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STRATEGIES FOR DECONTAMINATION AND ALLEVIATION OF MYCOTOXINS FOR SUSTAINABLE POULTRY FARMING – A REVIEW

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Abstract

Mycotoxins including aflatoxins (AF), zearalenone (ZEN), ochratoxin A (OTA), fumonisins (FUM), trichothecenes (TCN), deoxynivalenol (DON), and T-2 toxin had negative influences on poultry productivity causing a depression in performance, product quality, antioxidative properties, immunity, health status, economic value and sustainability of production. The liver and kidney are the organs most affected by dysfunction and genetic damage (carcinogenicity, mutagenicity, and teratogenicity). Chemical and physical approaches, including washing and extracting solvents, heat inactivation, irradiation, and chemical agents, are used to detoxify mycotoxins in feedstuff. Also, the dietary addition of adsorbents (zeolites, bentonites, hydrated sodium calcium aluminosilicate, glucomannan, etc.) is a strategy extensively used in poultry production. Additionally, several feed additives, including microorganisms, phytogenic additives, and natural antioxidants, can reduce the negative impacts of mycotoxins and achieve promising results in the poultry industry. However, the efficacies of these various strategies are different, showing distinct variations, and some limited effectiveness. Moreover, the minimum time required to induce a complete recovery from mycotoxins is lacking in the literature, as four weeks after removal, there are still adverse effects on performance and some physiological traits. This review focuses on the impact of different strategies for eliminating or mitigating the negative effects of mycotoxins on poultry productivity and their physiological and immunological traits by various means. In addition, the mycotoxicosis effect on the molecular pathways and the prevention and alleviation of different feed additives concerning the genetic pathways have been evaluated.

Key words: dietary manipulations, mycotoxins, growth, antioxidative status, immunity, recovery

Mycotoxins, or the silent killers, are secondary products of fungal metabolism. While more than 500 mycotoxins have been discovered, five fungal genera *Aspergillus, Fusarium, Penicillium, Claviceps,* and *Alternaria* are principally responsible for producing those that are significant for feed safety (Haque et al., 2020). Indeed, aflatoxins (AF), zearalenone (ZEN), ochratoxin A (OTA), fumonisins (FUM), trichothecenes (TCN), deoxynivalenol (DON), and T-2 toxin, are the most significant common mycotoxins that have negative impacts on health and performance of poultry species (Murugesan et al., 2015). The contamination of animal feed by mycotoxins not only affects poultry performance negatively but also reduces the quality, sustainability and safety of poultry products. Mycotoxins are metabolized in the liver, making it the primary target organ of mycotoxins toxicity. The negative impacts of mycotoxins depend on exposure time and dose. High levels of AF could cause acute liver and kidney disease or death within 72 hours (Ochieng et al., 2021). High levels of AF result in the loss of appetite, harming gut health, decreasing nutrient metabolism, weakening growth rate, impairing reproduction, causing muscle hemorrhage, and leading to immunosuppression (Tahir et al., 2022).

Several physical, chemical, biological, and nutritional strategies have been used to decrease the adverse influences of mycotoxins via decontamination and detoxification in the feed industry. The first is by altogether preventing the formation of mycotoxins by avoiding

mold growth using mold inhibitors. If molds have been formed, however, high levels of amino acids like methionine, lysine, glutamic acid, arginine, and aspartate, and antioxidants including vitamin E, vitamin C, vitamin B_1, selenium (Se), carotenoids, and flavonoids supplementation have been found to reduce the toxic effects (Liu et al., 2020 b). Adsorbents have been used for many years to deactivate mycotoxins by immobilization in the gastrointestinal tract (GIT); however, for other mycotoxins, these so-called "mycotoxin binders" have limitations. The inclusion of binders [e.g., hydrated sodium calcium aluminosilicate (HSCAS)] to AF-contaminated diets significantly reduces the negative impacts of the toxin on growth performance in broilers (Ghazalah et al., 2021). Microorganisms including *Bacillus, Lactobacillus, Bifidobacterium, Pseudomonas, Propionibacterium*, and *Lactococcus* showed biotransformation capabilities against specific mycotoxins in the GIT (Chang et al., 2020). It was reported that *Eubacterium* (BBSH 797) strain can detoxify TCN by reducing the epoxide ring (Karlovsky, 2011). Also, various fungal and yeast species have been shown to detoxify the AFB_1 (aflatoxin B1), OTA, ZEN, DON, and T-2 toxins (Chlebicz and Śliżewska, 2020). Several antioxidants and phytochemicals are safe and environmentally friendly supplements and can alleviate the negative impacts of mycotoxins via activating the antioxidative properties and immune response (Amminikutty et al., 2023). The present review addresses the influences of different strategies for eliminating and mitigating the harmful effects of mycotoxins on poultry productivity and sustainability and their physiological and immunological traits by other means. It will also study the mycotoxicosis effect on the molecular pathways and the prevention and alleviation of different feed additives concerning the genetic pathways.

General detrimental effects of mycotoxins in poultry

Mycotoxins harm poultry metabolism, product quality, production rate, immunity and health even at low concentrations (Hernandez-Valdivia et al., 2021). Several publications and reviews shed light on the detrimental effects of mycotoxins in poultry production; thus, only a brief amount of information will be introduced in this section. Mycotoxins impair growth performance, laying performance, and egg and meat quality and hurt the liver and kidneys in poultry species (Tahir et al., 2022). Diets contaminated with AF, OTA, DON, and ZEN reduced the feed intake (FI) and, consequently, growth rate in broilers (Metayer et al., 2019). Aflatoxicosis, primarily caused by aflatoxin B1, is a common disease in poultry and other animal species. AF ingestion induces severe pathological changes in most body organs, resulting in liver and kidney damage and dysfunction, impairing body weight gain (BWG), FI, feed conversion ratio (FCR), and increasing mortality % (Zou et al., 2023). In poultry, AF and OTA act as main immunosuppressive agents that suppress the immune system's growth and function, increasing susceptibility to severe diseases (Bhatti et al., 2018).

Moreover, the T-2 toxin-induced oxidative damage and damaged cell membranes and DNA, increase apoptosis in broiler chickens (Chen et al., 2019). It was reported that AF is involved in oxidative stress and immunosuppression in broilers (Ali et al., 2021). Diets contaminated with OTA (3.2 or 6.4 mg/kg diet) significantly decreased superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) concentrations in the liver and kidney of broiler chickens (Hameed et al., 2017). Moreover, Xue et al. (2010) investigated the immunopathological impacts of OTA and T-2 toxin. They documented that contamination with OTA and T-2 toxin decreased the antibody titers against Newcastle disease virus (NDV) by 10.4% in broiler chickens. These negative impacts of mycotoxins on immunity might be related to reducing the mRNA expression of interleukin-2 (IL-2), interferon-γ (IFN-γ), and deteriorating bursa of Fabricius, thymus, and spleen (Tahir et al., 2022). From another point of view, mycotoxins disturb gut microbiota, leading to an increase in pathogenic bacteria and a reduction at the expense of beneficial microbes. AFB_1 elevated the number of *Staphylococcus-xylosus,* and *Escherichia-coli-g-Escherichia-Shigella,* and minimized *Lactobacillus-aviarius* abundance in broilers (Guo et al., 2023). Thus, it might be indicated that mycotoxins disturb the intestinal microbial balance, antioxidative properties, and immune response, leading to sensibility to diseases and suppressing productivity.

Marin-Kuan et al. (2006) showed that oxidative stress can affect the OTA-induced nephrotoxicity. Oxidative stress can interfere with the signal transmission of PI3K/AKT pathway, modifying the activation of Nrf2 and reducing the Nrf2 total protein levels (Deng et al., 2013). The PI3K/AKT pathway is essential in modulating cell growth, differentiation, migration and apoptosis. The effects of OTA are often mediated through oxidative stress. Cavin et al. (2019) showed the role of Nrf2 in renal disorders. However, the mechanism of Nrf2 activation in response to OTA through PI3K/AKT signaling pathway in kidneys is still not well clarified. Loboda et al. (2017) reported that Nrf2 deficiency increased OTA-induced toxicity *in vitro* and *in vivo*. Furthermore, Nrf2 and its target genes, such as MnSOD, CAT, GSH-px, HO-1, and GLRX2 have a role in the endogenous redox system (Ge et al., 2019). Nrf2 and its target gene, HO-1, were reduced after OTA exposure in renal proximal tubular epithelial cells (Boesch-Saadatmandi et al., 2008). Se-Y activated Nrf2, improving the expression of Nrf2, MnSOD, CAT, GSH-px, HO-1, and GLRX2, and thus the redox balance and resistance of the chicken kidneys to oxidative stress induced by OTA (Rajput et al., 2019). The inflammatory genes (TLR4 and NF-κB) and cytokines (IL-6 and IL-8) were up-regulated in the liver of broiler exposed to AFB_1 (Wang et al., 2019). At 1 mg/kg, AFB_1 upregulated the expression of inflammatory genes (TLR4, myd88, and NF-κB) and markers (TNF-α, iNOS, IL-6, IL-1β), leading to an inflammatory response. Furthermore, the signal crosstalk TLR4/TNF-α triggers inflammation and RIPK1/RIPK3 mediating necroptosis in AFB_1-induced liver injury in broilers (Li et al., 2022).

Table 2. Effects of mycotoxins on gene expression in poultry

Gene/Pathway affected	Effect on gene expression	Potential health impacts	References
Immune response genes	Downregulation of MHC class I and II, TLR (Toll-like receptors)	Increased susceptibility to infections	Gimeno and Schat (2018)
Detoxification enzymes	Altered expression of CYP1A5, CYP3A37, GST	Variable detoxification efficiency, increased susceptibility to toxins	Dohnal et al. (2014)
Apoptosis regulators	Upregulation of Bax, downregulation of Bcl-2	Increased apoptosis leading to tissue damage	Li et al. (2020)
Carcinogenesis related genes	Changes in expression of proto-oncogenes and tumor suppressor genes	Elevated risk of cancer, especially liver cancer	Ghazi et al. (2020)
Lipid metabolism genes	Modulation of genes involved in fatty acid synthesis and degradation (e.g., SREBP)	Risk of fatty liver disease, metabolic disturbances	Tan et al. (2022)
Oxidative stress markers	Alteration in SOD (superoxide dismutase), CAT (catalase)	Increased oxidative stress leading to cellular damage	Mavrommatis et al. (2021)
Protein synthesis genes	Downregulation of genes involved in ribosomal activity and protein assembly	Impaired protein synthesis affecting growth and repair	Dietrich et al. (2012)
Cytokine production	Downregulation of IL-2, IL-6, TNF-alpha	Compromised immune responses, inflammation control	He et al. (2014)
Hepatic function genes	Changes in genes regulating bile acid synthesis and liver enzymes	Impaired liver function, potential for hepatic injury	Chen et al. (2023)
Endocrine system regulators	Effects on hormone synthesis genes, including those for estrogen and testosterone	Endocrine disruptions, potential reproductive issues	Ranzenigo et al. (2008)
Heat shock proteins (HSPs)	Upregulation in response to stress	Helps in protein stabilization and repair, mitigating damage	Balakrishnan et al. (2023)
P53 gene	Possible activation or suppression	Influences cell cycle control and apoptosis, affects carcinogenic potential	Godwin and Edu (2022)
NF-kB pathway	Activation by mycotoxins	Induces inflammatory responses, can lead to tissue damage	Tong et al. (2020)
Growth factors (e.g., IGF-1, TGF-β)	Alteration in expression levels	Impacts growth and development, leading to defects	Lahjouji (2021)
Xenobiotic metabolism genes (e.g., XRCC1, GSTM1)	Variation in expression or function	Affects detoxification and susceptibility to mycotoxins	Godwin and Edu (2022)
MicroRNA Involvement	Activation of miR-21, miR-200a leading to inflammation and EMT; miR-122 activates apoptosis via caspase-3.	Regulates inflammatory responses and apoptosis, impacting tissue health.	Balasubramanian et al. (2020)
Oxidative stress genes	Fluctuations in CYP1A2 expression in response to mycotoxins affecting oxidative stress response.	Influences oxidative stress levels, potentially leading to cellular damage.	Kövesi et al. (2024 a)
Apoptotic genes	Increase in caspase 3 and Bax expression; decrease in Bcl-2 expression.	Enhances apoptotic processes, contributing to tissue and organ damage.	Yang et al. (2017)
AhR signaling pathway genes	Variation in expression of AHRR and HSP90 due to mycotoxin exposure.	Affects detoxification and metabolic responses in poultry.	Kövesi et al. (2024 b)
MicroRNA (miR-21, miR-200a, miR-200c, miR-29b, miR-731, miR-122)	Various microRNAs regulate responses to OTA toxicity, affecting inflammation, EMT, nephrotoxicity, renal fibrosis, and apoptosis.	Impact cellular processes like inflammation, fibrosis, and apoptosis, potentially compromising organ function.	Chen et al. (2022)
Caspase 3, Bax (pro-apoptotic); Bcl-2 (anti-apoptotic)	Significant changes in expression promoting apoptosis in response to T-2 toxin.	Induces widespread apoptosis contributing to cell and tissue damage.	Yang et al. (2017)
Oxidative stress-related (CYP1A2, AHRR, HSP90)	Expression impacted by mycotoxins, influencing oxidative stress management.	Alters cellular responses to oxidative stress, affecting kidney and liver health.	Kövesi et al. (2024 b)
AhR signaling pathway (AHR, AHRR)	Expression levels change in response to *Fusarium* mycotoxins, affecting AhR pathway.	Modulates xenobiotic metabolism and toxic responses.	Kövesi et al. (2024 b)
Zearalenone impact on immune mediators (cytokines, MAPK signaling)	ZEA alters expression of immune mediators and signaling molecules in spleen, affecting immune responses.	Compromises immune function, influences inflammatory responses.	Pistol et al. (2015)

Table 3. Final comprehensive list of feed additives used to mitigate mycotoxins in poultry via gene expression pathways

Feed additive	Target mycotoxin	Gene expression pathway influenced	References
1	2	3	4
Beta-carotene	Aflatoxins	Influences immune system and oxidative stress genes	Ricke (2018)
Montmorillonite clay	Multiple mycotoxins	Modifies genes related to toxin absorption in gut	Kumar et al. (2020)
Lycopene	Ochratoxin A, zearalenone	Acts on liver protection and inflammation reduction genes	Rissanen et al. (2001)
Spirulina	Various mycotoxins	Modulates detoxification and immune system genes	Barone et al. (2023)
Astaxanthin	Various mycotoxins	Influences oxidative stress and immune enhancement genes	Hara et al. (2017)
Genetically modified yeasts	Various mycotoxins	Engineered to express enzymes for toxin degradation	Singh et al. (2008)
Omega-3 fatty acids	Multiple mycotoxins	Modulates inflammation and cellular repair genes	De Seymour et al. (2019)
Copper oxide nanoparticles	Multiple mycotoxins	Enhances antioxidant defense system genes	Mohamed et al. (2022)
Lutein	Various mycotoxins	Enhances gene expression related to visual health and immunity	Bowen et al. (2015)
Probiotic *Enterococcus faecium*	Multiple mycotoxins	Modulates gut health and detoxification genes	Darafsh et al. (2020)
Folic acid supplementation	Multiple mycotoxins	Influences genes related to cellular repair and growth	Koivu et al. (2023)
Essential oil blend (oregano, garlic, citrus oils)	Multiple mycotoxins	Affects metabolism processing genes	Śmiechowska et al. (2021)
Graphene oxide	Various mycotoxins	Impacts genes associated with intestinal barrier	Herreros et al. (2014)
Vitamin C (ascorbic acid)	Various mycotoxins	Enhances oxidative stress relief and immune system genes	Nosrati et al. (2017)
Calcium propionate	Various mycotoxins	Regulates genes reducing fungal growth	Lv et al. (2020)
Turmeric extract (curcuminoids)	Aflatoxins, ochratoxin	Modulates liver detoxification and anti-inflammatory genes	Kong et al. (2021)
Silver nanoparticles	Multiple mycotoxins	Affects genes related to microbial control	Gutiérrez et al. (2011)
Peppermint oil	Multiple mycotoxins	Acts on digestive system genes enhancing gut health	Stamilla et al. (2020)
Choline chloride	Aflatoxins	Affects liver health and fat metabolism genes	Jahn et al. (2019)
Sodium butyrate	Various mycotoxins	Modulates gut health and immunity genes	Warburton et al. (2022)
Yucca schidigera extract	Various mycotoxins	Modulates genes for ammonia reduction and liver detoxification	Wallace et al. (2010)
Milk thistle extract (silymarin)	Multiple mycotoxins	Enhances detoxification and antioxidant genes	El-Ghany (2022)
Zeolite clinoptilolite	Multiple mycotoxins	Affects genes related to toxin absorption and metabolism	Jard et al. (2011)
Naringin (from grapefruit)	Aflatoxins	Enhances detoxification pathways and liver function	Mazi-Kotwal and Seshadri (2012)
Hydrolyzed protein	Various mycotoxins	Boosts gut health and enhances gene expression for nutrient absorption	Duan et al. (2015)
Hops extract	Multiple mycotoxins	Modulates liver enzymes and immune response genes	Chen (2004)
Glucosamine	Various mycotoxins	Enhances gut barrier function genes	Hayes and Tiwari (2015)
Moringa oleifera extract	Multiple mycotoxins	Modulates detoxification and oxidative stress genes	Dudhatra et al. (2012)
Brewer's yeast	Multiple mycotoxins	Influences immune response genes	Thompson III et al. (2023)
Barley beta-glucans	Various mycotoxins	Modulates gut health genes	Thompson III et al. (2023)

Table 3 – contd.

1	2	3	4
Grape seed extract	Aflatoxins	Impacts liver health genes	Baron et al. (2024)
Selenium enriched algae	Various mycotoxins	Enhances antioxidant enzyme gene expression	Fernández-Luqueño et al. (2023)
Lignans from flaxseed	Zearalenone, aflatoxin	Influences liver detoxification enzyme genes	Chourasia et al. (2021)
Citrus bioflavonoids	Multiple mycotoxins	Modulates immune function and inflammation genes	Jaakola (2013)
Hydrolyzed collagen	Various mycotoxins	Affects gut barrier integrity genes	Riyazi et al. (2011)
Activated fenugreek fibers	Multiple mycotoxins	Binds mycotoxins and influences nutrient absorption genes	Mandal et al. (2023)
Protease enzymes	Various mycotoxins	Modifies nutrient absorption and immune response genes	Jeszeová et al. (2018)
Polysaccharides from mushrooms	Multiple mycotoxins	Affects immune system genes	McGorum et al. (2021)
Conjugated linoleic acid (CLA)	Various mycotoxins	Influences fat metabolism and immune modulation genes	Evans et al. (2002)
Artichoke extract	Multiple mycotoxins	Modulates liver detoxification pathways	Wang et al. (2020)
Pectin fiber	Multiple mycotoxins	Enhances gut health and immunity, binds mycotoxins	Zhu et al. (2023)

The mRNA expression of p53, Cyt-C, Bax, caspase-9, and caspase-3 were up-regulated, while that of Bcl-2 was down-regulated due to AFB_1 (Guo et al., 2022). The over-expression of such genes indicated the effect of AFB_1 in the hepatocellular injury and death (Salem et al., 2018). Sun et al. (2015) observed a reduction in the glutathione peroxidase (GPX) and catalase activities and an increase in malondialdehyde and exo-AFB_1-8,9-epoxide (AFBO) DNA concentrations in chicks' liver exposed to AFB1. See Table 2 for effects of mycotoxins on gene expression in poultry.

Some strategies for controlling the mycotoxicosis

Decontamination is majorly achieved via several approaches: (a) pre-harvest treatment to control mold growth and prevent toxin production, (b) removing the contaminated portion of feedstuffs physically, (c) treating the commodity with chemicals to destroy the toxin sources, and (d) adding additives that bind the toxins and make them unavailable during digestion or convert them to forms that animal system can counteract (Haque et al., 2020). The strategies employed must be cost-effective, with the cost being less than the value of the contaminated commodity. It must meet the following criteria: (i) mycotoxins must be destroyed (removed or inactivated), (ii) no carcinogenic or toxic compounds must be produced, (iii) the nutritional value and palatability must be preserved. (iv) the physical properties of the feedstuff should be maintained as much as possible, and (v) prevention of the formation of new toxins should be ensured by destroying fungal spores and mycelia (Liu et al., 2020 b). In addition in Table 3, we showed the effect of different feed additives on the mycotoxicosis through modulation of the gene expression. The most popular controlling strategies include:

Washing and extracting solvents

Mycotoxins can be decontaminated by washing using water or extracting with an organic solvent, depending on whether they are fat- or water-soluble (Karlovsky et al., 2016). The AF, TCN, ZEN, and FUM can be eliminated from grains by flotation and water washing by 51–72%, 64–69%, 2–61%, and 73–74%, respectively (Matumba et al., 2015). Remarkably, FUM removal from corn and wheat can be accelerated by floating the crop and washing it using a water solution containing 10–30% NaCl, 30% sucrose, or 1 mol/L sodium carbonate (Karlovsky et al., 2016). The FUM can be reduced by 84% when washing and hand sorting are combined (Van der Westhuizen et al., 2011). The most often used organic solvents for mycotoxins are methanol, ethanol, hexane, isopropanol, and acetone. It was demonstrated in earlier research that hexane-aqueous acetone-water (56:42:2%) and dimethyl ether could remove about 98% of AF in oil grains (Wang et al., 2016). However, these approaches have main weaknesses as they result in losing nutrients and are expensive, which limits their large-scale application (Figure 1).

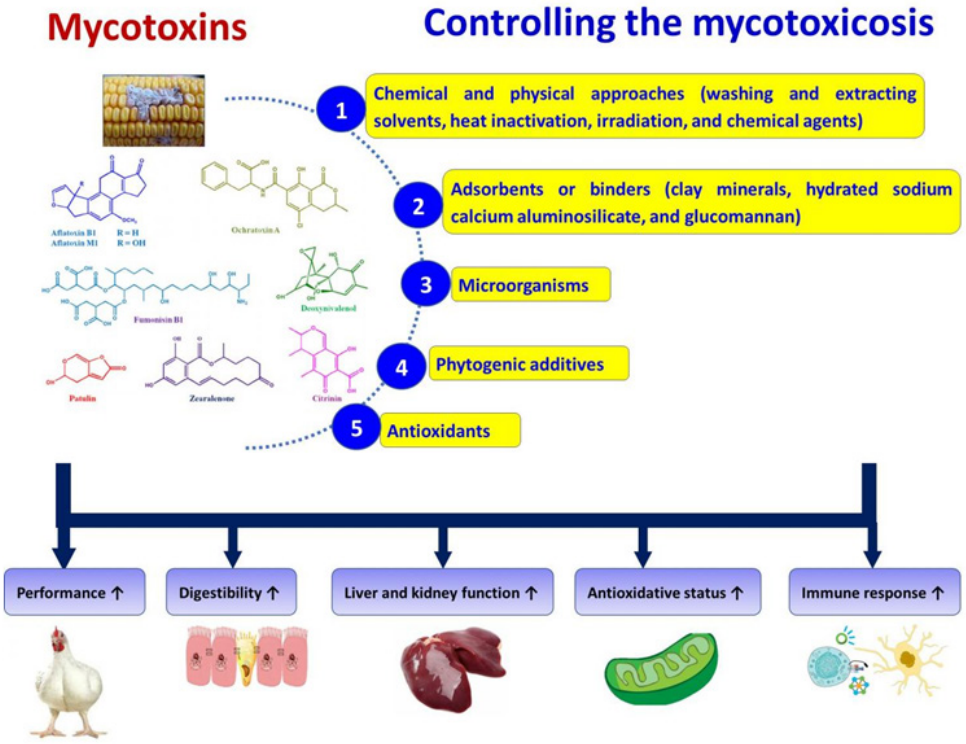

Figure 1. Strategies of controlling mycotoxicosis and its impacts on poultry's physiological and immunological response and productivity

Heat inactivation

For many years, heat processing has been used to remove mycotoxins from feed and feedstuff. Indeed, mycotoxins are heat-stable molecules. The AFB_1, DON, and ZEN are heat-stable molecules with breakdown temperatures greater than 237, 175, and 220°C, respectively (Yumbe-Guevara et al., 2003), that are difficult to remove by conventional heat treatment. Because the AF is very resistant to heat inactivation, the amount of AF produced by heat-using processes (such as boiling water, autoclaving, roasting, and baking) is rarely affected (Park and Liang, 1993). The effectiveness of this approach relies on the chemical composition and levels of mycotoxins, temperature, duration, moisture content, and pH throughout the process (Kabak et al., 2006). Various feed manufacturing procedures such as crumbling, pelleting, and extrusion can decrease mycotoxins in feed ingredients. Nonetheless, these procedures do not eliminate them (Čolović et al., 2019). Temperatures above 160°C effectively broke down the pure AFB_1 and OTA in soybeans (Raters and Matissek, 2008). Yumbe-Guevara et al. (2003) elucidated that exposure to 220°C for 85 min could destroy 90% of ZEN in barley powder. Thermal treatments accelerated the Maillard reaction, which might decrease the nutritive values of feed components such as amino acid lysine (Liu et al., 2020 a).

Irradiation

Three types of ionizing radiation are official in feed manufacturing in Europe, including γ-radiation, X-rays, and electron beams (Liu et al., 2022). Irradiation has reduced the AF content in contaminated grains and products. Irradiation could make physical, chemical, and biological changes that minimize or remove the mycotoxins (Pankaj et al., 2018). Peanut oil treated with short- and long-wave ultraviolet (UV) light significantly decreased AF concentrations (Park and Liang, 1993). γ-irradiation reduced AFB_1 and total aflatoxins concentration by 30% in chicken feed (Herzallah et al., 2008). AFB_1 concentration was decreased by 43.0–87.8%, 65.7–71.5%, and 22.0–100%, by γ-rays, electron beam, and ultraviolet rays, respectively, in grains (Pankaj et al., 2018). Also, ZEN was removed in grains by 25.0–86.0% and 60.0–100% via exposure to γ-rays and ultraviolet rays, respectively (Aziz et al., 1997). Likewise, γ irradiation (30 kGy) reduced peanut AFB_1 and fungal flora by about 61% (Prado et al., 2003). Furthermore, exposure to sunlight (solar radiation) for 30 hours destroyed about 60% of the AF presented in chicken feed (Herzallah et al., 2008). Numerous studies recognized that UV irradiation is a potential strategy to decontaminate mycotoxins, and the degradation ratio is 49–99% (He et al., 2021). The DON and ZEN were destroyed by about 37.0–82.4%, 17.2–56.3%, and 83.4–100% by γ-rays, electron beam, and UV rays, respectively, in feed ingredients (Murata et al., 2008). These variations in the efficacies of irradiation are related to the variation in the dose and period of irradiation, as well as the form and composition of feedstuffs. Even though irradiation can be considered a promising, effective method for detoxifying mycotoxins in feed ingredients, safety issues, including mutations in microorganisms and compromised nutritional values of feed, require additional studies.

Table 1. Role of feed additives in decontaminating and alleviating mycotoxicosis in poultry

Animal	Mycotoxin	Feed additives	Main impacts	References
1	2	3	4	5
Broiler chickens	0.05 mg aflatoxin B_1/kg diet and 0.5 mg ochratoxin A/kg diet	1–2 g clinoptilolite zeolite/kg diet	Enhanced feed conversion ratio. Improved average body weight gain. Improved serum concentration of glutamate-dehydrogenase. Decreased residue concentrations of aflatoxin B_1 in liver and ochratoxin A in spleen.	Raj et al. (2021)
Broiler chickens	0.25 mg aflatoxin B_1/kg diet	4 g bentonite/kg diet or 4 g zeolite/kg diet	Enhanced body weight gain, production efficiency factor, and feed conversion ratio. Improved dressing percentage. Improved apparent digestibility of crude protein, ether extract, and metabolizable energy. Increased serum levels of total protein, glucose, aspartate aminotransferase and alanine aminotransferase. Enhanced serum concentrations of total antioxidant capacity and total superoxide dismutase. Minimized aflatoxin B_1 residues in the liver.	Alharthi et al. (2022)
Broiler chickens	500 ppb aflatoxin B_1	0.2% smectite clay	Enhanced the final body weight, average daily gain, and feed conversion ratio. Reduced the severity of lesions (inflammatory and degenerative changes) in liver, kidney, heart, pancreas, and lymphoid organs. Increased serum concentrations of total protein and globulin. Elevated antibody titer against infectious bursal disease virus.	Zabiulla et al. (2021)
Broiler chickens	0.5 to 2 mg aflatoxin B_1/kg diet	0.5% hydrated sodium calcium aluminosilicate	Improved cumulative body weight gain. Elevated serum concentrations of albumin, total protein, globulin, phosphorus, glucose, alkaline phosphatase, and creatine phosphokinase. Enhanced liver gene expression of antioxidant enzymes (CAT and SOD).	Chen et al. (2014)
Broiler chickens	6.0 mg T-2 toxin/kg diet	0.05% modified hydrated sodium calcium aluminosilicate	Enhanced growth performance. Enhanced nutrient digestibility of gross energy, crude protein, calcium, and total phosphorus. Increased serum concentration of aspartate aminotransferase. Prohibited T-2 toxin-induced morphological changes and damage in the duodenum, jejunum, and ileum.	Wei et al. (2019)
Broiler chickens	427.2 µg/kg aflatoxin B_1, 5.45 µg/kg aflatoxin B_2, 2.23 µg/kg ochratoxin A and 206.31 µg/kg DON	0.05–0.1% esterified glucomannan	Improved feed intake, feed conversion ratio, and body weight gain. Increased liver % and bursa of Fabricius %. Elevated antibody titers against Newcastle disease and infectious bursal disease viruses. Increased serum concentration of alanine aminotransferase and aspartate aminotransferase.	Mohaghegh et al. (2017)
Broiler chickens	19.3 mg deoxynivalenol/kg diet	*Lactobacillus* spp. pool	Increased villi height and increased crypt depths. Improved the villi: crypt ratio in the duodenum and jejunum. Reduced oxidative stress (thiobarbituric acid reactive substances concentration in jejunum and ileum).	de Souza et al. (2020)
Broiler chickens	0.5 mg ochratoxin A/kg diet	*Bacillus subtilis* fermentation extract (1 mL/L water)	Enhanced antibody titers against avian influenza, Newcastle disease and infectious bronchitis. Enhanced cell-mediated immune response (lymphoproliferative response to PHA-P). Increased catalase activity and glutathione concentration. Reduced lipid peroxidation (malondialdehyde content). Reduced apoptosis (Bax and Caspase-3 and decreased Bcl-2 gene levels). Reduced serum concentrations of urea, uric acid, and creatinine.	Elhady et al. (2022)
Broiler chickens	100 µg aflatoxin B_1/kg diet	1 g *Saccharomyces cerevisia*e RC016/kg diet	Supported normal hepatocyte structure. Improved intestinal histomorphology (absence of hyperemia, normal villi, lower number of goblet cells, and atrophy). Decreased the residual concentrations of aflatoxin B_1 in the liver.	Poloni et al. (2020)

Table 1 – contd.

1	2	3	4	5
Broiler chickens	300 or 600 µg aflatoxins/kg	1 g *Pichia kudriazevii*/kg diet)	Enhanced antibody titer against sheep red blood cells. Enhanced lymphoproliferative response to phytohemagglutinin-P. Improved phagocytic response by carbon clearance. Enhanced total antioxidant capacity and total oxidant status.	Ali et al. (2021)
Broiler chickens	0.50 mg/kg diet of aflatoxin B_1 and/or 0.25 mg/kg diet of ochratoxin A	Chamomile flower extract (3 g/kg diet) and thyme-oil extract (3 g/kg diet)	Improved average daily gain and daily feed intake and decreased feed conversion ratio. Increased levels of IgG, IgM, and anti-Newcastle disease virus antibody titer. Improved villus height and the ratio of villus height to crypt depth in jejunum.	Nazarizadeh et al. (2019)
Broiler chickens	0.02 mg aflatoxin B_1/kg diet	400 mg of turmeric powder/kg diet	Established histological morphology of the liver tissues. Enhanced the gene expression of antioxidant enzymes (i.e., CAT and SOD2) and drug transporters (i.e., ABCG2) in the liver. Reduced hepatic lipid peroxidation (thiobarbituric acid reactive substances concentration).	Amminikutty et al. (2023)
Broiler chickens	1.0 mg aflatoxin B_1/kg diet	0.3 mg Se/kg diet	Enhanced glutathione peroxidase activity in the heart. Enhanced gene expression of glutathione peroxidase and thioredoxin reductase-3. Reduced selenoprotein M and selenophosphate synthetase 2 mRNA in heart.	Zhao et al. (2021)
Japanese quails	1.0 mg aflatoxin B_1/kg diet	0.5 mg Se nanoparticles/kg diet	Enhanced feed intake, body weight gain, and feed conversion ratio. Improved weight of lymphoid organs (bursa of Fabricius, thymus and spleen). Enhanced antibody titer against Newcastle disease, avian influenza viruses and sheep red blood cells. Enhanced serum concentrations of glutathione peroxidase and thioredoxin reductase.	Khazraei et al. (2022)
Broiler chickens	0.8 ppm aflatoxin B_1/kg diet	Vitamin E (80 mg) + Se (1.6 mg)	Enhanced liver function (increased serum concentrations of aspartate amino transferase and alanine aminotransferase). Decreased the cortex depletion and reduced the congestion, hemorrhage and necrosis in inflammatory cells in the thymus and Harderian gland.	Ulaiwi (2018)
Broiler chickens	172–200 µg ochratoxin A/kg diet	100 mg vitamin E/kg diet + 2200 mg polyphenols/kg diet	The superoxide dismutase and glutathione peroxidase activities are enhanced in blood, liver, and breast muscles. Reduced lipid peroxidation in the liver. Enhanced the concentrations of vitamin C, total tocopherols, and vitamin EEq in liver. No significant effect on growth performance parameters. No significant effect on carcass traits.	Mazur-Kuśnirek et al. (2019)

Chemical agents

Chemical agents can break down the construction of mycotoxins, which produce mild- or non-toxic outputs. Chemical detoxification of AF in feedstuffs and feeds using alkalis (hydroxides and bisulfites), chlorinating compounds, and oxidizing agents (ozone and hydrogen peroxide) is essential as a short-term solution post-harvest. Of the several chemical methods, ozonation is the most utilized and approved method for decontamination. Ozonation is a simple safety method, as it does not cause harmful residues after application (Conte et al., 2020). Protection from mycotoxins using chemical agents was demonstrated in contaminated corn, where oxidizing agents interact with various functional groups, eliminating their toxicity and leaving no residue in poultry (Celik et al., 2021). Several mycotoxins, including AF, ZEN, and FUM, were destroyed by ozone in poultry feedstuffs, with destruction efficiency reaching about 80% (Li et al., 2019). Ozone treatment decreased AFB_1 concentration significantly in poultry feed ingredients (corn, soybean meal, sunflower meal, barley, and peanuts) without increasing lipid oxidation (Torlak et al., 2016). Ozone handling with 100 mg/I ozone for 180 min decontaminated ZEN in corn by 90.7% (Qi et al., 2016).

Alkaline chemicals such as ammonia, sodium hydroxide, potassium hydroxide, and sodium carbonate could decontaminate mycotoxins in feed ingredients (Jalili et al., 2011). Alkaline hydrolysis opened the lactone ring AFB_1, leading to easy removal by washing with water (Liu et al., 2020 a). Also, ammonization and hydroxide salts are common strategies to eliminate AF and OTA from cereals, and the removal rate reached about 95% in poultry feedstuffs (Puvaca et al., 2018). Calcium hydroxide, sodium hydroxide, or potassium hydroxide treatments reduced fumonisin B_1, B_2, and B_3 concentrations in contaminated maize and sorghum (Odukoya et al., 2021). Despite all the positive aspects of the chemical procedures for deactivating mycotoxin-contaminated feed ingredients and diets, their restrictions also exist because the products being traded must be free of the used chemicals. Moreover, it should not be ignored that chemical treatments might possibly stimulate alterations in treated ingredients' nutritional, physical, and sensory characteristics.

Adsorbents or binders

Adsorbents or adsorption binders are not absorbed in the gut and can bind physically with mycotoxins, precluding their absorption in the GIT and consequently reaching the blood and organs of animals (Table 1). Mycotoxins could be bonded to adsorbents through various interactions, including hydrophobic bonding, hydrogen bonding, electrostatic interactions, and coordination bonds (Bočarov-Stančić et al., 2023). Adsorption therapy is one of the most vital approaches for avoiding toxicants' absorption in the gut of poultry and animal production (Kabak et al., 2006). However, it should be considered that adsorbents may also concurrently bind administered drugs used for therapeutic purposes. Several adsorption binders have been examined in the past decades, and their efficiency in detoxifying mycotoxins was documented (Liu et al., 2020 b). Thus, the adsorbent decontamination strategy is widely used in the feed industry. Possible absorbents comprise activated carbon, glucomannans, and aluminosilicates, including hydrated sodium calcium aluminosilicate (HSCAS), bentonite, zeolite, and phyllosilicates (Vila-Donat et al., 2018). Some mycotoxins like AF own an ionic charge; therefore, clay adsorbents like bentonite, illite, zeolite, and kaolin are active in eliminating mycotoxins from the feedstuffs with approximately 90% effectiveness (Hasheminejad et al., 2015).

Clay minerals

Adding non-nutritive clay minerals in animal and poultry feeds has been extensively used to minimize toxins' bioavailability in polluted feeds. Several investigations in poultry species documented that zeolite, bentonite clay, smectite clays, kaolinite, and sodium bentonite reduced AFB_1 residues in liver, meat, and egg by about 41–87% in broilers and ducks consuming AFB_1 contaminated diets (Bhatti et al., 2018). Moreover, Raj et al. (2021) postulated that the addition of modified clinoptilolite zeolite (1–2 g/ kg feed) to AFB_1- and OTA-contaminated feed alleviated the toxic effects of mycotoxins as it reduced residue concentrations of AFB_1 in liver and OTA in spleen, elevated serum concentration of glutamate dehydrogenase and improved growth performance parameters in broilers. Similarly, H-β zeolite can effectively adsorb OTA, and it gives the extra benefit of less interaction with vitamins in poultry (Rajendran et al., 2020). Studies revealed that dietary supplementation of 2% zeolite improved BW and FCR (Raj et al., 2021), enhanced egg albumin height and eggshell strength (Fendri et al., 2012), enhanced intestinal morphology and function (Wu et al., 2013), increased the antioxidative status (Wu et al., 2015), regulated the body's pH balance and boosted the immune system (Ivkovic et al., 2004). The administration of purified montmorillonite clay improved the adsorption of AFG_1 in the GIT and decreased its bioavailability and toxicosis in broiler chicks (Rejeb et al., 2020). Several studies elucidated that dietary bentonite reversed the adverse effects of mycotoxins in poultry (Alharthi et al., 2022). The dietary 0.75% bentonite clay ameliorated the lethal impacts of AFB_1 in broiler chickens (Dos Anjos et al., 2015).

Similarly, the dietary inclusion of 1% bentonite clay alleviated the detrimental effects of AFB_1 and OTA in broilers (Pappas et al., 2016). The dietary supplementation of 2% of bentonite, activated charcoal, and fuller's earth enhanced BW and alleviated the histopathological effects in broiler chickens fed AF-contaminated diets (Mgbeahuruike et al., 2018). Also, the dietary inclusion of 0.2% smectite clay in the feed contaminated with AFB_1 decreased the toxicological effects in the liver and enhanced growth performance parameters and humoral immune responsiveness in broiler chickens (Zabiulla et al.,

2021). The dietary inclusion of 4 g/kg bentonite alleviated the harmful effects of AFB_1 and enhanced growth performance and antioxidative status while supporting normal histomorphological structures of the liver in broilers (Alharthi et al., 2022). It is believed that the AF molecule is chemically absorbed onto the interlamellar surfaces of the clay and forms a stable conformation. Other possible methods of AFB_1 absorption to clay surfaces could be the interaction with water molecules in the interlayer or the chelation of interlayer cations (particularly Ca^{2+}) and other edge-site metals (Mitchell et al., 2014). Interestingly, dietary supplementation of clay minerals is a promising approach to minimizing mycotoxin bioavailability in polluted feeds in the poultry industry.

Hydrated sodium calcium aluminosilicate (HSCAS)

Hydrated sodium calcium aluminosilicate (HSCAS) (a phyllosilicate clay) is used to minimize concentrations of AF by selective chemical adsorption. The mechanism of action probably proceeds via either chemisorption (i.e., chemical solid bond formation) between HSCAS and AF (Attia et al., 2013) or interaction between HSCAS and other food management practices. Including 0.5% HSCAS in broiler feed contaminated with mycotoxins has been shown to protect against the poisonous effects of AF but not TCN or OTA. Dietary inclusion of HSCAS reduced the inhibitory actions of toxins and exhibited protecting effects against hepatic damages induced by AFB_1 (Attia et al., 2013). Adding HSCAS (0.1 and 0.2%) successfully alleviated the adverse impacts of AFB_1 on growth performance and liver impairment in broiler chickens (Zhao et al., 2010). These results follow (Chen et al., 2014), who showed that dietary supplementation of 0.5% HSCAS can efficiently improve BWG, elevate serum concentrations of albumin, total protein, globulin, phosphorus, glucose, alkaline phosphatase, and creatine phosphokinase and moderately ameliorate the aflatoxicosis in broilers consumed AFB_1-contaminated diets via enhancing liver gene expression of CAT and SOD.

Similarly, dietary 0.05% modified HSCAS enhanced growth performance and nutrient digestibility and prohibited T-2 toxin-induced histological variations and injury in small intestine fragments (i.e., duodenum, jejunum, and ileum) in broiler chicks fed diets contaminated with T-2 toxin (Wei et al., 2019). Likewise, the dietary inclusion of 3.0 g HSCAS/kg ameliorated AFB_1 toxicity in broilers' diet and improved growth performance, nutrient digestibility, and immunity (Liu et al., 2018). In overfed Landes geese, the addition of 0.3% HSCAS had a positive impact on liver weight % and gut microbiome contents in the form of increasing *Lactobacillus* and decreasing *Actinobacillus* counts in ileum as well as minimizing the presence of *Erysipelotrichia, Bacteroides* and *Escherichia* in the ceca (Tang et al., 2018). Adding HSCAS to AF contaminated diets of two-week-old chickens' reduced AFB_1 residuals in the liver and muscle compared with the control diet (Hassan et al., 2023). HSCAS decreased the negative effect of AF on the performance and relative weight of organs and increased plasma protein levels (Arab Abousadi et al., 2007). In addition, there was a significant increase in growth and feed utilization when broilers were fed a diet supplemented with 5 g HSCAS/kg diet but no significant influence on serum chemical constituents or relative weight of organs except a decrease in spleen % and proventriculus % (Prvulovic et al., 2008). An activated clay mixture (TOXFIN™ brand) supplementation at 5 kg/ton effectively ameliorated the adverse effects of toxicosis in broilers, as shown by the restoration of the feed utilization and liver morphology to that of the control (Manafi et al., 2009). Collectively, it might be documented that HSCAS could moderate the toxicity of mycotoxins in poultry, possibly through sequestration, reducing the bioavailability *in vivo*.

Glucomannan

The next generation of adsorbents originating from the cell wall component of microorganisms has been established. Glucomannan is an adsorbent that GIT microorganisms cannot utilize, and it is characterized by highly absorbable toxicants, mycotoxins, and pathogenic microbes in animals (Kolawole et al., 2019). Adding 0.1% glucomannan- containing yeast to an aflatoxin-contaminated diet (250 ppb) markedly prevented its toxic effect on serum biochemical measurements, and it was found to be the most effective treatment (Azizpour and Moghadam, 2015). Dietary supplementation of 0.1% esterified glucomannan is an efficient and safe mycotoxin detoxifier level in broiler chicken diets, and it improved FI, FCR, BWG, liver %, bursa of Fabricius %, antibody titer against NDV and infectious bursal disease viruses (Mohaghegh et al., 2017). Dietary 0.2% polymeric glucomannan mitigated the feed-borne *Fusarium* mycotoxins and activated the immune response in broilers infected with *Eimeria maxima* (Girgis et al., 2010). It was reported that modified yeast cell wall mannan-oligosaccharide (MOS), which possesses esterified glucomannan derived from the cell wall of *Saccharomyces cerevisiae*, has been shown to stimulate immunity (He et al., 2021). Moreover, the yeast cell wall extract (Mycosorb A+®) prevented the harmful effects of OTA in broiler chickens (Vartiainen et al., 2020). Mycosorb A+® (natural product containing 10% mannan oligosaccharide compound extract from *Saccharomyces cerevisiae*) supplementation to diets contaminated with 200 ppb AF at 0.1 and 0.2% resulted in improved serum total proteins, growth and feed efficiency without leading to significant alterations in gamma-glutamyl transferase activity, the weight of bursa of Fabricius, liver, spleen or gizzard (Vartiainen et al., 2020). It was reported that yeast cell walls comprising β-glucans and MOS could effectively bind with AFB_1 about 90% in poultry gastrointestinal medium (Attia et al., 2013). The adsorption was highest at pH 4.5 (Devegowda et al., 1998). In addition, there was a significant improvement in growth and feed utilization of Japanese quails fed a diet containing 2.5 mg/kg AF and 1 g/kg glucomannan (Parlat and Oguz, 2001). Adding glucoman-

nan improved feed utilization in both the control and contaminated diet groups but did not affect liver % and gizzard %, aspartate amino transferase (AST) and alanine amino transferase (ALT) activities and hematocrit values in broilers fed a diet polluted naturally with 168 ppb AF, 8.4 ppb OTA, 54 ppb ZEN and 32 ppb T2-toxin (Aravind et al., 2003). Similar results were obtained by Chowdhury and Smith (2004) in laying hens fed a diet contaminated with *Fusarium* mycotoxin with 0.2% glucomannan. Lower FI and better feed utilization in broilers receiving mannan-oligosaccharides were reported by Tokić et al. (2007). However, Chowdhury et al. (2005) found that glucomannan did not prevent the adverse effects of a diet contaminated with *Fusarium* on hematocrit and hematological parameters in duck and turkey. There was no effect of mannan-oligosaccharides (0.05, 0.10, 0.15%) on feed utilization and growth in broilers. Still, there was a decrease in AST and ALT levels due to a dietary addition of MOS (Yalçinkaya et al., 2008). In addition, a higher percentage of glucomannan (0.2%) was not effective in preventing the adverse effects of a lower concentration (1 ppm) of aflatoxin B_1 on performance (Nemati et al., 2015).

Microorganisms

Microorganisms can control mycotoxicosis via biotransformation of the mycotoxins into less toxic metabolites. Using microorganisms to detoxify mycotoxins is a successful strategy to alleviate the harmful impacts of non-adsorbable mycotoxins and microbial toxins. *Bacillus, Lactobacillus, Bifidobacterium, Pseudomonas, Propionibacterium*, and *Lactococcus* can bind with AF and suppress mold growth in poultry feed ingredients (Sangare et al., 2014). It was observed that adding *Lactobacillus* spp. in broiler chickens' feeds mitigated the toxic impacts of AFB_1, ZEN, and DON (Chang et al., 2020). *Bacillus subtilis* ANSB060 relieved the negative influences of AFB_1 in laying hens (Ma et al., 2012). After an *ex vivo* administration of AFB_1 into the lumen of the chicken duodenum, the addition of *Lactobacillus rhamnosus* GG (LGG) and *Propionibacterium freudenreichii* ssp. *shermanii* JS decreased AFB_1 uptake by 74% and 63%, respectively (El-Nezami et al., 2000). Also, *Lactobacillus rhamnosus* TMU094, *L. fermentum*, *P. pentosaceus* and *L. rhamnosus* PTCC1637 bound 25.64–75.06%, 38.63–72.15%, 24.86–63.21% and 19.41–35% of AFB_1 respectively during study incubation times (Bagherzadeh Kasmani et al., 2012). *Bacillus subtilis* fermentation extract ameliorated the poisonous effects of OTA and enhanced the humoral- and cell- mediated immune responsiveness and antioxidative properties in broilers (Elhady et al., 2022). The adverse effects of a 2 mg T-2 toxin/kg diet on growth and feed utilization were ameliorated by including a 2.0 kg *Eubacterium* BBSH 797/ton diet (Diaz et al., 2005). Dietary probiotic addition during AFB_1 exposure reduced AFB_1-induced expression alterations in genes such as 28S ribosomal RNA (RNA28S), serine/arginine repetitive matrix protein 1 (SRRM1), and ISG12-2 protein-related mRNA in domestic turkeys (Monson et al., 2015). The ameliorating effects were more significant in the spleen on immune genes like GZMA, THP2, and PRF1 (Monson et al., 2015). Probiotics did, however, have synergistic effects with AFB_1, and most of the expression alterations generated by it could not be corrected. For instance, combination therapy raised differential expression of ISG12-2 and RNA28S in the spleen and apolipoprotein A-IV (APOA4) in the liver. This showed that oral probiotics modulated expression in the liver and spleen but did not re-establish their normal outlines (Attia et al., 2013).

Various fungal and yeast species, including *Aspergillus, Alternaria, Absidia, Armillariella, Candida, Dactylium, Mucor, Penicillium, Peniophora, Pleurotus, Trichosporon,* and *Rhizopus* showed a detoxification ability of different mycotoxins in feedstuffs (Saleemi et al., 2020). *Aspergillus niger* RAF106 showed the capability of destroying the AFB_1 to levels of 98.7% (Fang et al., 2020). Also, several yeast strains, including *Saccharomyces cerevisiae, Trichosporon mycotoxinivorans,* and *Mastotermes darwiniensis* succeeded in relieving the toxic effects of AFB_1, OTA, ZEN, DON, and T-2 toxins and decreased their accumulation in tissues (Chlebicz and Śliżewska, 2020). Dietary *Saccharomyces cerevisiae* RC016 (1 g/kg diet) alleviated the harmful effects of AFB_1 and supported normal hepatocytes, improved intestinal histomorphology (absence of hyperemia, normal villi, lower number of goblet cells and atrophy), and decreased the residual concentrations of AFB_1 in the liver of broiler chickens (Poloni et al., 2020). Also, broilers receiving 2% *Saccharomyces cerevisiae* together with 200 µg AF/kg diet had more significant growth, FI, and improved protein, albumin, AST, and ALT concentrations and weight of bursa of Fabricius than those without *Saccharomyces cerevisiae* (Çelýk et al., 2003). *Saccharomyces cerevisiae* reduced the deleterious effects of adding AF at 1 and 2 ppm/kg diet on the growth, feed utilization, and serum protein, albumin, and enzyme levels of broilers (Ellakany et al., 2011). Also, the dietary inclusion of a novel yeast *Pichia kudriazevii* (1 g/kg diet), mitigated the AF contamination and enhanced humoral and cellular immune response and antioxidative properties in broiler chickens (Ali et al., 2021). Moreover, dietary 2% distillery yeast sludge can suppress the absorption of OTA and AFB_1 in the gastrointestinal tract and alleviate the immunotoxic impacts in White Leghorn laying hens (Khan et al., 2017). The *Saccharomyces cerevisiae* and *Lactobacillus acidophilus* are effective anti-aflatoxin agents (Attia et al., 2013). The proper amount of fungi and yeasts in poultry feed reduces the bioavailability of mycotoxins in the gastrointestinal tract, facilitating their elimination via feces (Saleemi et al., 2020).

Phytogenic additives

The use of phytochemical products such as medicinal plants, herbs, plant extracts, and essential oils offers a chance to obviate synthetic chemicals and drugs' risks

on human health and animal welfare (Al-Homidan et al., 2020). It was reported that phytochemicals are detrimental to fungi and might be used to protect crops, grains, feed ingredients, animals, and humans against toxic fungi and mycotoxins (Prabakar et al., 2016). Nearly 100 of the more than 280 plant species studied for their ability to suppress toxic *Aspergillus* growth or toxin production showed some action (Abd El-Ghany, 2024). The leaves, seeds, stem bark, or roots of plants with pesticidal value can be used to produce or create phyto-fungicides, which can then be administered as plant exudates, extracts, powders, or cakes (Prabakar et al., 2016), the phytochemical qualities of which could break down into a variety of potent antibacterial chemicals, including dithiins, ajoene, diallyl sulfide, diallyl disulfide, diallyl trisulfide, allyl methyl trisulfide, and many more (Elsamra et al., 2012).

Garlic (*Allium sativum* L.) has a broad antifungal spectrum and can limit the growth of *Aspergillus* and *Penicillium* fungi that are spread in seeds by 60–82% (Abd El-Ghany, 2024). The formation of aflatoxins (groups B and G) in fungal mycelia is inhibited by neem (*Azadirachta indica*) seed oil (Mossini et al., 2009). The growth of *A. parasiticus* is inhibited by crude extracts from ground red pepper, mint, sage, bay, and anise. Aflatoxin synthesis pathway precursor non-sorbic acid is effectively inhibited by plants such as *Ocimum gratissimum, Cymbopogon citratus, Xylopia aethiopica, Monodora myristica, Syzygium aromaticum, Cinnamomum verum,* and *Piper nigrum* (Tagoe et al., 2011). Aqueous extracts of beet root, garlic, leek, radish, rocket salad, and turnip might be an adequate natural food protective against fungi and mycotoxins (Salim, 2011). Additionally, lemon and orange oils (at concentrations of 0.05–2.0%) reduced about 90% of AF produced by *A. flavus* (Murali et al., 2012). Marjoram (*Origanum vulgare*) essential oil alleviated the toxic effects of AFB_1 on kidneys by enhancing the antioxidative properties, reducing inflammation, and minimizing DNA damage in growing rabbits (Hassan et al., 2023). The inclusion of chamomile flower extract (3 g/kg diet) and thyme-oil extract (3 g/kg diet) reduced the toxic effects of OTA and AFB_1 and they improved growth, intestinal histomorphology, and immune response in broilers (Nazarizadeh et al., 2019). Growth was more significant in the milk thistle-treated groups than in those contaminated with aflatoxin B_1 (Fani Makki et al., 2013). Utilization of milk thistle seeds decreased the toxicity of AFB_1, enhanced nutrients absorption, and lowered the metabolic needs of broilers' gut (Hasheminejad et al., 2015). In addition, photogenic plants such as pomegranate peels and clove powders can provide a proactive role from AF (Hussein, 2015).

The dietary supplementation of 400 mg turmeric powder/kg diet enhanced the gene expression of CAT and SOD2 and drug transporters (i.e., ABCG2) in the liver of broiler chickens fed AFB_1 contaminated rations (Amminikutty et al., 2023). Also, it was reported that curcumin (turmeric) ameliorated AFB_1 toxicity by downregulating CYP450 enzymes and enhancing ATPase activity in broiler chickens (Chen et al., 2019). The dietary inclusion of 74 mg curcumin/kg diet enhanced hepatic gene expression of antioxidative status [CAT, SOD, GSH-Px, glutathione S-transferase (GST)], biotransformation [epoxide hydrolase (EH), cytochrome P450 1A1 and 2H1 (CYP1A1 and CYP2H1)], and the immunity [interleukins 6 and 2 (IL-6 and IL-2)] in broilers fed AFB_1 (Yarru et al., 2009). Silymarin is a potent antihepatotoxic mediator that offers defense against the detrimental impacts of AFB_1 on the growth performance of broilers (Tedesco et al., 2004). Silymarin and curcumin administrations increased the survival of cells subjected to mycotoxins, inhibited free radicals' production, and stopped apoptosis in PK-15 cells exposed to mycotoxins (Ledur and Santurio, 2020). This is an attractive new area for further research as phytochemicals are safe and environmentally friendly substances without harming human and animal welfare (Ledur and Santurio, 2020).

Antioxidants

Mycotoxins are considered one of the most essential causes of oxidative stress in poultry production. Considering that the small intestine is regarded as the first organ to suffer from oxidative damage, it is interesting that adding antioxidants to the diet improves the antioxidant status in the small intestine in the form of enhancing the activities of antioxidant enzymes, including GSH-Px, SOD, and CAT (Ebeid et al., 2023). Thus, natural antioxidants, including Se and vitamins E, C, and A, could be a successful strategy to enhance the antioxidative status of the birds and consequently maximize their resistance to mycotoxins (Zhao et al., 2021). Natural antioxidants can improve the activity of antioxidative enzymes, scavenging and detoxifying free radicals (Ebeid et al., 2023). Numerous reports showed that dietary inclusion of Se granted efficient protection against AFB_1-induced mycotoxins hepatotoxicity, immunotoxicity, and genotoxicity due to its vital role in modulation of the antioxidative status, inflammatory process, and apoptosis in broiler chicks (Zhao et al., 2021) and Japanese quail (Khazraei et al., 2022). Dietary supplementation of 0.3 mg Se/kg diet alleviated the AFB_1 cardiotoxicity and cardiomyocyte damage via enhancing gene expression of GSH-Px-3 and thioredoxin reductase-3 in the heart of chicks (Zhao et al., 2021). Also, the dietary inclusion of Se nanoparticles (0.5 mg/kg diet) decreased the AFB_1 toxicity and enhanced serum concentrations of GSH-Px, thioredoxin reductase, and antibody titer against sheep red blood cells in Japanese quails (Khazraei et al., 2022). A dietary combination of vitamin E (80 mg) + Se (1.6 mg) minimized the detrimental effects of AFB_1 and enhanced liver function (increased serum concentrations of AST and ALT). It decreased cortex depletion and reduced the congestion, hemorrhage, and necrosis in inflammatory cells in the thymus and Harderian gland in broilers (Khazraei et al., 2022)

Moreover, Mazur-Kuśnirek et al. (2019) observed that the addition of 100 mg vitamin E/kg diet + 2200

mg polyphenols/kg diet enhanced the SOD and GSH-Px activities in blood, liver, and breast muscles in broiler chickens fed diets contaminated with OTA. Dietary supplementation of 100 mg vitamin C/kg diet alleviated the toxic effects of OTA and enhanced growth performance, liver %, kidney %, and bursa of Fabricius % in broiler chickens (Singh and Mandal, 2018). Antioxidants can collectively enrich the antioxidative capacity, activate antioxidant enzymes, and prevent excess production of free radicals (ROS), which protects the host from oxidative damage (Attia et al., 2016).

Recovery period

A few studies have been done on the effect of the withdrawal of AF from the poultry diet, the time needed for recovery, and the performance of poultry after withdrawal. Broilers were fed for four weeks on the AF-contaminated diet (at 50 ppb) and the next four weeks on the non-contaminated diet (Attia et al., 2016). They reported adverse effects on BWG, FI, and FCR due to treatment even after withdrawal of AF. The digestibility of all nutrients was slightly improved in the withdrawal period compared to the treatment period. The relative weight of organs, especially the liver and adrenal, was still higher after 4 weeks of withdrawal, but the adverse effects of AF on the mortality rate were reduced. Also, there was a decrease in Hgb, PCV, total protein, and globulin levels but an increase in ALT and alkaline phosphatase (ALP) levels after four weeks of AF withdrawal, with the recovery period not being influenced by the trend of alteration of all estimated criteria that happened after the treatment period (Attia et al., 2016). Moreover, Ahmed et al. (2010) reported that histologically, the liver of the affected bird after four weeks of withdrawal was the most affected organ characterized by infiltrations, necrosis, inflammatory cells, the thickness of the portal tract, and fibrosis along with fatty changes. The kidneys were also affected, showing interstitial nephritis, cloudy swelling of the proximal convoluted tubules, and some congestion. The heart of affected chicks showed inflammatory reactions, fibrin deposits, pericarditis, calcification, and edema. Growth of Pekin ducklings after 24 hours of withdrawal from 0.5–1 ppm of FA-contaminated diet was still negatively affected, but the levels of uric acid, AST, ALT, and ALP went back to normal (Das et al., 2023). They also added that blood parameters required more than a 24-day withdrawal period to return to average values. Resanovic and Sinovec (2006) concluded that the removal of contaminated feed only minimally alleviated the adverse effects of even small amounts of AF

During the recovery period (4 weeks), feed consumption and egg production were increased to a level comparable with all other treatments in laying hens (Lee et al., 2012). Growth performance did not wholly recover after 21 days of AF withdrawal from feeds, even though the adverse effects in the serum AST, ALP, and triglyceride were still significant (Attia et al., 2016). They added that most of the hematological parameters, apart from a reduction of eosinophils %, were overcome to normal by the end of the recovery period. The liver of AF-fed birds still exhibited histological damage at the end of the recovery period with portal inflammation and fibrosis, cell infiltration, and biliary hyperplasia. Supplementation with MOS resulted in better recovery, but HSCAS motivated the most favorable impact on liver tissues (Attia et al., 2016).

Conclusions

Strategies developed to control aflatoxicosis include preharvest treatments to eliminate fungal growth and postharvest treatments such as using dietary supplements and detoxification using either physical or chemical methods. The method of detoxification of AF must be cost-effective, must destroy, remove, or inactivate the AF, produce no carcinogenic or toxic compounds in the process, preserve the nutritional value and palatability of the diet, maintain the physical properties of the feedstuff, and prevent the formation of new toxins by destroying fungal spores and mycelia. The use of microbial inactivation, ammonization, ozone degradation, irradiation, and sequestering agents to decontaminate and remediate highly contaminated feedstuffs has been suggested. Still, most of these methods do not meet the criteria mentioned above. However, adsorbents that bind toxins, rendering them inactive, and are cost-effective, safe, and easy to administer seem to be preferred. Solar irradiation, ozonation, and natural products such as essential oil from the leaves of *Cinnamomum tamala*, milk thistle seed, antioxidants, *Saccharomyces cerevisiae,* and *Lactobacillus* are promising newly emerging methods but require further testing for safety and scalability. However, the effectiveness of the detoxification agents varies and depends on the concentration, temperature, pH, treatment time, duration of exposure, and age of chickens. The results showed that AF has a long-term negative effect on animal performance and investigated traits, suggesting further experiments to determine the time required to recover based on target criteria.

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