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Histopathological study in mice infected experimentally with *Aspergillus fumigatus*

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Aspergillosis is a highly prevalent and dangerous infectious zoonotic disease that poses a significant threat to public health and animal welfare globally. *Aspergillus fumigatus* is an opportunistic fungal pathogen that disseminates efficiently through contaminated water, agricultural soil, and decaying organic matter. This research aims to characterize the acute toxic impacts and subsequent pathomorphological alterations induced by *Aspergillus fumigatus* within the liver and small intestine of laboratory mice. A total of 30 mice, aged 10–12 weeks and weighing approximately 25 g, were acclimated for two weeks and then randomly divided into an infected group and a control group, each containing 15 animals. Group 1 served as the untreated control, while Group 2 was challenged with a single intraperitoneal injection of *Aspergillus fumigatus* spore suspension at a concentration of 2×10^7 cells/ml with a dose of 20 µl per mouse. Following the experimental period, all animals were humanely euthanized for subsequent visceral tissue collection. Detailed pathomorphological analysis of the liver from the infected group revealed prominent lymphocyte cuffing adjacent to the hepatic blood vessels, severe hepatocellular necrosis, dilation of the central vein, hydropic cellular swelling, and vascular congestion. Furthermore, histopathological examination of the small intestine documented severe mucosal barrier degradation, including villous epithelial hyperplasia, extensive mononuclear cell infiltration within the mucosa and submucosa, diffuse tissue edema, advanced villous blunting, and localized fibrosis. In conclusion, the obtained results demonstrate that *Aspergillus fumigatus* and its associated mycotoxins induce profound structural tissue ruin in vital internal organs. Given the ubiquitous environmental distribution of the pathogen, these findings highlight its high virulence, its capacity to breach local epithelial protective barriers, and its ability to trigger severe acute inflammation, resulting in profound pathomorphological alterations in essential internal organ systems.

Keywords: Aspergillosis, *Aspergillus fumigatus*, Histopathological lesions, Liver pathology, Mycotoxins, Intestinal damage.

Патоморфологічне дослідження мишей за експериментального зараження *Aspergillus fumigatus*

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Аспергільоз є надзвичайно поширеним і небезпечним інфекційним зоонозним захворюванням, яке становить значну загрозу для громадського здоров'я та благополуччя тварин у всьому світі. *Aspergillus fumigatus* є опортуністичним грибковим патогеном, який інтенсивно поширюється через забруднену воду, ґрунти та гниючу органічну речовину. Це дослідження мало на меті охарактеризувати гострі токсичні ефекти та патоморфологічні зміни, спричинені *Aspergillus fumigatus* у печінці та тонкому кишечнику лабораторних мишей. Загалом 30 мишей (віком 10–12 тижнів і вагою приблизно 25 г) пройшли двотижневу акліматизацію, після чого їх випадковим чином розділили на інфіковану та контрольну групи, по 15 тварин у кожній. Група 1 служила необробленим контролем, тоді як Групі 2 вводили одноразову внутрішньочеревну ін'єкцію суспензії спор *A. fumigatus* у концентрації 2×10^7 клітин/мл у дозі 20 мкл на мишу. Після завершення експериментального періоду всі тварини були гуманно евтаназовані для подальшого відбору зразків вісцеральних тканин. Детальний патоморфологічний аналіз печінки інфікованої групи виявив периваскулярні лімфоцитарні муфти кровоносних судин печінки, вогнищевий некроз гепатоцитів, розширення центральної вени, гідропічне набрякання клітин і судинне повнокрів'я. Крім того, гістопатологічне дослідження тонкого кишечника зафіксувало глибоку деструкцію слизового бар'єра, включаючи гіперплазію епітелію ворсинок, дифузну інфільтрацію мононуклеарними клітинами слизової та підслизової оболонок, набряк тканин, виражене згладжування ворсинок і локальний фіброз. У підсумку, отримані результати демонструють, що *Aspergillus fumigatus* та пов'язані з ним мікотоксини спричиняють глибоке руйнування структури тканин життєво важливих внутрішніх органів. Враховуючи повсюдне поширення патогену в навколишньому середовищі, ці висновки підкреслюють його високу вірулентність, здатність долати місцеві захисні епітеліальні бар'єри та викликати важке гостре запалення, що призводить до глибоких патоморфологічних змін у внутрішніх органах макроорганізму.

Ключові слова: аспергільоз, *Aspergillus fumigatus*, гістопатологічні ураження, патологія печінки, мікотоксини, ураження кишечника.

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Introduction

Both fungi and yeasts can cause a wide range of serious infections, varying from minor allergies and localized mucosal canal infections to potentially lethal systemic mycoses. The primary driver of the increasing prevalence of fungal infections is the growing population of immunocompromised individuals, such as cancer and HIV/AIDS patients [1]. Numerous opportunistic fungal infections and mycoses include candidiasis, aspergillosis, cryptococcosis, and mucormycosis [2].

Aspergillus spp. is one of the most common and earliest documented agents of the fungal kingdom, first described in 1729 by the scientist Micheli. Throughout the 20th century, numerous studies categorized the genus *Aspergillus* into more than 180 species. *Aspergillus* species are filamentous saprophytic fungi that can colonize and infect living hosts, including insects, plants, mammals, and birds. These agents are ubiquitous in the soil, where they thrive as saprophytes [3]. *Aspergillus* induces a broad spectrum of pathologies, ranging from saprophytic colonization of the bronchial tree to rapidly invasive and diffuse infections.

Aspergillus fumigatus is considered the most prevalent pathogenic species in both humans and animals. As a saprotrophic fungus, it survives vegetatively on decaying organic matter in the soil and disseminates via asexual sporulation [4,5]. This fungus can withstand high temperatures (exceeding 50°C) typically found in decomposing plant material. The fungus produces a massive amount of airborne asexual spores [6]. Consequently, these fungi pose a severe clinical risk, inducing conditions from allergic reactions and chronic infections to highly invasive aspergillosis in both humans and animals [4].

Fungal genera such as *Penicillium* and *Aspergillus* germinate, develop, and produce mycotoxins at humidity levels of 80–90 % and 80 %, respectively [7]. However, environmental conditions that stimulate fungal vegetative growth do not always trigger mycotoxin production. Generally, temperatures between 25–30°C, water activity above 0.78, and relative humidity ranging from 88 % to 95 % represent the most favorable conditions for fungal and yeast growth, as well as subsequent mycotoxin synthesis [8].

The aim of the study

This research aims to characterize the acute toxic impacts and subsequent pathomorphological alterations induced by *Aspergillus fumigatus* within the liver and small intestine of laboratory mice.

Materials and methods

Isolation and identification of Aspergillus fumigatus

A total of 40 nasal swabs were collected from dogs with respiratory diseases in the Diyala Governorate. The research samples were stored in sterile tubes containing fresh transport media and maintained at 4°C in ice containers until cultivation. In the laboratory, the samples were inoculated onto Sabouraud Dextrose Agar and incubated at 37°C for 7 days.

Preparation and standardization of inoculum

To prepare the fungal inoculum for animal infection, conidia were obtained by flooding the agar plates with 20 ml of sterile phosphate-buffered saline (PBS) containing 0.1 % Tween-80. The resulting suspension was filtered through two layers of sterile gauze to remove any remaining hyphae fragments and maintained at 4°C [9].

To standardize the concentration of this spore suspension, a McFarland standard solution No. 0.5 was prepared as a reference by mixing 9.95 ml of 1 % sulfuric acid with 0.05 ml of 1 % barium chloride in a sealed tube [10]. The density of the filtered fungal suspension was then adjusted according to this McFarland standard to achieve the precise target concentration of 2×10^7 cells/ml, which was required for the subsequent experimental challenge.

Experimental animals

A total of 30 mice, aged 10–12 weeks and weighing approximately 25 g, were acclimated for two weeks and then randomly divided into an infected group and a control group, each containing 15 mice.

Group 1: control mice (untreated).

Group 2: mice infected with *Aspergillus fumigatus* at a concentration of 2×10^7 cells/ml, administered via a single intraperitoneal injection at a dose of 20 µl per mouse, following the protocol described by Allawi [11].

At the end of the experimental post-infection period, all mice from both groups were humanely euthanized in strict accordance with international bioethical guidelines for the care and use of laboratory animals to minimize suffering, after which tissues were immediately harvested for further laboratory investigation.

Histopathological Study

Liver and intestine samples were collected and fixed in a 10 % formaldehyde solution to preserve the tissues in proper condition. The specimens were then processed routinely using an automated tissue processor (Histokinette) according to standard methods [12].

Results and discussion

Liver histopathology analysis

Histological examination of the liver sections from the control group (untreated mice, G1) demonstrated no significant pathological changes, as the tissue exhibited a well-preserved architecture with normal hepatocytes and clear sinusoids, which can be observed in ***Fig. 1***.

The hepatic parenchyma displays normal histological features characteristic of healthy murine tissue. The polyhedral hepatocytes are organized in neat radiating cords with distinct, centrally located spherical nuclei. The spaces between the cell cords, representing the hepatic sinusoids, are completely clear, showing no signs of congestion, endothelial damage, or cellular infiltration.

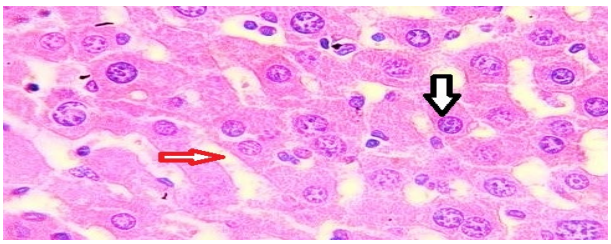

Fig. 1. Histological section of the liver from the control group (G1) showing normal hepatocytes (indicated by the white-and-black arrow) and intact sinusoids (indicated by the red arrow). (H&E stain, 40×)

In stark contrast, the pathomorphological examination of the liver from mice infected with *Aspergillus fumigatus* (G2) revealed severe structural alterations characteristic of acute parenchymal injury, heavily marked by a dense accumulation of inflammatory cells around the expanded vascular wall, as clearly demonstrated in ***Fig. 2***.

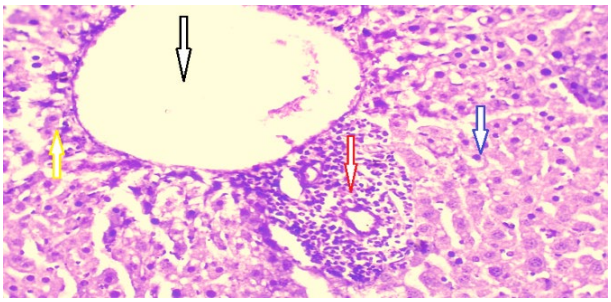

Fig. 2. Histopathological section of the liver from the infected group (G2) showing prominent lymphocytic cuffing around a blood vessel (red arrow), a severely dilated central vein (black arrow), acute cellular swelling of hepatocytes (blue arrow), and focal necrosis (yellow arrow). (H&E stain, 40×)

The microphotograph captures a severe acute inflammatory process within the hepatic tissue. The central vein is massively dilated and engorged, surrounded by a heavy peri-vascular sheath composed mostly of lymphoid cells (lymphocytic cuffing). The adjacent hepatocytes are severely altered, showing advanced hydropic degeneration or acute cellular swelling with a pale, vacuolated cytoplasm, along with focal zones of coagulative necrosis.

Further detailed assessment of the infected liver parenchyma (G2) confirmed the deep progression of the inflammatory response, specifically showing how a longitudinal section of the hepatic blood vessel becomes enveloped in a dense perivascular sheath, which is highlighted in ***Fig. 3***.

The longitudinal cut of the vascular channel displays a severe form of non-suppurative hepatitis. The perivascular connective tissue is heavily infiltrated by mononuclear inflammatory cells. This aggressive infiltration extends directly into the nearby sinusoidal spaces, actively breaking up the hepatic cords and causing widespread cellular dissolution, leaving behind ghost-like necrotic hepatocytes with fragmented or absent nuclei.

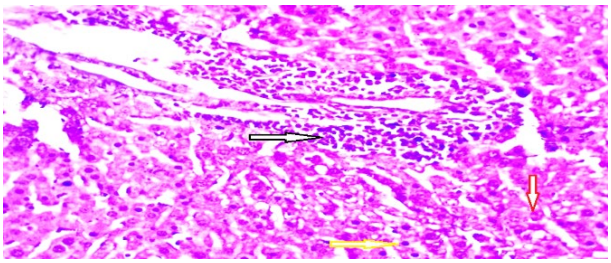

Fig. 3. Histopathological section of the liver from the infected group (G2) showing distinct lymphocytic cuffing around a longitudinal blood vessel (white arrow with black outline), diffuse mononuclear cell infiltration (yellow arrow), and necrotic hepatocytes (red arrow). (H&E stain, 40×)

The histopathological analysis of the liver from the infected group (G2) additionally demonstrated significant hemodynamic disturbances alongside advanced parenchymal damage, resulting in severe vascular congestion and microthrombi formation, as illustrated in ***Fig. 4***.

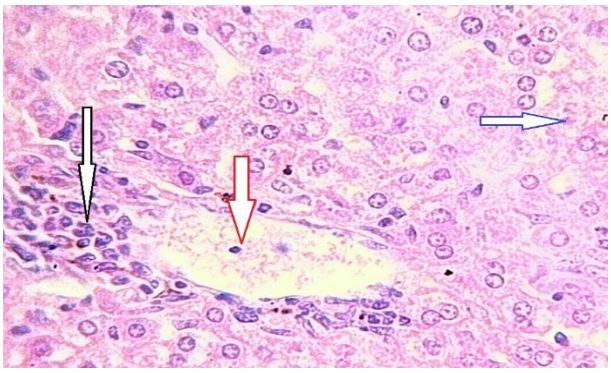

Fig. 4. Histopathological section of the liver from the infected group (G2) showing prominent lymphocyte cuffing around a blood vessel (white arrow), marked vascular congestion (red arrow), and a necrotic hepatocyte exhibiting nuclear dissolution (blue arrow). (H&E stain, 40×)

This region highlights the severe toxic and circulatory impacts of the fungal pathogen. The blood vessel lumen is heavily congested and filled with packed erythrocytes, indicating stasis. Persistent perivascular lymphocytic aggregates exert physical pressure on the hepatic architecture. The surrounding hepatocytes display terminal cellular damage, including advanced karyolysis (nuclear dissolution) and cellular shrinkage.

At a higher resolution, closer inspection of the infected liver parenchyma (G2) revealed localized cellular responses and small, well-defined focal aggregations of lymphocytes within the sinusoidal spaces away from the main vessel walls, as visualized in ***Fig. 5***.

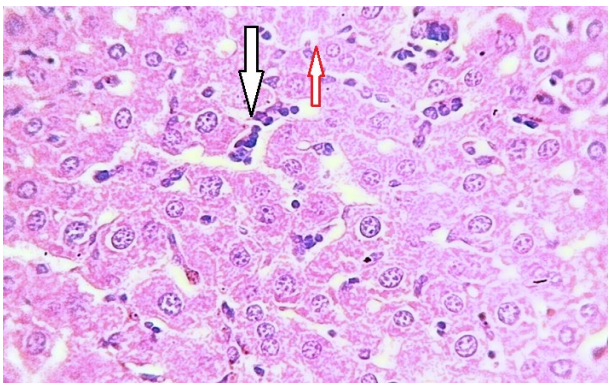

Fig. 5. Histopathological section of the liver from the infected group (G2) showing active nuclear division and slightly degenerated hepatocytes (red arrow), alongside a distinct focal aggregation of lymphocytes (white arrow). (H&E stain, 40×)

The microphotograph demonstrates a chronic-active cellular defense mechanism. A prominent focal cluster of lymphocytes is embedded directly within the hepatic cords. While many nearby cells show mild degenerative changes, there is clear evidence of nuclear division and binucleation among several hepatocytes, which represents a compensatory regenerative attempt by the liver tissue to overcome the destructive mycotoxins.

Intestine histopathology analysis

Histological examination of the intestinal sections from the control group (untreated mice, G1) demonstrated a completely normal and well-preserved tissue architecture, showing intact mucosal villi lined by a continuous epithelial layer, as shown in ***Fig. 6***.

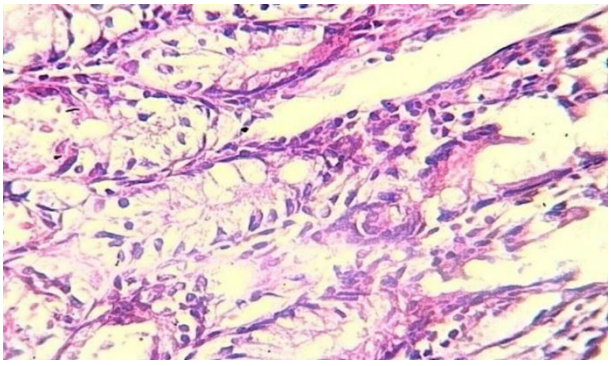

Fig. 6. Histological section of the intestine from the control group (G1) showing normal, intact architecture of the villi within the mucosal layer. (H&E stain, 40×)

The structural integrity of the small intestine is fully preserved. The finger-like intestinal villi project normally into the lumen, covered by a uniform layer of simple columnar epithelial cells with an intact brush border. The underlying lamina propria contains a normal, low density of resident immune cells, and no edema or vascular alterations are present in the submucosa.

On the contrary, the pathomorphological examination of the intestinal tissue from mice infected with *Aspergillus fumigatus* (G2) revealed early structural degradation and a pronounced local inflammatory response, marked by distinct cellular hyperplasia of the villi, as seen in ***Fig. 7***.

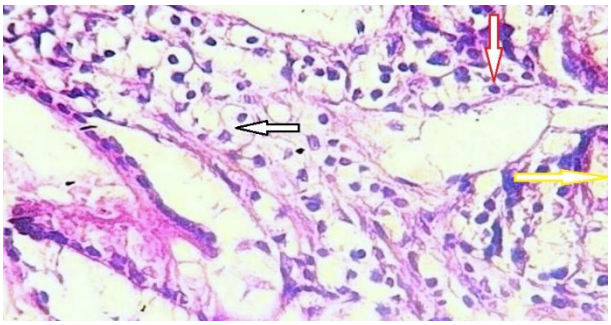

Fig. 7. Histopathological section of the intestine from the infected group (G2) showing prominent hyperplasia of the villi (white arrow with black outline), extensive mononuclear cell infiltration within the mucosa and submucosa (red arrow), and severe tissue edema (yellow arrow). (H&E stain, 40×)

The tissue responds to the fungal irritation with defensive remodeling. The epithelial layer of the villi displays noticeable hyperplasia, making the structures appear thickened. A heavy influx of mononuclear inflammatory cells is visible throughout the mucosa and submucosa. Furthermore, severe accumulation of fluid (edema) pushes the connective tissue fibers apart, widening the submucosal space.

With the continuous progression of the *Aspergillus fumigatus* infection, the intestinal mucosa (G2) displayed advanced structural lesions and acute vascular disturbances, which caused severe infiltration of the epithelial cells and localized hemorrhages, as documented in ***Fig. 8***.

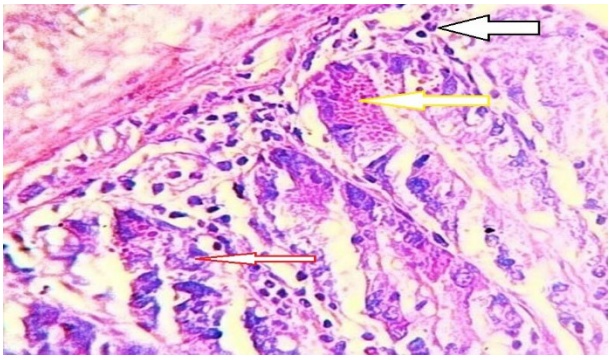

Fig. 8. Histographical section of the intestine from the infected group (G2) showing mononuclear cell infiltration within the mucosal layer (white arrow), damaged and disrupted intestinal villi (red arrow), and widespread hemorrhage (yellow arrow). (H&E stain, 20×)

At a lower magnification, a wider zone of destruction is visible. The normal architecture of the mucosal surface is lost, showing severe mechanical damage, blunting, and fragmentation of the villi. Masses of mononuclear cells

infiltrate the mucosal sheet, and prominent patches of free red blood cells (hemorrhage) are scattered across the tissue, showing that the local capillary walls have been damaged by the infection.

In the deeper layers and prolonged stages of tissue injury, the intestinal wall of the infected group (G2) exhibited chronic structural remodeling and a significant proliferation of connective tissue elements within the submucosa, which is clearly illustrated in ***Fig. 9***.

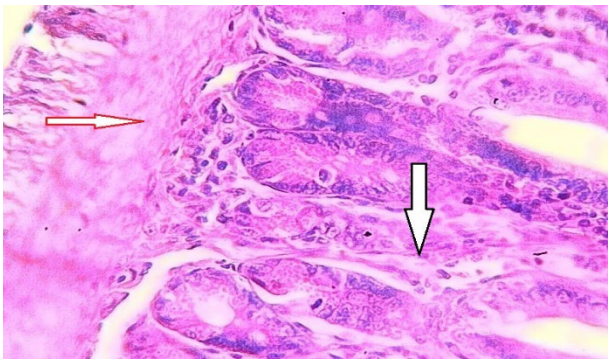

Fig. 9. Histopathological section of the intestine from the infected group (G2) showing advanced damage to the mucosal villi (white arrow with black outline) and areas of localized fibrosis within the tissue wall (red arrow).
(H&E stain, 40×)

The image illustrates a chronic pathological shift within the intestine. The mucosal villi are completely flattened and ruined. In response to this severe, long-term ulceration and inflammation, the tissue has activated fibroblastic pathways, resulting in an abnormal accumulation of collagen fibers (localized fibrosis) within the structural wall, which permanently alters intestinal function.

Detailed histopathological evaluation of the intestinal mucosa from the infected group (G2) finally highlighted significant cellular and functional adaptive responses, leading to widespread vacuolation and a massive increase in secretory structures, as captured in ***Fig. 10***.

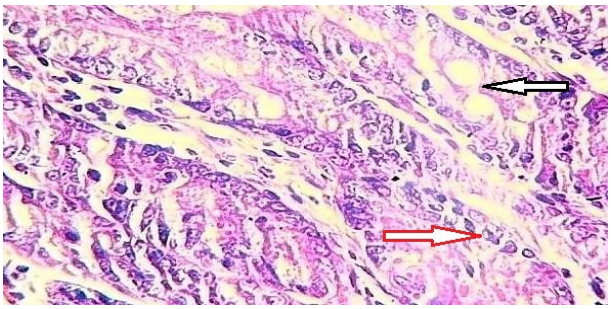

Fig. 10. Histopathological section of the intestine from the infected group (G2) showing prominent vacuolation of epithelial cells (red arrow) and a significant increase in the number and size of mucus-secreting goblet cells (white arrow with black outline).
(H&E stain, 40×)

The high-power view reveals severe intracellular pathology and a hyper-secretory state. The columnar epithelial cells contain large clear spaces (vacuolation), showing a breakdown of fluid balance inside the cells. Concurrently, the tissue shows a massive increase in both the size and number of goblet cells (goblet cell hyperplasia). This represents an intense physiological effort by the intestine to produce excessive mucus to shield itself from *A. fumigatus* and its toxic metabolites.

Infection with *Aspergillus* species has been extensively documented in both humans and animals [13, 14]. This opportunistic genus comprises pathogens capable of inducing a broad spectrum of mycoses, ranging from hypersensitivity reactions to highly invasive and lethal systemic aspergillosis, heavily facilitated by its ubiquitous nature as an airborne filamentous fungus [15–17]. Previous studies evaluated the impacts of *Aspergillus fumigatus* via intranasal inoculation in mice, demonstrating that a common host could suffer from systemic aspergillosis [18–20]. The current research concentrated on the pathobiological activity of this fungal species across vital internal organs when administered via the intraperitoneal route in a murine model, serving as a complementary study to map the dissemination patterns of aspergillosis.

The liver represents the primary target organ in cases of mycotoxin poisoning, although other systemic organs may also be progressively affected [21]. Numerous studies have documented severe histopathological changes in hosts suffering from systemic aspergillosis [18]. The histopathological alterations observed in the liver tissue of mice exposed to *A. fumigatus* in this study included extensive mononuclear cell infiltration, central vein dilation, acute cellular swelling of hepatocytes, severe vascular congestion, hepatocellular degeneration, and necrosis. It has been reported that *A. fumigatus* produces a wide variety of extracellular metabolites, including organic acids and proteolytic proteins [22]. Consistent with our findings, previous research noted that liver damage following *A. fumigatus* infection includes focal hemorrhages, lymphocyte infiltration, and hepatocellular necrosis, particularly localized near the portal spaces [18].

Furthermore, historical histopathological analyses revealed dose-dependent degenerative changes within specific hepatic cells, confirming that profound liver degeneration takes place during fungal infection [23]. These changes are typically accompanied by the influx of inflammatory cells across numerous anatomical locations, hemorrhagic expansions, and marked congestion developments within both the portal and central veins [23]. It has been documented that such hepatocellular necrosis is directly triggered by the specific metabolic products and toxins synthesized by *Aspergillus* fungi [24]. For instance, it was observed that within 48 hours of *A. fumigatus* and *Aspergillus flavus* injection, hepatocytes undergo acute necrosis, developing into cumulative inflammation and exerting severe harmful impacts on the murine liver [25]. Pathogenic *Aspergillus* species produce an array of distinct toxins, including endotoxins, oxalic acid, gliotoxins, and heparin factors,

which collectively induce tissue necrosis and systemic immunosuppression [26].

Regarding the intestinal tract, it was indicated that mice infected intraperitoneally with *A. fumigatus* for more than two weeks displayed marked mononuclear cell (MNC) infiltration within the tissue matrix, alongside prominent epithelial cell hyperplasia in the intestine [27]. Conversely, some studies observed widespread fungal-induced damage within the mucosal layers and external linings, noting a significant reduction in the regions settled by goblet cells and a depletion of mucins following exposure to varying levels of *Aspergillus cristatum* [28].

Furthermore, exposure to *Aspergillus* toxins at a dose of 0.6 mg/kg generally induces generalized hyperemia across all intestinal segments, accompanied by localized individual hemorrhages, with the duodenum being more deeply affected compared to other segments [29]. Under these toxic conditions, portions of the villous epithelium undergo desquamation and are sloughed into the intestinal lumen; this cellular disintegration, desquamation, and basement membrane hypertrophy are strictly associated with pyknosis and karyolysis of the nuclei [29]. When the toxic dose is increased to 0.8 mg/kg, the intestinal destruction becomes significantly more severe, leading to advanced necrotic alterations within the intestinal villi [29], which aligns with the widespread mucosal hemorrhages documented across multiple studies [30].

All *Aspergillus* species are considered opportunistic agents, with *A. fumigatus* being the primary etiological driver of aspergillosis in both humans and animals, even though other species within the genus may be concurrently involved [31]. These pathogens trigger severe clinical manifestations when predisposing risk factors are present, such as immunodeficiency, physiological stress, and adverse environmental conditions, including poor ventilation, toxin exposure, dusty atmospheres, and inappropriate humidity or temperature levels [32]. Ultimately, the pathogenicity of *A. fumigatus* is driven by its specialized virulence factors. These are represented by specific components of its genetic architecture responsible for pathogenicity, alongside the active secretion of mycotoxins and proteolytic enzymes [33]. These mechanisms effectively enable the fungus to penetrate biological barriers and invade vital internal organs despite the microscopic size of its airborne spores [33].

Conclusions

In conclusion, this study demonstrates that *Aspergillus fumigatus* exhibits profound virulence and pathogenicity, inducing severe acute inflammatory and degenerative pathomorphological alterations within vital visceral systems. The experimental intraperitoneal challenge in a murine model establishes that the dissemination of fungal elements and their secondary mycotoxins triggers profound tissue damage, characterized by severe vascular congestion, leukocyte infiltration, and focal necrosis in the hepatic parenchyma, alongside extensive mucosal degradation, villous blunting, localized fibrosis, and protective goblet cell hyperplasia in the small intestine. Ultimately, these findings highlight the significant public health risk posed by the ubiquitous environmental presence of *A. fumigatus*, underscoring its capacity to breach local epithelial barriers, suppress host tissue resistance, and cause multi-organ pathomorphological failure.

DECLARATIONS

Ethical Statement

The author confirms that all experimental procedures and studies involving biological objects were planned and conducted in strict accordance with the "European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes" (Strasbourg, 1986), Directive 2010/63/EU, national ethical norms, and international standards for the humane treatment of laboratory animals (NIH, ARRIVE). The research protocol and experimental scheme were officially reviewed and approved by the Bioethics Committee of the College of Veterinary Medicine, University of Diyala, Iraq (Protocol No. 50 dated 20/02/2026. To minimize animal stress, discomfort, and suffering, all handling, maintenance, inoculation, and subsequent tissue sampling procedures involving laboratory mice were executed in strict compliance with standard veterinary guidelines, recommendations of the American Veterinary Medical Association (AVMA), and current international principles of animal welfare.

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Conflict of Interest

The author states that there is no conflict of interest.

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Declaration of AI and AI-assisted technologies

The author declares that no generative AI or AI-assisted technologies were used during the preparation, writing, translation, or language polishing of this manuscript. The final content was fully authored and reviewed by the researcher, who takes sole responsibility for the work.

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