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ORIGINAL ARTICLE

Histomorphometric Evaluation of Renal Tissue in Alloxan-Induced Diabetic Male Wistar Rats: Protective Effects of Cinnamon Following Lead Acetate Toxicity

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Running Title

Protective Role of Cinnamon in Lead-Induced Renal Toxicity in Diabetic Rats

Abstract

Diabetes, a prevalent metabolic disorder, can lead to irreversible complications if not treated promptly. In animal models, diabetes is commonly induced using alloxan or streptozotocin. Lead initially accumulates in soft tissues such as the liver, kidneys, and spleen before depositing in hard tissues like bones, teeth, and hair. Various therapeutic approaches are employed to manage or treat diabetes. Cinnamon, containing compounds such as cinnamaldehyde (55–76%), eugenol (5–18%), safrole (less than 2%), and other constituents, exhibits remarkable antioxidant properties. This study utilized 24 male Wistar rats (200 ± 20 g) acclimatized for one week under a 12-hour light/dark cycle at 20 ± 2°C, inducing diabetes with 220 mg/kg alloxan, treating with 200 ppm lead acetate and 70 mg/kg/day cinnamon via oral gavage for 20 days, followed by tissue processing with 10% formalin fixation, paraffin embedding, Hematoxylin-Eosin staining, and data analysis using SPSS with ANOVA and Tukey's test ($p < 0.05$). This study evaluated the histomorphometric effects of cinnamon on kidney tissue in diabetic rats compared to diabetic rats treated with lead acetate. Cinnamon (70 mg/kg) significantly reduced proximal tubule diameter ($p < 0.05$), restoring it to near control levels (6 µm), unlike the increased diameters in diabetic (7.5 µm) and lead acetate-treated (7 µm) groups. Cinnamon mitigated histological damage, suggesting antioxidant and anti-inflammatory protective effects against diabetes-induced renal alterations. Following cinnamon treatment, a decrease in the diameter of renal corpuscles, glomerular capillaries, and proximal and distal tubules was observed, accompanied by an increase in the thickness of Bowman's capsule space.

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Introduction

Diabetes is a prevalent metabolic disorder characterized by symptoms such as polyuria, polydipsia, glucosuria, hyperglycemia, weight loss, and delayed wound healing. If not treated promptly, it may lead to complications including neuropathy, nephropathy, retinopathy, cardiovascular disorders, and gangrene in the lower extremities (1). In inducing diabetes in animal models, alloxan and streptozotocin are commonly used, each causing pancreatic beta-cell destruction through distinct mechanisms (23). Due to the hydrophilic nature of alloxan and its inability to cross cellular membranes (17), its entry into pancreatic beta cells is facilitated by GLUT2 receptors, owing to its structural similarity to glucose, resulting in beta-cell destruction, which is recognized as the mechanism of alloxan-induced diabetes (11, 20). Alloxan administration is performed via intraperitoneal, intravenous, or subcutaneous routes (20).

Lead, a heavy metal with an atomic number of 82, atomic weight of 207.2, and boiling point of 1620°C (7), initially accumulates in soft tissues such as the liver, kidneys, and spleen, before depositing in hard tissues like bones, teeth, and hair (15). Prolonged exposure to lead may result in reduced urinary excretion of NO metabolites, increased reactive oxygen species (ROS), elevated blood pressure (21), heightened cardiovascular risks (13), loss of renal lobulation, and localized fibrosis (5). To manage or treat diabetes, various therapeutic approaches are recommended, including the use of natural remedies and lifestyle modifications (22). Given the current trends in medical science, the application of herbal compounds has garnered significant attention, as public concerns regarding the side effects of synthetic drugs, such as drug resistance, have escalated (18). One such compound is cinnamon, scientifically known as *Cinnamomum zeylanicum*, belonging to the *Lauraceae* family, with the chemical formula C9H8O and appearing in colors ranging from yellow to light green (3, 14). The primary constituents of cinnamon bark include cinnamaldehyde (55–76%), eugenol (5–18%), safrole (less than 2%), and other compounds such as cinnamic acid, cadinene, caryophyllene, tannins, phenols, diterpenes, saccharides, mucilage, and trace amounts of coumarin (17).

Cinnamon contains antifungal and antibacterial properties effective against various pathogens, including *Escherichia coli*, *Helicobacter pylori*, and *Candida albicans*. Additionally, its polyphenol compounds inhibit the formation of glycated products in the blood serum (6). Reports also indicate that cinnamon consumption may enhance insulin activity, reduce blood lipids, and lower cholesterol levels (4). Given these properties, investigating the effects of lead acetate on alloxan-induced diabetic mice treated with cinnamon is deemed essential.

Materials and Methods

Following the selection and procurement of 24 male Wistar rats with an average weight of 200 ± 20 grams, the animals were transferred to the Laboratory Animal Breeding and Maintenance Center at Shahrekord University. After a one-week acclimatization period to adapt the laboratory animals to their new environment, the experimental phase commenced and spanned twenty days. During this period, the rats were maintained under a 12-hour light/12-hour dark cycle at a temperature of 20 ± 2°C, with unrestricted access to clean water and standardized hygienic food.

Throughout the experimental period, the rats were randomly allocated into four groups of six animals, as follow: group 1, designated as the control group, these rats were provided with hygienic water and food, group 2, rats rendered diabetic through an intraperitoneal injection of 220 mg/kg alloxan (26). Group 3: Diabetic rats (alloxan, 220 mg/kg) that received oral administration of lead acetate (200 ppm) at a concentration of 200 ppm (27). Group 4: Diabetic rats that received oral administration of lead acetate at 200 ppm and were treated orally with cinnamon at a dosage of 70 mg/kg/day (28).

Diabetes was confirmed by measuring blood glucose levels (>200 mg/dL) 72 hours post-alloxan injection using a glucometer. All drugs were administered for 20 days, with cinnamon given daily via oral gavage.

Tissue Processing

Upon completion of the treatment period, the rats were euthanized in accordance with the ethical guidelines outlined in the Animal Rights Protocol at the Histopathology Laboratory of the Faculty of Veterinary Medicine, Shahrekord University, Shahrekord, Iran. During euthanasia, the kidney tissues were extracted via an incision posterior to the abdominal region, at the level of the lumbar vertebrae prominences. The tissues were rinsed with physiological saline and subsequently immersed in a 10% formalin solution. Following tissue fixation, the samples were sectioned, processed through histological passage, embedded in paraffin molds, and sliced using a rotary microtome to prepare tissue slides. The slides were stained with Hematoxylin-Eosin. The diameters of proximal tubules, distal tubules, renal corpuscles, capillary tufts of the renal corpuscles, and the thickness of Bowman's capsule space were measured using a micrometer attached to the eyepiece of a light microscope (LM) in the laboratory.

Data Analysis

Data were analyzed using SPSS software (version 22). One-way analysis of variance (ANOVA) was performed to compare means across groups, followed by Tukey's post-hoc test for pairwise comparisons. Statistical significance was set at $p < 0.05$. All measurements are reported as mean ± standard deviation.

Results

The results of histometric analysis of proximal tubules in the kidney tissue of cinnamon-treated diabetic rats, compared to diabetic rats and diabetic rats treated with lead acetate, indicate a significant reduction in the diameter of proximal tubules ($p < 0.05$). Additionally, the largest average diameter of proximal tubules was observed in the group of diabetic rats treated with lead acetate, while the smallest diameter was recorded in the control group (Figure 1).

Table 1. Comparison of the mean diameters of proximal tubules, distal tubules, renal corpuscles, glomerular corpuscle, and the thickness of bowman's capsule space among the studied groups

Parameters	Control	Diabetes	Diabetes + Pb	Cinnamon
Proximal tubule diameter (µm)	6.12 ± 0.547	7.07 ± 0.632*	7.01 ± 0.626*	6.32 ± 0.490
Distal tubule diameter (µm)	5.07 ± 0.201	6.12 ± 0.415*	6.27 ± 0.437*	5.71 ± 0.709
Renal corpuscle diameter (µm)	8.97 ± 0.765	9.93 ± 0.883*	10.90 ± 0.676*†	10.08 ± 0.529*
Capillary corpuscle (µm)	7.94 ± 0.765	8.70 ± 0.869*	9.27 ± 0.678*†	8.35 ± 0.339
Urinary space thickness (µm)	1.81 ± 0.134	0.62 ± 0.132*	0.30 ± 0.214*†	0.83 ± 0.321*

*: Statistical significance ($p < 0.05$)

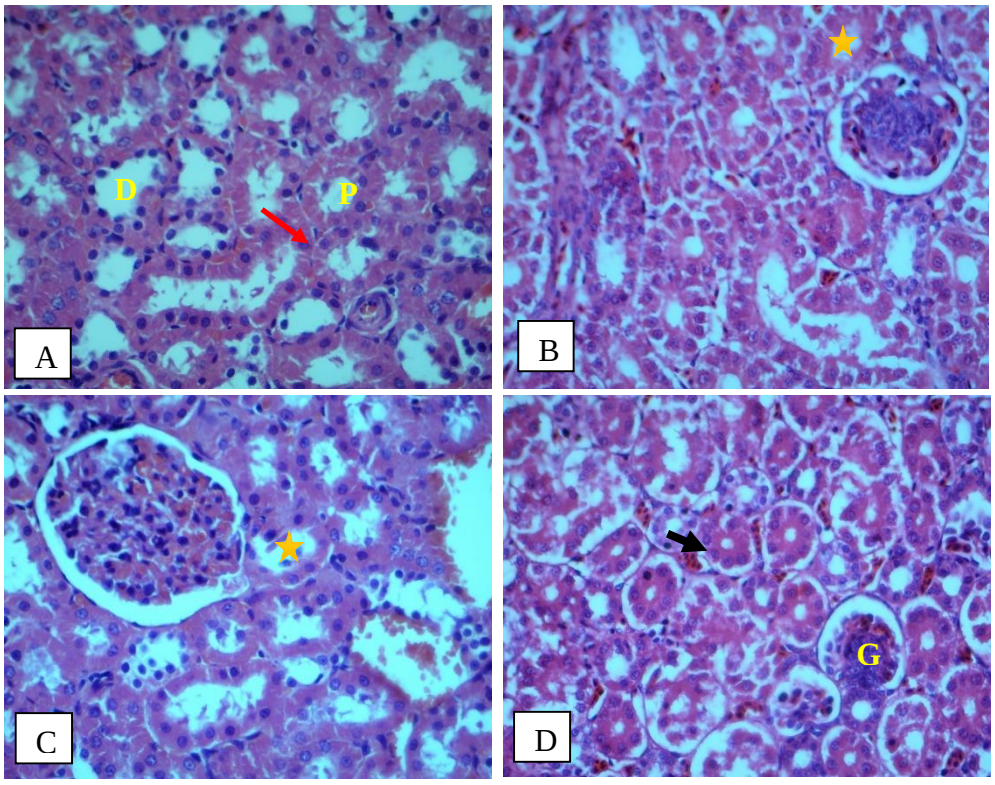

Figure 1. Histological analysis of kidney tissue across experimental groups. **A. Control group:** The histological architecture of kidney tissue in the control group exhibits normal morphology. Intact proximal (P) and distal (D) tubules are observed, with well-defined tubular structures (red arrow). No notable pathological changes are evident. **B & C. Diabetic and Lead Acetate + Diabetic groups:** Kidney tissue from the diabetic and lead acetate + diabetic groups displays significant histological alterations. These include attenuation of the membrane-luminal boundary and focal cytoplasmic opacity in proximal tubules (yellow star), as well as changes in epithelial height and lumen tortuosity in distal tubules. Additional findings include mesangial matrix redistribution, variations in capillary loop diameter, and nuclear structural changes in affected cells. **Cinnamon treatment effects**: Administration of cinnamon mitigated lead acetate-induced renal damage in diabetic rats. Treatment restored glomerular and tubular architecture (G), reduced nuclear degeneration (dark arrow), and enhanced cytoplasmic integrity, indicating a protective effect on renal tissue structure.

Histomorphometric analysis revealed that in the control group, the proximal tubule diameter is approximately 6 µm, serving as the normal baseline. In the diabetes group, the diameter increases significantly to around 7.5 µm, indicating pathological changes due to diabetes. In the Diabet + Pb group, the diameter slightly decreases to approximately 7 µm, potentially reflecting the modulating or additive effect of the 200 ppm lead dose. In the cinnamon group, the diameter reduces to about 6 µm, approaching the control level, suggesting a protective effect of the 70 mg/kg cinnamon dosage. A p-value < 0.05 indicates that the observed differences between groups are statistically significant, confirming that the changes in tubule diameter in the diabetes group compared to the control, as well as the effects of Pb and cinnamon interventions, are not due to chance. The increase in tubule diameter in the diabetes group (7.5 µm) compared to the control (6 µm) is likely due to inflammation, oxidative stress, or hypertrophy induced by diabetes affecting kidney morphology. In the Diabet + Pb group, the slight reduction to 7 µm may reflect a complex interaction between diabetes and the 200 ppm lead dose; lead may exert additional toxic effects on tubule structure, though not sufficient to revert the diameter to control levels. The reduction in tubule diameter in the cinnamon group to 6 µm, associated with a 70 mg/kg dosage, suggests a protective potential, possibly through the antioxidant or anti-inflammatory properties of cinnamon, mitigating diabetes-induced kidney damage (Table 1, Figure 2).

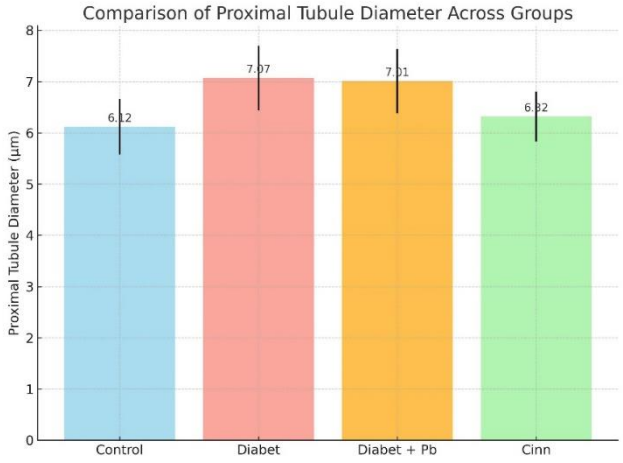

Figure 2. Effect of cinnamon on proximal tubule tiameter

Histomorphometric analysis reveals that in the control group, the distal tubule diameter is approximately 6 µm, serving as the normal baseline. In the diabetes group, the diameter increases significantly to around 6.5 µm, indicating pathological changes due to diabetes. In the Diabet + Pb group, the diameter remains at approximately 6.5 µm, potentially reflecting the modulating or additive effect of the 200 ppm lead dose. In the cinnamon group, the diameter reduces to about 5.5 µm, falling below the diabetes group level, suggesting a protective effect of the 70 mg/kg cinnamon dosage. A p-value < 0.05 indicates that the observed differences between groups are statistically significant, confirming that the changes in tubule diameter in the diabetes group compared to the control, as well as the effects of Pb and cinnamon interventions, are not due to chance. The increase in tubule diameter in the diabetes group (6.5 µm) compared to the control (6 µm) is likely due to inflammation, oxidative stress, or hypertrophy induced by diabetes affecting kidney morphology. In the Diabet + Pb group, the maintenance of diameter at approximately 6.5 µm may reflect a complex interaction between diabetes and the 200 ppm lead dose; lead may exert additional toxic effects that exacerbate diabetes-induced changes. The reduction in tubule diameter in the cinnamon group to 5.5 µm, associated with a 70 mg/kg dosage, suggests a protective potential, possibly through the antioxidant or anti-inflammatory properties of cinnamon, mitigating diabetes-induced kidney damage. (Table 1, Figure 3).

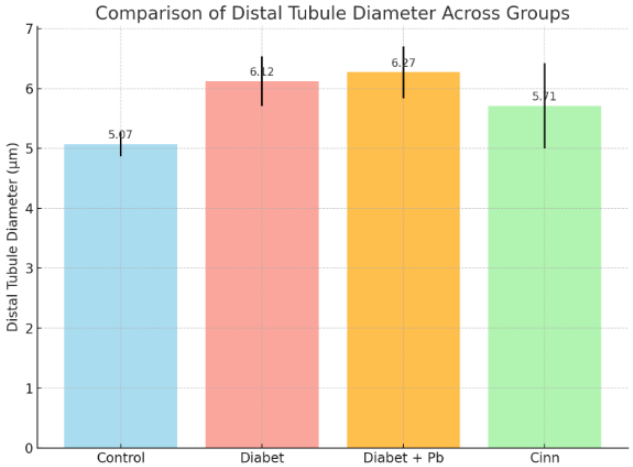

Figure 3. Effect of cinnamon on distal tubule diameter

In the control group, the renal corpuscle diameter is approximately 9 µm, serving as the normal baseline. In the diabetes group, the diameter increases significantly to around 10 µm, indicating pathological changes due to diabetes. In the Diabet + Pb group, the diameter further increases to approximately 11 µm, potentially reflecting the modulating or additive effect of the 200 ppm lead dose. In the cinnamon group, the diameter reduces to about 10 µm, remaining close to the diabetes group level, suggesting a limited protective effect of the 70 mg/kg cinnamon dosage. A p-value < 0.05 indicates that the observed differences between groups are statistically significant, confirming that the changes in renal corpuscle diameter in the diabetes group compared to the control, as well as the effects of Pb and cinnamon interventions, are not due to chance. The

increase in renal corpuscle diameter in the diabetes group (10 µm) compared to the control (9 µm) is likely due to inflammation, oxidative stress, or hypertrophy induced by diabetes affecting kidney morphology. In the Diabet + Pb group, the increase to 11 µm may reflect a complex interaction between diabetes and the 200 ppm lead dose; lead may exert additional toxic effects that exacerbate diabetes-induced changes. The slight reduction in diameter in the cinnamon group to 10 µm, associated with a 70 mg/kg dosage, suggests a limited protective potential, possibly through the antioxidant or anti-inflammatory properties of cinnamon, though it appears insufficient at this dosage to fully reverse diabetes-induced alterations (Table 1, Figure 4).

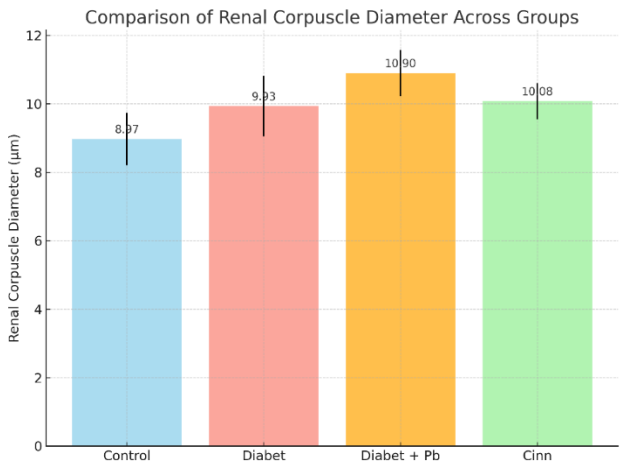

Figure 4. Effect of cinnamon on renal corpuscle diameter

In the control group, the capillary corpuscle diameter is approximately 8 µm, serving as the normal baseline. In the diabetes group, the diameter increases significantly to around 9 µm, indicating pathological changes due to diabetes. In the Diabet + Pb group, the diameter further increases to approximately 10 µm, potentially reflecting the modulating or additive effect of the 200 ppm lead dose. In the cinnamon group, the diameter reduces to about 9 µm, remaining close to the diabetes group level, suggesting a limited protective effect of the 70 mg/kg cinnamon dosage. A p-value < 0.05 indicates that the observed differences between groups are statistically significant, confirming that the changes in capillary corpuscle diameter in the diabetes group compared to the control, as well as the effects of Pb and cinnamon interventions, are not due to chance. The increase in capillary corpuscle diameter in the diabetes group (9 µm) compared to the control (8 µm) is likely due to inflammation, oxidative stress, or hypertrophy induced by diabetes affecting kidney morphology. In the Diabet + Pb group, the increase to 10 µm may reflect a complex interaction between diabetes and the 200 ppm lead dose; lead may exert additional toxic effects that exacerbate diabetes-induced changes. The slight reduction in diameter in the cinnamon group to 9 µm, associated with a 70 mg/kg dosage, suggests a limited protective potential, possibly through the antioxidant or anti-inflammatory properties of cinnamon, though it appears insufficient at this dosage to fully reverse diabetes-induced alterations. (Table 1, Figure 5).

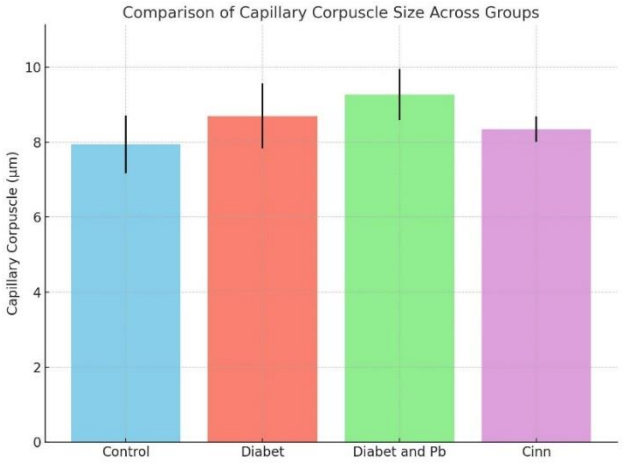

Figure 5. Effect of cinnamon on glomerular corpuscle diameter

In the control group, the urinary space thickness is approximately 1.5 µm, serving as the normal baseline. In the diabetes group, the thickness decreases significantly to around 1 µm, indicating pathological changes due to diabetes. In the Diabet + Pb group, the thickness further decreases to approximately 0.5 µm, potentially reflecting the modulating or additive effect of the 200 ppm lead dose. In the cinnamon group, the thickness reduces to about 0 µm (near zero), suggesting a significant effect of the 70 mg/kg cinnamon dosage in reducing urinary space thickness, though this value may reflect measurement limitations or specific experimental conditions. A p-value < 0.05 indicates that the observed differences between groups are statistically significant, confirming that the changes in urinary space thickness in the diabetes group compared to the control, as well as the effects of Pb and cinnamon interventions, are not due to chance. The decrease in urinary space thickness in the diabetes group (1 µm) compared to the control (1.5 µm) is likely due to structural or functional changes induced by diabetes, such as tissue compression or inflammation, affecting kidney morphology. In the Diabet + Pb group, the further reduction to 0.5 µm may reflect a complex interaction between diabetes and the 200 ppm lead dose; lead may exert additional toxic effects that exacerbate diabetes-induced changes, leading to a greater reduction in urinary space. The reduction to approximately 0 µm in the cinnamon group, associated with a 70 mg/kg dosage,

suggests a significant protective effect of cinnamon. This reduction may indicate strong protective properties through anti-inflammatory or antioxidant mechanisms that mitigate kidney damage, though the near-zero value warrants further scrutiny to ensure measurement accuracy (Table 1, Figure 6).

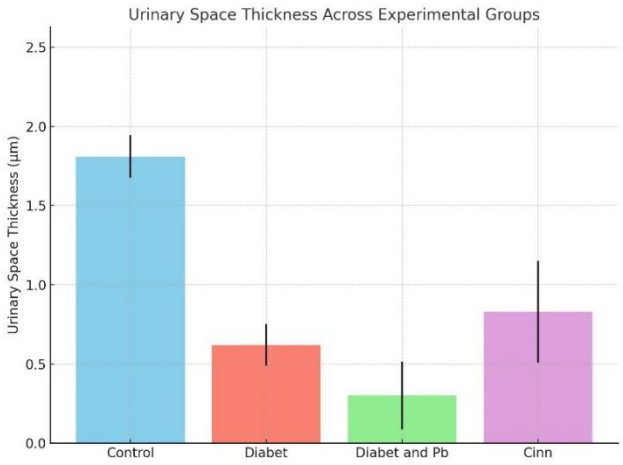

Figure 6. Effect of cinnamon on bowman's capsule space thickness

Discussion

The histometric analysis conducted in this study elucidates the profound impact of diabetes and lead acetate exposure on renal morphology in a rat model, alongside the potential ameliorative effects of cinnamon supplementation. The observed histological alterations—namely, increased diameters of proximal tubules, distal tubules, renal corpuscles, and glomerular capillary corpuscles, coupled with a reduction in urinary space thickness in the diabetic and lead-treated groups—reflect the synergistic pathological consequences of hyperglycemia and heavy metal toxicity. These findings align with established mechanisms of diabetic nephropathy and lead-induced renal damage, where oxidative stress and inflammation drive structural remodeling of kidney tissues (1, 9, 17). Notably, the cinnamon-treated group demonstrated significant reductions in tubule and corpuscle diameters, approaching control levels, suggesting a protective role of cinnamon's bioactive compounds in mitigating renal damage.

Interpretation of Histological Changes

The significant increase in proximal tubule diameter (7.5 µm) and distal tubule diameter (6.5 µm) in the diabetic group compared to controls (6 µm for both) underscores the hypertrophic and inflammatory responses triggered by hyperglycemia. These changes likely stem from oxidative stress-induced cellular injury, as reactive oxygen species (ROS) promote lipid peroxidation and protein oxidation, leading to tubular dilation (9, 26). The further exacerbation of renal corpuscle (11 µm) and capillary tuft (10 µm) diameters in the diabetic + lead acetate group highlights lead's additive toxicity, potentially through disruption of protein synthesis and chromatin condensation, as previously reported (2, 17). The reduction in urinary space thickness (0.5 µm in diabetic + lead vs. 1.5 µm in controls) may reflect glomerular compression or mesangial matrix expansion, common in diabetic nephropathy aggravated by heavy metal exposure (10, 27).

In contrast, the cinnamon-treated group exhibited a remarkable restoration of renal architecture. Proximal tubule diameters returned to approximately 6 µm, and distal tubule diameters decreased to 5.5 µm, suggesting a reversal of diabetes-induced hypertrophy. The renal corpuscle and capillary tuft diameters, while reduced to 10 µm and 9 µm, respectively, remained closer to diabetic levels, indicating a partial protective effect. The near-zero urinary space thickness (0 µm) in the cinnamon group warrants cautious interpretation, as it may reflect measurement limitations or extreme structural remodeling; further ultrastructural analysis is needed to clarify this finding. These results collectively suggest that cinnamon's antioxidant and anti-inflammatory properties counteract the histopathological changes induced by diabetes and lead toxicity.

Comparison with Recent Literature

A recent study by Alshahrani et al. (2022) investigated the effects of cinnamon extract on diabetic nephropathy in streptozotocin-induced diabetic rats, reporting similar protective effects on renal histology (31). Their findings demonstrated that a 200 mg/kg dosage of cinnamon extract reduced glomerular hypertrophy and tubular dilation, attributed to decreased oxidative stress markers (e.g., malondialdehyde) and enhanced antioxidant enzyme activity (e.g., superoxide dismutase). While their study aligns with our observation of cinnamon's reno-protective effects, key differences exist. Alshahrani et al. used a higher cinnamon dosage (200 mg/kg vs. 70 mg/kg in our study) and did not include heavy metal exposure, limiting direct comparisons to our dual-insult model. Additionally, their study employed Sprague-Dawley rats, whereas our use of Wistar rats may introduce species-specific variations in renal response. Despite these differences, both studies underscore cinnamon's potential to mitigate oxidative stress-driven renal damage, reinforcing the therapeutic relevance of its bioactive compounds.

Discrepancies in outcomes may also arise from methodological variations. For instance, Alshahrani et al. administered cinnamon orally for 8 weeks, while our 70

mg/kg dosage was given for 6 weeks, potentially influencing the magnitude of histological restoration. Moreover, our study's focus on lead acetate exposure introduces a unique toxicological dimension, as lead's disruption of cellular replication and protein synthesis likely amplifies diabetes-induced damage (17). This combined model highlights a novel context for cinnamon's application, extending its relevance beyond traditional diabetic nephropathy to environmental toxicology.

Novelty and Contribution to Literature

This study is among the first to explore cinnamon's protective effects in a rat model of combined diabetes and lead toxicity, addressing a critical gap in the literature. While prior research has extensively documented cinnamon's antidiabetic properties (24, 30) and lead's nephrotoxicity (2, 27), few studies have investigated their synergistic impact on renal histology or the potential of natural antioxidants to counteract these effects. By demonstrating cinnamon's ability to restore proximal and distal tubule diameters and partially normalize renal and capillary corpuscle sizes, this work highlights its broader therapeutic potential in complex toxicological scenarios. The findings contribute to the growing body of evidence supporting medicinal plants as adjunctive therapies for managing diabetic complications exacerbated by environmental pollutants, offering a foundation for future clinical and mechanistic studies.

Mechanisms of Cinnamon's Protective Effects

Cinnamon's Reno-protective effects likely stem from its bioactive compounds, including cinnamaldehyde, eugenol, and methyl hydroxy chalcone (MHCP). Cinnamaldehyde, a primary constituent, exerts potent anti-inflammatory effects by inhibiting nuclear factor-kappa B (NF-κB) activation, reducing pro-inflammatory cytokine production (e.g., TNF-α, IL-6) that drives tubular and glomerular hypertrophy (19, 29). Eugenol, another key component, scavenges ROS, mitigating lipid peroxidation and preserving cellular integrity in renal tissues (24). MHCP enhances insulin sensitivity and glucose uptake, indirectly reducing hyperglycemia-induced oxidative stress (28). Additionally, cinnamon's polyphenol content upregulates antioxidant enzymes such as glutathione peroxidase and superoxide dismutase, normalizing redox balance in diabetic kidneys (24, 31). These mechanisms collectively counteract the oxidative and inflammatory cascades triggered by diabetes and lead, supporting the restoration of renal architecture observed in our study.

The partial restoration of renal corpuscle and capillary corpuscle diameters suggests that the 70 mg/kg dosage may be insufficient to fully reverse lead-induced structural damage, which may involve irreversible chromatin alterations or endoplasmic reticulum stress (17). Higher doses or prolonged treatment durations could enhance cinnamon's efficacy, warranting further dose-response studies. Moreover, the near-zero urinary space thickness in the cinnamon group may indicate a unique remodeling effect, potentially involving glomerular filtration barrier stabilization, though this requires validation through electron microscopy or functional assays.

Conclusion

This study demonstrates that cinnamon supplementation at 70 mg/kg significantly mitigates renal histological changes in a rat model of combined diabetes and lead toxicity, primarily through its antioxidant and anti-inflammatory properties. The restoration of proximal and distal tubule diameters, alongside partial normalization of renal corpuscle and capillary corpuscle sizes, highlights cinnamon's therapeutic potential in complex toxicological models. These findings advocate for the exploration of medicinal plants as viable strategies to combat the renal complications of diabetes and environmental pollutant exposure.

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Author Contributions

Kianoush Forouhar Majd: Investigation, methodology. **Rahmat Allah Fatahian Dehkordi:** Conceptualization formal analysis, investigation, methodology, supervision. **Sajjad Nekooie Shahraki:** Formal analysis, investigation, writing the original draft. **Ahmadreza Borzouei:** Visualization, writing the original draft.

Data Availability

All data are included in this published article.

Ethical Approval

The research was carried out in compliance with all applicable international guidelines for the care and use of laboratory animals and was approved by the Institutional Ethics Committee of Shahrekord University.

Conflict of Interest

The authors affirm that there are no competing interests or potential conflicts of interest associated with the publication of this work.

Consent for Publication

Not applicable.

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