Journal of Basic Research in Medical Sciences

Journal HomePage : https://jbrms.medilam.ac.ir

Ilam University of Medical Sciences Publications

Impact of Folate Supplementation on Liver Oxidative Stress Indicators in Diabetic Rats Induced by Streptozotocin

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Article Info

Article type:

Original Article

Article History:

Received: May. 09, 2026
Revised: Jun. 16, 2026
Accepted: Jun. 23, 2026
Published Online: Sep. 19, 2026

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A B S T R A C T

Introduction: Diabetes can cause metabolic disorders and the liver is an organ at risk due to its crucial role in glucose and lipid metabolism. Oxidative stress and inflammation play key roles in the development of diabetic liver disease. Folate, an antioxidant water-soluble B-vitamin, might prove beneficial in the treatment of these conditions through decreasing oxidative stress and regulating the metabolism of homocysteine. The present study was designed to investigate the effect of folate supplementation on glucose metabolism, redox status and liver dysfunction in streptozotocin-induced diabetic rats.

Materials & Methods: Adult male Wistar rats (200 +/- 20 g) were randomly divided into three groups (n=6): control, STZ-induced diabetic and folate-treated diabetic. Diabetic status in the two diabetic groups was induced by a single intraperitoneal (i.p.) injection of streptozotocin (55 mg/kg). Folate (15 mg/kg, i.p.) was administered once daily for 4 weeks in the therapy group. At end of the study, fasting blood sugar (FBS), serum liver enzymes, hepatic MDA, SOD activity and TAC were determined. Data were analyzed by one-way ANOVA and Dunnett's post hoc test.

Results: Folate supplementation resulted in mild improvement in body weight, FBS, ALT and AST levels in diabetic rats. However, these changes were not significant when compared to untreated diabetic animals. There were no significant changes in the hepatic levels of MDA and TAC, and a mild non-significant increase in SOD activity after the administration of folate.

Conclusion: Folate exerted small, possibly beneficial effects on metabolic and hepatic oxidative stress in STZ-induced diabetic rats. The slight improvement in antioxidant status, although not statistically significant, suggests that folate may have protective effects in diabetic conditions. Its therapeutic efficacy may be enhanced when used as an adjunct to conventional antidiabetic treatments.

Keywords: Diabetes, Oxidative Stress, Liver Function, Folate, Malondialdehyde, Total Antioxidant Capacity, Streptozotocin

➢ **Cite this paper**

Mohammadi R, Vatannejad A, Kheirollahi A. Impact of Folate Supplementation on Liver Oxidative Stress Indicators in Diabetic Rats Induced by Streptozotocin. *J Bas Res Med Sci*. 2026; 13(4):49-57.

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Introduction

The liver is well placed to receive a steady supply of nutrient-rich blood from the portal vein and thus plays a central role in directing absorbed nutrients to the peripheral tissues. The liver is one of the few organs that can metabolize in two different ways. It can produce glucose (gluconeogenesis and glycogenolysis), and it can take up glucose and store it as glycogen. These interconnected metabolic pathways are tightly controlled by the availability of substrates, allosteric regulation by metabolic intermediates, and hormonal signals, particularly insulin, glucagon, and other counter-regulatory hormones (1). Diabetes mellitus is a chronic metabolic disease in which the regulation of blood glucose concentrations is defective, usually because of deficiencies in insulin secretion or action. The International Diabetes Federation (IDF) estimates that some 590 million adults, or 11.1% of all adults worldwide, had diabetes in 2025 (2). Diabetes complications continue to be among the leading causes of disease and death worldwide.

Indeed, oxidative stress and inflammation are considered the main mechanisms that contribute to the various complications of diabetes. Oxidative stress is, in its simplest terms, an imbalance between the production of reactive oxygen species (ROS) and the body's natural ability to defend against these harmful compounds. These damaging effects are based on several key mechanisms such as activation of NADPH oxidase, formation of Advanced Glycation End-products (AGEs), mitochondrial dysfunction, and chronic inflammation. To summarize, these processes are major contributors to the development of specific diabetic complications and hepatopathies, including non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) (3).

ROS directly interfere with the phosphorylation of insulin receptor substrate (IRS) proteins in diabetes. This disruption interferes with the critical PI3Kinase/Akt signaling pathway. Consequently, the liver cells' ability to efficiently uptake and utilize glucose is compromised, contributing to both the insulin resistance in the liver and the blood glucose regulation defects that define diabetes (4, 5). Oxidative stress can also induce endoplasmic reticulum (ER) stress, which subsequently activates specific kinases such as JNK and IKK-β. These kinases further inhibit the insulin signaling of the liver and aggravate the insulin resistance. Moreover, the persistent oxidative process reduces the activity of key endogenous antioxidant enzymes such as superoxide dismutase (SOD) and catalase (CAT) (4, 5). A significant consequence of this oxidative imbalance is lipid peroxidation, wherein polyunsaturated fatty acids in cell membranes are degraded by ROS. Ultimately, this results in impaired membrane integrity and disturbed cellular signaling, leading to programmed cell death of hepatocytes. Besides direct cellular damage, oxidative stress is also important in initiating chronic inflammation by increasing the release of pro-inflammatory cytokines like TNF-α, IL-6, and IL-1β. This sustained inflammatory response aggravates the diabetic liver complications to a great extent (4, 5).

Due to the strong implication of oxidative stress in the diabetic tissue injury, antioxidant-based interventions have been considered supportive therapies (6). Antioxidants may also be cytoprotective by limiting DNA damage and reducing apoptosis (7). Folate (vitamin B9) is a water-soluble antioxidant that operates within the glutathione peroxidase (GPx) pathway (8). Folate has several functions that are central to the reduction of oxidative stress, including the regulation of homocysteine metabolism and the support of endothelial cell function, which results in limiting lipid peroxidation and reducing ROS in biological environments (9, 10). Insufficient folate and excess homocysteine accumulation negatively affect cellular function and metabolism, including increased ROS production, increased risk of cardiovascular diseases, increased apoptosis,

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epigenetic changes, and dysregulation of gene expression (11, 12).

The effect of folate supplementation on oxidative stress in the liver in diabetic conditions is, however, poorly understood. The main objective of this study is to evaluate the effect of diabetes on oxidative stress in the liver of experimental rats. A secondary objective is to study the possible protective role of folate as an antioxidant against such diabetes-induced hepatic damage.

Materials and methods

Study Design

The present work was conducted as part of a broader experimental project using the same animal cohort (13), from which renal biochemical findings have been reported previously (14). This approach was used to reduce the number of animals required, in accordance with the 3Rs principle. The current study specifically investigates hepatic oxidative stress and liver-related biochemical parameters following folate treatment, and includes data that have not been published before.

Setting and Participants

Animals were accommodated in individually ventilated cages under standardized laboratory conditions, including a controlled temperature (24 ± 1°C), relative humidity (55 ± 5%), and a 12-hour light/dark cycle. Throughout the experiment, they had unrestricted access to commercial rodent chow and fresh water.

Induction of Diabetes

After overnight food deprivation, diabetes was induced in the diabetic groups by a single intraperitoneal injection of STZ at 55 mg/kg body weight. STZ was freshly dissolved in cold 0.1 M citrate buffer (pH 4.5) immediately before injection. To minimize early post-STZ hypoglycemia, rats were provided with 5% sucrose solution in drinking water for 24 hours.

Sample Size

A total of 18 male Wistar rats, weighing approximately 200 ± 20 grams at baseline, were sourced from the Royan Institute in Tehran, Iran.

Randomization

Random assignment of the animals resulted in three groups, with six rats per group:

- Group I (control): Non-diabetic rats that received no treatment.
- Group II (STZ): Diabetic rats that remained untreated throughout the experimental period.
- Group III (STZ + Folate): Diabetic rats treated with a daily dose of folate at 15 mg/kg administered via intraperitoneal injection in saline for a duration of four weeks (16, 17).

During the experimental period, one rat in the STZ-induced diabetic group died after diabetes induction. No mortality was observed in the control or folate-treated diabetic groups. Therefore, the final number of animals included in the statistical analysis was six in the control group, five in the STZ group, and six in the STZ + Folate group.

Measurements & Validity and Reliability

Body Weight

On the final day of the experiment, body weight was recorded and compared across all groups.

Fasting Blood Sugar (FBS)

Seventy-two hours after STZ injection, blood glucose was measured from tail-vein blood using a portable glucometer (Mini Glucocard 01, Japan) after a 6-hour fasting period. Rats exhibiting fasting blood glucose concentrations exceeding 150 mg/dL were considered diabetic and were included in the study cohort (15).

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Sample Collection and Biochemical Analyses

At the four-week time point, euthanasia was performed, and blood was withdrawn via cardiac puncture into gel clot activator tubes. The blood was then centrifuged at 3000 × g for 10 minutes at 4°C to separate serum. The resulting serum samples were immediately frozen and maintained at −70 °C pending biochemical measurements. FBS levels and serum concentrations of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were subsequently determined following procedures outlined in our earlier work (13).

Malondialdehyde (MDA) Levels in Liver Tissue

Liver tissue was removed, washed with cold phosphate-buffered saline (PBS), and homogenized in PBS (pH 7.4) to obtain a 10% (w/v) suspension. Before MDA analysis, protein concentration in the tissue homogenate was measured using the Bradford assay and used to normalize MDA values. The homogenates were then centrifuged at 1,600 × g for 10 min at 4°C, and the supernatant was collected for MDA determination. MDA levels were assessed using a commercial assay kit (Kushan Zist Laboratory, Iran; Cat. No. KZMA-OB) according to the manufacturer's instructions. This assay is based on the reaction of MDA with thiobarbituric acid (TBA) under acidic conditions, producing a pink MDA–TBA adduct. The intensity of the resulting color was quantified spectrophotometrically at 530–540 nm.

Total Antioxidant Capacity (TAC) Levels in Liver Tissue

TAC was determined using a commercial kit (Kushan Zist Laboratory, Iran; Cat. No. KZTA-OB) according to the manufacturer's protocol. In liver tissue, TAC was assessed based on the ability of endogenous antioxidants to reduce Cu^{2+} to Cu^{+}, resulting in the formation of a stable-colored complex detected at 412 nm. Quantitative values were obtained using a standard curve prepared with Trolox.

Superoxide Dismutase (SOD) Activity in Liver Tissue

To measure SOD activity in liver tissue, a 10% (w/v) homogenate was prepared in cold phosphate-buffered saline (pH 7.4) and centrifuged at 14,000 × g for 5 min at 4°C, after which the supernatant was collected. Tissue protein concentration was measured using the Bradford assay before SOD analysis. SOD activity was then determined using a commercial assay kit (Kushan Zist Laboratory, Iran; Cat. No. KZSO-OB), which is based on inhibition of WST-1 tetrazolium salt reduction by superoxide radicals generated through the hypoxanthine/xanthine oxidase system. Absorbance was recorded at 440–460 nm.

Statistical and Data Analysis

Statistical analyses were carried out in GraphPad Prism 10.6.1 (GraphPad Software, CA, USA). The Shapiro–Wilk test was used to examine whether the data followed a normal distribution. Variables with normal distribution were compared among groups by one-way ANOVA, followed by Dunnett's multiple comparison test. Data are expressed as mean ± standard deviation (SD). Differences were considered statistically significant when p values were less than 0.05.

Results

As previously reported, STZ-induced diabetic rats exhibited metabolic and hepatic alterations compared with controls (13). Folate supplementation resulted in slight improvements in body weight, FBS, and liver enzyme levels; however, these changes were not statistically significant (Table 1).

Folate treatment slightly reduced hepatic MDA levels (25.82 ± 10.55 μM/mg protein) compared with untreated diabetic rats, although the change

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was not statistically significant. Likewise, TAC levels showed no significant differences among groups (Fig. 1A, B). Hepatic SOD activity showed an upward trend in the folate group (226.7 ± 74.28 U/mg protein) compared to the STZ group (171.0 ± 89.91 U/mg protein) and the control group (147.9 ± 64.62 U/mg protein); however, this increase did not reach statistical significance (Fig. 1C).

Table 1. Effect of folate supplementation on hepatic enzymes in diabetic rats.

Biochemical parameters	*Control (n=6)*	*STZ (n=5)*	*Folate (n=6)*	p value
body weight (g)	292.6 ± 20.89	168.2 ± 52.50 a***	194.2 ± 42.08	ns
FBS (mg/dl)	235.8 ± 67.24	562.8 ± 70.03 a**	505.8 ± 164.2	ns
ALT (u/l)	80.60 ± 11.17	207.0 ± 88.23 a**	168.2 ± 45.99	ns
AST (u/l)	95.80 ± 9.884	220.5 ± 93.49 a*	170.0 ± 51.44	ns

Data are shown as mean±SD. ns; non-significant. Control and STZ baseline values were previously reported [13]; current analysis focuses on the effect of folate treatment.

Control: Non-diabetic group, STZ: diabetic group, Folate: diabetic group treated with folate

a. Comparison between control group and STZ group b. Comparison between STZ group and Folate group

* p < 0.05 ** p < 0.01 ***p < 0.001

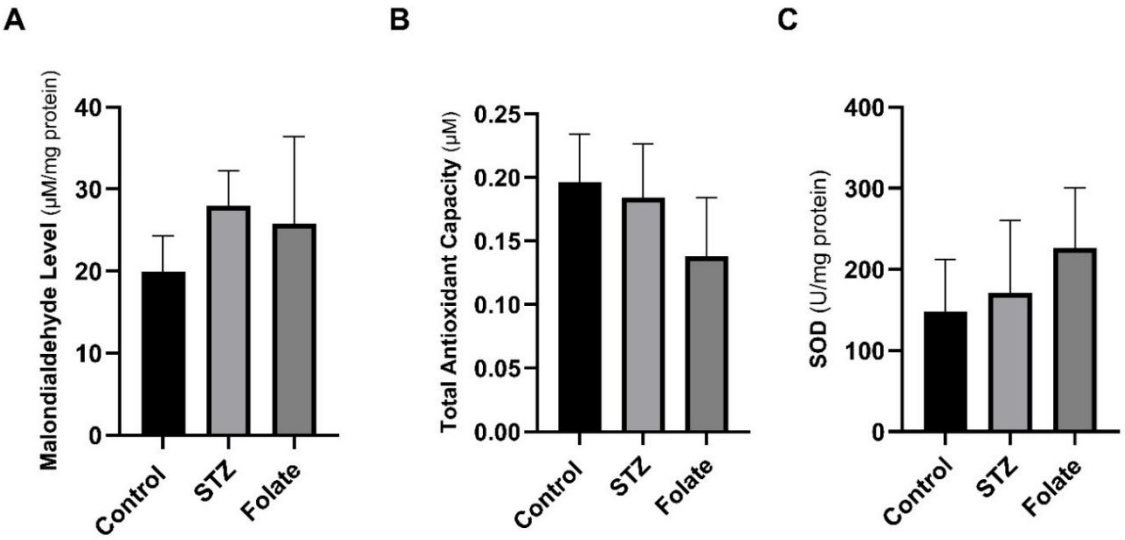

Figure 1. Tissue levels of MDA (A), TAC (B), and SOD (C) in different experimental groups. Data are presented as mean ± SD. Control: Non-diabetic group, STZ: diabetic group, Folate: diabetic group treated with folate

Discussion

In the present study, diabetic animals treated with folate tended to improve their body weight and fasting blood glucose level, but these changes were not significantly different from untreated diabetic controls. This finding is in agreement with earlier reports that folate supplementation can partially improve the diabetes-associated weight loss and hyperglycemia, but not fully normalize these parameters (8). Failure to normalize body weight may be related to persistent insulin deficiency, which favors the use of adipose tissue and protein catabolism as alternative energy sources. Likewise, the continued elevation of blood glucose in the folate-treated group indicates that folate does not directly enhance insulin sensitivity or glucose uptake. Instead, its biological effects are believed to be primarily mediated via mechanisms related to one-carbon metabolism and antioxidants, such as methyl-group donation, regulation of antioxidant

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gene expression, and involvement in nucleotide and amino acid metabolism (8).

Similarly, in the present study, serum ALT and AST levels in folate-treated diabetic rats showed a downward trend as compared to untreated diabetic controls, but these reductions were not statistically significant (18). The absence of statistical significance suggests that folic acid has a limited hepatoprotective effect against the type of cellular injury that causes AST and ALT elevation at the dose and duration used. Aminotransferases are released into the circulation mainly when hepatocyte membrane damage is associated with intracellular and mitochondrial injury, and the present data suggest that folic acid may not have a strong effect on these specific injury pathways. The trend toward improvement seen may be due to some modulation of the liver injury, but the effect was not strong enough to be statistically significant, perhaps due to the severity of the diabetic injury, the duration of treatment, or limitations in sample size (18).

A non-significant decrease of hepatic MDA levels was observed in folate-treated diabetic rats as compared to untreated diabetic controls. This is in line with previous reports showing that treatment with folate alone was able to reduce but not fully restore the diabetes-induced lipid peroxidation (8). The marginal effect on MDA may be due to the antioxidant effect of folate being mainly indirect, as a methyl group donor to regulate the transcription of genes encoding proteins involved in antioxidant defense and supporting glutathione synthesis, rather than directly scavenging lipid radicals. Thus, folate appears to be more effective in improving enzymatic antioxidant systems, including glutathione peroxidase, catalase, and glutathione reductase, than in rapidly reducing the accumulation of products of lipid peroxidation. The persistence of elevated MDA despite folate treatment may also be associated with the relatively short period of treatment, the dose used, or the inherent variability of the TBARS assay, which is known to have limited sensitivity for detecting modest changes in lipid peroxidation. Furthermore, the diabetic liver is subjected to severe oxidative stress due to chronic hyperglycemia, mitochondrial dysfunction, and chronic inflammation, which may demand a more potent or combined antioxidant regimen to bring down MDA levels (8).

There was no statistically significant improvement in hepatic TAC after folate treatment. This finding is in line with the results of a recent systematic review and meta-analysis of randomized controlled trials, indicating that although folate supplementation may improve TAC in general, the effect was not consistently statistically significant, especially in studies with longer durations of intervention or specific population subgroups (6). The reason for the absence of a measurable increase in systemic antioxidant capacity in the experiment may be that folate was given intraperitoneally for 4 weeks, which may not have been long enough. Moreover, as the antioxidant effect of folate is mainly mediated by indirect mechanisms (e.g., reduction of homocysteine and modulation of antioxidant gene expression), the small change in TAC may also be a reflection of the severity of oxidative stress and the short duration of the intervention (19).

The activity of hepatic SOD was increased non-significantly in diabetic and folate groups and highest activity was observed in folate group. Most of the studies have shown a decrease in SOD activity in diabetic conditions due to the decrease in antioxidant defenses caused by oxidative stress (6, 20). However, paradoxical increases in SOD activity have been reported in early or moderate stages of diabetes, probably as a compensatory response to enhanced superoxide generation (16,21). Thus, the marginal increase in SOD in diabetic group of this study may be an index of such an adaptive response (16). Folate supplementation further non-significantly increased SOD activity. Thus, the antioxidant potential of folate may be partly associated with the upregulation or stabilization of

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enzymatic defenses (6). The lack of statistical significance may be related to the relatively short duration of treatment, the dose used or the small sample size (19).

Limitations and Strengths

This study provides experimental evidence and proposes biologically plausible explanations for the limited effects of folate in diabetic liver injury. The interpretation of oxidative stress markers should consider relevant methodological factors such as the duration of treatment and severity of disease. However, the discussion is largely based on non-significant results, and several mechanistic interpretations go beyond the data collected, as insulin signaling, homocysteine, glutathione and molecular antioxidant pathways were not directly measured. Moreover, the relatively small sample size and treatment duration should be considered when interpreting the non-significant findings and their biological relevance.

Conclusion

Folate supplementation showed minor beneficial trends in numerous metabolic and oxidative stress parameters in diabetic rats including body weight, liver enzyme activity and antioxidant status. However, none of these alterations were statistically significant in the experimental settings utilized in this investigation. These data imply that the protective effect of folate alone on diabetes-induced hepatic oxidative stress may be limited. Further trials with various dosages, longer treatment durations or combination treatments may assist to understand the putative therapeutic effect of folate in diabetic liver impairment.

Funding

This study was funded by the Iran National Science Foundation (INSF), Project No. 4037647.

CRediT authorship contribution statement

Conceptualization, Methodology, Supervision: AV., AK, Validation, Project Administration, Funding Acquisition: AV, Formal Analysis, Investigation, Data Curation, Writing–Original Draft Preparation, Visualization: RM, Resources: RM, AV, Writing–Review & Editing: RM, AV, AK.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work, AI-assisted technologies were used for language editing and improvement of academic writing. After using these tools, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Conflict of interest

All authors declare that they have no conflict of interest.

Ethical considerations

The authors avoided data fabrication, falsification, plagiarism, and other forms of research misconduct. This study was approved by the Ethics Committee of University of Tehran (IR.UT.VETMED.REC.1403.045).

Data availability statement

Data available on request from the authors.

Acknowledgements

The authors would like to thank the University of Tehran for supporting this study.

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