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REVIEW ARTICLE

Aflatoxin B1 in Animals: Metabolism and Immunotoxicity

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ABSTRACT

Aflatoxin B1 (AFB1) is a derivative of the difuranocoumarin class, which is most toxic and harmful. In livestock production, exposure to AFB1 has been demonstrated to induce growth retardation, immune dysfunction, and increased mortality in livestock and poultry species, including cattle, sheep, pigs, chickens, and ducks, thereby posing a significant constraint to sustainable animal husbandry practices. Current review article focuses on the toxic mechanisms of AFB1 in animals, including oxidative stress, apoptosis, and autophagy. Integrated high-throughput sequencing analysis and experimental investigations have demonstrated that dietary AFB1 intake compromises immune cell function, consequently enhancing the susceptibility of livestock and poultry to pathogenic infections. Animal experiments reveal that AFB1 exerts immunotoxicity (immunosuppression and immunostimulation). However, the specific mechanisms underlying AFB1-induced immunotoxicity remain unclear. This review provides a detailed summary of the known types of aflatoxins (AFs) and the transformation processes of their various metabolites. To sum up, this review comprehensively reviews the immunotoxic mechanisms of AFB1 in livestock and poultry, establishing a theoretical framework to guide early diagnosis, immunomodulatory interventions, and feed toxin mitigation strategies in veterinary clinical practice.

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INTRODUCTION

Aspergillus flavus is a widespread soil fungus. The growth of this fungus is dependent on water activity and temperature (Shabeer *et al.*, 2022). Studies have shown that *A. flavus* can grow under high water activity conditions at temperatures of 25-35°C. Meanwhile, the genes involved in the synthesis of aflatoxins (AFs) would also be expressed (Norlia *et al.*, 2020). Therefore, tropical regions face a greater risk of AFs pollution especially in Asia and Africa. Due to climatic conditions and improper food storage methods, this poses significant challenges to food and agricultural production (Jallow *et al.*, 2021), and also increases the risk of liver cancer in human (Kinyenje *et al.*, 2023). Hence, AFs pollution has become an urgent global public health and safety issue.

Aflatoxins are present in moldy grains, nuts, meats, and dairy products (Pożarska *et al.*, 2024; Hoteit *et al.*, 2024). Their discovery can be traced back to the "Turkey X disease" incident where numerous turkeys abruptly perished due to intoxication. It was caused by toxins produced by fungi and was named aflatoxin (Nesbitt *et al.*, 1962). Due to its toxicity, AFs are designated as Group 1 carcinogens and have a significant link to the onset of cancer (Vainio *et al.*, 1994). Aflatoxin B1 (AFB1) is regarded as the most toxic and important among all known forms of AFs. It has oncogenic, fetotoxic and immunosuppressive properties (Pauletto *et al.*, 2020; da Silva *et al.*, 2021).

AFB1 has harmful effects on many organs and systems, including damage to organs (Ye *et al.*, 2024; Rashad *et al.*, 2024), neurons (Song *et al.*, 2024), genital and developmental systems (Huang *et al.*, 2024; He *et al.*, 2023a). Immunotoxicity is a key feature of AFs. It inhibits the size of immune organs and causes immunosuppression (Ülger *et al.*, 2020). Multi-omics analyses, including transcriptomics, proteomics, and metabolomics, have revealed how AFB1 induces changes in inflammatory pathways, immune-related genes, and gut microbiota in various animals such as turkeys or chickens (Monson *et al.*, 2015; Liew *et al.*, 2022; Yue *et al.*, 2022). *In vivo* experiments have shown that AFB1 can induce intestinal or spleen damage in livestock and poultry such as rabbits, pigs and ducks, thereby causing inflammatory responses

(Cheng *et al.*, 2023b; Wan *et al.*, 2022; Zhang *et al.*, 2024c). This emphasizes the importance of studying the immunogenic role of AFB1 in animals. However, the mechanisms underlying AFB1-induced immunotoxicity in livestock and poultry remain poorly understood. Therefore, summarizing the immunotoxicity of AFB1 is of great significance for early diagnosis, immunomodulatory interventions, and feed toxin mitigation strategies in veterinary clinical practice.

Livestock and poultry consuming AFB1-contaminated feed suffers inhibited growth and development, leading to reduced production capacity (Kassaw *et al.*, 2022; Niu *et al.*, 2025), and pose a threat to human health through food chain accumulation. Therefore, understanding the toxic mechanisms of AFB1 in animals is of vital importance. Although the immunotoxicity of AFB1 has received relatively limited attention in previous research, it represents a critically important area of study. In summary, this review gives an extensive summary of the distinct kinds of AFs and the transformations that occur in their metabolites. Additionally, we provide a comprehensive discussion on the mechanisms by which AFB1 induces immunotoxicity in animals, with a focus on innate and adaptive immunity. The objective is to provide novel insights and research directions for AFB1-associated immunosuppression, thereby highlighting the critical importance of addressing AFB1's impact on animal health and its profound implications for livestock production and public health.

Aflatoxins

Types: AFs represent a group of compounds with similar chemical structures. Currently, 25 distinct structures have been identified (Table 1). Among these toxins, four are primarily synthesized by different toxin-producing fungal species: Aflatoxin B1 (AFB1), Aflatoxin B2 (AFB2), Aflatoxin G1 (AFG1), and Aflatoxin G2 (AFG2) (Fig. 1). Other AFs primarily function as metabolites of animals or microorganisms, such as aflatoxin M1, GM1, P1, M2 and Q1 (Khani *et al.*, 2024). Additional examples include aflatoxicol, aflatoxicol H1, Q2a, M1 and aspertoxin (Grove *et al.*, 1984; Scott, 1989; Karabulut *et al.*, 2014; Benkerroum, 2020; García-Nicolás *et al.*, 2023; García-Nicolás *et al.*, 2023; Choi *et al.*, 2024; Liu *et al.*, 2024) (Fig. 1).

Classification: The aflatoxin family contains various compounds, which are usually named according to their fluorescence color, chemical structure, or order of discovery. These compounds can be classified into B-group toxins, G-group toxins, M-group toxins, GM-group toxins, and aflatoxicols. Under UV-light, the B-group and G-group toxins respectively signify blue and green fluorescence, such as AFB1 and AFG1 (Shabeer *et al.*, 2022). The "M" in M-group toxins refers to "milk," as these toxins were initially detected in the milk of contaminated cows and are mainly found in milk and dairy products, such as AFM1 (Giovati *et al.*, 2015). Furthermore, aflatoxicols are derivatives of AFB1. For instance, AFB1 can be enzymatically reduced to aflatoxicol (AFL) by cytosolic reductases (Gerdemann *et al.*, 2023).

Physicochemical properties: AFs contamination is an inevitable concern. Alterations in the global climate offer suitable conditions for fungal growth (Kos *et al.*, 2023). Among mycotoxins, AFs, fumonisins (FBs), deoxynivalenol (DON), ochratoxins (OTs) and zearalenone (ZEN) are the five most prevalent ones. AFs has a stable molecular structure. It can directly or indirectly pollute grains and feed, and transfer to the human food chain, causing acute or chronic poisoning (Alshannaq and Yu, 2017) (Fig. 2). Given that eliminating AFB1 from food remains challenging and poses significant health risks to consumers (Wan *et al.*, 2020), a comprehensive understanding of *Aspergillus flavus* growth habits and toxin properties is crucial for formulating effective prevention and elimination strategies against AFB1.

AFs appear yellow and their relative molecular weight are from 312 to 346g/mol. (Popescu *et al.*, 2022). They only begin to decompose at temperatures as high as 237-306°C. So ordinary cooking temperatures are insufficient to eliminate AFs from food (Afsah-Hejri *et al.*, 2020). But AFs can be degraded under specific conditions, such as alkalinity, strong oxidants, and UV-light (Liu *et al.*, 2024). For instance, in alkaline solutions with pH ranging from 9.0 to 10.0, the lactone ring of AFB1 will rapidly hydrolyze to form coumarin sodium salt, and its fluorescence and toxicity will weaken (Fan *et al.*, 2013). The main detoxification strategy is to remove the methoxy groups on the side chains of the benzene ring and the double bonds on the terminal furan ring (Anjum *et al.*, 2022; Tang *et al.*, 2023).

Metabolism in animals: After animals ingest food contaminated with AFs, the toxins are absorbed by the duodenum (Newcomer, 2022). It can produce toxic metabolites in organisms, which can damage various organs (Rajaura *et al.*, 2024; Ye *et al.*, 2024). The liver in animals exhibits marked vulnerability to diverse toxic insults (Newcomer, 2022). The cytochrome P450 (CYP450) enzyme family are crucial in the metabolism of exogenous substances. However, the key enzymes involved in AFB1 metabolism differ between animals and humans. In poultry species, these include cytochrome P450 2A6 (CYP2A6), cytochrome P450 3A37 (CYP3A37), cytochrome P450 1A5 (CYP1A5), and cytochrome P450 1A1 (CYP1A1), whereas in humans, the predominant enzymes are cytochrome P450 1B1 (CYP1B1) (Chen *et al.*, 2023), cytochrome P450 1A2 (CYP1A2), and cytochrome P450 3A4 (CYP3A4) (Deng *et al.*, 2018).

To illustrate, let's consider the metabolism of AFB1 in the liver. The phase I metabolic processes involve chemical reactions such as epoxidation, hydroxylation, hydration, and demethylation (Fig. 3). These processes produce metabolites with less toxicity, such as AFQ1, AFM1, and AFP1, which can be excreted via bile and urine. However, they also produce the highly toxic exo-AFB1-8,9-epoxide (AFBO) (Popescu *et al.*, 2022). AFBO promptly engages with guanine components in DNA, leading to the formation of AFB1-N7-guanine adducts (Gramantieri *et al.*, 2022). Furthermore, AFBO has the ability to combine with lysine units in proteins to create adducts (Popescu *et al.*, 2022). The formation of these adducts leads to DNA damage and cytotoxicity, thereby causing hepatocyte damage (Wang *et al.*, 2023b). The phase II involves the reduction and conjugation reactions of the above-mentioned metabolites. These reactions mainly convert the metabolites into less

toxic or non-toxic compounds through processes such as glutathione conjugation, microsomal epoxide hydrolase (mEH) activity, and the action of aflatoxin aldehyde reductase (AFAR). The transformed compounds are subsequently excreted from the body via urine (Popescu *et al.*, 2022) (Fig. 3).

Immunotoxicity: AFB1 is a highly toxic substance that mainly causes immunotoxicity in livestock and poultry. Surprisingly, RNA sequencing data have uncovered the differential gene expression patterns related to immune responses from the livers of turkeys, rats, and cattle. This includes the upregulation of fatty acid binding protein 4 (FABP4) and B cell lymphoma 6 (BCL6) mRNA levels, as well as Toll-like receptor 2 (TLR2) activation (Iori *et al.*, 2022; Reed *et al.*, 2018; Yan *et al.*, 2022). Furthermore, RNA-seq data have shown that AFB1 activates inflammatory signaling pathways in mouse macrophages and turkey spleen, while inhibiting transcripts related to immune function (Ma *et al.*, 2021; Monson *et al.*, 2015). After exposure to AFB1, significant changes occur in the proteomics of ducks, rats and lambs. AFB1 can induce an imbalance of intestinal microbiota, leading to intestinal damage (Chen *et al.*, 2024b; Liew *et al.*, 2022; Tansakul *et al.*, 2019). Metabolomic analyses further indicate that AFB1 changes the metabolite's level in the plasma of many animals. These metabolites affect the pathways related to the metabolism of amino acids, lipids and nucleotides in

Table 1: The formula and source of aflatoxins.

Aflatoxin	Formula	Source	References
AFB1	$C_{17}H_{12}O_6$	Section Flavia: A. flavus, A. pseudotamarii, A. togoensis. A. aflatoxiformans, A. austwickii, A. cerealis, A. arachidicola, A. minisclerotigenes, A. mottae, A. luteovirescens (formerly A. bombycis), A. nomius, A. novoparasiticus, A. parasiticus, A. pseudocaelatus, A. pseudonomius, and A. sergii, and A. transmontanensis Section Ochraceorosei: A. ochraceoroseus and A. rambellii Section Nidulantes: A. astellatus, A. venezuelensis, A. miraensis andA. olivicola	(Frisvad *et al.*, 2019; Pildain *et al.*, 2008; Chen *et al.*, 2016)
AFB2	$C_{17}H_{14}O_6$	Section Flavi: A. flavus, A. pseudotamarii, A. togoensis. A. aflatoxiformans, A. austwickii, A. cerealis, A. arachidicola, A. minisclerotigenes, A. mottae, A. luteovirescens (formerly A. bombycis), A. nomius, A. novoparasiticus, A. parasiticus, A. pseudocaelatus, A. pseudonomius, and A. sergii, and A. transmontanensis Section Ochraceorosei: A. ochraceoroseus and A. rambellii Section Nidulantes: A. astellatus	(Frisvad *et al.*, 2019; Pildain *et al.*, 2008)
AFG1	$C_{17}H_{12}O_7$	Section Flavi: A. flavus[a], A. aflatoxiformans, A. austwickii, A. cerealis, A. arachidicola, A. minisclerotigenes, A. mottae, A. luteovirescens (formerly A. bombycis), A. nomius, A. novoparasiticus, A. parasiticus, A. pipericola, A. pseudocaelatus, A. pseudonomius, and A. sergii, and A. transmontanensis	(Frisvad *et al.*, 2019)
AFG2	$C_{17}H_{14}O_7$	Section Flavi: A. flavus[a], A. aflatoxiformans, A. austwickii, A. cerealis, A. arachidicola, A. minisclerotigenes, A. mottae, A. luteovirescens (formerly A. bombycis), A. nomius, A. novoparasiticus, A. parasiticus, A. pipericola, A. pseudocaelatus, A. pseudonomius, and A. sergii, and A. transmontanensis	(Frisvad *et al.*, 2019)
AFM1	$C_{17}H_{12}O_7$	A hydroxylated metabolite of AFB1 and the major CYP450 isoenzyme is CYP1A2.	(Min *et al.*, 2021; Rushing and Selim, 2019)
AFQ1	$C_{17}H_{12}O_7$	A hydroxylated metabolite of AFB1 and the major CYP450 isoenzyme is CYP3A4、CYP3A7.	(Deng *et al.*, 2018; Rushing and Selim, 2019)
AFB2a	$C_{17}H_{14}O_7$	A hydroxylated metabolite of AFB1 and forms a terminal hemiacetal ring by adding water to the 8,9-double bond under dilute acidic conditions; It is metabolized in a NADPH-dependent manner.	(Rushing and Selim, 2019)
Aflatoxicol H1	$C_{17}H_{14}O_7$	A hydroxylation metabolite of AFB1 or AFQ1 and its metabolism depends on the microsomal hydroxylase and cytoplasmic reductase systems.	(Rushing and Selim, 2019)
AFP1	$C_{16}H_{10}O_6$	A demethylated metabolite of AFB1 and the major CYP450 isoenzyme is CYP2A13, CYP2A3, and CYP321A1.	(Min *et al.*, 2021; Rushing and Selim, 2019)
Aflatoxicol R0/Aflatoxicol	$C_{17}H_{14}O_6$	An aldehyde-reducing metabolite of AFB1, which was formed by NADPH reductase.	(Deng *et al.*, 2018; Rushing and Selim, 2019)
AFM2	$C_{17}H_{14}O_7$	A hydroxylation metabolite of AFB2.	(Kuilman *et al.*, 2000)
AFG2a	$C_{17}H_{14}O_8$	A hydroxylation metabolite of AFG1 which is obtained by catalytic addition of water to the terminal furan double bond under acidic conditions.	(Benkerroum, 2020)
AFGM1	$C_{17}H_{12}O_8$	A hydroxylation metabolite of AFG1.	(Yabe *et al.*, 2012)
AFGM2	$C_{17}H_{14}O_8$	A hydroxylation metabolite of AFG2.	(Yabe *et al.*, 2012)
AFGM2a	$C_{17}H_{14}O_8$	Metabolites of aflatoxin GM1 or aflatoxin M1.	(Benkerroum, 2020)
AFB3	$C_{16}H_{14}O_6$	A metabolite of aflatoxin G1 is produced by the microbic hydrolysis and decarboxylation reactions.	(Benkerroum, 2020)
AFM2a	$C_{17}H_{14}O_8$	Acid hydration of the terminal furan ring of aflatoxin M1.	(Benkerroum, 2020)
AFQ2a	$C_{17}H_{14}O_8$	Acid hydration of aflatoxin Q1.	(Benkerroum, 2020)
Aflatoxicol M1	$C_{17}H_{14}O_7$	Reduced metabolite of aflatoxin B1, aflatoxin R0, or aflatoxin M1.	(Benkerroum, 2020)
Aspertoxin[b]	$C_{19}H_{14}O_7$	A. flavus and A. parasiticus.	(Benkerroum, 2020)
AFD1	$C_{16}H_{14}O_5$	The main transient degradation product formed by the hydrolysis of AFB1 lactone ring mediated by Aspergillus oryzae or the reductase BacC followed by decarboxylation.	(Choi *et al.*, 2024; Liu *et al.*, 2024)
AFD2	$C_{11}H_{10}O_4$	The reduction enzyme BacC mediates the hydrolysis of AFB1 lactone ring and then breaks the peptide bond to form AFD2.	(Liu *et al.*, 2024)
AFM4	$C_{17}H_{12}O_7$	Aflatoxin M4 is a metabolite of Aspergillus flavus and Aspergillus parasiticus.	(García-Nicolás *et al.*, 2023; Scott, 1989)
AFP2	$C_{16}H_{12}O_6$	NA	(García-Nicolás *et al.*, 2023)
Aflatoxicol B	$C_{17}H_{14}O_6$	Aflatoxicol isomer of R0/AFL	(García-Nicolás *et al.*, 2023; Karabulut *et al.*, 2014)

a: Not a typical producer of G-types of aflatoxins, but some strains were reported to produce them in addition to B1 and B2; b: Usually considered as a sperate mycotoxin produced by A. flavus because of structural differences with the difurocoumarin structure that characterizes the aflatoxins; NA: Not available (Benkerroum, 2020).

Table 2: Immunotoxicity of AFB1 to different tissues and organs.

Species	Tissues or organs	Treatment	Immunotoxicity	References
Pacific white shrimp	Hepatopancreas and intestine	Shrimp were fed diets containing 2 mg/kg AFB1 or 2 mg/kg AFB1 and 0.3 g/kg bile acids for 28 days.	Total hemocyte counts, phagocytic activity of hemocytes and antibacterial activity of plasma were decreased.	(Su *et al.*, 2023)
Newborn chick	Liver and kidney	Chickens were intragastric with 5 mg/kg AFB1 for 24 h.	The expression of inflammatory factors decreased, such as TNF-α, IL-6 and IL-1β.	(Gao *et al.*, 2022)
Broiler chicken	Immune organs (bursa of Fabricius and thymus)	Chickens were given orally 0.1, 0.2, and 0.6 mg/kg AFB1 daily for 42 days.	The immune response to SRBCs and PHA-P-mediated cutaneous basophilic hypersensitivity response were decreased.	(Bhatti *et al.*, 2021)
Swine	3D4/21 cell	The cells were treated with 0, 0.1, 0.5, 1, 1.5, 2, 4 and 8 μg/mL OTA and 0, 0.01, 0.02, 0.04、0.08, 0.16, 0.32 and 0.64 μg/mL AFB1 for 48 h.	The phagocytosis index was decreased, and the release of inflammatory cytokines such as TNF-α and IL-6 was increased.	(Hou *et al.*, 2018)
Broiler	Bursa tissues	Broilers were fed with 2 mg/kg of AFB1 or 2 mg/kg of AFB1 and 50 mg/kg of Lico A for 28 days.	AFB1-induced damage and apoptosis in bursa of broilers.	(Xia *et al.*, 2024)
Broiler	Liver and kidney	Broilers were fed with 0.5 mg /kg AFB1 or 2.5 g/kg ITM, ACTM50 and ACTM100 for 42 days.	Immunoglobulin Y levels and antioxidant enzyme activity were decreased.	(Mohammadi *et al.*, 2024)
Broiler	Immune organs (thymus, spleen and bursa of Fabricius)	Broilers were fed with 5 mg/kg AFB1 or 150, 300 and 450 mg/kg curcumin for 28 days.	AFB1 exposure impaired the development of immune organs and down-regulated the IL-2 and IFN-γ mRNA levels.	(Li *et al.*, 2022)
Mice	Mouse spleen mononuclear cells	The cells were treated with 5–50 μM AFB1, 25–250 μM FB1, and AFB1–FB1 mixtures for 68 h.	AFB1 enhanced the Treg/Th17 cell ratio and led to immunosuppression.	(Mary *et al.*, 2024)
Pig	Porcine alveolar macrophages	The cells were treated with 3.01 μM AFB1, 624.33 nM DON and 3.11 μM OTA for 24 h.	AFB1 disrupted the RLR pathway by increasing RIG-1, MAVS and NF-κB expression and decreasing IRF3 expression.	(Lai *et al.*, 2024)
C57BL/6 male mice	Small intestine	Mice were taken orally 0.06, 0.18, or 0.6 mg/kg AFB1 for 21 days.	AFB1 impaired intestinal immune function through the inhibition of macrophages and Paneth cells.	(Wang *et al.*, 2023a)
Chicken	Liver	Chickens were administered with 2.8 mg/kg AFB1 and/or treated with 24 mg/kg PHI for 33 days.	AFB1 caused immunotoxicity through modulating the NF-κB and the NRF2 pathway.	(Guo *et al.*, 2022b)
Chicken	Spleen and the bursa of Fabricius	Chickens were administered with 0.3, 0.6, 1.2 mg/kg AFB1 for 5 weeks.	AFB1 was able to trigger the expression of genes involved in cancer development and immune response pathways.	(Xu *et al.*, 2022)
Mice	RAW264.7 cell line	The cells were administered with 0, 3.125, 6.25, 12.5, 25, 50 or 100 μM AFB1 for 24 and 48 h.	AFB1 caused oxidative stress and activated inflammatory pathways	(Ma *et al.*, 2021)
BALB/c mice	Spleen	AFM1 was administered intraperitoneally at doses of 25 and 50 μg/kg for 28 days to BALB/C mice.	Spleen weight and proliferation of splenocytes was reduced in mice.	(Shirani *et al.*, 2021)
Cobb male broiler	Spleen	Broilers were fed with 1.0 mg/kg AFB1 and 0.3 mg/kg Se for 3 weeks.	AFB1 induced spleen damage.	(Zhao *et al.*, 2019)
Pig	3D4/21 Cell	The cells were administered with 0, 0.02, 0.04, 0.08 and 0.16 μg/ml AFB1 for 48 h.	AFB1 induced apoptosis, pro-inflammatory factors and decreased phagocytotic capacity.	(Zhou *et al.*, 2019b)
C57BL/6 mice	Liver	Mice were treated with 30 mg/kg celecoxib and 1 mg/kg AFB1 for 4 weeks.	AFB1 activated NLRP3 inflammasome, and promote inflammatory infiltration.	(Zhang *et al.*, 2019)
Litopenaeus vannamei	Hepatopancreas and intestine	Shrimp were fed with 5 ppm AFB1, three times a day for 30 days.	AFB1 damaged organs of hepatopancreas and intestine, and resulted in damage of immune system.	(Wang *et al.*, 2019c)
Broiler chicken	Spleen	Broilers were fed with 1mg/kg AFB1 and 250 mg/kg GSPE for 28 days.	AFB1 induced immunotoxicity via modulation of NF-κB and NRF2 signaling pathways.	(Rajput *et al.*, 2019)
Chicken	Cecal tonsil	Chickens were fed with 0.6 mg/kg AFB1 and 0.4 mg/kg Se for 21 days.	AFB1 decreased the percentages of T cell subsets, and suppressed the cytokine levels.	(Wang *et al.*, 2019a)
C57BL/6 male mice	Spleen	Mice were fed with 5 mg/kg curcumin, 0.01 mg/kg AFB1 and 0.1 mg/kg DON for 21 days.	DON and AFB1 induced immune dysfunction.	(Muhmood *et al.*, 2024)
Male F344 rats	Spleen	Rats were fed with 5-75 μg/kg AFB1 for 1 or 5 weeks.	AFB1 regulated splenic lymphocyte phenotype and cell-specific cytokine production.	(Qian *et al.*, 2014)
Male BALB/c mice	Liver and gut	BALB/c mice were fed with 0, 5, 25, 50 μg/kg bw/day AFB1, and the mice were sacrificed on 3, 7, 14, 21, 35 and 49 day, respectively.	AFB1 induced steatohepatitis in mice.	(Zhang *et al.*, 2024b)
Turkey poults	Ileum	Turkey poults were fed with 0.25% HA and 250 ng/g AFB1 for 28 days.	AFB1 induced immunosuppression.	(Maguey-González *et al.*, 2024)
Rabbit	Liver	Rabbits were fed with 0.3 mg/kg AFB1 and LACP (1×10^9 cfu/g/kg diet) for 8 weeks.	AFB1 induced inflammation and decrease in immunoglobulins (IgG and IgM).	(Saghir *et al.*, 2024)
Juvenile white Leghorn males	Lymphoid tissue	The White Leghorn breeder males were fed with 400 ppb AFB1, 100 ppm vitamin E and 1% Moringa oleifera for 2 months.	AFB1 inhibited potential immunological parameters including sheep erythrocyte antibody titers, lymphocyte proliferation response to avian tuberculin, and macrophage phagocytosis.	(Saleemi *et al.*, 2024)

Landes geese	Immune organs (Fabricius bursae, thymus, spleen)	Geese were fed with 10, 50 μg/kg AFB1 for 63 days.	AFB1 increased the expression levels of TLR3 and NF-κB, and decreased the immunoglobulin levels.	(Li *et al.*, 2024)
Turkey poults	Gut	Turkey poults were fed with 250 ng/g AFB1 and 0.5% (w/w) adsorbent for 8 days.	AFB1 induced immunosuppression.	(Nava-Ramírez *et al.*, 2024)
Broiler chicken	Liver	Broilers were fed with 0.5 g/kg CPP, 0.5 mg/kg AFB1, and 0.5 g/kg CSP for 42 days.	AFB1 decreased immunoglobulin levels (IgG, IgM, and IgA) and increased pro-inflammatory factors such as TNF-α and IL-6.	(Oloruntola *et al.*, 2024)
Broiler	Bursa of Fabricius	Broilers were fed with 3 mg/kg AFB1, 10 ml/kg Yin-Chen-Hao Tang extract, and 1, 2, and 3 g/kg Penthorum chinense Prush extract for 35 days.	AFB1 decreased NRF2 pathway related gene expression, the average weight gain and relative weight of the broilers.	(Nabi *et al.*, 2024)
C57 and BTBR Mice	Spleen	Mice were fed with 1250 μg/kg AFB1 for 28 days.	AFB1 induced an inflammatory response in the spleen.	(Almanaa *et al.*, 2024)
BALB/c mice	Colon	BALB/c mice were fed with 5, 25 and 50 μg/kg/day AFB1 by gavage.	AFB1 induced colitis via AHR/TLR/STAT3 signaling axis.	(Zhang *et al.*, 2023)
Kunming mice	Liver and intestinal tissues	Mice were administered with 0.75 mg/kg AFB1 and HAs in their drinking water (0.4%, m/v) for 54 days.	AFB1 damaged organs, triggered inflammatory cell infiltration and lipid accumulation, reduced immunoglobulin levels, and elevated inflammatory factors.	(Xu *et al.*, 2023)
Grass carp	Gill	Grass carp were fed with 30–150 μg/kg AFB1, four times a day, for 60 days.	AFB1 disrupted the immune barrier, activated NF-κB signaling to trigger an inflammatory response and inhibited the TOR pathway.	(He *et al.*, 2023b)
C57 and BTBR Mice	Spleen and brain tissues	Mice were fed with 1250 μg/kg/day AFB1 daily for 28 days.	AFB1 increased the proportion of Th1, Th9, Th17 and Th22 cells in the spleen, but decreased the proportion of Treg cells.	(Alwetaid *et al.*, 2023)
Kunming male mice	Ileum	Mice were administered 300 μg/kg bw/day AFB1 and 100 mg/kg bw/day Polydatin by gavage for 18 days.	AFB1 induced ileal inflammation through up-regulation of the NLRP3/NF-κB pathway.	(Cheng *et al.*, 2023a)
Broiler chicken	Spleen and thymus	Broiler were fed with 2.8 mg/kg AFB1 and 4, 8, 12 g/kg Penthorum chinense Pursh Compound for 28 days.	AFB1 increased the organ weight of spleen and decreased the organ weight of thymus and the immunoglobulin level.	(Lu *et al.*, 2023)
Duckling	Spleen	Duckling were fed with 0.1 mg/kg AFB1 and 400 mg/kg curcumin-containing for 21 days.	AFB1 destroyed splenic tissue through the activation of NF-κB pathway.	(Wan *et al.*, 2022)
Mice	Spleen	Mice were fed with 0, 0.5, 0.75 and 1 mg/kg AFB1 for 28 days.	AFB1 exposure activated PINK1/Parkin-mediated mitochondrial autophagy.	(Guo *et al.*, 2022a)

BTBR: a BTBR $T^{+}Itpr3^{tf/}J$.

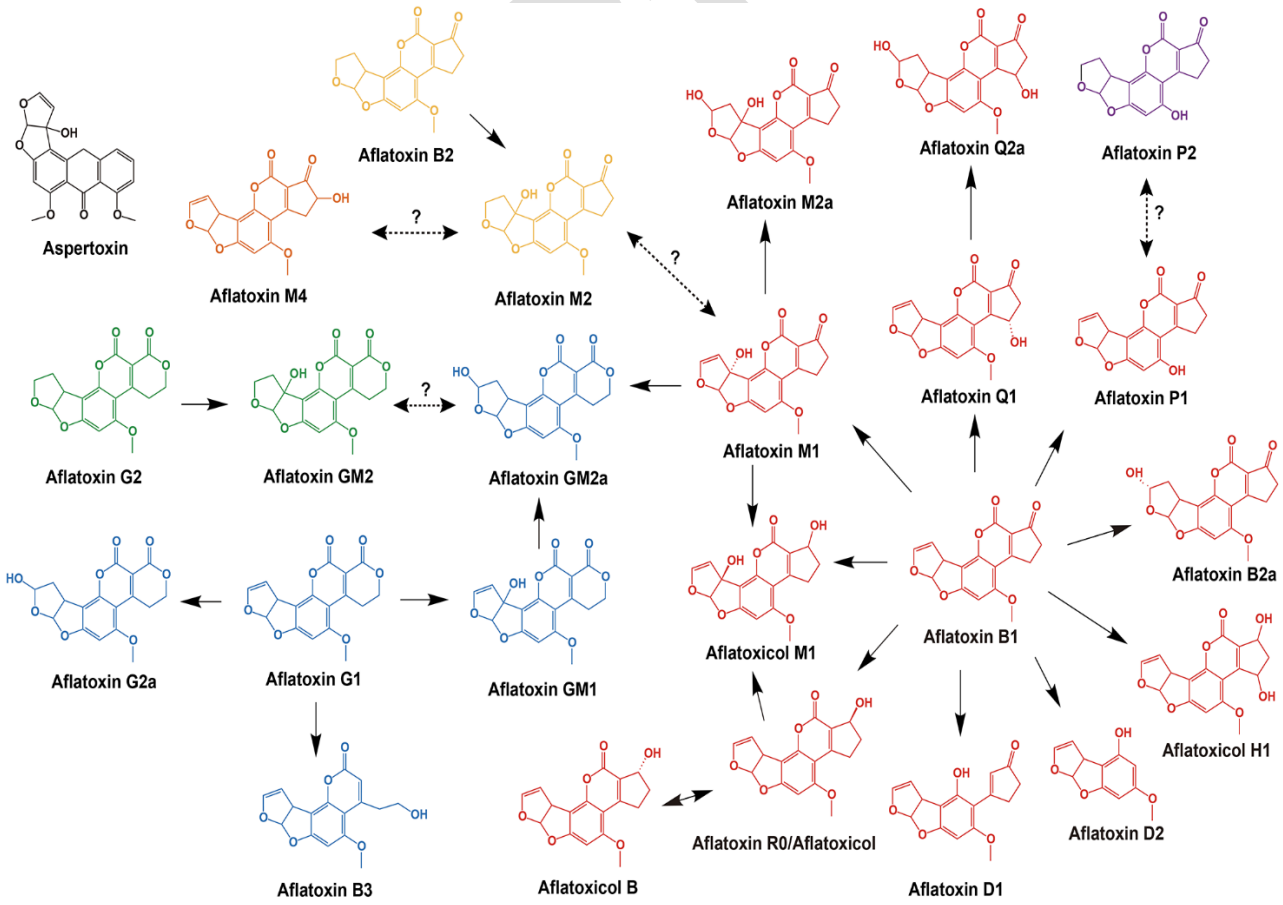

Fig. 1: Types of aflatoxins and their structures. The diversity structures of 25 different structures of aflatoxins have been identified.

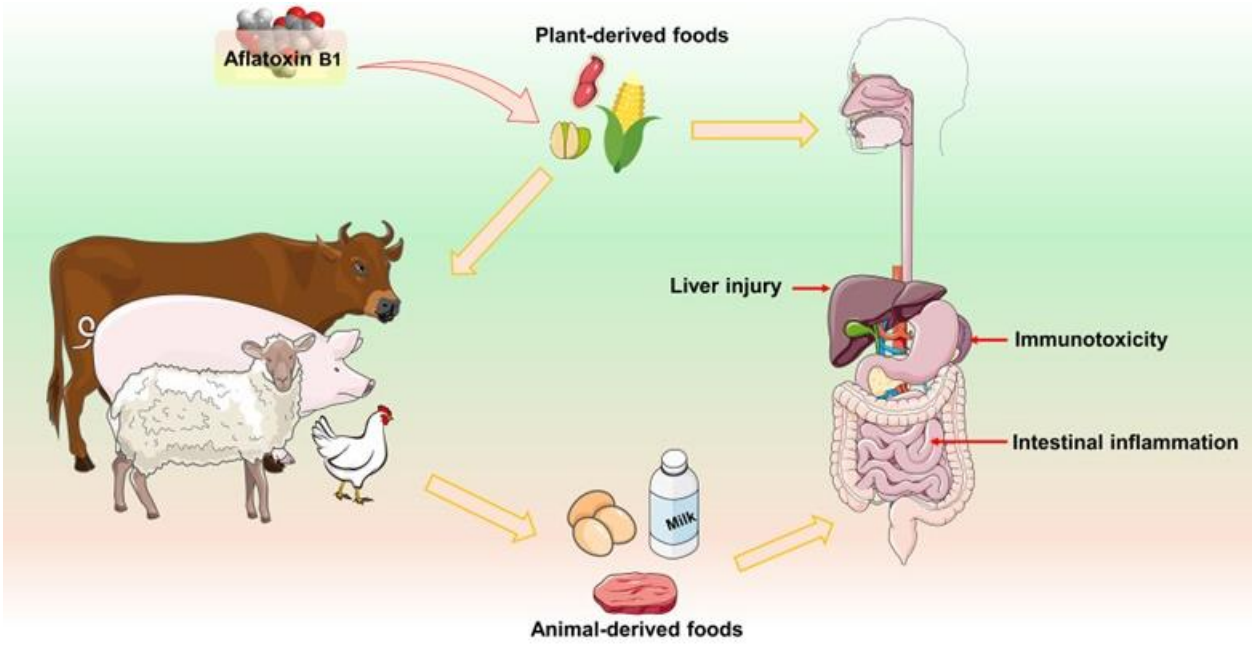

Fig. 2: Transmission routes of AFB1. AFB1, a prevalent toxin often present in plant-derived foods, can lead to harm in various tissues and organs of both humans and animals. Moreover, when animals ingest feed polluted with AFB1, it can result in AFB1 metabolites being present in animal-derived foods consumed by humans, hence indirectly introducing toxins into the human body and posing health risks.

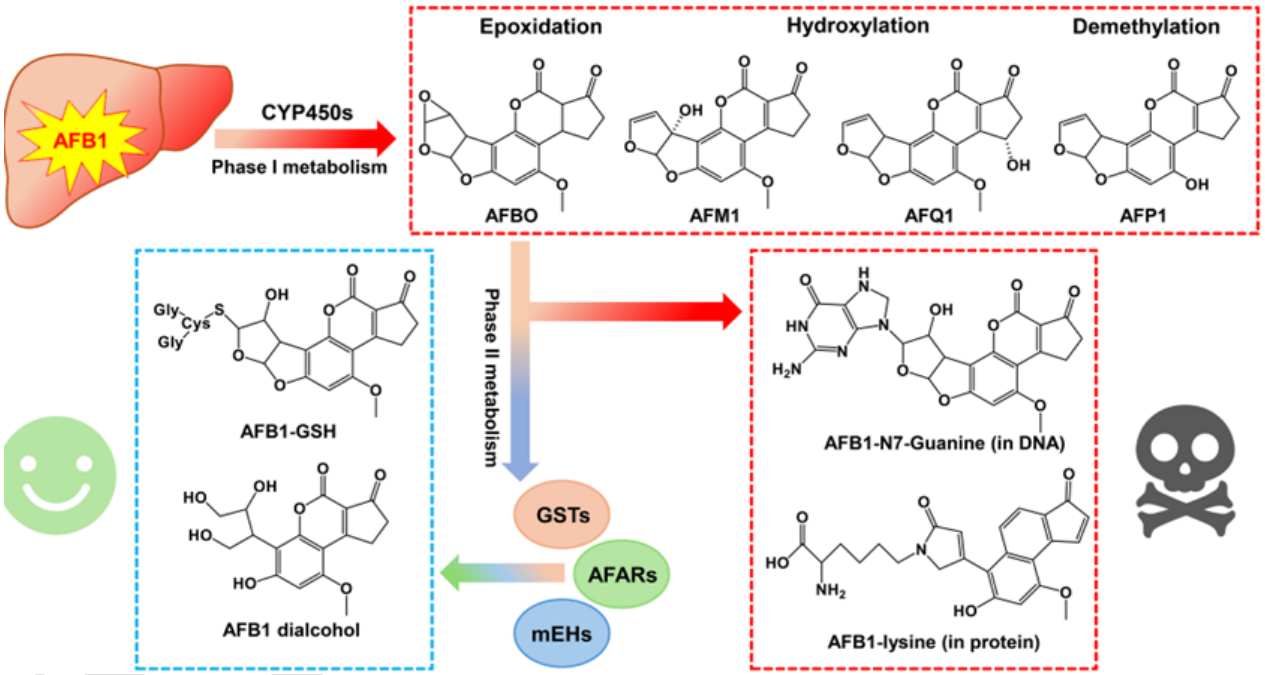

Fig. 3: The metabolism process of AFB1 in animal liver**.** AFB1 undergoes primary metabolism in the liver, where it is primarily metabolized by CYP450 enzymes. This process involves hydroxylation and demethylation, leading to the formation of less toxic metabolites such as AFM1, AFQ1, and AFP1. Alternatively, AFB1 can be metabolized into the highly toxic AFBO through epoxidation. On one hand, AFBO can form adducts with DNA and proteins, resulting in cellular damage. On the other hand, detoxification mechanisms occur when AFBO conjugates with GSH or is metabolized by AFAR and mEH.

turn. This will eventually lead to organs damage and immunotoxicity (Shi *et al.*, 2022; Wang *et al.*, 2019b; Zhou *et al.*, 2019a). These omics data suggest that AFB1 has a dual effect on immune systems. It involves stimulation and inhibition of immunity.-The impact of AFB1 on the immune system is determined by multiple factors, including species, exposure time, and dosage (Su *et al.*, 2023; Sun *et al.*, 2018).

The immunotoxicity of AFB1 is commonly categorized into two parts: non-specific and specific immunity. This includes studying the proliferation and differentiation of immune cells, cytokine synthesis, and even the sensitivity to pathogens (Hou *et al.*, 2018; Maroui *et al.*, 2024; Saha Turna *et al.*, 2023) (Fig. 4).

Effects on non-specific immune responses: Non-specific immunity, also known as innate immunity, functions as the body's essential primary barrier to resist pathogenic microbes. Immune cells are vital components of innate immunity. They use pattern recognition receptors (PRRs) to identify and eliminate pathogens (Locati *et al.*, 2020).

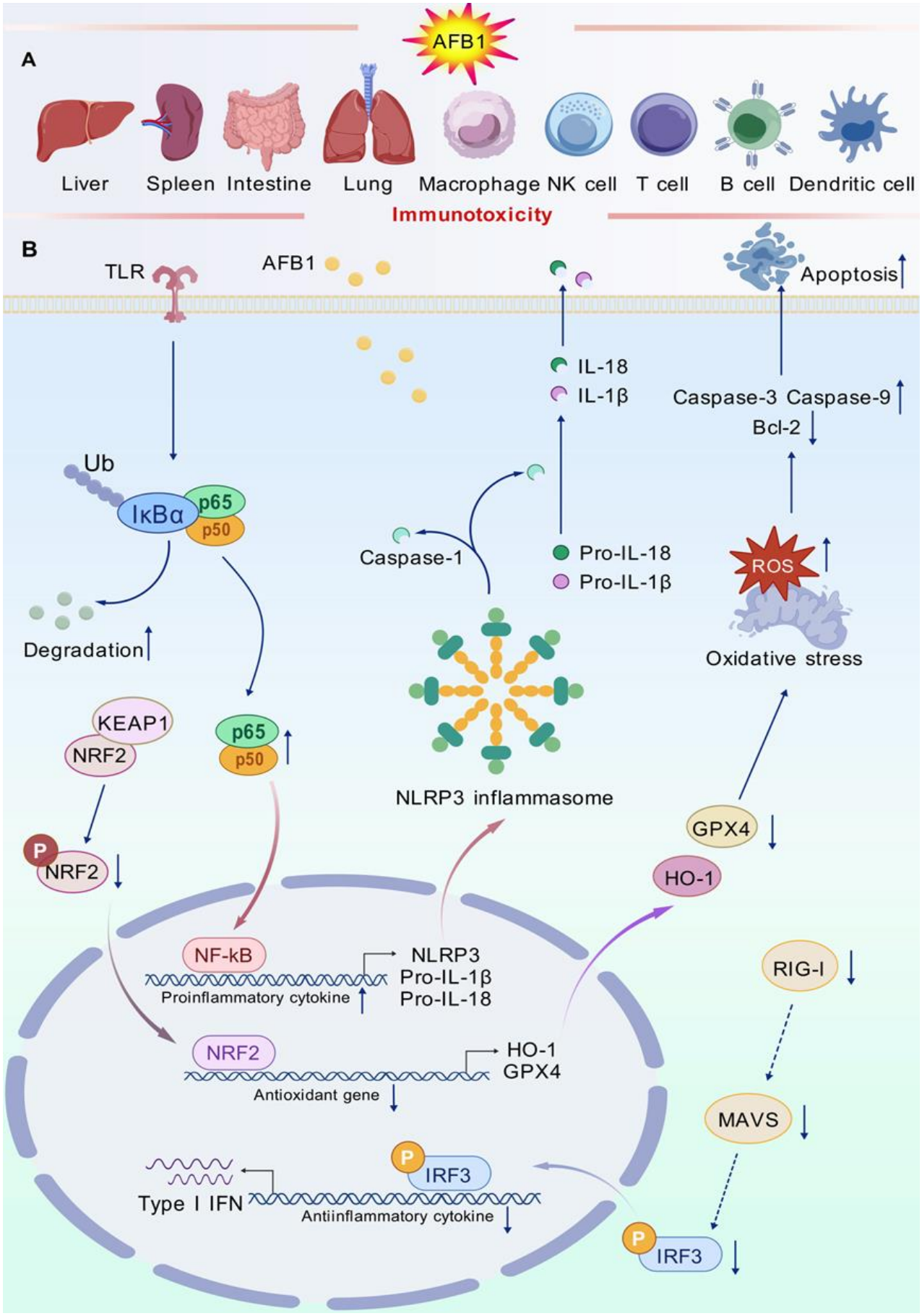

Fig. 4: Schematic representation of the effects of AFB1 on immunity. AFB1 exhibits immunotoxicity in two main ways: immunosuppression and immunostimulation. Immunosuppression gives rise to cellular oxidative stress and apoptosis, such as the inhibition of the NRF2/KEAP1 signaling pathway. Conversely, immunostimulation is mediated by the activation of the NF-κB pathway and NLRP3 inflammasome, and the downregulation of the IRF pathway.

PRRs can be divided into cell surface receptors and intracellular receptors. Cell surface receptors include Toll-like receptors (TLRs), scavenger receptors, and C-type lectins. Intracellular receptors include NOD-like receptors (NLRs), RIG-I-like receptors (RLRs), inflammasomes, and DNA sensors (Carpenter and O'Neill, 2024; Mantovani and Garlanda, 2023; Wu and Lu, 2019). AFB1 significantly impacts the immune systems, particularly affecting innate immunity through its effects on macrophages (Chao *et al.*, 2022; Zhang *et al.*, 2024b; Zhang *et al.*, 2023).

AFB1 exerts immunosuppressive effects through multiple mechanisms, including impairing immune cell viability, phagocytic function, and transcriptional regulation of core immune-related genes (Mehrzad *et al.*, 2018), as well as suppressing macrophage proliferation via activation of calcium signaling pathways (Tian *et al.*, 2023). Aquatic invertebrates are important components of the food chain. They can enhance the movement and deposition of AFB1 from the surroundings to living organisms. However, research in this area is still in its early stages (Su *et al.*, 2023). Shrimp mainly rely on innate immune responses to resist pathogens and other threats. TLR and immune deficiency (IMD) pathways are vital components of innate immunity, playing significant roles in resisting pathogen (Wu and Lu, 2019). Su *et al*. (2023) found that when Pacific white shrimp were fed with AFB1 for 28 days, total hemocyte count (THC), hemocyte phagocytic activity (PA), and plasma antibacterial activity (AB) decreased, and the Toll and IMD pathways were suppressed. After 3 to 30 days of AFB1 treatment in *Litopenaeus vannamei*, the expressions of immune genes such as Toll and glutathione S-transferase (GSTs) first increased and then decreased in tissues. These results showed that AFB1 could inhibit innate immunity in shrimp (Wang *et al.*, 2019c). Currently, research studies are focused on the toxicity of AFB1 to vertebrates, especially poultry and livestock. Studies on vertebrates have found that oral AFB1 administration in male C57BL/6 mice reduced the quantity of M2-type macrophages and Paneth cells, impairing intestinal immunity. They also found that soluble epoxide hydrolase was crucial in mediating AFB1-induced intestinal immunotoxicity (Wang *et al.*, 2023a). Besides, AFB1 can induce immunotoxicity in animals by promoting cell apoptosis, oxidative stress, and ferroptosis (Xia *et al.*, 2024). Therefore, AFB1 primarily impairs innate immune responses by compromising phagocytic function.

AFB1 exerts immunostimulatory effects by activating the inflammatory pathways to boost the production of pro-inflammatory factors. The NF-κB pathway is closely related to AFB1-induced immunotoxicity. AFB1 activates this pathway to trigger inflammation (He *et al.*, 2023b), thereby increasing release of pro-inflammatory factors (Hou *et al.*, 2018). Beyond NF-κB pathway, inflammasomes can regulate innate immunity. AFB1-induced tissue damage and inflammation were associated with NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome activation (Liao *et al.*, 2024). Moreover, NLRP3 inflammasome were triggered by AFB1, inducing gasdermin D-mediated pyroptosis and expression of inflammatory cytokines (Zhang *et al.*, 2022). AFB1 upregulates pro-inflammatory mediators, thereby activating multiple immune cell populations including macrophages, circulating monocytes, NK cells, lymphocytes, and basophils (Zhou *et al.*, 2019b; Dey and Kang, 2020). Macrophages induced by AFB1 can activate immune responses through ROS production (Ma *et al.*, 2021). AFB1 also triggered inflammation through the ERMCS/Ca^{2+}/ROS cascade (Wu *et al.*, 2023) and damaged intestinal mucosa. However, the porcine antimicrobial peptide, porcine beta-defensin-2 (pBD-2) can mitigate intestinal inflammation and damage caused by AFB1, due to its antioxidant properties (Li *et al.*, 2023). AFB1 exerts immunostimulatory effects by activating inflammatory pathways such as NF-κB and NLRP3 inflammasome to promote the release of pro-inflammatory factors.

Effects on specific immune responses: Specific immunity, also known as adaptive immunity, relies on immune organs (thymus, lymph nodes, spleen) and immune cells (lymphocytes, phagocytes). AFB1 also impacts adaptive immunity. AFB1 exhibits dual effects on adaptive immunity. Qian *et al*. (2014) reported that high-dose AFB1 (75 μg/kg for 1 week) suppressed the percentage of $CD8^+$ T cell subsets and inflammatory factor expression, showing immunosuppression. However, low doses AFB1 (5 and 25 μg/kg for 5 weeks) increased the percentages of $CD3^+$ and $CD8^+$ T cells, indicating immunostimulation.

Numerous studies show that long-term AFs exposure directly suppresses adaptive immunity. Prolonged exposure to AFB1 impairs egg quality and immune organs, leading to a decrease in production performance and an increase in susceptibility to pathogens (Xu *et al.*, 2022). Plasma cells produce antibodies upon antigen or cytokine stimulation, participating in humoral immune responses. Li *et al*. (2022) found that AFB1 reduced the plasma cells in broilers, suppressing humoral immunity. Broilers fed a long-term AFB1 diet had lower serum immunoglobulin levels (IgY and IgA) but higher inflammatory cytokines (NF-κB, IL-6, IFN-γ), suggesting suppressed humoral immunity and reduced immune function (Guo *et al.*, 2022b; Mohammadi *et al.*, 2024; Oloruntola *et al.*, 2024). Similar immunosuppression occurs in other animals. For example, rabbits fed AFB1 for 8 weeks showed decreased expression of immunoglobulins (IgG and IgM) and anti-inflammatory gene (NRF2 and IL-10) (Saghir *et al.*, 2024). Juvenile white Leghorn fed AFB1 for 2 months showed decreased immunoglobulin levels and lymphoid hyperplasia responses (Saleemi *et al.*, 2024). Thus, numerous animal studies have confirmed that AFB1 affects antibody levels, leading to increased susceptibility of animals to pathogens. Besides, AFB1 also induces T cell immunotoxicity (Frangiamone *et al.*, 2023). Medium and low doses of AFB1 may increase the regulatory T (Treg)/Th17 ratio via the aryl hydrocarbon receptor (AHR) pathway, leading to immunosuppression (Mary *et al.*, 2024). Taken together, AFB1 inhibits adaptive immunity by reducing antibody or cytokine levels and the proportion of T cells.

AFB1 crosses intestinal epithelial cells, enters into the bloodstream and then damages the immune system and organs via lymphatic circulation. For instance, AFB1 impaired the intestinal barrier, allowing microbial toxins like lipopolysaccharides to reach the spleen and trigger cell death (Chen *et al.*, 2024a). As a key immune organ, the spleen produces lymphocytes and immune proteins. Guo *et*

al. (2022a) found that AFB1 activated mitophagy through the PINK1/Parkin pathway, damaging the bone marrow, thymus, and spleen. Multiple studies indicated that AFB1 changed the immune organs' weight and disrupted inflammatory factors' balance (Lu *et al.*, 2023). Increase in the spleen weight indicates the severity of inflammation. AFB1 caused spleen damage in poultry, shown by a higher spleen index, fewer lymphocyte and splenic cell proliferation (Shirani *et al.*, 2021; Zhao *et al.*, 2019). This involves modulating the NF-κB and NRF2 pathways, leading to increase in the level of inflammation and decrease the antibody levels (Li *et al.*, 2024; Rajput *et al.*, 2019; Wan *et al.*, 2022). Furthermore, the bursa of Fabricius in broilers is a vital immune organ, with its structure and function holding a unique position in the avian immune system. AFB1 reduced the size of the bursa of Fabricius in broilers and suppressed the NRF2 pathway (Nabi *et al.*, 2024; Khatoon *et al.,* 2024). This indicates that AFB1 has adverse effects on immune organs. Overall, AFB1 significantly impairs the immune systems of various animal species.

Discussion and conclusions: AFs pollution, especially the highly toxic AFB1, leads to significant economic losses in farming and animal husbandry (Yang *et al.*, 2020). AFB1's carcinogenic, toxic, and teratogenic effects on livestock and poultry are well-documented (Cao *et al.*, 2022). It exerts toxicity through oxidative stress, immunotoxicity, developmental disorder, and gut microbiota imbalance (Aljazzar *et al.*, 2023; Chen *et al.*, 2024a; Dai *et al.*, 2024; He *et al.*, 2023a). Thus, the harm caused by AFB1 is complex and multifaceted, but currently there is a lack of specific antidrug for AFB1 poisoning. Current decontamination approaches include physical, chemical, and biological techniques, such as high-temperature and high-pressure treatments, alkaline and ozone treatments, and biodegradation by microorganisms or enzymes (Guan *et al.*, 2021; Liu *et al.*, 2024). But these strategies have limitations. Because they can only partially remove toxins and may impact on the nutritional content and taste of foods. Plant-based active substances have been shown to alleviate AFB1-induced immunotoxicity, such as licochalcone A, grape seed proanthocyanidin, quercetin, lycopene, curcumin, alfalfa, and resveratrol (Hidayat *et al.*, 2023; Li *et al.*, 2022; Nava-Ramírez *et al.*, 2024; Pauletto *et al.*, 2023; Rajput *et al.*, 2019; Sarker *et al.*, 2021; Xia *et al.*, 2024; Yang *et al.*, 2024; Zhu *et al.*, 2024). Probiotics have been reported to alleviate aflatoxin's toxicity, including *Lactobacillus rhamnosus*, *Lactobacillus salivarius*, *Bacillus licheniformis*, and yeast (*Geotrichum candidum XG1*) (Ahlberg *et al.*, 2015; Aloui *et al.*, 2024; Zhang *et al.*, 2024a). Vitamins have been demonstrated to alleviate AFB1's toxicity (Abdel-Hamid and Firgany Ael, 2015). Overall, the detoxification strategy based on plant active substances represents a promising direction.

AFB1 exhibits significant immunotoxicity in poultry, rodents, and marine organisms. It not only causes inhibitory immunity at high doses but also triggers stimulating immunity at low doses. This will damage many immune system organs such as spleen and intestines, causing immune dysregulation. And it also increases the risk of diseases. In summary, this article systematically reviews the known types of AFs and their metabolic transformations, while providing a comprehensive synthesis of AFB1-induced immunotoxic mechanisms in livestock and poultry. These findings establish a theoretical framework to guide early AFB1 diagnosis, immunomodulatory interventions, and feed toxin mitigation strategies in veterinary clinical practice.

Abbreviations:

AB	Antibacterial activity
AFAR	Aflatoxin aldehyde reductase
AFBO	Exo-AFB1-8,9-epoxide
AFB1	Aflatoxin B1
AFB2	Aflatoxin B2
AFB2a	Aflatoxin B2a
AFB3	Aflatoxin B3
AFD1	Aflatoxin D1
AFD2	Aflatoxin D2
AFG1	Aflatoxin G1
AFG2	Aflatoxin G2
AFG2a	Aflatoxin G2a
AFGM1	Aflatoxin GM1
AFGM2	Aflatoxin GM2
AFGM2a	Aflatoxin GM2a
AFL	Aflatoxicol
AFM1	Aflatoxin M1
AFM2	Aflatoxin M2
AFM2a	Aflatoxin M2a
AFM4	Aflatoxin M4
AFP1	Aflatoxin P1
AFP2	Aflatoxin P2
AFQ1	Aflatoxin Q1
AFQ2a	Aflatoxin Q2a
Afs	Aflatoxins
BCL6	B cell lymphoma 6
CCL22	Chemokine ligand 22
CYP1A1	Cytochrome P450 1A1
CYP1A2	Cytochrome P450 1A2
CYP1A5	Cytochrome P450 1A5
CYP1B1	Cytochrome P450 1B1
CYP2A6	Cytochrome P450 2A6
CYP3A4	Cytochrome P450 3A4
CYP3A37	Cytochrome P450 3A37
CYP450	Cytochrome P450
DON	Deoxynivalenol
EBV	Epstein-Barr Virus
ERMCS	Endoplasmic reticulum (ER)-Mitochondria Contact Sites
FABP4	Fatty acid binding protein 4
FB	Fumonisins B
GST	Glutathione-S-transferase
IFN-γ	Interferon-gamma
IMD	Immune deficiency
mEH	Microsomal epoxide hydrolase
NF-κB	Nuclear factor-kappaB
NLR	NOD-like receptor
NLRP3	Nucleotide-binding oligomerization domain (NOD)-like receptor (NLR) family pyrin domain containing 3AHR, Aryl hydrocarbon receptor
OTs	Ochratoxins
PA	Phagocytic activity
PAM	Macrophage
pBD-2	Porcine beta-defensin-2

PRRs	Pattern recognition receptors
RLR	RIG-I-like receptor
THC	Total hemocyte count
TLR	Toll-like receptor
TLR2	Toll-like receptor 2
TNF-α	Tumor necrosis factor alpha
Treg	Regulatory T
ZEN	Zearalenone

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