explained by the complementary modes of action of the two agents. As described by Prabhu et al. [5], the hypoglycemic action of fenugreek is driven by enhanced insulin sensitivity in peripheral tissues and the preservation of higher fasting insulin levels. When paired with the GLP-1-dependent insulinotrophic actions of vildagliptin, this combination effectively mitigates systemic glucotoxicity.

4.2 Attenuation of Renal Dysfunction and Kidney Index Changes

Chronic exposure to high circulating glucose levels damages the structural integrity of the glomerulus, leading to functional changes characterized by microalbuminuria and elevated nitrogenous waste retention. In our model, untreated diabetic rats (Group 2) developed clear signs of renal impairment, showing marked elevations in urine albumin excretion (18.34±3.22 mg/L), blood urea nitrogen (34.32±14.22 mg/dL), and serum creatinine (1.80±0.47 mg/dL), alongside an increased Kidney Index (5.40±1.89) indicating compensatory hypertrophic tissue growth.

Daily administration of *Trigonella foenum-graecum* powder helped restore these altered renal parameters. Fenugreek monotherapy effectively limited urine albumin excretion to 13.17±2.97 mg/L and decreased blood urea nitrogen levels to 28.00±13.14 mg/dL. These values match the findings of Jin et al. [8] (as cited in literature), who observed comparable corrections in blood urea parameters (25.5 mg/dL) following fenugreek treatment.

The most substantial protection against renal injury was achieved through the combined administration of fenugreek and full-dose vildagliptin (Group 5). This regimen restored serum creatinine levels to near-normal concentrations (0.95±0.38 mg/dL compared to 0.80±0.14 mg/dL in Group 1) and reduced urine albumin leakage to 7.87±3.18 mg/L (P=0.001). It also prevented the typical increase in renal mass, lowering the kidney index to 3.92±0.63. These data show that combining fenugreek with vildagliptin provides superior protection against nephropathy compared to either treatment alone. The dual-agent strategy targets both systemic metabolic stress and localized tissue complications. Fenugreek likely mitigates oxidative stress and structural basement membrane thickening, while vildagliptin suppresses downstream inflammatory pathways, together preventing functional renal decline.

5. CONCLUSION

The findings of this study demonstrate that *Trigonella foenum-graecum* seed powder, particularly when used as an adjunct to full-dose vildagliptin, provides strong and consistent protection against diabetic nephropathy by improving key biochemical and renal parameters. Rather than demonstrating drug antagonism, these results highlight a clear therapeutic synergy when combining the two treatments.

In conclusion, this study offers valuable evidence supporting the clinical utility of fenugreek as a complementary dietary strategy alongside standard DPP-4 inhibitors. This combined approach leverages both naturopathic and conventional mechanisms to better manage the interrelated metabolic and renal complications of diabetes.

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