# Effects of Fusarium Toxins on Antioxidant Capacity and the Distribution and Expression of Interleukin-1 and Interleukin-6 in the Spleen of Weaned Piglets: Postprint

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## Abstract

This experiment aimed to investigate the effects of Fusarium toxins in naturally moldy feed on the antioxidant capacity of spleen and the distribution and expression of interleukin-1 (IL-1 ) and interleukin-6 (IL-6) in weaned piglets. Forty healthy crossbred (Duroc × Landrace × Large White) weaned piglets with an average body weight of (8.45±0.94) kg at 35 days of age were selected and randomly divided into 2 groups with 20 piglets per group. The control group was fed a basal diet, while the Fusarium toxin group was fed an experimental diet containing Fusarium toxins [zearalenone (ZEN) 0.90 mg/kg; deoxynivalenol (DON) 1.43 mg/kg; fumonisin (FUM) 5.85 mg/kg]. The pre-trial period was 7 days, and the formal trial period was 35 days. The results showed: 1) Compared with the control group, Fusarium toxins significantly decreased the activities of glutathione peroxidase (GSH-Px) and total superoxide dismutase (T-SOD) in serum and spleen of weaned piglets ($P<0.05$), and significantly increased the malondialdehyde (MDA) content ($P<0.05$). 2) Fusarium toxins caused the white pulp area of the spleen to be significantly reduced, the red pulp area to be expanded with nearly circular small cavities, and the number of lymphocytes in the periarterial lymphatic sheath to be decreased. 3) Fusarium toxins led to IL-1 and IL-6 positive cells in the spleen of weaned piglets being mainly concentrated at the margin of the white pulp, with more positive spots near the sinusoids. 4) Compared with the control group, Fusarium toxins significantly increased the relative mRNA expression levels of IL-1 and IL-6 in the spleen of weaned piglets ($P<0.05$). In conclusion, Fusarium toxins in the diet significantly affected the antioxidant capacity of serum and spleen in weaned piglets, and reduced the immune function of the spleen by altering the distribution and expression of IL-1 and IL-6 in the spleen.

## Full Text

# Effects of Fusarium Toxins on Antioxidant Capacity and Distribution and Expression of Interleukin-1 and Interleukin-6 in Spleen of Weaned Piglets

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### Abstract

This study investigated the effects of Fusarium toxins in naturally contaminated diets on antioxidant capacity and the distribution and expression of interleukin-1 (IL-1 ) and interleukin-6 (IL-6) in the spleen of weaned piglets. Forty healthy female weaned piglets (Duroc×Landrace×Yorkshire) aged 35 days with an average body weight of (8.45±0.94) kg were randomly allocated into two groups of 20 piglets each. The control group received a basal diet, while the Fusarium toxins group received an experimental diet contaminated with Fusarium toxins [0.90 mg/kg zearalenone (ZEN); 1.43 mg/kg deoxynivalenol (DON); 5.85 mg/kg fumonisin (FUM)]. The experiment lasted 35 days following a 7-day adaptation period. The results showed that: 1) Compared with the control group, Fusarium toxins significantly decreased the activities of glutathione peroxidase (GSH-Px) and total superoxide dismutase (T-SOD) in serum and spleen ($P<0.05$), while significantly increasing malondialdehyde (MDA) content ($P<0.05$). 2) Fusarium toxins markedly reduced the white pulp area in the spleen, expanded the red pulp area with near-circular small cavities, and decreased lymphocyte numbers in the periarterial lymphatic sheath. 3) IL-1 and IL-6 positive cells were primarily concentrated at the white pulp margins, with more positive staining observed near sinusoids. 4) Fusarium toxins significantly elevated the relative mRNA expression of IL-1 and IL-6 in spleen ($P<0.05$). These findings indicate that dietary Fusarium toxins significantly impair antioxidant capacity in serum and spleen, and compromise splenic immune function by altering the distribution and expression of IL-1 and IL-6.

**Keywords:** weaned piglets; Fusarium toxins; interleukin-1 ; interleukin-6; spleen

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Fusarium species are among the primary fungal genera contaminating grains and feedstuffs, with zearalenone (ZEN), deoxynivalenol (DON), and fumonisin (FUM) representing the most hazardous mycotoxins to animal health and production. These toxins are ubiquitous in nature, contaminating both human food and animal feed, and can cause acute or subacute poisoning and even death in humans and animals. Previous research demonstrated that diets contaminated

with multiple Fusarium toxins [2 or 3 mg/kg DON, 1.3 mg/kg nivalenol (NIV), 1.5 mg/kg ZEN] induced pathological damage in liver, small intestine, and lymphoid organs of piglets, with apoptosis observed in lymph nodes and spleen. Cytotoxicity studies further revealed that combined exposure to subclinical doses of individual Fusarium toxins (DON, NIV, ZEN, and fumonisin B1) significantly reduced viability of porcine jejunal epithelial cells, with the four-toxin combination showing the strongest toxicity. Moreover, multiple Fusarium toxins can disrupt cytokine balance and induce production of various cytokines including IL-1 , IL-1 , IL-6, IL-8, TNF- , and MCP-1, thereby exacerbating inflammatory responses at both tissue and systemic levels.

While most Fusarium toxin research has focused on liver and intestine in pigs and mice, and primarily investigated single toxins, few studies have examined the effects of naturally occurring toxin combinations on weaned piglet spleen under practical production conditions. This study systematically investigated the impact of Fusarium toxins on antioxidant capacity in serum and spleen, and explored their effects on the distribution and expression of IL-1 and IL-6 at histological and molecular levels, providing reference for mitigating immune damage and guiding healthy production in weaned piglets.

### 1.1 Experimental Materials

Our research group collected feed ingredient samples from multiple feed mills and farms in Shandong Province to survey mycotoxin contamination. Ingredients with toxin levels below detection limits were selected for the basal diet, while naturally contaminated corn and corn gluten meal were used to prepare the Fusarium toxin diet.

### 1.2 Experimental Animals and Management

Forty healthy 35-day-old weaned piglets (Duroc×Landrace×Yorkshire) with an average body weight of (8.45±0.94) kg were randomly divided into two groups of 20 piglets each, with no significant difference in initial body weight between groups ($P>0.05$). Piglets were housed individually with ad libitum access to feed and water. The control group received the basal diet, while the Fusarium toxins group received a diet in which 50% of corn and corn gluten meal were replaced with naturally contaminated equivalents, containing 0.90 mg/kg ZEN, 1.43 mg/kg DON, and 5.85 mg/kg FUM. The experiment consisted of a 7-day adaptation period followed by a 35-day formal trial period. All experimental diets were prepared at the beginning of the trial and stored in a dry, cool place. The basal diet was formulated according to NRC (2012) standards, with composition and nutrient levels shown in Table 1 .

### 1.3 Sample Collection

On day 35, blood samples were collected from the anterior vena cava of 10 randomly selected piglets per group before morning feeding. Approximately 10

mL of blood was collected into vacuum coagulation-promoting tubes, centrifuged at 3,000 r/min for 10 minutes to prepare serum, which was aliquoted into 1.5 mL tubes for antioxidant analysis. After blood collection, piglets were euthanized by electric shock. The abdominal cavity was opened and approximately 10 cm of spleen tissue was excised from the middle section, washed with physiological saline, and divided into two equal portions. One portion was fixed in Bouin' s solution for immunohistochemical sectioning, while the other was placed in a 5 mL sterile cryotube, snap-frozen in liquid nitrogen, and stored at -80°C for mRNA expression analysis. Remaining spleen tissue was stored at -20°C for antioxidant measurements.

### 1.4.1 Dietary Toxin Content

Diet samples were collected at the beginning and end of the experiment to analyze toxin content and crude protein levels. ZEN, aflatoxin (AFL), T-2 toxin, and FUM were determined by enzyme-linked immunosorbent assay (ELISA) and fluorometric methods, while DON was measured by high-performance liquid chromatography (HPLC). Detection limits were 0.1 mg/kg for ZEN and DON, 1.0 µg/kg for AFL, 0.25 mg/kg for FUM, and 1.0 µg/kg for T-2 toxin. Dietary toxin contents are shown in Table 1; AFL and T-2 toxin were either not detected or below detection limits.

### 1.4.2 Serum Antioxidant Indices

Serum total superoxide dismutase (T-SOD) activity was measured by xanthine oxidase (hydroxylamine) method, glutathione peroxidase (GSH-Px) activity by chemical colorimetry, and malondialdehyde (MDA) content by colorimetric assay. Test kits for T-SOD (A001-1), GSH-Px (A005), and MDA (A003) were purchased from Nanjing Jiancheng Bioengineering Institute, with procedures performed according to manufacturer instructions.

### 1.4.3 Spleen Antioxidant Indices

Spleen tissue was thawed on ice and homogenized mechanically (10,000-15,000 r/min) in 9 volumes of physiological saline under ice-water bath conditions. The homogenate was centrifuged at 4°C and 3,000 r/min for 15 minutes, and the supernatant was collected for analysis. GSH-Px, T-SOD, and MDA were measured as described in section 1.4.2.

### 1.4.4 Hematoxylin-Eosin (HE) Staining

Spleen tissue fixed in Bouin' s solution was rinsed, dehydrated through graded ethanol, cleared in xylene, and embedded in paraffin. Sections (5 µm) were prepared using a microtome (LEICA RM2135, Germany), deparaffinized in xylene, and rehydrated through graded alcohol to distilled water. Sections were stained with hematoxylin for 10 minutes, differentiated in hydrochloric alcohol for 5 seconds, blued in tap water for 15 minutes, and counterstained with eosin for

10 seconds. After dehydration through 95% and 100% ethanol, clearing in xylene, and mounting with neutral resin, sections were observed under bright-field microscopy.

### 1.4.5 Immunohistochemistry (Streptavidin-Biotin Complex Method)

Spleen tissue fixed in Bouin's solution was trimmed, dehydrated through graded ethanol, cleared in xylene, and embedded using a BMJ-23 embedding machine. The procedure was as follows: 1) Sections (5 μm) were prepared using a microtome (LEICA RM2135, Germany) and deparaffinized. 2) Antigen retrieval was performed in citrate buffer (0.01 mol/L, pH 6.0), followed by three 5-minute washes in phosphate-buffered saline (PBS) (0.01 mol/L, pH 7.2). 3) Endogenous peroxidase was blocked with 3% H O for 30 minutes at room temperature in the dark, followed by three PBS washes. 4) Sections were incubated with 10% fetal bovine serum at 37°C for 1 hour. 5) Primary antibodies—rabbit anti-IL-6 polyclonal antibody (1:150, bs-4587R, Beijing Biosynthesis Biotechnology Co., Ltd.) and rabbit anti-IL-1 polyclonal antibody (1:150, bs-0812R, Beijing Biosynthesis Biotechnology Co., Ltd.)—were applied and incubated overnight at 4°C, followed by three PBS washes. 6) Biotinylated goat anti-rabbit IgG secondary antibody (1:200, SPN-9001, Beijing Zhongshan Golden Bridge Biotechnology Co., Ltd.) was applied and incubated at 37°C for 1 hour, followed by three PBS washes. 7) Horseradish peroxidase-conjugated streptavidin (1:200) was applied and incubated at 37°C for 45 minutes, followed by three PBS washes. 8) Color development was performed using diaminobenzidine (DAB) [ZLI-9018, Beijing Zhongshan Golden Bridge Biotechnology Co., Ltd., concentrate:buffer (V/V) = 1:20] under microscopic observation to control development time. 9) Sections were counterstained with hematoxylin, dehydrated, cleared, mounted, and observed under bright-field microscopy to determine distribution of immunopositive cells (positive products appeared brownish-yellow).

### 1.4.6 Relative mRNA Expression of IL-6 and IL-1 in Spleen

Specific primers for porcine IL-1 , IL-6, and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) reference gene were designed using Primer 6.0 based on GenBank sequences and synthesized by Shanghai Bioengineering Co. (Table 2 ). Total RNA was extracted from 50-100 mg of spleen samples stored at -80°C using Trizol reagent (Invitrogen, USA). RNA quality and concentration were assessed using a UV spectrophotometer, with OD ratios between 1.8-2.0. Total RNA was immediately reverse-transcribed using PrimeScript® RT Master Mix Perfect Real Time kit (TaKaRa Code: DDR036A, Lot: BK1302) in a 20 μL reaction volume. Real-time quantitative PCR was performed using SYBR Premix Ex Taq kit (TaKaRa, Dalian) in a 20 μL reaction containing 10 μL SYBR Premix Ex Taq, 0.4 μL each of forward and reverse primers (10 μmol/L), 0.4 μL ROX Reference Dye, 2 μL cDNA, and 6.8 μL dH O. Amplification conditions were: 95°C for 30 s, followed by 40 cycles of 95°C for 5 s and 60°C for 34 s, with fluorescence detection at 60°C. Each sample was run in triplicate.

### 1.5 Statistical Analysis

Real-time PCR data were analyzed using the 2^(-ΔΔCt) method to determine relative mRNA expression of IL-1 and IL-6. Experimental data were analyzed by one-way ANOVA using SAS 9.2 software, with Duncan' s multiple range test for post-hoc comparisons. Results are expressed as mean±SD, with $P<0.05$ considered statistically significant.

### 2.1 Effects of Fusarium Toxins on Growth Performance and Relative Spleen Weight

Fusarium toxins in naturally contaminated diets significantly reduced average daily gain (ADG) in weaned piglets compared with the control group ($P<0.05$). However, relative spleen weight was not significantly affected ($P>0.05$), and no gross pathological changes were observed in spleen tissue.

### 2.2 Effects of Fusarium Toxins on Antioxidant Indices in Serum and Spleen

As shown in Table 3 , Fusarium toxins significantly decreased GSH-Px and T-SOD activities in both serum and spleen ($P<0.05$), while significantly increasing MDA content ($P<0.05$). These results demonstrate that Fusarium toxins caused oxidative damage to the spleen of weaned piglets.

### 2.3 Effects of Fusarium Toxins on Splenic Histopathological Changes

Histopathological examination revealed that control piglets showed no obvious lesions, with uniform cell arrangement in the white pulp and evenly stained pale blue or blue nuclei (yellow arrows in panel A). In contrast, Fusarium toxins induced marked morphological changes, including significantly reduced white pulp area, expanded red pulp with near-circular small cavities (red arrows in panel B), and decreased lymphocyte numbers in the periarterial lymphatic sheath. These histological findings confirm that Fusarium toxins caused pathological damage to the spleen [Figure 1: see original paper].

### 2.4 Effects of Fusarium Toxins on Distribution of IL-1 and IL-6 in Spleen

Immunohistochemical analysis showed that in control piglets, IL-1 and IL-6 positive cells were scattered throughout the white pulp with light staining and low numbers (red arrows). In the Fusarium toxins group, positive cells were concentrated at the white pulp margins, particularly near sinusoids (yellow circles) [Figure 2: see original paper]. The clearly visible positive staining further confirms significant splenic damage induced by Fusarium toxins.

### 2.5 Effects of Fusarium Toxins on Relative mRNA Expression of IL-1 and IL-6 in Spleen

As shown in Figure 3 [Figure 3: see original paper], Fusarium toxins significantly increased the relative mRNA expression of both IL-1 and IL-6 in spleen compared with the control group ($P<0.05$). These molecular findings provide further evidence of splenic injury caused by Fusarium toxins.

In this study, naturally contaminated corn and corn gluten meal with known Fusarium toxin concentrations were used to prepare the contaminated diet. Due to the prevalence of Fusarium contamination, strict ingredient selection was implemented to ensure valid results. However, trace amounts of Fusarium toxins were detected in the control diet, though all levels were well below Chinese feed hygiene standards [11-12] (ZEN <0.5 mg/kg, GB13078.2-2006; DON <1 mg/kg, GB13078.3-2007; no standard for FUM) and EU maximum limits for piglet diets (ZEN <0.1 mg/kg, DON <0.9 mg/kg, FUM <5 mg/kg) [13]. Since toxin levels in the Fusarium toxins group far exceeded these standards, the trace contamination in the control group did not affect interpretation of results.

### 3.1 Effects of Fusarium Toxins on Antioxidant Capacity in Serum and Spleen

Oxidative damage represents a key mechanism of Fusarium toxin toxicity. GSH-Px, T-SOD, and MDA are important indicators of antioxidant capacity. ZEN and DON can block sphingomyelin metabolism, generating excessive MDA and causing lipid peroxidation. Combined cytotoxicity studies demonstrate that Fusarium toxins impair cellular antioxidant systems and accelerate free radical production, leading to oxidative damage in various organs. Previous research in broilers fed naturally contaminated diets (102.08 μg/kg AFL, 281.92 μg/kg ZEN, 5,874.38 μg/kg FUM, 2,038.96 μg/kg DON) showed significantly decreased serum T-SOD activity and increased MDA content. The current findings of reduced T-SOD and GSH-Px activities and elevated MDA in serum and spleen confirm that Fusarium toxins induce oxidative stress and splenic damage.

### 3.2 Effects of Fusarium Toxins on Splenic Histopathological Injury

The spleen, the largest peripheral immune organ composed of red and white pulp, plays a crucial role in immune responses. Red pulp destroys damaged erythrocytes and filters antigens, while white pulp (periarterial lymphatic sheath, follicles, and marginal zone) is the primary site of humoral immunity. Previous studies showed that dietary ZEA at 40 mg/kg body weight (equivalent to 1 mg ZEA/day) altered splenic histopathology in mice, reducing lymphocyte numbers and causing red pulp swelling and white pulp atrophy. However, another study in weaned female mice fed 10 mg/kg ZEA (1.5 mg/kg/day) for 8 weeks observed no histological changes. The current study found reduced white pulp area, expanded red pulp with vacuolar degeneration, and decreased lymphocyte numbers in the periarterial lymphatic sheath, indicating splenic injury

likely resulting from combined effects of three Fusarium toxins. The specific mechanisms require further investigation.

### 3.3 Effects of Fusarium Toxins on Distribution and mRNA Expression of IL-1  and IL-6

IL-1  and IL-6 levels serve as important physiological indicators of tissue damage. IL-1  is a polypeptide regulator that mediates acute inflammatory responses; sustained synthesis accelerates local inflammation and can trigger systemic inflammatory responses. IL-6 is a pleiotropic inflammatory cytokine with both pro- and anti-inflammatory functions, playing a critical regulatory role in inflammatory reactions. Studies on individual and combined mycotoxin immunotoxicity demonstrated increased splenic IL-1  and IL-6 mRNA expression in mice, piglets, and broilers. Fusarium toxins can impair immune function by inducing apoptosis or altering immune-related gene expression. The current results show that IL-1  and IL-6 were concentrated at white pulp margins, particularly in ellipsoids, suggesting Fusarium toxin-induced splenic inflammation. Furthermore, significantly elevated mRNA expression of both cytokines confirms splenic injury at the molecular level. The precise mechanisms of inflammatory cytokine action in splenic immunity warrant further investigation.

Under the conditions of this study, dietary contamination with Fusarium toxins (0.90 mg/kg ZEN, 1.43 mg/kg DON, 5.85 mg/kg FUM) impaired antioxidant function, altered the distribution of inflammatory cytokines IL-1  and IL-6, increased their mRNA expression, and caused histopathological damage, thereby compromising splenic function in weaned piglets.

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*Note: Figure translations are in progress. See original paper for figures.*