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Histomorphological assessment of T-2 toxin, ochratoxin A, and aflatoxin B1-induced renal damage in a rat model

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Abstract. *Fungal toxins are a prevalent cause of food contamination and can induce pathological changes in various organs of both humans and animals. This study aimed to investigate the histomorphological changes and immune response in rat kidneys exposed to aflatoxin B1, ochratoxin A, and T-2 toxin.*

Methods. A total of 44 albino rats were used, divided into four groups: three groups receiving different doses of toxins (24 mg/kg of aflatoxin B1, 64 mg/kg of ochratoxin A, and 25 mg/kg of T-2 toxin) for 20 days. Kidney samples were stained with hematoxylin-eosin, and picrofuchsin along with the Giemsa and May-Grünwald solutions.

Results. Histopathological analysis revealed specific changes, including vacuolization, necrosis with hemorrhagic foci, pyknosis, and inflammation in the renal tissue. A significant increase in mast cells and degenerative changes in renal tubular epithelial cells were also observed.

Conclusions. These findings suggest that ochratoxin A and aflatoxin B1 are potent nephrotoxins, causing severe damage to renal epithelial cells and their nuclei, while the T-2 toxin had a relatively less pronounced effect. This study highlights the detrimental effects of mycotoxins on kidney tissue, underscoring the need for further research on their prevention and mitigation to ensure food safety.

Keywords: *aflatoxin B1, ochratoxin A, T-2 toxin, mast cells, nephrotoxicity, food contamination.*

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Гістоморфологічна оцінка пошкодження нирок, спричиненого Т-2 токсином, охратоксином А та афлатоксином В1 у моделі щурів

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Резюме. *Грибкові токсини є поширеною причиною забруднення харчових продуктів і можуть викликати патологічні зміни в різних органах людини та тварин. Це дослідження мало на меті вивчити гістоморфологічні зміни та імунну відповідь у нирках щурів, підданих впливу афлатоксину В1, охратоксину А та Т-2 токсину.*

Методи. Дослідження провкдено на 44 альбіносних щурах, поділених на чотири групи: три групи отримували різні дози токсинів (24 мг/кг афлатоксину В1, 64 мг/кг охратоксину А та 25 мг/кг Т-2 токсину) протягом 20 днів. Зразки нирок фарбували гематоксилин-еозином, пікрофуксином, а також розчинами Гімзи та Май-Грюнвальда.

Результати. Гістопатологічний аналіз виявив специфічні зміни, включаючи вакуолізацію, некроз із геморагічними осередками, пікноз та запалення в нирковій тканині. Також спостерігалося значне збільшення кількості тучних клітин і дегенеративні зміни в епітеліальних клітинах ниркових канальців.

Висновки. Ці результати свідчать, що охратоксин А та афлатоксин В1 є потужними нефротоксинами, які спричиняють серйозне пошкодження епітеліальних клітин нирок та їх ядер, тоді як Т-2 токсин мав відносно менш виражений ефект. Це дослідження підкреслює шкідливий вплив мікотоксинів на ниркову тканину, наголошуючи на необхідності подальших досліджень щодо їх профілактики та пом'якшення для забезпечення безпеки харчових продуктів.

Ключові слова: *афлатоксин В1, охратоксин А, Т-2 токсин, тучні клітини, нефротоксичність, забруднення харчових продуктів.*

Introduction. Ensuring food safety is a paramount concern for both individuals and entities on a global scale. The growing importance of food supply availability and safety has become a significant issue for many countries, which are increasingly dependent on one another [1]. However, the health of both humans and animals is at risk due to the presence of mycotoxins—chemical toxins produced by fungi. These toxic fungal metabolites are naturally occurring in numerous foods and feed, and they can cause severe harm to public health, resulting in economic losses and safety issues worldwide due to the fungal contamination of agricultural commodities [2-7]. Approximately 25% of wheat worldwide is contaminated with mycotoxins, which have not been adequately studied for their complex structures and properties [8].

Mycotoxins, including aflatoxins, ochratoxins, and trichothecenes, are produced by various mold fungi such as Aspergillus, Fusarium, Penicillium, Claviceps, and Alternaria. These toxins can cause a range of acute and chronic health issues when ingested, including liver toxicity, nephrotoxicity, and immunosuppressive effects [9-14]. Of particular concern is the impact on kidney function, as mycotoxins have been shown to induce nephropathy in both animals and humans, though the specific renal effects of these toxins are not fully understood [2, 10, 14].

Research has primarily focused on the general toxicological effects of mycotoxins, but studies specifically addressing their renal-specific impacts remain limited. While the effects of aflatoxins, ochratoxins, and trichothecenes on other organs have been studied in detail, fewer studies have investigated the histological and immunological responses of kidney tissues to these toxins. This gap in renal-specific research is particularly critical given the kidney's role in detoxifying harmful substances and its susceptibility to toxin-induced damage.

This study aims to address this gap by investigating the histomorphological and immunological response in rat kidneys following exposure to aflatoxin B1, ochratoxin A, and T-2 toxin. By examining these toxins' specific impacts on kidney structure and immune reactions, this study provides valuable insights into the renal toxicity of mycotoxins, contributing to a deeper understanding of their effects on kidney function and structure.

Materials and methods. Experimental design. Our study aimed to evaluate histomorphological changes in rat kidneys under the influence of specific mycotoxins, namely aflatoxin B1, ochratoxin A, and T-2 toxin. We

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utilized a sample of 44 albino rats, aged between 3-4 months, with a body weight range of 150-200g. The animals were randomly divided into four groups (n=11 in each). The rats were subjected to a constant 12-hour light/dark cycle with 45–55% humidity conditions and were given a standard pellet diet and tap water ab libitum. The first group that served as a control group received a standard diet. While the second experimental group was fed a diet containing 24mg/kg of aflatoxin B1 for 20 days, the third group received a diet containing 64mg/kg of ochratoxin A for 20 days. Finally, the fourth third group was fed with T-2 toxin at 25mg/kg for 20 days. The doses were determined based on literature data, considering the concentrations of toxins commonly appearing in natural food crops and foodstuffs [15].

Each mycotoxin was first weighed using a high-precision balance. The powdered feed was thoroughly mixed with the prepared mycotoxins to provide its homogeneity. The toxins were dissolved in a small volume of solvent before mixing into the powdered feed. The size and weight of the pellets were standardized to ensure consistent dosing for each animal. After pellet preparation, the toxin concentrations in the final pellets were maintained consistent with the target doses. The number of pellets given to each rat was adjusted so that the total amount of toxin administered matched the calculated dose based on the animal's weight. This process was designed to minimize any potential variability in toxin exposure among the animals, ensuring consistent delivery to all subjects.

All experimental procedures have been performed according to the principles of the "International Recommendations on Carrying out of Biomedical Research with Use of Animals" (CIOMS, 2016), the European Convention for the Protection of Vertebral Animals Used for Experimental and Other Scientific Purposes (CE, 2005), the guidelines outlined in Directive 2010/63/EU [16], and approved by the National Center of Bioethics (Armenia).

Histological examination. During the experiment, the rats were euthanized using an intraperitoneal injection of ketamine hydrochloride (37 mg/kg) [17] immediately after the final doses of toxins were administered in the third week of the study. The kidneys were then removed and fixed using Bouin's solution and 10% formalin. The fixed tissues underwent standard histological processing, which included sequential dehydration with 70%, 80%, 90%, and 96% ethyl alcohol. Following dehydration, the tissues were cleared with xylene, embedded in paraffin, and coverslipped with DPX.

Paraffin sections approximately 5-6 μm thick were cut and stained using hematoxylin-eosin, picrofuchsin by Van Giesen, and Giemsa and May-Grünwald by Pappenheim [18]. The hematoxylin-eosin and picrofuchsin-stained preparations were utilized to examine the morphological changes in the rat kidneys due to mycotoxin exposure, including the sizes of the renal epithelial cell nuclei. Additionally, to assess the inflammatory responses to the mycotoxins, the number of mast cells within a standardized section area was counted across 50 fields of view. Cell counts were conducted on all sections from the studied animals and processed for microscopic reporting using magnifications of 200x, 400x, 600x, and 1000x. The microscope used was a B-293, equipped with an Optikam B5 Digital Camera (Model M-114, Italy). Images were recorded and analyzed using Optika Liteview software.

Data analysis. The numerical data obtained were analyzed using statistical methods to calculate the mean values, expressed as the mean ± standard deviation, with the assistance of Statistica 11 software. The significance of the differences between the mean values was determined using the Student's t-test (unpaired, two-tailed), with a p-value less than 0.05 considered statistically significant.

Results. Histopathological analysis. The present study aimed to investigate the effects of exposure to different mycotoxins on the kidneys in a rat model. It should be mentioned that the animals did not receive a high-fat diet to increase their weight, and as such, no weight data were collected. As a result, the toxin doses were not adjusted based on body weight.

The histomorphological examination of the aflatoxin B1-exposed rats revealed significant differences in both the ventromedial and dorsolateral zones of the kidneys compared to the control group (Fig. 1A-D).

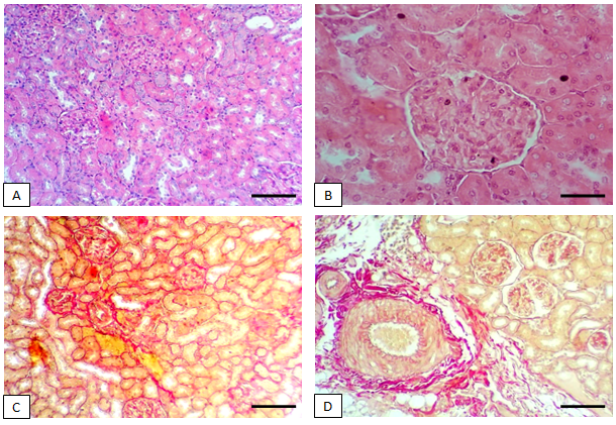

Fig. 1. Histological sections of the control rat kidneys (A-D). Glomerulus with proximal and distal convoluted tubules (A-ventromedial zone, B-dorsolateral zone), H&E (magnifications ×200 and ×400, scale bar = 50um). Blood vessels next to the renal corpuscle and tubular structures within the ventromedial zone (C). Cross-sectional view of connective tissue surrounding blood vessels in the dorsolateral zone, (D), picrofuxin, (magnifications ×200, scale bar = 75μm, 400, scale bar = 50μm).

Most of the cells in the kidneys of aflatoxin B1-exposed rats underwent pyknotic changes, and the proximal and distal tubes became more tightly spaced. Hemorrhagic foci were also observed, indicating functional inactivity of the kidneys after the daily intake of aflatoxin B1 (Fig. 2A-D).

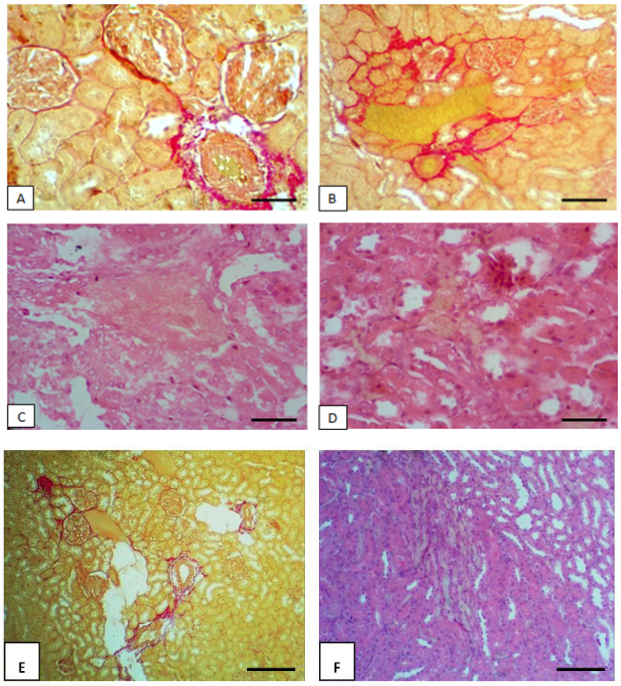

Fig. 2. Histological section of the kidney of a rat exposed with aflatoxin B1 (A), picrofuxin (magnifications ×400, scale bar = 50μm, (B), (magnification ×200, scale bar = 100μm). Hemorrhagic foci in the kidney of an aflatoxin B1-exposed rat (C, D), H&E (magnification ×400, scale bar = 50μm), (E), (picrofuxin, magnification ×200, scale bar = 100μm), (F), (H&E, magnification ×200, scale bar = 100μm).

Degenerative alterations were also evident in the kidneys of T-2 toxin-exposed rats, particularly in the renal tubules, where cells displayed widened margins, flattened structures, pyknotic changes, and cytoplasmic vacuolization (Fig. 4 A-D). Furthermore, a layer of heterochromatin was present in both the proximal and distal tubular cell nuclei, indicating decreased functional activity of the kidneys.

Similarly, the kidneys of rats exposed to ochratoxin A showed severe changes. These changes were characterized by degeneration of the epithelial cells in the renal tubules, including swelling and vacuolization, along with the accumulation of connective tissue around the affected areas. In some regions, necrosis of the tubules and atrophy of the glomerular capillaries were also observed (Fig. 3 A-D).

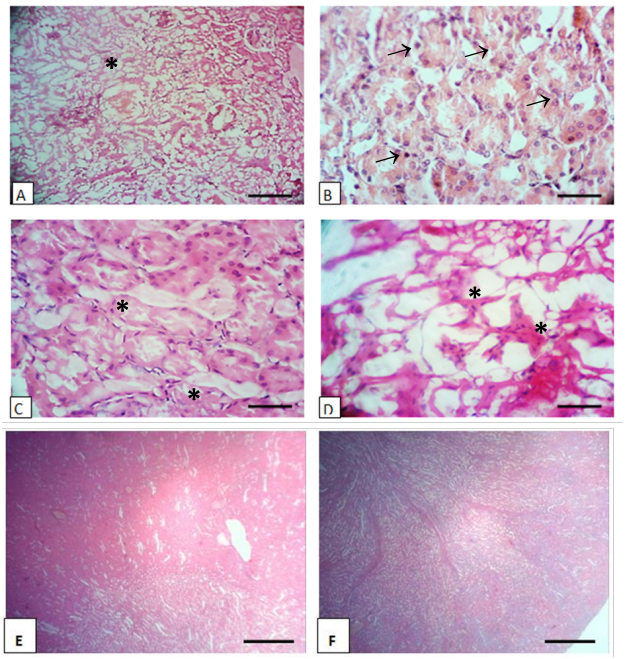

Fig. 3. Histological section of the kidney of an ochratoxin A-exposed rats. Pyknotic cells (arrows) of renal tubules and atrophy of glomerular capillaries. The swelling areas (asterisks) between the epithelial tubules and accumulated connective tissue elements, (A) (magnification ×100), (B,C,D) (H&E, magnification ×400, scale bar = 50μm), (E) (magnification ×40), (F) kidney of control group rats (H&E, magnification ×40).

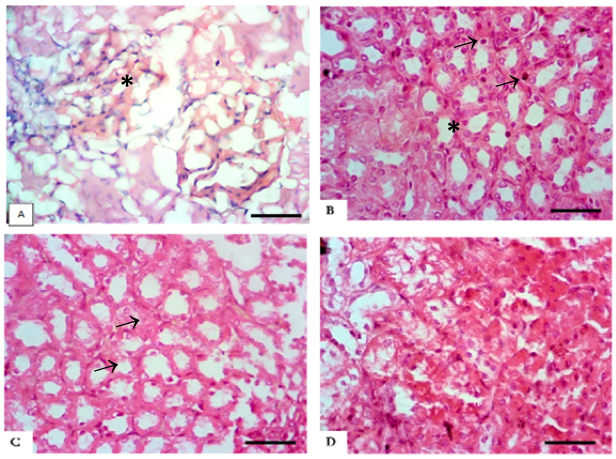

Fig. 4. Photomicrograph of T-2-toxin-exposed kidneys tissue sections. Degenerated renal corpuscles with pyknotic cells (arrows) and vacuolated cytoplasm (asterisk) (A). Proximal renal tubules have defected; cells are characterized by a vacuolated cytoplasm (asterisk) (B,C,D) (H&E, magnification ×400, scale bar = 50μm).

To assess the kidney's response to mycotoxin exposure, we examined the epithelial cells and their nuclei. Nuclear size was evaluated according to established criteria [19]. The results showed significant differences in the size of the epithelial cell nuclei in rats exposed to aflatoxin B1 and ochratoxin A, compared to the control group.

The diameter of cell nuclei was smaller in aflatoxin B1 and ochratoxin A-exposed groups compared to the control animals (p=0.001), whereas no significant alterations were observed in T-2 toxin-exposed rats (Table 1).

Table 1

Changes of epithelial cell nuclei in renal tubules of the rat kidneys with a daily intake of mycotoxins (n = 11/group)

Experimental groups	The diameter of the cell nuclei (μm) / mean±SD
Control	31.4±0.75
Aflatoxin B1	25.05±0.26*
Ochratoxin A	16.77±0.46*
T-2 toxin	33.21±0.63*

Significant difference (*p< 0.05) vs the control group

Consequently, the most remarkable changes were observed in ochratoxin A-exposed kidneys. Notably, the diameter of cell nuclei is smaller in aflatoxin B1-exposed and ochratoxin A-exposed groups compared to the control animals (Fig. 5).

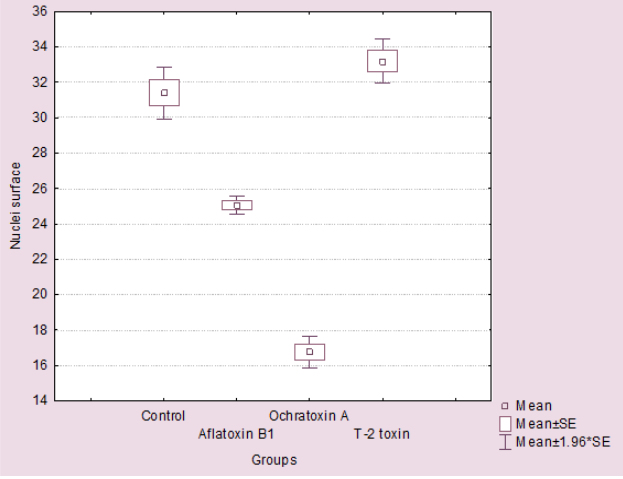

Fig. 5. Changes in sizes of the epithelial cell nuclei in aflatoxin B1, ochratoxin A, and T-2-toxin exposed rats' kidneys.

Based on the measurements obtained, it was observed that the average size of the renal epithelial nuclei decreased in animals that were exposed to aflatoxin B1 and ochratoxin A. This can be attributed to degenerative changes in the nuclei after the intake of these toxins, which testifies to their severe nephrotoxic effects.

Effects of mycotoxins on mast cells. Mast cells are a type of cell found in tissues that play an important role in maintaining local homeostasis by participating in inflammation, immunogenesis, blood coagulation, and circulation [20]. Exposure to mycotoxins has been linked to the activation of mast cells, and IgE antibodies to mycotoxins stimulate mast cells to release heparin, histamine, and pro-inflammatory cytokines [21]. The number of mast cells was counted to evaluate the immune responses of kidneys under exposure to mycotoxins. The quantitative changes in the number of these cells were compared between the control group and the mycotoxins-exposed animals.

Table 2 shows the number of mast cells in the kidneys of rats exposed to aflatoxin B1 and ochratoxin A significantly differs from the control group showing an increased number of mast cells. However, in animals exposed to T-2 toxin, the number of these cells did not demonstrate significant changes.

Table 2

Changes in the number of mast cells in control and mycotoxins-exposed rat kidneys (n = 11/group)

Experimental groups	Number of mast cells in each group/ (M ± SD)
Control	16.75 ± 2.3
Aflatoxin B1	17.75 ± 1.38*
Ochratoxin A	17.56 ± 0.26*
T-2 toxin	16.92 ± 0.33

Significant difference (*p< 0.05) *vs* the control group

The examination of animals that were exposed to mycotoxins revealed a considerable presence of degranulated mast cells, particularly around basement membranes (Fig. 6). These cells displayed a significant polymorphism, characterized by diverse granule sizes and densities in the cytoplasm, suggesting the presence of inflammatory reactions in the kidneys of mycotoxin-exposed rats. This reaction resulted in the destruction of the basal plates of the renal tubule walls.

Discussion. Recent medical literature suggests that the inhalation of mycotoxins may pose risks to human health. In animals, the ingestion of ochratoxin can lead to severe lesions, including glycogen accumulation, mitochondrial alterations, and extensive liver necrosis. Kidney damage is characterized by thickening of the glomerular basal membrane, lymphocytic infiltration of the interstitium, and IgG deposits in the glomeruli [22]. While most absorbed mycotoxins are excreted through urine, residues can accumulate in the liver, kidneys, and muscles, presenting a threat to both animal and human health [23].

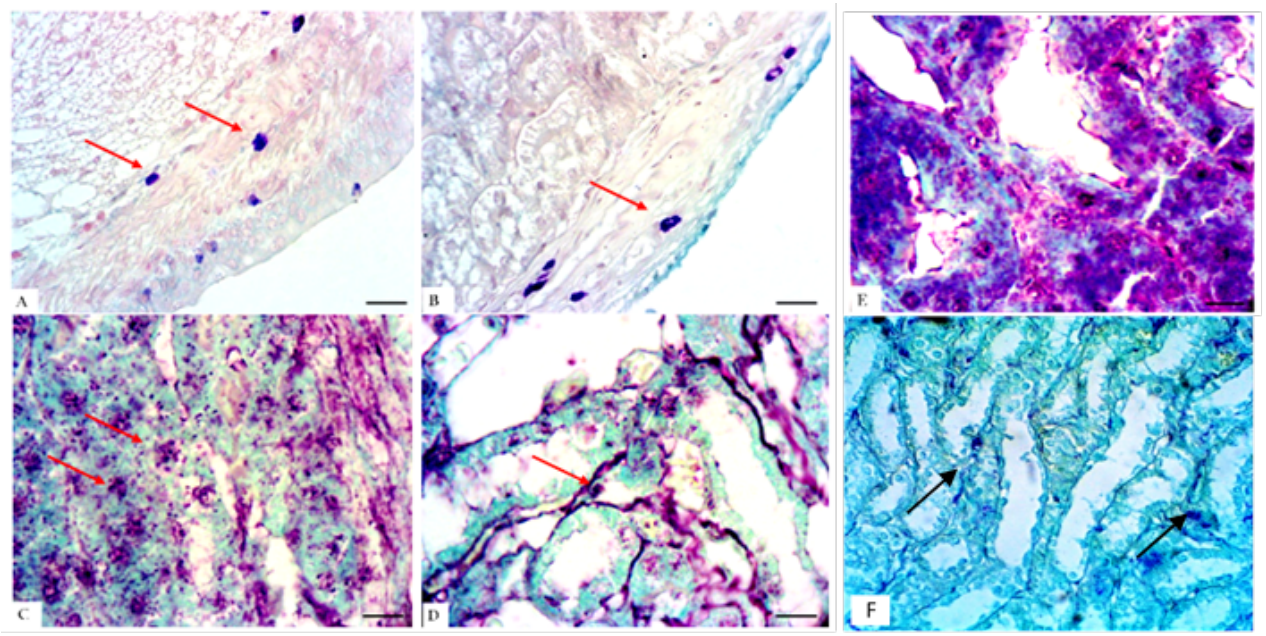

Fig. 6. Granulated mast cells in T-2 (A, B) and ochratoxin A (C) exposed rat kidneys. Degranulated mast cells (D, E) in aflatoxin B1 exposed rat kidneys (red arrows), Giemsa and May-Gr nwald staining (magnifications 400, scale bar = 50μm and x600, scale bar = 25μm). Mast cells in the control group (F), (magnifications 400, scale bar = 50μm).

The kidney is particularly susceptible to nephrotoxic attack, owing to its high blood flow and specialized metabolism. Environmental pollutants that target the kidney including mycotoxins can target the renal tissue as the majority of nephrotoxic compounds or their derivatives occur via the renal glomeruli and the proximal tubules [24]. The kidney and liver are predominantly affected, while immune cells in the thymus, spleen, and lymph nodes undergo structural and functional alterations, thereby influencing the function of immune organs. However, understanding of the mechanisms underlying ochratoxin A-induced immunotoxicity remains limited, particularly within the context of innate immunity [25]. The nephrotoxicity mechanism of mycotoxins involves multiple factors including oxidative stress, endoplasmic reticulum stress, mitophagy, inflammatory responses, and apoptosis, which are intertwined and interdependent [26]. This, in turn, can upregulate the proline dehydrogenase (PRODH) and pro-apoptotic factors (Bax, Caspase-3), and downregulate the apoptosis inhibitor Bcl-2 in mRNA and protein expression. Particularly, the ocharatoxin A may disrupt several cell functions, including cell proliferation, division, and signaling pathways. It also has a synergistic effect on other co-occurring mycotoxins [27]. Inflammation is one of the most important risk factors influencing the development of kidney disease. It has been reported that exposure to mycotoxins affects the transcription of the pro-inflammatory factor TNF-α and the production of the pro-inflammatory mediators [28-30]. This can contribute to the accumulation of inflammatory cells in the renal interstitium, thus creating an inflammatory infiltration composed of diverse immune cells. Prolonged inflammation eventually leads to chronic interstitial inflammation, tubular atrophy, and prominent fibrosis [31]. Mast cells in this case can contribute to the immune response as mycotoxins stimulate them to secrete pro-inflammatory cytokines and chemokines that activate the immune system leading to the stimulation of chronic neuroinflammatory symptoms [32-33].

Histopathological observations in visceral organs have highlighted the toxic effects of aflatoxin. Aflatoxin is primarily eliminated through the kidneys, and the accumulation of high concentrations of the toxin impairs excretory function, leading to congestion and pathological alterations. Aflatoxin-induced nephrotoxicity is believed to result from interference with the transport function in collecting tubular cells, along with diffuse impairment of proximal tubular function [34-36]. Most toxicological studies on mycotoxins have focused on exposure to a single toxin, without considering the potential interactions and combined effects—synergistic or antagonistic—that can occur in nature. Data on the toxic effects of mycotoxin mixtures are limited, and thus, the risks of exposure to multiple toxins remain uncertain [37].

In the present study, a significant decrease in the severity of histopathological and morphometric changes was observed in animals exposed to mycotoxins. Chronic administration of low doses of ochratoxin led to morphological and functional changes in the renal tubules, resulting in tubule tissue damage [38]. These findings suggest that simultaneous exposure to these toxins is likely, though the combined effects on human and animal toxicity remain unclear [39].

Among the mycotoxins studied, ochratoxin A exhibited the most pronounced nephrotoxic effects on the kidneys, while the effects of T-2 toxin were relatively

mild. In the kidneys of rats exposed to aflatoxin B1, the number of cells in the renal tubules was reduced. In contrast, in the kidneys of rats exposed to ochratoxin A, there were significant degenerative processes, marked by changes in renal tubule cells, the presence of numerous pyknotic cells, and cytoplasmic vacuolization. The number of cells in the kidneys of rats with various pathological alterations of the nuclei significantly increased following exposure to these mycotoxins. Additionally, the toxic effects of aflatoxin B1, ochratoxin A, and T-2 toxins were evident in changes in mast cells, which indicate an inflammatory response in the kidneys. The most pronounced immune responses were observed in rats exposed to ochratoxin A. These findings suggest that mycotoxins contribute to the progression of inflammation and cellular damage in kidney tissue [**40-42**].

Given the harmful effects of the studied mycotoxins, possible mitigation strategies, such as the use of dietary binders or detoxifying agents, are suggested. These agents could help alleviate the harmful effects of fungal metabolites and protect cells. Several studies have demonstrated that nutritional binders, such as bentonite clay, activated charcoal [**43-45**], and silymarin [**46**], can effectively adsorb aflatoxins and ochratoxins in the gastrointestinal tract, preventing their absorption and reducing systemic toxicity. These binders could be considered a preventive measure for individuals or animals at risk of exposure to contaminated food. Additionally, the application of certain antioxidants, such as vitamin C and E, and curcumin, may have potential protective effects against aflatoxicosis and ochratoxicosis. Evidence suggests that curcumin offers protective potential against tissue injury caused by certain drugs and environmental toxins. It has been shown to ameliorate aflatoxin B1-induced duodenal toxicity and liver injury by downregulating CYP450 enzyme activity and regulating hepatic long non-coding RNAs [**47-49**]. One of the most effective biological strategies to reduce the harmful effects of fungal toxins is the inclusion of probiotic yeasts and bacteria in the diet. Since probiotics can bind to toxins in the gastrointestinal tract, they can prevent toxin absorption and mitigate the effects on animal and human health [**50-52**].

Study limitations. This study has several limitations concerning the investigation of specific molecular biomarkers to further clarify the mechanisms of nephrotoxicity. The 20-day exposure period may not capture the long-term or chronic effects of mycotoxins on kidney health, which warrants further investigation over extended periods. The use of a rat model may not fully replicate human kidney toxicity, limiting the direct applicability of the findings to human health. Additionally, the study is restricted by the separate investigation of the mycotoxins instead of the combined version which should enhance our insights about the synergistic effects of those fungal toxins. Another key limitation is the variability in toxin administration. Despite our effort to provide the toxin's homogeneity in the feed, nevertheless, possible uneven mixing could have led to inconsistencies in exposure levels across animals. Albeit, these limitations may impact the reliability of the results, therefore future studies should provide more compelling findings into the interactions between multiple mycotoxins and warrant a better understanding of the collective effects of these toxins.

Conclusions. The present study reveals that prolonged exposure to mycotoxins results in nephrotoxic effects on the kidneys, causing cellular and histomorphological changes in the renal tubule walls. In cases of ochratoxicosis and aflatoxicosis, an elevated number of mast cells indicates inflammation in the kidneys. However, exposure to T-2 toxin produced only minor effects on kidney tissue and immune responses. The histopathological findings suggest that ochratoxin A and aflatoxin B1 are potent nephrotoxins, causing significant damage to epithelial cells and their nuclei, while the T-2 toxin had a less deleterious effect on kidney tissue. These findings contribute to a more precise understanding of the pathological effects of fungal toxins on renal histomorphology and their varied impact on kidney tissue.

Conflict of interest. The authors declare no conflict of interest.

Author contributions.

Anna Karapetyan: supervision, project administration, visualization;

Anna Karapetyan, Anna Grigoryan, Tamara Abgaryan: conceptualization, methodology, validation.

Tamara Abgaryan, Marietta Mkhitaryan, Lyudmila Niazyan, Ruzanna Adamyan: investigation, resources.

Anna Karapetyan, Anna Grigoryan, Marietta Mkhitaryan, Ruzanna Shushanyan: writing - original draft, writing - review & editing.

Data availability statement. The original contributions presented in the study are included in the article; further inquiries can be directed to the corresponding author.

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