



Nifuroxazide protects against diabetic neuropathy in rats by enhancing Nrf2/HO-1 signaling and inhibiting the NF-κB and JAK-1/STAT3 pathways

Nifuroxazide and sciatic nerve protection

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Abstract

Aim: Diabetic neuropathy remains one of the most debilitating complications of diabetes, driven by oxidative stress, chronic inflammation, and neuronal apoptosis. This work explored the protective role of nifuroxazide (NIF), a known signal transducer and activator of transcription 3 (STAT3) inhibitor, in a rat model of streptozotocin-induced peripheral neuropathy.

Methods: Forty male albino rats were divided into four groups: healthy controls, NIF-treated controls, diabetic controls, and diabetic rats receiving NIF. After induction of diabetes and stabilization, NIF was administered orally for four weeks.

Results: Biochemical evaluation revealed that diabetes markedly increased lipid peroxidation and reduced antioxidant enzyme activity, while NIF treatment restored superoxide dismutase and catalase activities and lowered malondialdehyde levels. These antioxidant effects were accompanied by activation of the nuclear factor erythroid 2-related factor 2 (Nrf2)/heme oxygenase-1 (HO-1) pathway. Inflammatory analysis showed that diabetes elevated phosphorylated Janus kinase 2 (JAK2)/STAT3, nuclear factor kappa B (NF-κB), and pro-inflammatory cytokines, whereas NIF significantly suppressed these mediators. Apoptotic markers, including caspase-3 and B-cell lymphoma 2 (Bcl-2)-associated X protein (Bax), were upregulated in diabetic nerves, with a parallel decline in Bcl-2; NIF reversed these changes, indicating anti-apoptotic efficacy. Histological examination further confirmed that NIF preserved sciatic nerve architecture, reducing vacuolation, demyelination, and endoneurial disruption.

Conclusion: Overall, NIF demonstrated a multifaceted neuroprotective effect by attenuating oxidative stress, dampening inflammatory signaling, and preventing apoptosis. These findings suggest that NIF may represent a promising therapeutic candidate for diabetic neuropathy, acting through coordinated modulation of antioxidant, inflammatory, and apoptotic pathways.

Keywords

diabetes, nifuroxazide, neuropathy, STAT3, oxidative stress, inflammation

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Introduction

Diabetic peripheral neuropathy (DPN) is the most frequent complication of diabetes mellitus (DM), affecting around half of all DM patients.^{1,2} This condition contributes to a decline in skeletal muscle mass and elevates the risk of falls and fractures.³ Consequently, slowing the onset and advancement of DPN is crucial for preventing fall-related fractures and lowering associated illness and death rates.⁴ The sciatic nerve (SN), given its role in innervating the lower limbs, is commonly used as a model to investigate the mechanisms underlying DPN.⁵

Currently, there is no clinically available cure specifically for DPN, and management focuses on prevention through blood sugar control and lifestyle changes.⁶ While certain drugs like anticonvulsants, antidepressants, and opioids are prescribed for neuropathic pain, this symptom is not universal in DPN. Furthermore, these treatments often provide inadequate relief even for patients who experience pain.⁷

Oxidative stress is thought to play a key role in triggering DPN. High blood sugar levels induce lipid peroxidation and lead to excessive generation of reactive oxygen species (ROS) in the sciatic nerves of mice.⁸ Such oxidative stress has been demonstrated to impair sciatic nerve function in these models.⁹ Supporting this, the antioxidant resveratrol was shown to reduce diabetes-induced oxidative stress and improve DPN in rat sciatic nerves.¹⁰ Thus, mitigating oxidative stress may help delay the development or onset of DPN.

Nifuroxazide (NIF) is a broad-spectrum nitrofurantoin antibiotic with a long-established safety profile in humans, primarily used as an intestinal anti-infective and antidiarrheal agent.¹¹ Recent evidence, however, indicates it possesses significant antioxidant and anti-inflammatory properties, suggesting potential benefits in managing various disease states.^{12,13} Despite these insights, its specific role in diabetic peripheral neuropathy (DPN) remains largely unexplored.

Given this background, the present study aims to evaluate the therapeutic potential of nifuroxazide—an existing drug with novel applications—against experimentally induced diabetic neuropathy. A further objective is to elucidate the mechanistic pathways underlying its proposed therapeutic effects.

Materials and Methods

Animals

Forty male Albino rats, weighing between 150 and 200 grams, were used in the study. They were maintained under standardized environmental conditions, including a temperature of 25 °C ($\pm$ 2 °C), relative humidity of 65% ($\pm$ 5%), and a 12-hour light/dark cycle. The rats were housed in standard polypropylene cages fitted with wire-mesh tops, with corn cob as bedding material. They had unrestricted access to both standard commercial rodent feed and water throughout the acclimatization and experimental periods.

Experimental Design

The forty rats were allocated into four experimental groups (n = 10 per group) as follows:

Group I (Control): Animals received a single intraperitoneal (i.p.) injection of 1 ml citrate buffer (0.1 M, pH 4.5), the vehicle for streptozotocin (STZ).

Group II (NIF-treated Control): Non-diabetic rats received no treatment for 4 weeks, followed by oral nifuroxazide (NIF; 20 mg/kg/day) for 4 weeks.

Group III (Diabetic Control): Diabetes was induced by a single i.p. injection of STZ (60 mg/kg in citrate buffer). After a 4-week stabilization period, this group received no further treatment.

Group IV (Diabetic + NIF): Following STZ-induced diabetes and a 4-week stabilization period, rats received oral NIF (20 mg/kg/day) for 4 weeks.

Diabetes was confirmed 3 days post-STZ injection by measuring tail vein blood glucose; rats with levels >250 mg/dL on two consecutive days were included.

Sample Collection and Tissue Preparation

Following the 8-week experimental period, blood samples were obtained from all rats to measure plasma glucose and insulin levels. Animals were then euthanized via an overdose of pentobarbital (40 mg/kg, i.p.). Both sciatic nerves were immediately dissected out. One nerve from each animal was processed for histopathological examination by light microscopy. The contralateral sciatic nerve was used for biochemical analysis. A weighed portion (50–100 mg) of the nerve tissue was homogenized on ice in 1–2 ml of cold potassium phosphate buffer (50 mM, pH 7.5) containing 1 mM EDTA, using a mortar and pestle. The homogenate was centrifuged at 4,000 rpm for 15 minutes at 4 °C. The resulting supernatant was collected and stored at -20 °C for subsequent assessment of oxidative stress markers and other biochemical parameters by enzyme-linked immunosorbent assay (ELISA).

Light Microscopic Study

A portion of the sciatic nerve was fixed in 10% neutral buffered formalin, processed, and embedded in paraffin. Sections were cut at a thickness of 3 μ m and stained with hematoxylin and eosin (H&E). The prepared slides were examined for histopathological alterations using a Leica DM500 light microscope equipped with a Leica ICC50HD camera. Images were captured and analyzed with the accompanying LEICA Application Suite (LAS) EZ software, Version 3.1.1 (Leica Microsystems, Heerbrugg, Switzerland).

Assay of Oxidative Stress Markers

The concentration of malondialdehyde (MDA), an indicator of lipid peroxidation, was measured in the tissue supernatant using a standardized colorimetric assay kit (Bio-Diagnostics, Egypt, Cat. # MD2529). The enzymatic activities of the antioxidant enzymes superoxide dismutase (SOD) and catalase (CAT) were also assessed. SOD activity was determined using a colorimetric biochemical kit (Bio-Diagnostics, Egypt, Cat. # SD 2521). CAT activity was measured biochemically using a corresponding kit (Bio-Diagnostics, Egypt, Cat. # CA 25 17). All assays were performed strictly according to the respective manufacturers' protocols.

ELISA Assay

ELISA was performed according to the manufacturers' instructions to quantify the following markers: phosphorylated JAK-2 (p-JAK2; MBS7269637) with a sensitivity of 0.1 ng/mL; phosphorylated signal transducer and activator of transcription 3 (STAT3) (p-STAT3; EK721641, 3.75–100 U/mL); nuclear factor kappa B (NF- κ B) (ER1186, 0.156–10 ng/mL); the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway components Nrf2 (ER0666, 15.625–1000 pg/mL) and heme oxygenase-1 (HO-1) (ER1041, 0.313–20 ng/mL); pro-inflammatory cytokines tumor necrosis factor alpha (TNF- α) (QT-ER1393, 3.906–250 pg/mL), interleukin-6 (IL-6) (ER0042, 62.5–4000 pg/mL), and interleukin-1 beta (IL-1 β) (ER1094, 31.25–2000 pg/mL); and apoptosis-related proteins cleaved Caspase-3 (ER0143, 0.313–20 ng/mL), B-cell lymphoma 2 (Bcl-2)-associated X protein (Bax) (ER0512, 0.313–20 ng/mL), and Bcl-2 (ER0762, 0.156–10 ng/mL).

Ethical Approval

This study was approved by the Ethics Committee of Umm Al-Qura University, Makka, Saudi Arabia (Date: 14.02.2025, Decision No: HAPO-02-K-012-2025-12-3128).

Statistical Analysis

Data were processed and analyzed using GraphPad Prism software, Version 8.0 (GraphPad Software, Inc., San Diego, CA, USA). Results are expressed as the mean ± standard deviation (SD). Statistical comparisons among all groups were performed using a one-way analysis of variance (ANOVA), followed by Tukey's post hoc test for pairwise comparisons. A probability value (p) of less than 0.05 was considered statistically significant.

Reporting Guidelines

This experimental animal study was reported in accordance with the ARRIVE guidelines.

Results

Antioxidant Effect of NIF Against Diabetic-Induced Sciatic Nerve Oxidative Stress

Oxidative stress markers were assessed in sciatic nerve homogenate. As shown in Figure 1, the sciatic nerves of diabetic rats exhibited a significant ($P < .05$) elevation in MDA, a marker of lipid peroxidation, and a significant reduction in the antioxidant enzymes SOD and CAT, relative to normal controls. In contrast, the NIF-treated diabetic group showed a marked inhibition of nerve oxidation, demonstrated by the restoration of SOD and CAT activities and a reduction in MDA levels. This protective effect was associated with the upregulation of the Nrf2/HO-1 signaling pathway, as shown by increased protein expression in the NIF-

treated group (Figure 1D, E). Collectively, these results indicate that NIF mitigates experimental diabetic neuropathy by inhibiting oxidative damage.

Histological Results

Histological examination of H&E-stained sciatic nerve sections is presented in Figure 2. Transverse sections from control rats displayed normal nerve architecture (Figure 2A-D). In contrast, sections from diabetic rats exhibited features of neurodegeneration, including edematous axoplasm with areas of vacuolation, endoneurial separation, and demyelination within affected nerve fascicles (Figure 2E, F). The Diabetic+NIF-treated group showed marked histological improvement, characterized by restored nerve fascicle structure and reduced endoneurial separation (Figure 2G, H). These findings demonstrate the neuroprotective effect of NIF against diabetic neuropathy in rats.

Impact of NIF on Diabetic Induced Sciatic Nerve Inflammation

Protein analysis revealed a significant increase in the inflammatory transcription factor NF- κ B in the sciatic nerve of diabetic rats, concomitant with elevated transcription of the pro-inflammatory cytokines TNF- α , IL-6, and IL-1 β compared to the control group (Figure 3C-F). Treatment with NIF significantly reduced the levels of these inflammatory indicators. This suggests that the therapeutic effect of NIF on diabetic neuropathy may be mediated, in part, by its anti-inflammatory properties.

Impact of NIF on Diabetic-Induced Sciatic Nerve Apoptosis

The impact of diabetes on sciatic nerve apoptosis was confirmed by ELISA (Figure 3G-I), which showed elevated levels of the pro-apoptotic factors caspase-3 and Bax and reduced levels of the anti-apoptotic protein Bcl-2. NIF administration counteracted these diabetes-induced changes, significantly reducing caspase-3 and Bax levels while upregulating Bcl-2. This demonstrates the anti-apoptotic efficacy of NIF and its relevance to the mechanisms underlying diabetic neuropathy.

Discussion

This study was designed to investigate the neuroprotective effect of NIF against STZ-induced peripheral neuropathy using the sciatic nerve as a model. The main findings demonstrate that oral administration of NIF for one month effectively halts diabetes-induced oxidative damage in the sciatic nerve. This protection is associated with enhanced Nrf2 signaling. As NIF is recognized as a selective STAT3 inhibitor, it suppresses the JAK2/STAT3 pathway, thereby preventing activation of the NF- κ B inflammatory pathway and reducing the secretion of inflammatory cytokines. Furthermore, NIF decreases apoptotic changes in the sciatic nerve, ultimately leading to improved sciatic nerve morphology.

Hyperglycemia-induced oxidative stress exacerbates nerve damage through elevated levels of reactive oxygen species (ROS) and nitric oxide, leading to neuronal injury, reduced pain thresholds, and slower nerve conduction velocities. Consistent with this, our study demonstrated that the sciatic nerves of diabetic rats exhibited a marked increase in lipid peroxidation, accompanied by a significant decline in the activities of antioxidant enzymes such as SOD and CAT, in agreement with the findings of Adki et al.¹⁴ In contrast, coadministration of NIF to diabetic rats produced a protective effect, evidenced by enhanced antioxidant enzyme activity and reduced lipid peroxidation in sciatic nerve homogenates. This beneficial action can be attributed to the activation of the Nrf2/HO-1 signaling pathway, which promotes the transcription of antioxidant enzymes. Our results are in line with those of Abd-Alhameed et al., who reported that NIF exerted protective effects

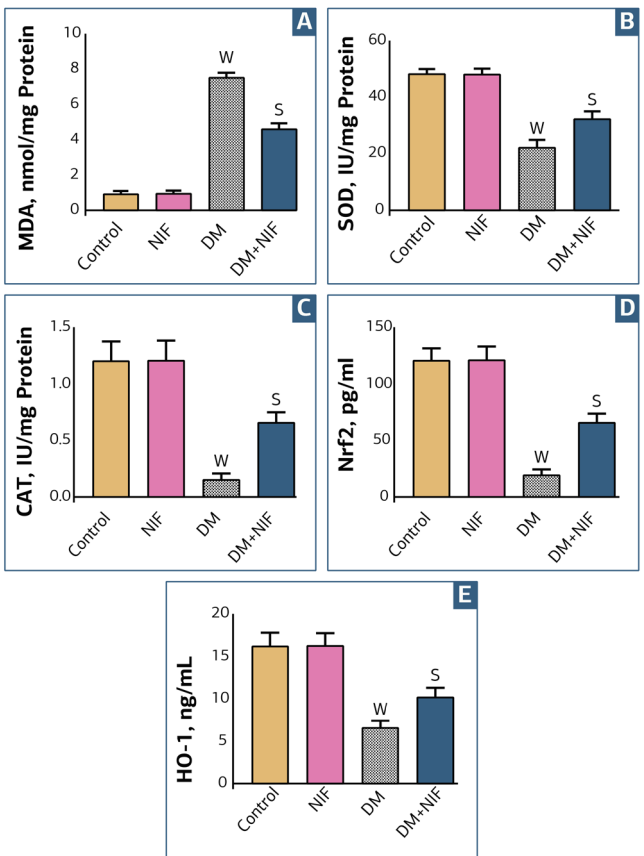


Figure 1. The level of (A) MDA, (B) SOD, (C) CAT, (D) Nrf2, and (E) HO-1 in Sciatic Nerve Supernatant in Different Groups

Data are presented as mean ± SD. * $P < .05$ vs. control group; # $P < .05$ vs. diabetic group.

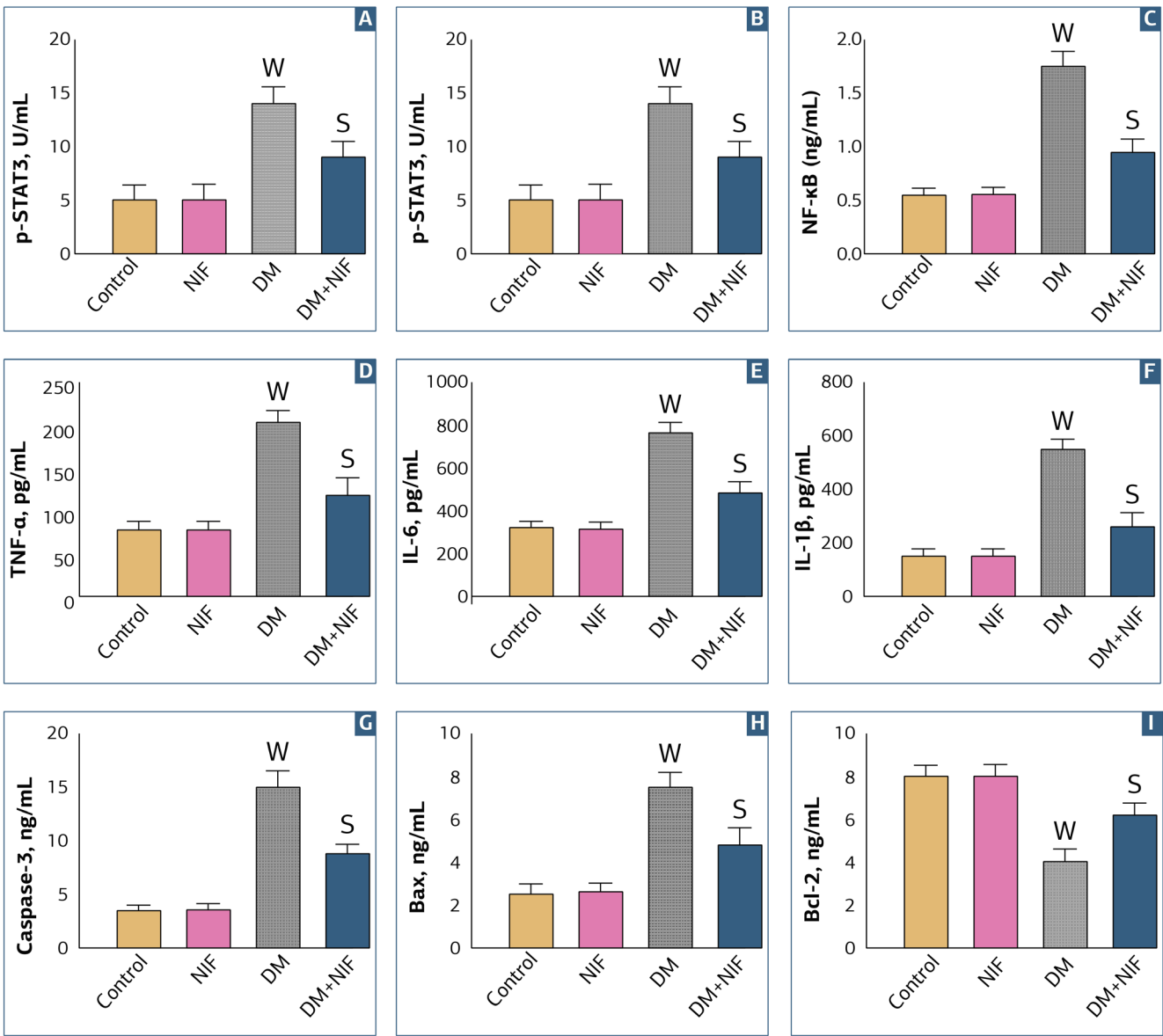


Figure 2. (A, B) Cross Sections of H&E-Stained Sciatic Nerve from Control and NIF Groups Showing Epineurium, Blood Vessel, Thin Perineurium Surrounding the Closely Packed Nerve Fiber Fascicles that are Separated by a Small Endoneurial Area

Nerve fiber fascicles consist of myelinated nerve fibers with central axoplasm surrounded by a myelin sheath and well-packed with Schwann cells. (C) Sciatic nerve from the diabetic group showing loosely packed nerve fiber fascicles with increased endoneurium, separation of nerve fibers with a wide area on endoneurium (Star), swollen axoplasm with vacuolations, and demyelinated nerve fiber. (D) Sciatic nerve from the Diabetic+NIF group showing normal nerve fascicle arrangement with slightly increased endoneurium. **Magnifications:** X: 100 bar 100 and X: 400 bar 50. Epineurium (Ep), blood vessel (red arrow), perineurium (Pn), endoneurium (En), axoplasm (yellow arrow), myelin sheath (arrowhead), Schwann cells (blue arrow), demyelinated nerve fiber (curved arrows), vacuolations (thick arrow)

against methotrexate-induced enteropathy through upregulation of Nrf2 and reduced glutathione, along with inhibition of MDA formation in intestinal homogenates.¹⁵

The JAK2/STAT3 signaling pathway is a fundamental and highly conserved intracellular cascade that regulates genes involved in cell survival, proliferation, differentiation, the cell cycle, angiogenesis, and inflammation.¹⁶ Increasing evidence highlights its critical role in the nervous system, particularly in neural cell development, differentiation, and responses to neuronal injury.¹⁷ Notably, activation of STAT3 by high glucose has been identified as a key contributor to the progression of diabetic neuropathy (DN).¹⁸ Consequently, the STAT3 signaling pathway represents a promising therapeutic target for the management of DN.

In line with this, our study demonstrated a significant elevation in JAK2/STAT3 protein levels in diabetic rats compared with the control group. Conversely, diabetic rats treated with NIF exhibited a marked reduction in pathway activation in sciatic nerve

supernatants relative to untreated diabetic rats. This protective effect is consistent with the findings of Said et al., who reported that NIF mitigates diabetic nephropathy through inhibition of STAT3 signaling.¹⁹

Phosphorylated STAT3, activated by JAK2, translocates to the nucleus and interacts with NF-κB signaling pathways, leading to enhanced secretion of inflammatory cytokines.²⁰ Schwann cell injury is further aggravated by pro-inflammatory mediators such as TNF-α and IL-1β, which promote inflammation and oxidative stress.²¹ Supporting previous data, our results showed a marked elevation in NF-κB, TNF-α, IL-6, and IL-1β protein levels in the sciatic nerves of diabetic rats compared with controls. In contrast, NIF coadministration significantly reduced these inflammatory cytokines, paralleling the findings of Hassan et al., who documented the protective effect of NIF against ureteral obstruction-induced renal fibrosis through suppression of p-STAT3 and NF-κB protein levels, accompanied by decreased TNF-α and IL-1β expression.²²

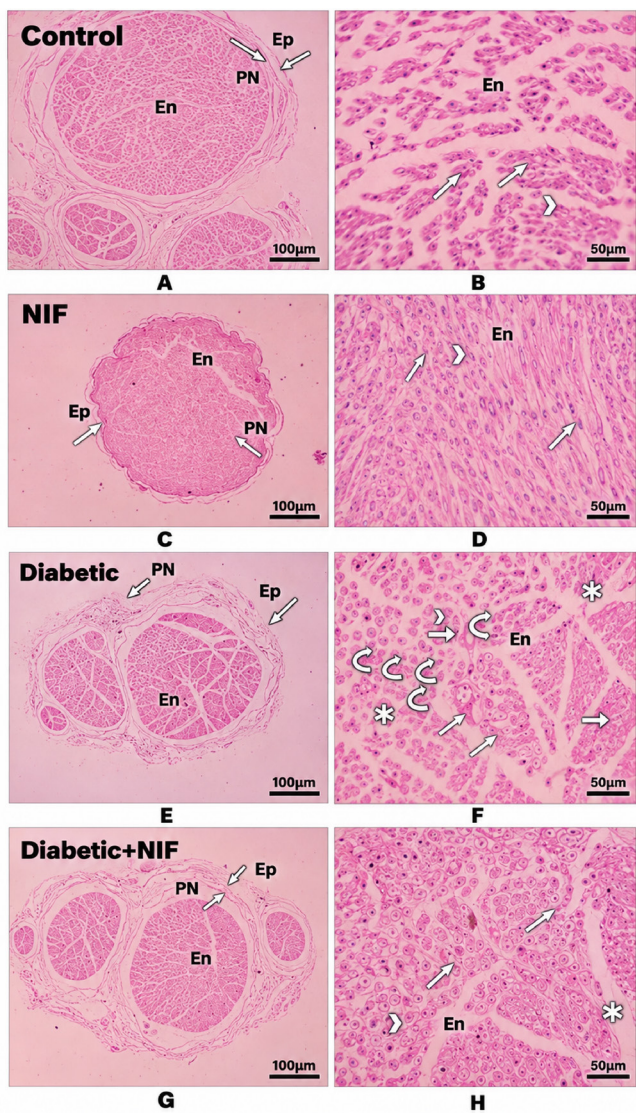


Figure 3. ELISA Measurements of Key Signaling, Inflammatory, and Apoptotic Proteins In Sciatic Nerve Supernatant: (A–B) JAK/STAT Pathway Proteins (p-JAK, p-STAT3); (C–F) Inflammatory Mediators (NF- κ B, TNF- α , IL-6, IL-1 β); (G–I) Apoptosis-Related Markers (caspase-3, Bax, Bcl-2)

Data are mean $\pm$ SD. Wp < 0.05 compared to the control; Sp < 0.05 compared to the diabetic group

The inhibitory effect of NIF on STAT3/NF- κ B signaling can be explained by its ability to directly block JAK2-mediated phosphorylation, thereby preventing STAT3 activation and nuclear translocation. In addition, NIF suppresses NF- κ B indirectly by reducing upstream inflammatory signals—including ROS, cytokines, and NADPH oxidase activity—thus stabilizing I κ B and preventing NF- κ B nuclear translocation, ultimately attenuating pro-inflammatory gene expression.

In diabetic neuropathy, elevated levels of inflammatory cytokines trigger neuronal apoptosis. This process is further intensified by oxidative stress, driven by excessive free radical production. The resulting neuronal damage disrupts communication with Schwann cells, thereby impairing their function.²³ Our findings are consistent with this mechanism, as diabetic rats exhibited increased expression of apoptotic markers such as caspase-3 and Bax in the sciatic nerve, accompanied by a reduction in anti-apoptotic markers. In contrast, coadministration of NIF with diabetic rats significantly attenuated sciatic nerve apoptosis through modulation of these markers. This observation concurs with the study by Salama and

Omar, who demonstrated the protective role of NIF against skin aging in a rat model by reducing caspase-3 immunoexpression and thereby limiting apoptosis.²⁴

Limitations

The present study has several limitations that should be acknowledged. First, the mechanistic scope was restricted to oxidative stress, inflammation, and apoptosis, while other relevant pathways, such as mitochondrial dysfunction, autophagy, and neurotrophic signaling, were not investigated. Second, the sciatic nerve was used as the sole model of peripheral neuropathy, without examination of other peripheral nerves or central nervous system structures, which may limit the generalizability of the findings. Third, the study relied primarily on biochemical and histological markers and did not include functional or behavioral assessments such as pain threshold, nerve conduction velocity, or behavioral performance, which are critical for correlating molecular changes with clinical outcomes. Finally, nifuroxazide was not compared against established therapeutic agents for diabetic neuropathy, including antioxidants, anti-inflammatory drugs, or neuroprotective compounds, thereby limiting conclusions regarding its relative efficacy.

Conclusion

In summary, nifuroxazide (NIF) demonstrated significant neuroprotective effects against streptozotocin-induced diabetic neuropathy in rats. Its therapeutic efficacy was mediated through attenuation of oxidative stress via Nrf2/HO-1 activation, suppression of JAK2/STAT3 and NF- κ B signaling, reduction of pro-inflammatory cytokines, and modulation of apoptotic markers. These combined actions preserved sciatic nerve morphology and function, highlighting NIF as a promising candidate for the management of diabetic neuropathy.

Declarations

Animal and Human Rights Statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments, or comparable ethical standards.

Informed Consent

Not applicable.

Data Availability

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflict of Interest

The authors declare no conflict of interest.

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None.

Author Contributions (CRediT Taxonomy)

Conceptualization: O.B.
Methodology: O.B.
Software: O.B.
Validation: O.B.
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Resources: O.B.
Data curation: O.B.
Writing – original draft: O.B.
Writing – review & editing: O.B.
Visualization: O.B.

Supervision: O.B.

Project administration: O.B.

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AI Usage Disclosure

The authors declare that no AI-assisted technologies were used.

Abbreviations

ANOVA: Analysis of variance

Bax: Bcl-2-associated x protein

Bcl-2: B-cell lymphoma 2

CAT: Catalase

DM: Diabetes mellitus

DN: Diabetic neuropathy

DPN: Diabetic peripheral neuropathy

ELISA: Enzyme-linked immunosorbent assay

H&E: Hematoxylin and eosin

HO-1: Heme oxygenase-1

IL-1β: Interleukin-1 beta

IL-6: Interleukin-6

JAK2: Janus kinase 2

MDA: Malondialdehyde

NF-κB: Nuclear factor kappa b

NIF: Nifuroxazide

Nrf2: Nuclear factor erythroid 2-related factor 2

ROS: Reactive oxygen species

SD: Standard deviation

SN: Sciatic nerve

SOD: Superoxide dismutase

STAT3: Signal transducer and activator of transcription 3

STZ: Streptozotocin

TNF-α: Tumor necrosis factor alpha

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