Advances in Research on Mycotoxin-Induced DNA Damage in Multiple Cell Types: Postprint

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Abstract

Mycotoxins are widely present in feed raw materials and human food, posing a serious threat to animal and human health while also exerting negative impacts on economic benefits. Mycotoxins affect cell growth, induce oxidative stress by increasing intracellular reactive oxygen species levels, and cause DNA damage in cells. Based on existing research both domestically and internationally, this paper provides a comprehensive review of the DNA damaging effects of mycotoxins on intestinal, hepatic, renal, and neuronal cells.

Full Text

Research Progress of Mycotoxins on DNA Damage of Different Cells

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Abstract: Mycotoxins are widely present in feed ingredients and human food, posing serious threats to animal and human health while causing significant economic losses. These toxins affect cell growth by increasing intracellular reactive oxygen species (ROS) levels, leading to oxidative stress and DNA damage. This review summarizes current research on the DNA-damaging effects of mycotoxins on intestinal, hepatic, renal, and neural cells.

Keywords: mycotoxins; DNA damage; mechanism

Animal feed is susceptible to fungal contamination during production and storage, resulting in the generation of secondary metabolites known as mycotoxins. The primary mycotoxins include aflatoxin B1 (AFB1), ochratoxin A (OTA), zearalenone (ZEA), fumonisin B1 (FB1), and deoxynivalenol (DON). These toxins can increase animal body weight and relative organ weights, cause gastrointestinal dysfunction, diarrhea, reduced appetite, hepatomegaly, and impair kidney function in birds, leading to apoptosis of renal tubular epithelial cells [1].

The intestine serves as the primary route for mycotoxin entry into the body. Under normal structural and functional conditions, the intestinal tract forms a physical barrier against invading pathogens and toxins [2]. As the first line of defense against food contaminants, intestinal epithelial cells exhibit high sensitivity to mycotoxins [3]. These toxins can cause intestinal damage in animals, triggering inflammation, ulceration, and hemorrhage, while disrupting intestinal epithelial cells [4]. The liver is the body' s most important detoxification organ, and mycotoxin-induced hepatocellular damage directly affects metabolic capacity. Approximately 50% of ingested mycotoxins are absorbed in the duodenum and primarily distributed to the liver. As a major immune, detoxification, and digestive organ, liver damage initiates a cascade of pathological changes that negatively impact animal health and performance, causing reproductive disorders and potentially leading to death [5].

Primary metabolites of various mycotoxins are frequently detected in animal urine and feces [6]. Most are excreted in urine conjugated with glucuronic acid, while some toxins are eliminated without metabolism [7]. These unmetabolized toxins can damage renal tubules and kidney cells, causing tubular edema and cellular vacuolation that impair kidney function. The nervous system regulates signal transmission and coordinates tissues and organs throughout the body, establishing and receiving external information. Neurological damage consequently affects overall bodily function [8]. Mycotoxins stimulate nerve cells, trigger immune responses, and can induce autoimmune diseases, allergies, and inflammatory pain [9]. Numerous studies have demonstrated that mycotoxins affect cell growth and cause oxidative stress, resulting in DNA damage. This review examines the DNA-damaging effects of mycotoxins on intestinal, hepatic, renal, and neural cells, providing a theoretical foundation for more comprehensive future research on mycotoxin impacts in animals.

1. Mycotoxin-Induced DNA Damage in Intestinal Cells

Extensive literature has focused on mycotoxin effects on intestinal mucosal barrier function, including mechanical, chemical, immune, and biological barriers [10]. In vitro models such as porcine intestinal epithelial cells (IPEC-J2) [11], colon cancer cells (Caco-2) [3], and their differentiated derivative cell line TC7 are commonly employed, with differentiated cells showing greater sensitivity

than undifferentiated cells [12]. IPEC-J2 cells are frequently used to investigate mycotoxin cytotoxicity and oxidative damage [13]. Caco-2 cells exhibit structural and functional similarities to human small intestinal epithelium, possessing microvilli structures and brush border enzyme systems with identical cell polarity and tight junctions. When grown on porous, permeable polycarbonate membranes, these cells fuse and differentiate into intestinal epithelial cells, making them suitable for studying mycotoxin effects on intestinal barrier function and tight junction proteins [14].

DNA damage represents a primary cause of carcinogenesis and teratogenesis. Bony et al. [15] applied DON to both differentiated and undifferentiated human colon cancer Caco-2 cells, with comet assay results demonstrating that DON increased comet tail length in a time- and dose-dependent manner. Differentiated cells exhibited greater sensitivity to toxic effects than undifferentiated cells, likely because they more closely approximate physiological conditions and produce more signaling factors, making differentiated Caco-2 cells more appropriate for evaluating mycotoxin genotoxicity. ROS generation can cause DNA damage, which in turn indirectly promotes further ROS production, creating a destructive cycle. Taranu et al. [16] conducted transcriptome analysis of porcine intestinal epithelial IPEC-1 cells treated with 10 mol/L ZEA, a concentration that did not affect cell viability. ZEA modulated expression of glutathione peroxidase (GPx) genes (GPx6, GPx2, GPx1), promoting ROS production. Thus, even at non-cytotoxic concentrations, mycotoxins can cause oxidative damage through DNA alterations, with oxidative damage representing the manifestation and DNA changes representing the underlying cause. Antioxidant supplementation can inhibit mycotoxin-induced DNA damage.

Abid-Essefi et al. [17] treated undifferentiated Caco-2 cells with ZEA, with agarose gel electrophoresis revealing dose-dependent DNA fragmentation and inhibition of DNA adduct formation, producing characteristic DNA ladders. However, vitamin E supplementation reduced DNA fragmentation while prolonging the cell cycle, demonstrating its capacity to repair DNA damage through antioxidant activity. This confirms the close relationship between ROS generation and DNA damage. Other intestinal cells such as porcine IPEC-1 cells can evaluate mycotoxin effects on epithelial membrane integrity. Pacheco et al. [18] found that DON decreased transepithelial electrical resistance (TEER) values and cell viability in IPEC-1 cells, while phytic acid acted as a damage inhibitor that attenuated DON-induced injury.

Since feed ingredients are typically contaminated with multiple mycotoxins simultaneously, researchers have investigated their interactive effects. Kouadio et al. [19] examined DON, ZEA, and FB1 interactions using undifferentiated human colon cancer Caco-2 cells as an in vitro model. Malondialdehyde (MDA) production was higher when DON was combined with ZEA or FB1 compared to individual treatments or triple combinations. All three mycotoxins individually inhibited DNA synthesis by 45%, 70%, and 43%, respectively. Binary combinations showed more pronounced inhibition (62%, 35%, and 65%), while

triple combination exhibited weaker inhibition (25%). This suggests that cellular substances produced in response to three mycotoxins may attenuate the toxicity of the initial two toxins, highlighting the importance of understanding each mycotoxin' s mechanism of action.

These studies demonstrate that single or combined mycotoxins affect intestinal function, with consistent results across in vivo, in vitro, and ex vivo experiments. Intestinal cell models can simulate intestinal structure to investigate damage mechanisms, with differentiated cells providing more physiologically relevant environments and greater sensitivity. Antioxidant supplementation reduces mycotoxin damage, making oxidative stress control crucial for protecting DNA integrity. Different mycotoxins employ distinct mechanisms, and cell interactions vary accordingly. Investigating mycotoxin combinations present in the same food source is essential for developing strategies to eliminate their harmful effects.

2. Mycotoxin-Induced DNA Damage in Hepatocytes

Hep-G2 cells exhibit high morphological differentiation and are widely used to model mycotoxin-induced hepatocellular damage. These cells and their derivatives serve as model systems for studying xenobiotic metabolism and toxicity, cell viability, and anti-genotoxic effects. Kang et al. [20] and Gazzah et al. [21] utilized Hep-G2 cells to investigate toxin hepatotoxicity, while Sahu et al. [22] and Rumora et al. [23] studied oxidative damage. Other models including HepaRG cells and hepatocytes from adult male Wistar rats have also been employed to assess mycotoxin-induced DNA damage in liver cells.

Mycotoxins can cause DNA strand breaks in hepatocytes. Sahu et al. [24] demonstrated that high concentrations (2 g/mL) of DON disrupted mitochondrial function in rat hepatocytes, causing double-strand DNA breaks and DNA damage. Comet assay tail moment and length reflect DNA damage severity. Le Hégarat et al. [25] investigated DNA damage in HepaRG cells exposed to carcinogenic substances, using comet tail length as an indicator. AFB1 increased comet tail length in a dose-dependent and significant manner. DNA damage typically accompanies apoptosis. Animal studies on FB1 hepatotoxicity and carcinogenicity showed that FB1 induced apoptosis and lipid peroxidation in adult male Wistar rat hepatocytes in a dose- and time-dependent manner. Comet assay results revealed that a single oral dose of 5 g/kg FB1 did not cause DNA damage after 24 hours, while high doses (500 g/kg) significantly increased comet tail length. This suggests that induced apoptosis was not caused by DNA damage, and low-dose FB1 does not affect DNA replication during mitosis [26].

Caspase-3/7 expression serves as an apoptosis marker and is representative for studying the relationship between apoptosis and DNA damage. Ayed-Boussema et al. [27] demonstrated that ZEA inhibited Hep-G2 cell proliferation in a dose-dependent manner, with necrotic cells comprising 6% of the 55% dead cells at high concentrations (120 g/mL). ZEA altered mitochondrial membrane poten-

tial, and microarray analysis revealed that ZEA upregulated the p53 gene family via the ataxia telangiectasia mutated (ATM) pathway, increasing caspase-9 and caspase-3 protein expression to induce apoptosis. However, Takakura et al. [28] found that when HepaRG cells were treated with various DON concentrations for 24 hours, DON promoted caspase-3/7 expression and induced apoptosis without increasing comet tail length or causing DNA damage. The authors hypothesized that DON may lack in vitro genotoxicity.

These studies indicate that Hep-G2 cells serve as an appropriate in vitro model for evaluating mycotoxin effects on hepatocyte proliferation, apoptosis, and DNA damage. Other models such as Wistar rat hepatocytes and HepaRG cells can also assess DNA damage and mechanisms. However, the mechanisms of hepatocyte proliferation inhibition vary, with apoptosis representing only one form. Investigating apoptosis provides a more representative approach for understanding mycotoxin-induced growth inhibition. Mycotoxins produce hepatotoxicity within short timeframes, promoting apoptosis and apoptotic protein expression, though DNA damage may not be detectable. Therefore, the relationship between mycotoxin-induced apoptosis and DNA damage requires further investigation with extended exposure times and higher concentrations.

3. Mycotoxin-Induced DNA Damage in Renal Cells

Mycotoxin-induced kidney damage primarily manifests as injury to renal tubules and glomeruli [29-30]. Researchers commonly use African green monkey kidney epithelial cells (Vero) and human embryonic kidney cells (HEK293) as in vitro models [31]. Other models including renal tubular epithelial cells (HK-2), male rat kidney cells (NRK), and human primary cells have also been employed.

Mycotoxins alter cellular ROS levels, causing oxidative stress accompanied by DNA fragmentation. MDA is a major product of membrane lipid peroxidation, and ROS accumulation-induced lipid peroxidation is closely associated with cellular damage under stress conditions. T-2 toxin, a trichothecene mycotoxin, can cause leukopenia. Bouaziz et al. [32] found that T-2 toxin reduced Vero cell viability and increased MDA release in a dose-dependent manner, causing oxidative damage. Agarose gel electrophoresis revealed DNA strand breaks and increased DNA fragmentation, inducing DNA damage in Vero cells. Additionally, T-2 toxin activated caspase-3 protein, with production increasing with concentration and inducing apoptosis. OTA primarily targets the kidney, causing endemic nephropathy. Arbillaga et al. [33] confirmed OTA-induced DNA damage in HK-2 cells, though comet assay results showed that OTA did not cause single-strand DNA break-mediated damage. Cysteine supplementation inhibited OTA-induced ROS generation, suggesting no observable DNA damage in renal cells. Conversely, Lebrun et al. [34] demonstrated via comet assay that OTA increased comet tail length in Madin-Darby canine kidney (MDCK) cells, causing DNA damage that was inhibited by methotrexate. Mycotoxins induce renal cell DNA damage through ROS generation, and using amino acids and purine-pyrimidine drugs to modulate cytotoxicity represents an innovative

approach requiring further molecular-level investigation.

Mycotoxins can indirectly alter DNA levels by modifying enzyme and protein expression. p38 kinase and mitogen-activated protein kinases (MAPK) regulate cell cycle and protein expression pathways. Patulin (PAT), produced by Aspergillus, did not affect HEK293 cell viability or DNA damage but induced apoptosis in a time- and dose-dependent manner by promoting p38 kinase (rather than MAPK) expression [35]. Cavin et al. [36] showed that OTA treatment of male rat kidney NRK cells induced inducible nitric oxide synthase (iNOS) generation, significantly increasing nitrotyrosine residues and causing nitrosative stress that elevated DNA base site levels. iNOS inhibitors did not reduce this increase, indicating that OTA-induced oxidative damage is a major cause of DNA damage and providing insights into OTA' s carcinogenic mechanism.

DNA content alterations affect mitosis. Weidner et al. [37] demonstrated that low concentrations (0.1 g/mL) of T-2 toxin did not change G1 phase DNA content in human primary renal cells or induce apoptosis. High concentrations (1 g/mL and 10 g/mL) also did not alter G1 DNA content after 24 hours, but significantly increased it after 48 hours, causing G1/M phase arrest and necrosis. Chang et al. [38] found that the nephrotoxic mycotoxin citrinin (CTN) arrested HEK293 cells in G2/M phase in a dose-dependent manner, with chromosome number changes 4.3-fold higher than controls. Both in vivo and in vitro studies showed that CTN inhibited tubulin polymerization in a dose-dependent manner, indicating that CTN-induced chromosome aberrations and G2/M arrest are associated with disrupted microtubule polymerization and spindle formation. Thus, mycotoxins affect mitosis by altering DNA content and reducing cell viability.

These results demonstrate that while various renal cell models are used, HEK293 cells are suitable for studying both protein expression and DNA damage. Mycotoxins may alter renal cell DNA levels by modifying ROS expression and activating or inhibiting DNA synthesis-related enzymes and proteins, causing chromosomal abnormalities that arrest the mitotic cycle and affect cell growth. Different mycotoxin doses affect renal cell viability differently, suggesting that apoptosis is one toxicity pathway and that dose-dependent mechanisms may vary. Whether multiple mycotoxins share common mechanisms requires further investigation.

4. Mycotoxin-Induced DNA Damage in Neural Cells

Mycotoxins affect brain development [39] and neural cell growth [40] through mechanisms that remain unclear but are likely closely related to oxidative stress, DNA damage, and mitochondrial dysfunction. Oxidative stress can cause mitochondrial dysfunction and DNA damage, which are considered major factors damaging brain regions [41]. Mycotoxins invading the brain damage the hippocampus, causing memory and learning impairments. Many researchers have compared glial and neural cell sensitivity to mycotoxins [42-43], though no stan-

dardized in vitro model exists for studying mycotoxin neurotoxicity.

Neural cells are distributed throughout the body, making them more susceptible to damage and causing diverse disease types. OTA specifically damages hippocampal neurons, leading to neurological disorders such as depression and memory impairment. Sava et al. [40] found that OTA inhibited proliferation and differentiation of mouse hippocampal neural stem cells in a dose- (0.01–100.00 g/mL) and time- (6–72 h) dependent manner, increasing superoxide dismutase (SOD) release and causing oxidative stress that affected DNA fragmentation. Differentiated neurons showed greater toxin sensitivity than undifferentiated cells, and sodium benzoate maleate diethyl ester alleviated OTA-induced DNA damage.

Mycotoxins also cause DNA damage and promote apoptosis and apoptotic protein expression in neural cells. Satratoxin G (SG), a macrocyclic trichothecene mycotoxin produced by Stachybotrys chartarum found in damp environments, is pathogenic. Islam et al. [44] used rat pheochromocytoma PC-12 cells to investigate SG-induced neuronal cell death mechanisms. Agarose gel electrophoresis showed that 10 ng/mL SG induced DNA fragmentation after 48 hours, with mRNA expression of p53 protein, double-stranded RNA-activated protein kinase (PKR), and caspase apoptotic protein genes increasing significantly with exposure time. These results indicate that SG induces apoptosis by activating PKR pathway-related gene expression. SG also induced caspase apoptotic protein expression in differentiated PC-12 cells without causing apoptosis, possibly due to dosage and exposure time effects.

FB1, produced by Fusarium species, commonly contaminates corn and other crops in humid environments. Stockmann-Juvala et al. [42] treated four different cell types with FB1: human neuroblastoma SH-SY5Y, mouse hypothalamic GT1-7, rat glioblastoma C6, and human glioblastoma U-118MG cells. FB1 promoted apoptotic protein caspase-3 production and DNA fragmentation while increasing p53 and Bcl-2 family protein expression in a time- and dose-dependent manner. Caspase-3 expression in SH-SY5Y cells increased significantly after 48–144 hours of FB1 exposure, indicating that FB1 induces apoptosis by altering DNA fragments and p53 and Bcl-2 family protein expression. Cell sensitivity to FB1 varied as follows: U-118MG > GT1-7 > C6 > SH-SY5Y, demonstrating that glial cells are more sensitive than neural cells.

These studies show that low-dose, short-term mycotoxin exposure does not induce DNA damage, requiring extended exposure to manifest genotoxicity and proving that organisms possess short-term defense capabilities. The mechanisms by which high-concentration mycotoxins cause double-strand DNA breaks and their relationship to mitosis require further investigation. Antioxidant supplementation not only reduces oxidative damage but also inhibits DNA damage, confirming the close connection between mycotoxin-induced oxidative and DNA damage. Molecular biology approaches integrating transcriptomics and proteomics should be applied to further elucidate mycotoxin mechanisms, and appropriate detoxifying agents should be identified to fundamentally address

mycotoxin hazards.

Mycotoxins exhibit hepatotoxicity, nephrotoxicity, intestinal toxicity, and neurotoxicity. Consumption of grains contaminated with multiple mycotoxins inevitably causes complex and diverse clinical manifestations in animals. The intestine, kidney, and liver are essential absorption and metabolic pathways for mycotoxins, while the nervous system coordinates organ function and is continuously exposed throughout the body. Current research has focused extensively on liver and kidney effects, with less attention to intestinal and neural impacts, and minimal investigation of protein expression regulatory mechanisms underlying mycotoxin-mediated damage. Future research should employ molecular biology and transcriptomics to explore damage mechanisms at the molecular level. To protect animal and human health, mycotoxin production must be controlled in production through proper mold prevention and detoxification. Developing safe, suitable detoxification technologies that do not compromise nutritional value is crucial. With advancing molecular biology techniques and dedicated research efforts, safe, efficient, and environmentally friendly mycotoxin degradation methods will undoubtedly be developed, bringing value and benefits to the feed industry and animal husbandry.

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