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Protective Effects of *Moringa oleifera* Aqueous Leaf Extract against Dexamethasone-Induced Multi-Organ Injury in Mice: A Histopathological Study

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Abstract

Introduction: The potent synthetic glucocorticoid dexamethasone (DEX) is used widely in clinical practice, but has a high level of multi-organ toxicity, partially through oxidative stress and inflammatory pathways. *Moringa oleifera* (MO), a medicinal plant, is rich in bioactive compounds having established antioxidant and anti-inflammatory properties.

Methods: Twenty-one male albino mice were randomly divided into three groups of seven mice per group, namely control group (21 days received distilled water), DEX group (1 mg/kg intramuscular injection for 21 days) and DEX+MO group (1 mg/kg intramuscular injection and 50 mg/kg MO aqueous leaf extract orally for 21 days). Histopathological examination of liver, kidney and heart tissues was done using haematoxylin and eosin staining. The semi-quantitative scoring system (0–3) for degeneration, necrosis, inflammation, congestion, and architectural disruption was used to assess tissue injury.

Results: There was significant histopathological damage in all organs of the body that were examined, as indicated by the mean injury score of 2.43±0.53 for liver, 2.57±0.53 for kidney and 2.71±0.49 for heart following DEX treatment. These changes were significantly reduced by co-administration of MO, with scores of 1.14±0.38 (liver), 1.29±0.49 (kidney) and 1.29±0.49 (heart) ($p<0.001$ for all comparisons). MO therapy improved near-normal tissue architecture and decreased tissue degeneration, necrosis and inflammatory infiltration.

Conclusion: The *Moringa oleifera* aqueous leaf extract showed a remarkable protective effect against DEX-induced multi-organ injury in mice. These results suggest that MO may be a natural adjunctive agent to reduce the tissue toxicity induced by GC, probably due to its antioxidant and anti-inflammatory activity.

Keywords: *Moringa oleifera*; Dexamethasone; Drug induced organ injury; Histopathology; Phytotherapy

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Introduction

Historically, medicinal plants have been of great scientific interest because of their traditional applications as a source of nutritional and pharmacological compounds. They have been used extensively to treat a variety of diseases as well as to improve health (1).

Moringa oleifera (MO) is a very popular species in the family *Moringaceae* of which it is a member, and is native to South Asia, the sub-Himalayan region (including India) and parts of the Sahara Desert (2). The plant is well known for its exceptional nutritional profile, being rich in proteins, essential amino acids, vitamins (A, E, C), and minerals such as calcium, potassium, iron, and phosphorus. Owing to these properties, different parts of the plant have been extensively used in traditional medicine, particularly in Asian and African healthcare systems (3, 4, 5). In recent years, *Moringa oleifera* has gained increasing research attention due to its high content of bioactive compounds, including flavonoids, phenolic acids, alkaloids, carotenoids, and tocopherols (6, 7). These constituents are largely responsible for its wide range of pharmacological activities, such as antioxidant, antidiabetic, cardioprotective, anti-asthmatic, anticancer,

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antimicrobial, antiviral, anti-inflammatory, and hepatoprotective effects. Among its various parts, the leaves are the most utilised, either as dietary supplements or in the preparation of herbal extracts (8, 9, 10, 11).

Dexamethasone (DEX), a potent synthetic glucocorticoid with significantly higher anti-inflammatory potency than cortisol, is widely used in clinical practice for the management of autoimmune diseases, allergic conditions, inflammatory disorders, and, more recently, COVID-19 (12, 13, 14). Its therapeutic action is mainly mediated through suppression of pro-inflammatory cytokine production and inhibition of immune cell activation (15). Although clinically useful, a major side effect of long-term use or high doses of dexamethasone is metabolic disturbance, immunosuppression, and injury to vital organs (16). Oxidative stress, DNA damage, inflammation, hepatotoxicity, nephrotoxicity, and cardiotoxicity have been reported in previous studies after administration of DEX (17).

Considering the antioxidant and anti-inflammatory effects of Moringa oleifera, this study aimed to investigate the potential protective effect of Moringa oleifera aqueous leaf extract against dexamethasone-induced tissue damage in the liver, kidney, and heart of male mice, especially the histopathological changes.

Methods

Experimental Animals

In the present experimental study, we used twenty-one (21) male albino mice of 6 weeks with a weight of 27-30 g. Animals were acquired from the Animal House of the College of Medicine, Tikrit University, Iraq. Mice were kept under standard laboratory conditions with a controlled (20 ± 2 °C) temperature and a 12-hour light/dark cycle in well-ventilated cages. For the duration of the experiment, animals received commercial feed and tap water ad libitum. The animal procedures were approved by the Institutional Animal Ethics Committee of Samarra University (SU/IAEC/2025-021) and followed ARRIVE guidelines.

Sample Size and Randomisation

Based on the number of similar studies completed and the resources available, sample size (n=7 per group) was determined. Randomisation of animals into experimental groups was performed by a computer-generated randomisation sequence. All the histological evaluations were conducted by a pathologist who was blinded to treatment allocation.

Chemicals and Reagents

Dexamethasone sodium phosphate (8 mg/2 mL ampoules) was purchased from H-Tech International Enterprises Co., Ltd. DEX was injected intramuscularly (IM) at a dose of 1 mg/kg body weight once daily for 21 consecutive days based on an experimental protocol described previously. (18). The chosen dose was chosen for its known reproducible tissue injury.

Preparation of Moringa oleifera Extract

The fresh leaves of Moringa oleifera were obtained from a cultivated source, Samarra, Iraq. The plant material was identified by the botanist of the Department of Biology, Samarra University (Voucher Specimen No. MO-2025-003). To remove dust and impurities, the leaves were washed thoroughly twice with distilled water and air-dried at room temperature (25 ± 2 °C) for 7 days. The dried leaves were then powdered using an electric grinder. Thirty grams of the powdered material were extracted in 200 mL of double-distilled water with continuous stirring for 24 hours at room temperature. The mixture was filtered with Whatman No. 1 filter paper to get a clear filtrate. The extract was preserved at 4 °C and employed during the experimental period. The extraction yield was determined to be 12.4% (w/w). The phytochemical screening of the extract revealed the presence of phytochemicals such as flavonoids, phenolic compounds and alkaloids (19).

Experimental Design

Based on the body weight of the animals, they were randomly assigned to three experimental groups (n=7 each), and there was minimal difference between the groups.

Animals of group I (Control) were given distilled water orally (1 mL/kg) for 21 consecutive days.

In group II (dexamethasone), the animals were injected with dexamethasone intramuscularly (IM) once a day for 21 days at the dose of 1 mg/kg body weight.

The animals in Group III were treated with dexamethasone (1mg/kg IM) once a day, and one hour after injection, Moringa oleifera aqueous extract (50mg/kg) was administered orally via gastric gavage for 21 consecutive days, as described by Ahmad et al. (20). One hour was chosen to ensure sufficient systemic absorption of dexamethasone before giving the extract. The MO dose was chosen according to previous studies showing that this dose is effective in protection without toxicity.

Tissue Collection and Histological Preparation

Animals were sacrificed at the end of the experiment by cervical dislocation under light anaesthesia. Liver, kidneys and heart were immediately removed, washed with sterile normal saline (0.9% NaCl), and immersed in 10% neutral buffered formalin (Fisher Scientific) for 24 hours. Fixed tissues were dehydrated through a graded series of ethanol concentrations (70%, 80%, 90%, 95%, and 100%), cleared with xylene, and embedded in paraffin wax using standard techniques. Sections of 4–5 µm thickness were cut on a rotary microtome and stained with haematoxylin and eosin (H&E) according to standard protocols (21). For each organ, three non-overlapping sections per animal were examined at 100× and 400× magnification using an Olympus BX43 light microscope.

Histopathological Scoring

Histopathological changes were assessed using a semi-quantitative scoring system. For each organ, parameters including cellular degeneration, necrosis, inflammatory cell infiltration, vascular congestion, and architectural disruption were evaluated and assigned scores as follows:

Grade 0: Normal histology

Grade 1: Mild changes (<25% of field affected)

Grade 2: Moderate changes (25–50% of field affected)

Grade 3: Severe changes (>50% of field affected)

A total injury score for each organ was calculated as the sum of individual parameter scores. The scoring was performed by a pathologist blinded to group allocation.

Statistical Analysis

Histopathological scores are presented as mean ± standard deviation (SD). Data were assessed for normality using the Shapiro–Wilk test. Differences among groups were analysed using one-way analysis of variance (ANOVA) followed by Tukey's post-hoc test for multiple comparisons. Statistical analyses were performed using GraphPad Prism version 9.5 (GraphPad Software, San Diego, CA, USA). A p-value < 0.05 was considered statistically significant.

Results

Histomorphological Evaluation of the Liver

Control Group (G1): Examination of liver sections from control animals revealed normal hepatic architecture. Hepatocytes were arranged in radiating cords around the central vein, with centrally located nuclei and eosinophilic cytoplasm. Hepatic sinusoids were patent and well-preserved. Kupffer cells were inconspicuous. No pathological changes were observed (Figure 1A).

Dexamethasone-Treated Group (G2): Liver sections from DEX-treated animals demonstrated severe histopathological alterations, including marked congestion and dilation of central veins, extensive hepatocyte degeneration, and focal areas of necrosis. Hepatocyte cords showed abnormal arrangement, with loss of radial organisation. Prominent lymphocytic infiltration was observed in the periportal and sinusoidal areas. Vascular congestion and evidence of erythrocyte extravasation were also noted (Figures 1B and 1C). The mean total injury score was 2.43±0.53 (Table 1).

DEX + MO-Treated Group (G3): Co-administration of MO significantly ameliorated DEX-induced hepatic injury. Liver sections showed near-normal architecture, with well-organised hepatocyte cords. Hepatocyte degeneration and necrosis were markedly reduced. Central veins appeared normal in calibre with reduced congestion. Kupffer cell hyperplasia was noted, possibly reflecting hepatic immune system activation. Inflammatory infiltration was minimal (Figure 1D). The mean total injury score was 1.14±0.38, significantly lower than the DEX group ($p<0.001$) (Table 1, Figure 2).

Table 1: Semi-Quantitative Histopathological Injury Scores in Liver, Kidney, and Heart

Organ	Control (G1)	DEX (G2)	DEX + MO (G3)	p-value (G2 vs G3)
Liver	0.00 ± 0.00	2.43 ± 0.53	1.14 ± 0.38	< 0.001
Kidney	0.00 ± 0.00	2.57 ± 0.53	1.29 ± 0.49	< 0.001
Heart	0.00 ± 0.00	2.71 ± 0.49	1.29 ± 0.49	< 0.001

Data are presented as mean ± SD. Statistical analysis: One-way ANOVA with Tukey's post-hoc test. Significance threshold: $p < 0.05$

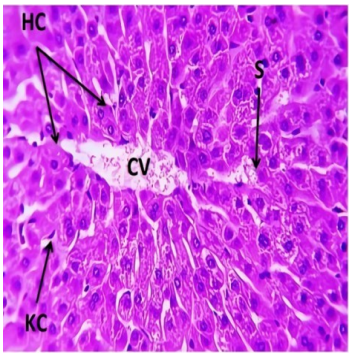


Figure 1A — Control group (G1), liver, H&E, 100×

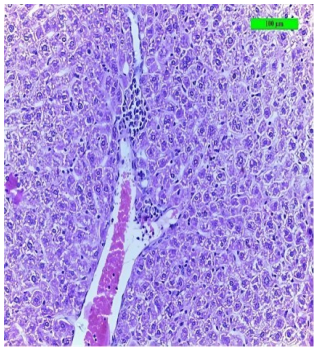


Figure 1B — DEX group (G2), liver, H&E, 100×

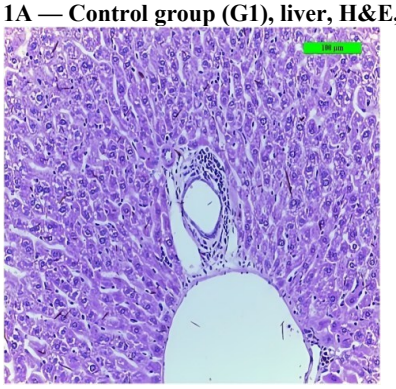


Figure 1C — DEX group (G2), liver, H&E, 400×

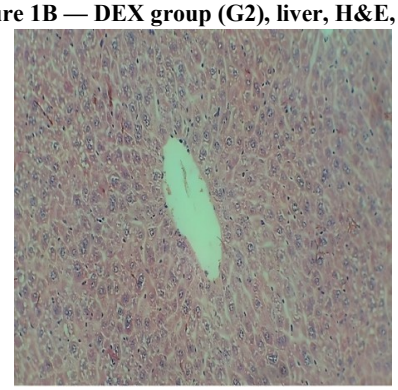


Figure 1D — DEX + MO group (G3), liver, H&E, 100×

Figure 1: Histopathological Evaluation of Liver Tissues (H&E Stain)

(A) Control Group (G1, 100×): Normal hepatic architecture showing central vein (CV), hepatocyte cords (HC) radiating from the central vein, hepatic sinusoids (S), and Kupffer cells (KC). **(B) DEX-treated group (G2, 100×):** Marked congestion of the central vein (CV) and sinusoidal dilation. Note the disruption of hepatocyte cord arrangement. **(C) DEX-treated group (G2, 400×):** Higher magnification showing hepatocyte degeneration (arrowheads), necrosis (N), and lymphocytic infiltration (arrows). **(D) DEX + MO Group (G3, 100×):** Near-normal hepatic architecture with well-preserved hepatocyte cords and central vein. Minimal sinusoidal congestion is evident. Kupffer cell hyperplasia (KC) is noted

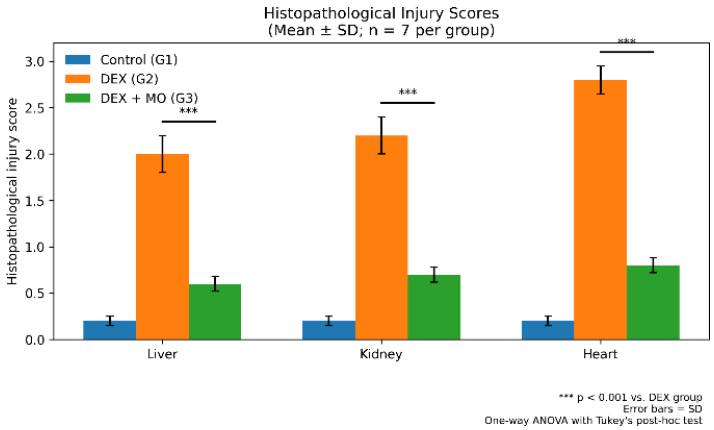


Figure 2: Comparison of Histopathological Injury Scores Among Groups

Histomorphological Evaluation of the Kidneys

Control Group (G1): Kidney slices taken from control animals showed a normal renal architecture. In the glomeruli, the Bowman's capsules were clearly visible, and the glomeruli were intact. The proximal and distal convoluted tubules showed no abnormalities in lining or lumen diameter. No inflammatory infiltrates or vascular congestion were seen (Figure 3A).

In the Dexamethasone-Treated Group (G2), DEX treatment caused severe renal damage, including glomerular shrinkage and distortion, widening of Bowman's spaces, and significant degeneration and necrosis of tubular epithelial cells. Loss of integrity of tubular lumina and infiltration of inflammatory cells into the interstitium were seen. Vascular congestion was prominent (Figures 3B and 3C). The mean total injury score was 2.57±0.53 (Table 1).

DEX + MO-Treated Group (G3): Treatment with MO resulted in substantial histological improvement. Glomeruli appeared nearly normal with minimal widening of Bowman's spaces. Renal tubules showed restoration of epithelial lining with reduced degeneration and necrosis. Interstitial inflammation and vascular congestion were significantly diminished (Figure 3D). The mean total injury score was 1.29±0.49, significantly lower than the DEX group ($p<0.001$) (Table 1, Figure 2).

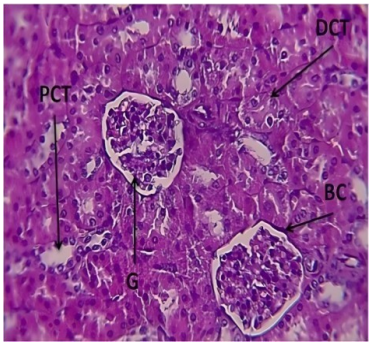


Figure 3A — Control group (G1), kidney, H&E, 100×

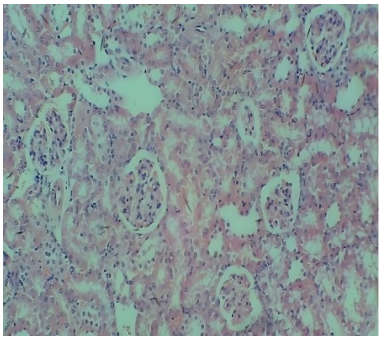


Figure 3B — DEX group (G2), kidney, H&E, 100×

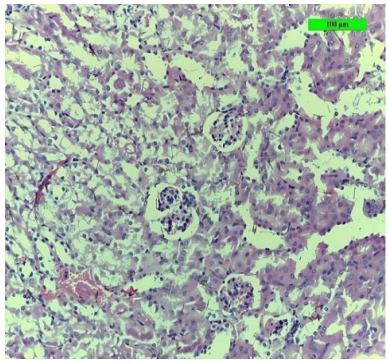


Figure 3C — DEX group (G2), kidney, H&E, 400×

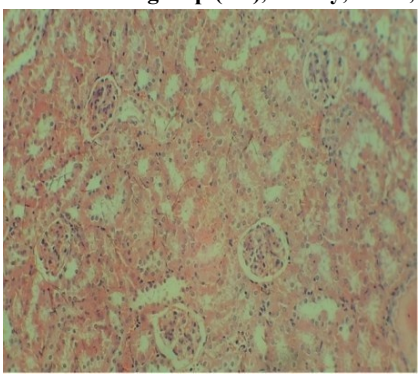


Figure 3D — DEX + MO group (G3), kidney, H&E, 100×

Figure 3: Histopathological Evaluation of Kidney Tissues (H&E Stain)

(A) Control Group (G1, 100×): Normal renal architecture showing intact glomerulus (G) within Bowman's capsule (BC). Proximal convoluted tubules (PCT) and distal convoluted tubules (DCT) demonstrate normal epithelial lining. **(B) DEX-treated group (G2, 100×):** Glomerular shrinkage (G) with widened Bowman's space (arrowhead). Tubular epithelial degeneration is evident. **(C) DEX-treated group (G2, 400×):** Higher magnification showing tubular epithelial necrosis (arrowheads), interstitial inflammatory cell infiltration (arrows), and vascular congestion. Pyknotic nuclei (P) are visible. **(D) DEX + MO Group (G3, 100×):** Marked improvement in renal architecture. Glomeruli appear nearly normal with minimal Bowman's space widening. Renal tubules show restoration of epithelial lining. Minimal vascular congestion and inflammatory cell infiltration are present

Histo-morphological Evaluation of the Heart

Control Group (G1): Cardiac sections from control animals showed normal myocardial architecture. Cardiac muscle fibres were well-organised, with branching and anastomosing patterns. Cardiomyocytes exhibited centrally located nuclei and eosinophilic cytoplasm. No inflammatory infiltrates, oedema, or fibrosis were observed (Figure 4A). Dexamethasone-Treated Group (G2): DEX treatment caused significant myocardial injury, including myofibre disorganisation, loss of normal branching, and extensive myonecrosis. Pyknotic nuclei were frequently observed. Interstitial oedema, fibrosis, and vascular congestion were prominent. There was an infiltration of inflammatory cells in several areas (Figure 4B and 4C). The mean total injury score was 2.71±0.49 (Table 1).

In the DEX + MO-treated group (G3), MO administration had a significant positive effect on the myocardial histology. Cardiac muscle fibres showed better organisation with restored branching patterns. Pyknotic nuclei were infrequent. Interstitial oedema and vascular congestion were significantly reduced. Fibrosis was minimal (Figure 4D). The mean total injury score was 1.29±0.49, significantly lower than the DEX group ($p<0.001$) (Table 1, Figure 2).

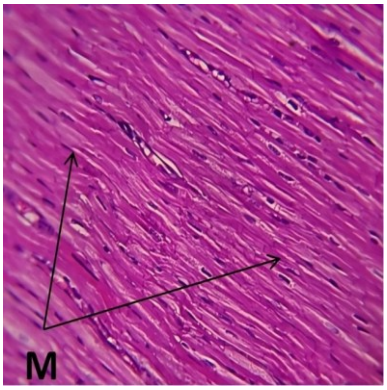


Figure 4A — Control group (G1), heart, H&E, 100×

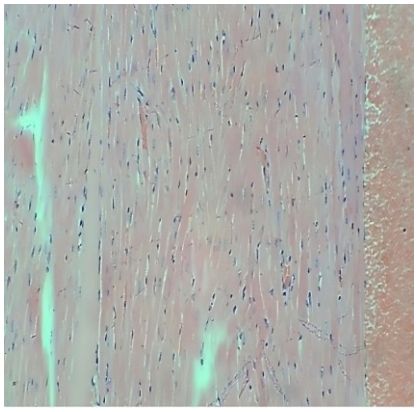


Figure 4B — DEX group (G2), heart, H&E, 100×

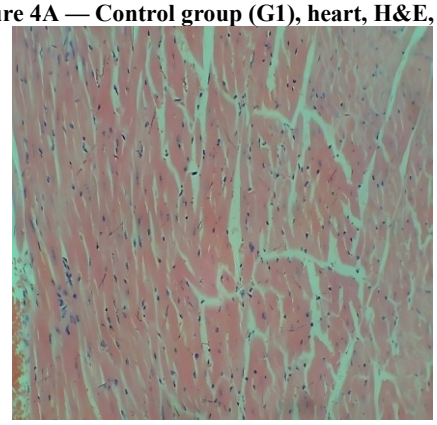


Figure 4C — DEX group (G2), heart, H&E, 400×

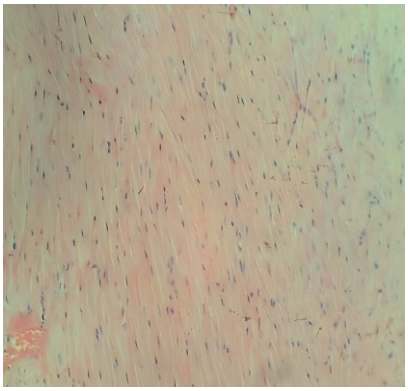


Figure 4D — DEX + MO group (G3), heart, H&E, 100×

Figure 4: Histopathological Evaluation of Cardiac Tissues (H&E Stain)

(A) Control Group (G1, 100×): Normal myocardial architecture showing well-organised, branching cardiac muscle fibres (M) with centrally located nuclei and eosinophilic cytoplasm. **(B) DEX-treated group (G2, 100×):** Disorganisation of myocardial fibres with evident degeneration and pyknotic nuclei (arrows). Interstitial oedema (E) is present. **(C) DEX-treated group (G2, 400×):** Higher magnification showing myofibre disorganisation, pyknotic nuclei (P), interstitial oedema, and vascular congestion (VC). **(D) DEX + MO Group (G3, 100×):** Marked improvement in myocardial architecture with better-organised cardiac muscle fibres. Fewer pyknotic nuclei are observed. Minimal interstitial oedema and vascular congestion are present

Discussion

The present study demonstrates that chronic administration of dexamethasone (DEX) induces significant histopathological injury in the liver, kidneys, and heart of male mice. These findings confirm DEX-associated multi-organ toxicity, consistent with previous reports (22, 23, 24). Importantly, co-administration of *Moringa oleifera* (MO) aqueous leaf extract substantially attenuated DEX-induced tissue damage across all examined organs, suggesting a protective role for this medicinal plant.

DEX-Induced Organ Injury

In this study, DEX treatment resulted in severe hepatic damage characterised by hepatocyte degeneration, necrosis, sinusoidal congestion, and inflammatory infiltration. These findings align with previous studies reporting DEX-induced hepatotoxicity, attributed to oxidative stress and disruption of cellular homeostasis (22, 23, 24). The observed central vein congestion and hepatocyte cord disruption are consistent with glucocorticoid-mediated vascular and metabolic disturbances (25).

Similarly, DEX caused significant renal injury, evidenced by glomerular shrinkage, widening of Bowman's spaces, tubular degeneration, and interstitial inflammation. These findings corroborate earlier reports of DEX-associated nephrotoxicity (26, 27, 28). The mechanisms likely involve glucocorticoid-induced oxidative stress, mitochondrial dysfunction, and activation of inflammatory pathways (29, 30).

Cardiac tissue also exhibited extensive damage, including myofibre disorganisation, myonecrosis, interstitial oedema, fibrosis, and vascular congestion. These observations support previous findings that DEX induces cardiotoxicity via oxidative stress, apoptosis, and fibrotic signalling pathways (31, 32). Glucocorticoids may upregulate pro-fibrotic and pro-apoptotic signals in cardiomyocytes, leading to structural and functional impairment (32).

Mechanisms of DEX Toxicity

The histopathological changes observed in this study can be mechanistically linked to established effects of glucocorticoids. Prolonged DEX exposure is known to increase reactive oxygen species (ROS) production, elevate lipid peroxidation, and deplete endogenous antioxidant defences such as glutathione and catalase (24, 29, 32). This oxidative stress activates inflammatory, apoptotic, and pro-fibrotic pathways, ultimately resulting in cellular death and tissue injury (30, 33, 34, 35).

Protective Effects of Moringa oleifera

Co-treatment with MO significantly improved the histopathological damage of all organs studied in DEX-induced rats. In the MO+DEX group, tissues were near normal with minimal degeneration, necrosis, inflammation and vascular congestion compared to the DEX-only controls. The protective effects of MO are thought to be due to its phytochemical content, especially flavonoids, phenolic compounds, and other bioactive components (36, 37, 38). Phenolic compounds have been shown to directly scavenge ROS and free radicals, as well as indirectly, via enhancing antioxidant enzyme activity (36, 37). The bioactive compounds like quercetin, kaempferol, vitamins (A, C, E), and natural antioxidants in MO have been reported to have anti-lipid peroxidation activity and modulate oxidative stress-related signalling pathways (39, 40). Moreover, MO shows anti-inflammatory, anti-apoptotic, and cytoprotective effects to help maintain cellular integrity and tissue repair (41, 42, 43, 44).

Comparison with Previous Studies

Our results are in line with recent reports which have shown the chemoprotective activity of MO. An infusion of MO leaves effectively mitigated methotrexate-induced tissue damage in mice, as noted by De Barros et al. (44). Likewise, Nayak et al. (2020) showed that MO leaf ethanolic extract helped to alleviate the toxic effects of cyclophosphamide on the testicles, restore functional integrity of the sperm and prevent DNA damage (45). These findings of improvement in the histological structure of the liver, kidney and heart in the present study suggest a protective effect of MO against oxidative stress-induced organ damage and maintenance of organ architecture during chronic treatment with GC. It is believed that the protective mechanisms involve more than one, such as direct scavenging of free radicals, increased levels of endogenous antioxidants and modulation of inflammatory and apoptotic pathways.

Study Limitations

Several limitations of this study should be acknowledged. First, the findings are based exclusively on histopathological assessment without corresponding biochemical markers (e.g., serum ALT, creatinine, CK-MB) or oxidative stress indicators (e.g., MDA, SOD, GSH). Such measurements would strengthen the evidence for MO's protective mechanisms. Second, the sample size (n=7 per group) is relatively small, and no power calculation was performed. Third, the study lacks a group receiving MO alone, which prevents assessment of any potential inherent effects or toxicity of the extract. Fourth, the MO extract was not subjected to detailed phytochemical quantification (e.g., HPLC analysis), limiting reproducibility and understanding of active constituents. Fifth, the study did not include a dose-response assessment for MO, which would help establish the optimal protective dose. Sixth, the duration of DEX exposure (21 days) may not fully reflect chronic clinical use scenarios.

Future Directions

Future studies should include biochemical studies of biochemical markers of oxidative stress and organ function in addition to histopathology studies. Mechanistic insights could be gained from molecular studies of MO effects on specific signalling pathways, such as Nrf2/HO-1, NF-κB, and MAPK. Optimal therapeutic regimen should be determined by dose-response studies. Further long-term studies are needed to determine if MO provides long-lasting protection and to determine toxicity from future use. The usefulness of MO as a supplementary treatment to the glucocorticoids would be evaluated in clinical translation studies in human subjects.

Conclusion

This study shows that Moringa oleifera aqueous leaf extract offers substantial protection against histological changes in several organs of the mouse when induced by dexamethasone. The liver, kidneys and heart were also significantly damaged by DEX treatment, and the co-treatment with MO resulted in a restoration to near-normal architecture of these tissues and decreased pathological changes. These protective effects are likely mediated through MO's rich content of bioactive compounds with established antioxidant and anti-inflammatory properties. While these findings are promising, further studies incorporating biochemical and molecular endpoints are warranted to fully elucidate the mechanisms involved and to translate these findings to clinical applications. MO shows potential as a natural adjunctive agent for mitigating glucocorticoid-induced tissue toxicity.

Abbreviations

ALT: Alanine aminotransferase
ANOVA: Analysis of variance
AST: Aspartate aminotransferase
BUN: Blood urea nitrogen
CAT: Catalase
CK-MB: Creatine kinase-MB
DEX: Dexamethasone
GSH: Glutathione
H&E: Haematoxylin and eosin
HPLC: High-performance liquid chromatography
IM: Intramuscular
LDH: Lactate dehydrogenase
MDA: Malondialdehyde
MO: Moringa oleifera
NF-κB: Nuclear factor kappa B
Nrf2: Nuclear factor erythroid 2-related factor 2
ROS: Reactive oxygen species
SD: Standard deviation
SOD: Superoxide dismutase
TNF-α: Tumour necrosis factor-alpha

Declarations

Ethics Approval and Consent to Participate: All experimental procedures involving animals were approved by the Institutional Animal Ethics Committee of Samarra University (Approval No. SU/IAEC/2025-021, dated 15 October 2025). All procedures were conducted in accordance with the ARRIVE guidelines and the principles of the Declaration of Helsinki for animal research.

Data Availability: The datasets generated and/or analysed during the current study are available from the corresponding author upon reasonable request. Raw histopathological scores and images are archived at the Department of Pathological Analyses, Samarra University.

Competing Interests: The authors declare that they have no competing interests, financial or otherwise, that could have influenced the work reported in this manuscript.

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Author contributions: HSF: Conceptualisation, methodology, investigation, data curation, writing- original draft, writing- review and editing, visualisation, project administration. SNI: Methodology, investigation, formal analysis, validation, writing- review and editing. ARH: Conceptualisation, resources, supervision, writing- review and editing, funding acquisition (institutional). All authors read and approved the final manuscript.

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