Official Journal of Erciyes University Faculty of Medicine

DOI: 10.14744/cpr.2024.11149
J Clin Pract Res 2024;46(6):584–592

Neuroprotective Effects of *Ficus carica* Seed Oil in Diabetic Neuropathy: A Preclinical Study in Wistar Rats

Serap Oktay,[1] Aysegul Turkkol,[1] Ozlem Bozkurt-Girit,[1,2] Mehmet D. Bilgin,[1,2] Mehmet Bilgen[1,2]

[1]Department of Biophysics, Aydın Adnan Menderes University, Institute of Health Sciences, Aydın, Türkiye
[2]Department of Biophysics, Aydın Adnan Menderes University, Faculty of Medicine, Aydın, Türkiye

ABSTRACT

Objective: Exploring novel therapeutic approaches for diabetic neuropathy (DN) is crucial, and *Ficus carica* seed oil (FCSO) emerges as a promising candidate due to its rich composition of fatty acids, phenolics, antioxidants, and anti-inflammatory compounds. This study aimed to investigate the effects of FCSO treatment on the progression of DN.

Materials and Methods: Adult male Wistar rats were randomly assigned to control, untreated diabetic, and FCSO-treated diabetic groups. Diabetes was induced by a single intraperitoneal injection of streptozotocin (STZ) at a dose of 50 mg/kg, confirmed by hyperglycemia (>250 mg/dL). The treatment group received FCSO orally at a dose of 4 mL/kg/day for 5 weeks. Blood glucose was monitored at the initiation and conclusion of the treatment, while insulin and glycated hemoglobin (HbA1c) were assessed at the study's endpoint. The hot plate test was conducted at the 3rd and 5th weeks of treatment. Sciatic nerve electrophysiology was performed, followed by biochemical analyses for markers of inflammation and oxidative stress.

Results: Diabetes resulted in elevated blood glucose and HbA1c levels, along with decreased insulin levels, indicative of diabetic conditions. Increased oxidative stress and inflammation were observed, alongside reductions in nociceptive response and nerve conduction velocity, indicating DN progression. However, FCSO treatment mitigated these effects, restoring markers to levels comparable to those of normal controls.

Conclusion: Early intervention with FCSO appears to counteract the mechanisms leading to DN, exerting neuroprotective and preventive effects. These findings underscore the therapeutic potential of FCSO and highlights its role as a promising treatment against DN.

Keywords: Diabetic neuropathy, *Ficus carica* seed oil, nerve conduction, neuroinflammation nociception, oxidative stress.

Cite this article as:
Oktay S, Turkkol A, Bozkurt-Girit O, Bilgin MD, Bilgen M. Neuroprotective Effects of *Ficus carica* Seed Oil in Diabetic Neuropathy: A Preclinical Study in Wistar Rats. JClinPractRes2024;46(6):584–592.

Address for correspondence:
Mehmet Bilgen.
Department of Biophysics, Aydın Adnan Menderes University, Faculty of Medicine, Aydın, Türkiye
Phone: +90 537 284 01 49
E-mail:
mehmet.bilgen@yahoo.com

Submitted: 08.05.2024
Revised: 29.08.2024
Accepted: 05.11.2024
Available Online: 21.11.2024

Erciyes University Faculty of Medicine Publications - Available online at www.jcpres.com

INTRODUCTION

Diabetic neuropathy (DN) is a common complication of diabetes mellitus, characterized by long-term nerve damage and deterioration of nerve functions.[1] Mechanisms of inflammation in the etiology of DN are actively studied experimentally.[2,3] Hyperglycemia, dyslipidemia, and

insulin resistance trigger oxidative stress and inflammatory responses, leading to pathological changes such as DNA damage, endoplasmic reticulum stress, and mitochondrial dysfunction, ultimately causing DN.

There is no effective remedy for completely reversing the pathogenetic mechanisms responsible. However, good control of blood sugar is currently the only approved way to reduce the risk. Despite a better understanding of the disease, current research also focuses on developing new interventions with preventive or protective potential. Potential treatments are expected to alter the natural course of the disease by slowing its progression; controlling pain; providing rapid and adequate management of complications; and/or preserving function.[4,5] For this purpose, plant extracts or pharmaceutical agents are extensively investigated in experimental studies.[6]

In this context, our attention was directed to *Ficus* plant varieties, based on previous research exploring their traditional uses, photochemistry, and pharmacological activities.[7] Reports indicate that the leaves, fruits, bud extracts, and other parts of *Ficus carica* (a tree native to Southwest Asia and the eastern Mediterranean) possess antioxidant, antimicrobial, anticonvulsant, anti-inflammatory, analgesic, hepatoprotective, dermoprotective, and nephroprotective properties.[8] Additionally, *Ficus carica* inherently exhibits antidiabetic activity.[7,9] During a preliminary review, we observed that oil extracted from the seeds of *Ficus carica* by cold pressing or other methods was the least studied component in the literature for its potential in disease treatment.[10,11] Besides various nutrients and bioactive compounds, *Ficus carica* seed oil (FCSO) contains significant amounts of fatty acids, phenolics, antioxidants, and anti-inflammatory compounds.[12] These ingredients are considered effective against diabetes; however, no study has yet tested the impact of FCSO treatment on DN.[13,14] Therefore, such an investigation is essential and would be novel, providing important insights for future clinical applications and implications.

This study addresses this need by experimentally examining the progression of DN, specifically the peripheral form, when treated with FCSO. We used a chemically induced diabetic rat model and documented the pathobiological changes observed during the disease course in control, FCSO-treated, and untreated groups. The degree of peripheral DN was characterized by in vivo nociceptive and electrophysiological tests from the sciatic nerve, with additional blood-based biochemical analyses conducted.

KEY MESSAGES

- *Ficus carica* seed oil (FCSO) reduces the detrimental effects of diabetes-related neuropathy by:
- Regulating blood glucose and inflammation,
- Preserving nerve conduction and nociceptive pain perception,
- Managing oxidative stress.

Table 1. Laboratory analysis of *Ficus carica* seed oil (FCSO)

Analysis	Result
Alpha Tocopherol	55.50±9.99 mg/kg
Delta tocopherol	87.20±7.85 mg/kg
Gamma tocopherol	3515.60±351.56 mg/kg
Myristic acid (C 14:0)	0.02%
Pentadecanoic acid (C 15:0)	0.02%
Palmitic acid (C 16:0)	7.24%
Palmitoleic acid (C 16:1)	0.07%
Heptadecanoic acid (17:0)	0.06%
cis-10-Heptadecanoic acid (17:1)	0.03%
Stearic acid (C 18:0)	2.93%
Oleic acid (C 18:1)	17.42%
Linoleic acid (C 18:2)	28.81%
Gondoic acid (C 20:1)	0.25%
Linolenic acid (C 18:3)	43.00%
cis-11,14-Eicosadienoic acid (C 20:2)	0.03%
Behenic acid (C 22:0)	0.07%
cis-11,14-17- Eicosatrienoic acid (C 20:3n3)	0.01%
Tricosanoic acid (C 23:0)	0.01%
Lignoceric acid (C 24:0)	0.03%
Iron	2.249±0.593 mg/kg
Calcium	94.580±36.413 mg/kg
Magnesium	9.178±2.241 mg/kg
Potassium	1.170±0.395 mg/kg
Zinc	0.302±0.066 mg/kg

MATERIALS AND METHODS

Ficus Carica Seed Oil

Ficus Carica seed oil was purchased from a local company (Egesia, Nazilli, Aydın, Türkiye info@egesia.com.tr). The oil was extracted from the seeds of figs grown regionally in Aydın province. The laboratory analysis shown in Table 1 presents the chemical composition of the oil used in this study.

Animals

The study was performed with 27 adult male Wistar-albino rats, following approval from Aydın Adnan Menderes University (approval date: 26. 08. 2021, approval number: 2021/64583101-116). Rats were bred and housed in a local facility according to standard procedures.

Diabetes Model

Our laboratory used a diabetic rat model induced chemically by streptozotocin (STZ).[15] Briefly, in this model, diabetes was induced in rats by a single intraperitoneal (i.p.) administration of STZ at a dose of 50 mg/kg (Cayman, Michigan, USA), dissolved in 0.05 M citrate buffer (pH 4.5). To prevent hypoglycemic shock, a 5% dextrose solution was provided in water bottles for the first 6 hours. Two days after STZ administration, blood glucose levels were measured with a glucometer (IME-DC Glucometer, Santek, Germany) using blood from the rat's tail vein. Rats with blood glucose levels greater than 250 mg/dL were considered diabetic.

Experimental Groups

In this randomized controlled experimental study, rats were randomly divided into three groups and followed for 5 weeks.

Group 1: Sham group (non-diabetic, NC): Rats were not subjected to any treatment but received a daily administration of physiological saline phosphate buffer (pH 7.4, 4 mL/kg/day) via oral gavage (n=7).

Group 2: Diabetic control group (DC): After being confirmed diabetic (blood glucose level ≥250 mg/dL at 48 hours post-STZ administration), rats received saline phosphate buffer (pH 7.4, 4 mL/kg/day) by oral gavage (n=10).

Group 3: Diabetes + *Ficus carica* seed oil (FCSO) group (D+FCSO): Following diabetes confirmation, rats received 4 mL/kg/day of FCSO daily by oral gavage for 5 weeks (n=10).

The FCSO dose of 4 mL/kg/day was selected based on previous studies.[11,16] Groups 2 and 3 initially included more rats to account for potential losses due to complications of diabetes.

Measurements

Before and after inducing diabetes, rat weights were recorded weekly, and blood glucose levels were measured from the tail vein using a test strip. Additionally, nociceptive pain responses of the rats were assessed at the 3rd and 5th weeks of treatment. At the end of the experiment (5 weeks), before the rats were sacrificed, electrophysiological measurements were recorded, and 3 mL of blood was collected from the heart for analysis. Blood samples were analyzed to determine levels of proinflammatory cytokines, including IL-1β (interleukin-1 beta), IL-6 (interleukin-6), and TNF-α (tumor necrosis factor alpha), as well as oxidative stress parameters, including superoxide dismutase-1 (SOD1), malondialdehyde (MDA), and catalase (CAT), alongside insulin and glycated hemoglobin (HbA1c) levels.

Nociceptive Test

The hot plate (HP) test was performed to assess sensory nerve function and observe changes in nociceptive pain perception at the third week following the onset of diabetes and at the end of 5 weeks. A hot-plate device (May AHP0603 Analgesic Hot Plate, Commat Ltd., Ankara, Türkiye) with a circular metal surface preheated to 55±0.3°C was used. After the rats were placed on the device, reaction times, such as licking their hind legs, jumping, and urinating, were evaluated as responses to thermal stimulation in the experiment. To prevent potential harm from heat, 15 seconds was set as the cut-off time, based on literature.[15] Latency values were recorded for all experimental groups.

Electrophysiological Measurements

Diabetic neuropathy is a condition that develops due to nerve damage in diabetic patients. During diagnosis, electromyography (EMG) is commonly used to evaluate the severity of nerve damage and detect DN. Nerve conduction velocity (NCV) measures how quickly nerves communicate. At the end of the fifth week, electrophysiological measurements were performed on the left sciatic nerve just before the rats were sacrificed under intraperitoneal anesthesia with a combination of ketamine (50 mg/kg) (Alfamine 10%, Alfasan, Netherlands) and xylazine (10 mg/kg) (Alfazyne 2%, Alfasan, Netherlands). Stimulation and nerve conduction measurements were conducted with the 2-channel Nicolet Viking Quest® (VIASYS, Natus Medical Inc., USA) EMG system. The areas where electrodes were placed were shaved, and the skin was cleaned with 10% alcohol to ensure proper electrode-skin contact. The animal was placed on a thermal pad (thermophore) to maintain body temperature and to prevent any ambient temperature effects on nerve conduction. Stimulation was applied to the sciatic nerve from the skin surface, targeting the dorsolateral region of the hind limb at the level of the trochanter major for proximal stimulation and the backside of the knee for distal stimulation. Compound muscle action potentials (CMAPs) were recorded from the plantar muscles of the hind paw. Bipolar surface electrodes were used for stimulation, and disc electrodes were used to record CMAPs. The ground electrode was placed on the tail. The EMG device frequency range was set to 10Hz–10kHz, with a stimulation duration of 0.5/1 ms, sweep speed of 1 ms, gain of 10 mV, and supramaximal stimulation intensity. To ensure repeatability, five stimulations were given, producing and recording five muscle action potentials. The system's software was used to analyze and evaluate the recorded CMAPs, determining distal and proximal latencies.[17] Motor nerve conduction velocity was calculated using the distal and proximal latencies with the following formula:

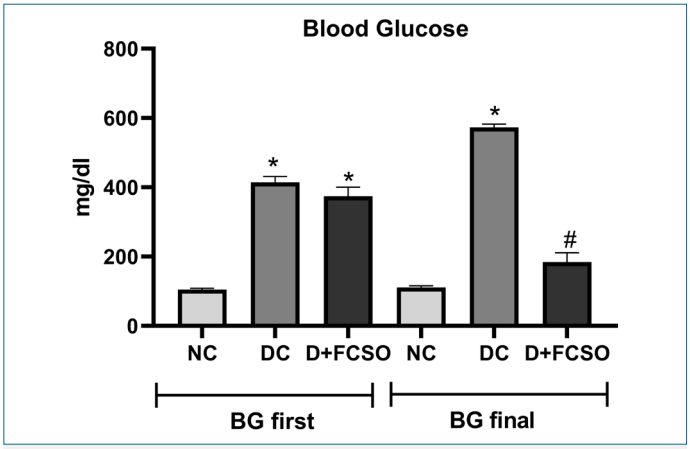

Figure 1. Blood glucose (BG) levels measured 2 days after streptozotocin (STZ) administration (BG first) and at the end of the experiment (BG final) in the experimental groups.

NC: Healthy control; DC: Diabetic control; D+FCSO: Diabetes+*Ficus carica* seed oil administered. Statistical significance compared to the NC group is indicated with *, and statistical significance compared to the DC group is indicated with # ($p<0.05$). Data are presented as the mean±standard error of the mean.

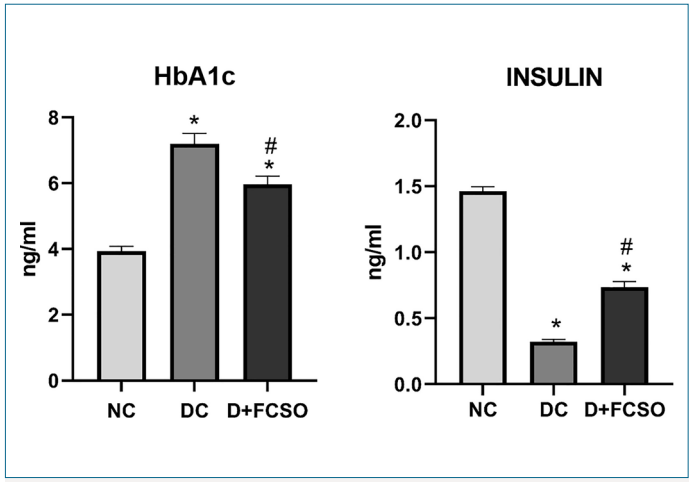

Figure 2. Variations in serum levels of insulin and glycated hemoglobin (HbA1C) in the experimental groups.

NC: Healthy control; DC: Diabetic control; D+FCSO: Diabetes+*Ficus carica* seed oil administered. Statistical significance compared to the NC group is indicated with *, and statistical significance compared to the DC group is indicated with # ($p<0.05$). Data are presented as the mean±standard error of the mean.

$$NCV = \frac{Distance\ between\ proximal\ and\ distal\ stimulations\ (mm)}{Proximal\ latency\ (ms) - Distal\ latency\ (ms)}.$$

Biochemical Analysis

Inflammation is a defense mechanism that the body responds to and initiates to heal damaged tissue. Diabetes triggers inflammation as caused by high blood glucose levels and increased oxidative stress. When the oxidative balance in cells is disrupted, cells are exposed to free radicals, and the inflammatory process damages nerve tissues, leading to nerve fiber degeneration.[16,18–21] Blood drawn at the fifth week was analyzed for levels of proinflammatory cytokines and oxidative stress parameters. The serum levels of IL-1β (Catalog No: ER1094), IL-6 (Catalog No: ER0042), TNF-α (Catalog No: ER1393), SOD1 (Catalog No: ER0332), MDA (Catalog No: ER1878), and CAT (Catalog No: ER0264) activity were examined using Fine Test ELISA (Enzyme-Linked Immunosorbent Assay) kits (Wuhan Fine Biotech Co., Wuhan, China) in accordance with the prescribed protocol. In addition, serum levels of insulin (Catalog No: ER1113) and HbA1c (Catalog No: ER1030) were also determined using test kits from the same source.

Statistical Analysis

The collected data included body weights, blood glucose levels, latency values from nociceptive tests, motor nerve conduction velocity values from electrophysiological tests, proinflammatory cytokines (IL-1β, IL-6, and TNF-α), oxidative stress parameters (MDA, SOD, CAT), as well as serum levels of insulin and HbA1c from all rats in the healthy control, diabetic control, and diabetic plus FCSO-treated groups. The measurements were organized in columns corresponding to each group. Statistical analysis was conducted using GraphPad Prism 9 (GraphPad Software, Boston, USA). The statistical normality of data within each group was assessed using the Kolmogorov-Smirnov test. Values with a normal distribution were analyzed using One-Way Analysis of Variance (ANOVA) with Tukey's test as a post-hoc test, while data with non-normal distribution were analyzed using the Kruskal-Wallis test. A p value of less than 0.05 was considered statistically significant. Significance levels were indicated with an asterisk (*) when comparing the control group with the diabetic and treatment groups, and with a pound sign (#) when comparing the diabetic group with the treatment group.

RESULTS

The experimental procedures were successfully completed without any loss over the 5-week period. The administration of STZ induced diabetes in groups 2 and 3, as evidenced by a significant increase in blood glucose levels compared to group 1 at the beginning (Fig. 1). By the end of the study, blood glucose levels remained elevated in diabetic rats, though they were comparatively lower in those administered FCSO, approaching the levels of the control group. Similarly, measurements of serum insulin and blood plasma HbA1c at 5 weeks revealed consistent trends (Fig. 2). The findings suggested that FCSO may influence the regulation of glucose and energy mechanisms in diabetes.

Table 2. Weekly changes in body weights (g) in experimental groups

Time (week)	NC (n=7)	DC (n=10)	D+FCSO (n=10)	p
1	261.04±26.10[a]	258.31±21.63[a]	249.84±17.24[a]	0.498
2	283.65±27.41[b]	231.60±27.62[c]	246.81±17.54[ac]	<0.001
3	303.88±28.11[c]	220.11±22.97[b]	258.06±24.07[a]	<0.001
4	318.57±28.31[d]	210.17±17.64[e]	273.70±30.82[b]	<0.001
5	331.41±25.47[e]	200.77±12.94[d]	293.67±37.61[c]	<0.001
p	<0.001	<0.001	<0.001	

Time Effect: p<0.001; Group Effect: p<0.001; Group x Time Interaction Effect: p<0.001. NC: Healthy control; DC: Diabetic control; D+FCSO: Diabetes+*Ficus carica* seed oil administered. Data are represented as arithmetic mean±standard deviation. Similar letters within the same rows and columns indicate statistical similarity, while different letters indicate statistical differences.

Table 3. Intergroup comparison of nerve conduction velocities (NCV) from electromyography (EMG) measurements

	NC (n=7)	DC (n=10)	D+FCSO (n=10)	p
NCV (m/s)	68.00 (67.30–68.10)[a]	34.70 (33.30–35.90)[b]	53.50 (50.00–54.30)[c]	<0.001

NC: Healthy control; DC: Diabetic control; D+FCSO: Diabetes+*Ficus carica* seed oil administered. Data are represented as median and interpercentile ranges. Similar letters in the same row indicate statistical similarity, while different letters indicate statistical differences.

Over the 5-week period, control rats exhibited weight gain, while diabetic rats experienced steady weight loss, as shown in Table 2. In contrast, rats administered FCSO showed weight gain, although not as much as those in the control group. These results indicated that FCSO may prevent weight loss in diabetes.

Diabetes led to delayed neuronal responses to thermal stimuli, as demonstrated in Figure 3. Significant increases in latency periods were observed in diabetic rats following heat exposure, likely due to DN affecting sensory neurons. FCSO treatment significantly shortened the response time and enhanced nociceptive pain perception, providing evidence of its potential to prevent and protect against sensory neuron damage.

Compound muscle action potential measurements recorded at the end of the 5-week period revealed a significant slowing of NCV in the sciatic nerves of diabetic rats. However, these effects were effectively reversed by FCSO administration (Table 3). This reflected the level of neuronal damage caused by DN and highlighted the potential of FCSO to preserve motor function in neuropathy.

Diabetes triggered inflammation, as evidenced by significant increases in proinflammatory cytokine levels in diabetic rats (IL-1β, IL-6, and TNF-α), as shown in Figure 4. However, these levels were close to those of healthy rats in the group administered FCSO, indicating that FCSO supplementation effectively controlled inflammation. Consistent with these findings, results regarding oxidative stress, presented in Figure 5, showed significant deviations in the levels of MDA and SOD, as well as CAT activity in diabetes. However, FCSO administration maintained these parameters close to those of the control group, suggesting an effective suppression of oxidative stress.

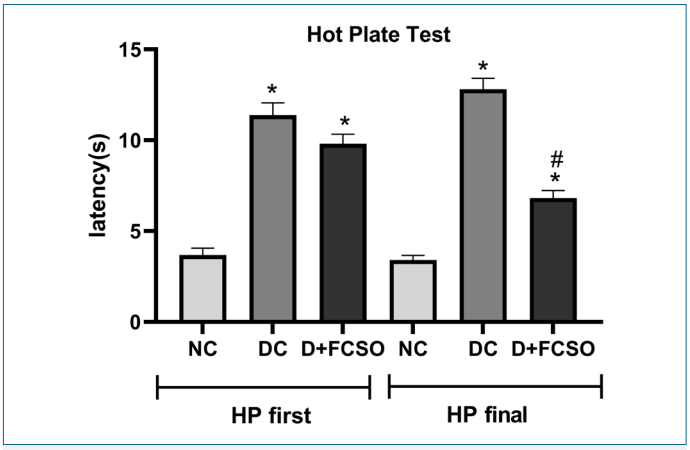

Figure 3. Comparative measurement of hot plate latency (s) at the 3rd week (hot plate, HP first) and the 5th week (HP final) in the experimental groups.

NC: Healthy control; DC: Diabetic control; D+FCSO: Diabetes+*Ficus carica* seed oil administered. Statistical significance compared to the NC group is indicated with *, and statistical significance compared to the DC group is indicated with # (p<0.05). First and final measurements have been compared within their respective NC and DC values. Data are presented as the mean ± standard error of the mean.

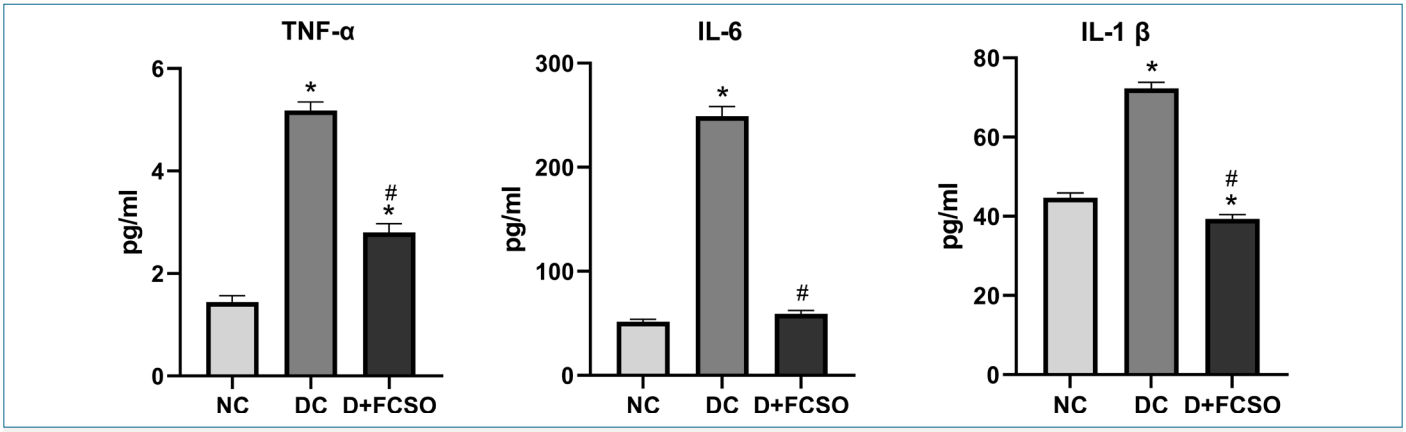

Figure 4. Changes in inflammatory cytokines: tumor necrosis factor-alpha (TNF-α, pg/mL), IL-6 (pg/mL) and interleukin-1 beta (IL-1β, pg/mL).

NC: Healthy control; DC: Diabetic control; D+FCSO: Diabetes+*Ficus carica* seed oil administered. Statistical significance compared to the NC group is indicated with *, and statistical significance compared to the DC group is indicated with # ($p<0.05$). Data are presented as the mean±standard error of the mean.

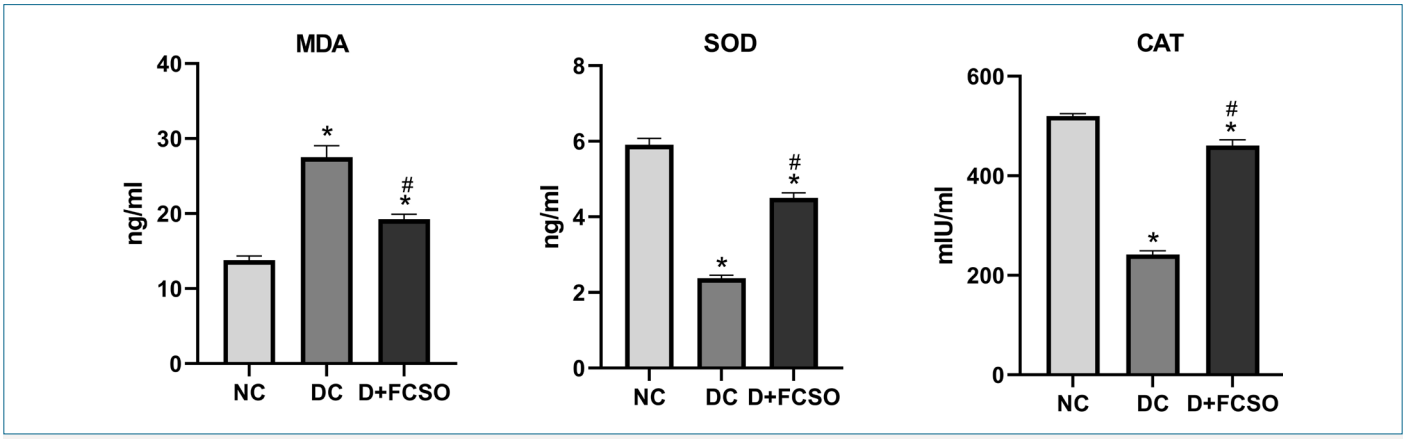

Figure 5. Changes in oxidative stress parameters: levels of malondialdehyde (MDA, ng/mL), superoxide dismutase (SOD, ng/mL), and catalase (CAT) activity (mIU/mL).

NC: Healthy control; DC: Diabetic control; D+FCSO: Diabetes+*Ficus carica* seed oil administered. Statistical significance compared to the NC group is marked with *, and statistical significance compared to the DC group is indicated with # ($p<0.05$). Data are presented as the mean ± standard error of the mean.

DISCUSSION

Our data, gathered through electrophysiological, nociceptive, and biochemical examinations, demonstrated that the progression of peripheral DN in diabetes induced by STZ in rats can be mitigated by oral FCSO administration when applied at the onset of the disease at an appropriate dose and timing. FCSO treatment decreased blood glucose and HbA1c levels, which were elevated with diabetes, increased insulin levels and improved nociceptive pain perception and sciatic nerve conduction, which were impaired by diabetes. FCSO administration in diabetic rats also maintained oxidative stress parameters and inflammation biomarkers closer to those of healthy controls. Based on these findings, FCSO administration appears to exert both neuroprotective and preventive effects against DN by slowing disease progression and alleviating damage to the nervous system, thus potentially reducing associated complications. In a limited number of studies on other disease conditions, such as experimental ischemia-reperfusion and acute kidney injuries, FCSO was also reported to improve serum parameters and reduce functional and morphological tissue damage. These effects were attributed to the enhanced antioxidant and anti-inflammatory capacities of FCSO.[1,11,22–24]

The FCSO used in this study naturally contained physiochemical compounds and minerals listed in Table 1. The main ingredients were tocopherols (vitamin E group: alpha, delta, gamma) and fatty acids (linolenic acid as omega-3, linoleic acid as omega-6, and oleic acid as omega-9). This composition was also confirmed by other studies.[13,14] Research has shown that oils with similar contents to FCSO (omega-3 fatty acids, linoleic acid, oleic acid, etc.) can reduce HbA1c and blood glucose levels in diabetic models, thereby reducing diabetes-associated complications, demonstrating neuroprotective effects, and enhancing antioxidant enzyme activity. In previous experimental studies, these compounds were extracted from medicinal plants and tested separately and individually. As discussed below, treatment responses of each isolated form have been evaluated, and their potential benefits in diabetes-related complications have been characterized. Our data suggest that the components in FCSO, especially those present in large amounts, likely contributed to the favorable outcomes observed against DN.

Early research demonstrated that vitamin E plays a central role in extracellular free radical defense and in preventing the development of vascular complications in diabetes.[25] Vitamin E supplementation has been shown to mitigate hyper-inflammatory responses in diabetic animals.[26,27] Its antioxidant properties, combined with anti-inflammatory actions, counteracted nerve damage by protecting against lipid peroxidation and reducing HbA1c levels, thereby exerting a positive effect on the prevention and progression of neurodegenerative diseases, including DN.[28,29]

More recently, clinical research has provided additional support: a phase II double-bind, randomized controlled clinical trial showed that vitamin E supplementation improved nerve conduction velocity in diabetic patients.[30] In another clinical study, the intake of vitamin E, omega-3, and omega-6 was found to improve glycemia, HbA1c, and insulin resistance, resulting in lower fasting blood glucose levels in patients.[31] A close correlation is well-known between the severity, degree, and duration of hyperglycemia and the development of DN.[32,33] Our data in Figure 1 and Figure 2 align with these reports, suggesting that vitamin E present in FCSO may have contributed to effective short-term glycemic control in diabetic rats.

Monosaturated and polyunsaturated fatty acids were also abundant in our FCSO extract. Experimental studies have indicated these fatty acids as promising pharmacological therapeutic agents due to their effects in central and peripheral neurotrauma models.[34–36] Polyunsaturated lipids are implicated in all stages of neurogenesis, including neuronal growth, differentiation, maturation, and neurite outgrowth.[37,38] Their administration has been shown to accelerate nerve regeneration, inhibit neuropathic pain, improve sensory-motor function, and reduce neuroinflammation. A ketogenic diet, which is high in fat and low in carbohydrates, was reported to prevent neuropathy and inhibit neuroinflammation in rats.[39] The mechanism of action associated with fatty acid administration in nerve damage and neurodegenerative diseases has been reported to involve the modulation of peroxisome proliferator-activated nuclear receptors (PPARs). Specifically, PPAR-α was reported to decrease neuroinflammation and oxidative stress, thereby supporting neurotransmission processes,[40] while PPAR-γ signaling was found to be upregulated by a ketogenic diet, alleviating the severity of neuropathic nociception.[39] Consequently, reducing or controlling inflammation offers a potential strategy for preventing the progression of DN or alleviating its symptoms. Our data presented in Figure 5 and Table 3 align with these reports, as fatty acids in FCSO likely contributed to the neuroprotective and preventive effects observed in diabetic rats.

The data presented collectively indicate that the mechanisms by which FCSO potentially influences the course of DN are related to oxidative stress and inflammatory responses. Although we minimized factors that could have influenced the outcomes, our study had limitations. First, it consisted of preliminary experiments conducted with a limited number of subjects and was restricted to a duration of only five weeks. We used a fixed dose of FCSO based on previous studies investigating different pathological conditions. However, this dose was consistent with the biochemical composition of FCSO shown in Table 1, where each isolated component has been used individually as a supplement in clinical alternative medicine. How varying doses might affect the course of neuropathy needs further exploration. Future investigations should also be planned and conducted at molecular and histological levels.

CONCLUSION

The findings of this study highlight the remarkable potential of FCSO as a therapeutic intervention for DN. By effectively mitigating the harmful effects of diabetes on nerve function and inflammation, FCSO demonstrates its ability to address key mechanisms underlying the progression of DN. This emphasizes the importance of exploring natural compounds like FCSO for their neuroprotective and preventive properties in managing or slowing diabetic complications. Further research into the specific mechanisms of action and clinical efficacy of FCSO holds promise for developing novel therapeutic strategies to combat DN during the post-induction period corresponding to the chronic phase of diabetes, ultimately improving the quality of life for individuals living with diabetes. Additionally, investigating the long-term effects of FCSO treatment or evaluating its efficacy in different models of DN or diabetes-induced damage in other tissues or organs could prove valuable.

Ethics Committee Approval: The Aydın Adnan Menderes University Animal Experiments Ethics Committee granted approval for this study (date: 26.08.2021, number: 64583101/2021/116).

Author Contributions: Concept – SO, MDB, MB; Design – SO, MDB, MB; Supervision – MDB, MB; Resource – MDB, MB; Materials – SO, MDB; Data Collection and/or Processing – SO, AT, OBG, MB; Analysis and/or Interpretation – SO, AT, OBG, MDB, MB; Literature Search – SO, MDB, MB; Writing – SO, MB; Critical Reviews – OBG, MDB, MB.

Conflict of Interest: The authors have no conflict of interest to declare.

Use of AI for Writing Assistance: Not declared.

Financial Disclosure: The research was supported by Aydın Adnan Menderes University Scientific Research Projects Coordinatorship through the grant no TPF-21056.

Peer-review: Externally peer-reviewed.

REFERENCES

1. Ziegler D, Keller J, Maier C, Pannek J. Diabetic neuropathy. Experimental and Clinical Endocrinology & Diabetes 2023; 131(01/02): 72-83.
2. Zhu J, Hu Z, Luo Y, Liu Y, Luo W, Du X, et al. Diabetic peripheral neuropathy: pathogenetic mechanisms and treatment. Frontiers in Endocrinology 2024; 14: 1265372.
3. Yalçın MB, Bora ES, Çakır A, Akbulut S, Erbaş O. Autophagy and anti-inflammation ameliorate diabetic neuropathy with Rilmenidine. Acta Cirúrgica Brasileira 2023; 38: e387823.
4. Kobayashi M, Zochodne DW. Diabetic neuropathy and the sensory neuron: new aspects of pathogenesis and their treatment implications. Journal of diabetes investigation 2018; 9(6): 1239-54.
5. Baum P, Toyka KV, Blüher M, Kosacka J, Nowicki M. Inflammatory mechanisms in the pathophysiology of diabetic peripheral neuropathy (DN)-new aspects. International Journal of Molecular Sciences 2021; 22(19): 10835.
6. Pathak R, Sachan N, Chandra P. Mechanistic approach towards diabetic neuropathy screening techniques and future challenges: A review. Biomedicine & Pharmacotherapy 2022; 150: 113025.
7. Shim KH, Sharma N, An SSA. Mechanistic insights into the neuroprotective potential of sacred ficus trees. Nutrients 2022; 14(22): 4731.
8. Mawa S, Husain K, Jantan I. Ficus carica L. (Moraceae): phytochemistry, traditional uses and biological activities. Evidence-Based Complementary and Alternative Medicine 2013; 2013.
9. El Ghouizi A, Ousaaid D, Laaroussi H, Bakour M, Aboulghazi A, Soutien RS, et al. Ficus Carica (Linn.) leaf and bud extracts and their combination attenuates type-1 diabetes and its complications via the inhibition of oxidative stress. Foods 2023; 12(4): 759.
10. Deepa P, Sowndhararajan K, Kim S, Park SJ. A role of Ficus species in the management of diabetes mellitus: A review. J Ethnopharmacology 2018; 215: 210-32.
11. Orak C, Şirinyıldız F, Yılmaz EG, Cesur G, Ek RO. Protective effects of Ficus carica seed oil on ischemia and reperfusion injury in a rat model of acute mesenteric ischemia. Turkish J Trauma & Emer Surgery 2021; 27(4): 402-9.
12. Rajendran EGMG. Fig (Ficus carica) Seed Oil. Fig (Ficus carica): Production, Processing, and Properties. Springer; 2023: pp. 357-68.
13. Güven N, Gökyer A, Koç A, Temiz NN, Selvi S, Koparal B, et al. Physiochemical composition of fig seed oil from Turkey. Journal of pharmacy and pharmacology 2019; 7: 541-5.
14. Baygeldi N, Küçükerdönmez Ö, Akder RN, Çağındı Ö. Medicinal and nutritional analysis of fig (Ficus carica) seed oil; a new gamma tocopherol and omega-3 source. Progress in Nutrition 2021; 23(2): 1-6.
15. Oktay S, Bilgen M, Girit ÖB, Bilgin MD. Neuroprotective potential of 20 (S)-Ginsenoside Rg3 against the progression of diabetic neuropathy: experiments on rat sciatic nerve. J Clin Prac and Res 2023; 45(5): 480-6.
16. Alharthy N, Bawazir A. Effects of the mixture dried figs (Ficus Carica) and olive oil on amnesia model of Alzheimer's induced by scopolamine in male albino rats. Pharmacophore 2019; 10(4): 62-71.
17. Ünsal C, Turan E, Dilek ÖG, Sabanci SS, Sarierler M. Evaluation of proximal and distal motor nerve conduction using the electrical root stimulation technique in the femoral and obturator nerves. Veterinary and Comparative Orthopaedics and Traumatology 2017; 30(02): 111-7.
18. Berraaouan A, Abderrahim Z, Hassane M, Abdelkhaleq L, Mohammed A, Mohamed B. Evaluation of protective effect of cactus pear seed oil (Opuntia ficus-indica L. MILL.) against alloxan-induced diabetes in mice. Asian Pacific J Tropical Med 2015; 8(7): 532-7.
19. Ojo OA, Okesola MA, Ekakitie LI, Ajiboye BO, Oyinloye BE, Agboinghale PE, et al. Gongronema latifolium Benth. leaf extract attenuates diabetes-induced neuropathy via inhibition of cognitive, oxidative stress and inflammatory response. J Scien Food and Agriculture 2020; 100(12): 4504-11.
20. Aslam F, Iqbal S, Nasir M, Anjum AA, Swan P, Sweazea K. Evaluation of white sesame seed oil on glucose control

and biomarkers of hepatic, cardiac, and renal functions in male Sprague-Dawley rats with chemically induced diabetes. J Med food 2017; 20(5): 448-57.

21. Yıldız BB, Sunay FB, Yılmaz HF, Girit ÖB. Low-intensity low-frequency pulsed ultrasound ameliorates sciatic nerve dysfunction in a rat model of cisplatin-induced peripheral neuropathy. Sci Rep 2022; 12(1): 8125.
22. Sandireddy R, Yerra VG, Areti A, Komirishetty P, Kumar A. Neuroinflammation and oxidative stress in diabetic neuropathy: futuristic strategies based on these targets. Int J Endocrinol 2014; 2014: 674987.
23. İşler D, Şirinyildiz F, Ek RO. Effect of Ficus carica (fig) seed oil administration on GSH levels, necrosis and cast formation in myoglobinuric acute kidney injury. Cukurova Med J 2022; 47(1): 152-60.
24. Pang L, Lian X, Liu H, Zhang Y, Li Q, Cai Y, et al. Understanding diabetic neuropathy: focus on oxidative stress. Oxidative Med and Cellular Longevity 2020; 2020: 1-13.
25. Rösen, Toeller. Vitamin E in diabetes: increased oxidative stress and its prevention as a strategy to prevent vascular complications? Int J Vitamin and Nutrition Res 1999; 69(3): 206-12.
26. Shin J, Yang SJ, Lim Y. Gamma-tocopherol supplementation ameliorated hyper-inflammatory response during the early cutaneous wound healing in alloxan-induced diabetic mice. Experimental Biology and Med 2017; 242(5): 505-15.
27. Lee H, Lim Y. Gamma-tocopherol ameliorates hyperglycemia-induced hepatic inflammation associated with NLRP3 inflammasome in alloxan-induced diabetic mice. Nutrition Res and Practice 2019; 13(5): 377-83.
28. Pazdro R, Burgess JR. The role of vitamin E and oxidative stress in diabetes complications. Mech Ageing Dev 2010; 131(4): 276-86.
29. Roldi LP, Pereira RV, Tronchini EA, Rizo GV, Scoaris CR, Zanoni JN, et al. Vitamin E (α-tocopherol) supplementation in diabetic rats: effects on the proximal colon. BMC Gastroenterol 2009; 9: 88.
30. Chuar PF, Ng YT, Phang SCW, Koay YY, Ho J-I, Ho LS, et al. Tocotrienol-Rich Vitamin E (Tocovid) improved nerve conduction velocity in Type 2 diabetes mellitus patients in a phase II double-blind, randomized controlled clinical trial. Nutrients 2021; 13(11): 3770.
31. Asbaghi O, Nazarian B, Yousefi M, Anjom-Shoae J, Rasekhi H, Sadeghi O. Effect of vitamin E intake on glycemic control and insulin resistance in diabetic patients: An updated systematic review and meta-analysis of randomized controlled trials. Nutrition J 2023; 22(1): 1-22.
32. Bondar A, Popa AR, Papanas N, Popoviciu M, Vesa CM, Sabau M, et al. Diabetic neuropathy: A narrative review of risk factors, classification, screening and current pathogenic treatment options. Experimental and Therapeutic Med 2021; 22(1): 1-9.
33 Shaidullina MR, Valeeva FV, Yakupov EZ. Risk factors for diabetic autonomic cardiovascular neuropathy in children and adolescents with type 1 diabetes mellitus. Diabetes mellitus 2013; 16(3): 84-9.
34. Galán-Arriero I, Serrano-Muñoz D, Gómez-Soriano J, Goicoechea C, Taylor J, Velasco A, et al. The role of Omega-3 and Omega-9 fatty acids for the treatment of neuropathic pain after neurotrauma. Biochimica et Biophysica Acta (BBA)-Biomembranes 2017; 1859(9): 1629-35.
35. Granado-Casas M, Mauricio D. Oleic acid in the diet and what it does: Implications for diabetes and its complications. Bioactive Food as Dietary Interventions for Diabetes. Elsevier; 2019: pp. 211-29.
36. de Oliveira MR, Nabavi SF, Nabavi SM, Jardim FR. Omega-3 polyunsaturated fatty acids and mitochondria, back to the future. Trends in Food Scie & Techn 2017; 67: 76-92.
37 Liu JW, Montero M, Bu L, De Leon M. Epidermal fatty acid-binding protein protects nerve growth factor-differentiated PC 12 cells from lipotoxic injury. J Neurochemistry 2015; 132(1): 85-98.
38. Falomir-Lockhart LJ, Cavazzutti GF, Giménez E, Toscani AM. Fatty acid signaling mechanisms in neural cells: fatty acid receptors. Frontiers in Cellular Neuroscience 2019; 13: 162.
39. Zhong S, Zhou Z, Lin X, Liu F, Liu C, Liu Z, et al. Ketogenic diet prevents paclitaxel-induced neuropathic nociception through activation of PPARγ signalling pathway and inhibition of neuroinflammation in rat dorsal root ganglion. European J Neuroscience 2021; 54(4): 5341-56.
40. Wójtowicz S, Strosznajder AK, Jeżyna M, Strosznajder JB. The novel role of PPAR alpha in the brain: promising target in therapy of Alzheimer's disease and other neurodegenerative disorders. Neurochemical Res 2020; 45: 972-88.