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Molecular antioxidant and immunological mechanisms of phytogenics in the mitigation of aflatoxicosis in poultry

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Primary Audience: Researchers, Poultry Microbiologists, Poultry Farmers, Poultry Industry

SUMMARY

The poor quality and safety of poultry feed in developing countries pose significant concerns as they negatively impact poultry performance and present potential health risks to human consumers. Aflatoxicosis, resulting from postharvest contamination of feed ingredients by certain mold species, severely affects birds' overall health and productivity. To address these challenges, various feed additives have become increasingly important in poultry nutrition. Phytogenics, natural plant-derived products, have gained popularity for their ability to mitigate aflatoxicosis by their rich composition of bioactive compounds that offer beneficial effects on physiological and immunological functions. In light of the growing significance of aflatoxicosis in poultry nutrition, this review provides an overview of aflatoxins and their harmful effects on poultry health. It highlights the role of phytogenic compounds as growth and health stimulators, emphasizing their potential application in poultry nutrition. Furthermore, the review explores the antioxidant and immunological mechanisms through which phytogenics mitigate aflatoxicosis in poultry, including specific compounds and pathways involved. The findings reveal that aflatoxins induce inflammation, and oxidative stress in poultry, resulting in cellular damage and immune dysfunction. Phytogenics play a crucial role in ameliorating the harmful effects of aflatoxins in birds by countering aflatoxin-induced oxidative stress, reducing inflammation, and restoring gut health and immune functions. In conclusion, phytogenics offer an invaluable tool for the mitigation of aflatoxicosis in poultry and serve as potent natural and safe alternatives to antibiotics and synthetic antioxidants, promoting sustainable production practices.

Key words: Aflatoxin, poultry health, phytogenics, antioxidant, immune response

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DESCRIPTION OF PROBLEM

In many developing countries, poultry feed is usually seen to be of low quality and in many instances, heavily contaminated with various toxins (Jutzi, 2004). This is partly due to the use of feed ingredients such as maize that are contaminated and often considered unfit for human consumption and feed production, coupled with the absence of regulatory policies for the effective monitoring and certification of the quality and safety of animal feeds and ingredients (Ravindran, 2013). The development and proliferation of fungi is a major issue arising pre-harvest and postharvest, from the high temperature, drought stress, crop rotation and poor storage of feed materials and are known to produce several biological toxins that cause mycotoxicosis in poultry species (Adeyeye, 2016). Aflatoxicosis is a form of mycotoxicosis that is caused by the ingestion of aflatoxins which are toxic metabolites of certain fungi species that can contaminate animal feeds products (Fouad et al., 2019). Aflatoxicosis can adversely impact feed utilization and growth performance (Bai et al., 2014; Dos Anjos et al., 2015), immune functions (Peng et al., 2017), meat and egg production, (Silversides et al., 2012; Fouad et al., 2019), as well as the integrity and functionality of the liver and other organs (Denli et al., 2009; Magnoli et al., 2011). Therefore, to ameliorate these negative impacts and improve the health and performance of poultry birds, several additives including binders, activated charcoal, modifiers, antioxidants, pro and prebiotics, and medicinal plant products are increasingly being used in postharvest processing and storage of plant products to limit the presence of aflatoxins (Boudergue et al., 2009; Kolawole et al., 2019; Elliott et al., 2020).

Phytogenics are natural compounds derived from plants that have been shown to have antioxidant and immunomodulatory activities in poultry (Puvača et al., 2013; Paraskeuas et al., 2017; Mnisi et al., 2023).These phytogenics are majorly composed of bioactive compounds including essential oils like flavonoids, polyphenols, resveratrol, cineole, capsaicin, carvacrol, and eugenol that provides a variety of physiological and pharmacological benefits to birds (Ahmed et al., 2015; Galli et al., 2020). Generally, the positive health impact of phytogenic compounds have been attributed to their roles in modulating multiple biochemical pathways involved in normal physiological and immunological functions of birds (Mannelli et al., 2019). Hence, phytogenics have gained popularity in the prevention and mitigation of aflatoxicosis conditions in poultry species as they can lower inflammations, improve gut health, and boost immune functions and overall performance (Abd El-Aziz et al., 2015; Rahman and Kim, 2016; Kim et al., 2016; Paraskeuas et al., 2017; Damaziak et al., 2018; Armanini et al., 2021). For example, administration of turmeric extract has been observed to lower liver and blood levels of birds exposed to aflatoxins and reduce the severity of liver damage in infected birds (Uzunhisarcikli and Aslanturk, 2019).

A detailed review of the chemical structure of aflatoxins and their harmful impacts on poultry has been presented earlier (Fouad et al., 2019). Also, a general overview of the various methods namely physical, chemical, biological and the use of antioxidants for ameliorating the impacts of aflatoxins have also been studied (Abedi and Talebi, 2015). Additionally, studies have reported the ameliorative effects of phytogenic feed additives such as phytobiotics and toxin binders (Tavangar et al., 2021), Chinese gallnut tannic acid (Zhang et al., 2022), licorice extract (Rashidi et al., 2020), on aflatoxin-exposed poultry species. In view of the rapidly growing interest and literature on this area, there is need for a more holistic study of the physiological and molecular processes and pathways through which these mitigating effects of phytogenics are exerted. This review paper therefore presents an overview of aflatoxins and their harmful effects on poultry health and performance. It also seeks to highlight the importance of phytogenic compounds as growth and health-stimulatory agents, in addition to their potential application in poultry production. Furthermore, the review examines the current state of knowledge regarding the antioxidant and immunological mechanism of phytogenics in mitigating aflatoxicosis in poultry species, including the role of specific compounds and pathways.

OVERVIEW OF AFLATOXINS AND THEIR HARMFUL EFFECT ON POULTRY

Aflatoxin is a group of naturally occurring carcinogenic mycotoxins produced by certain species of fungi, primarily *Aspergillus flavus* and *Aspergillus parasiticus* (Nadeem and Hadeel, 2022). These fungi species grow on a variety of crops, including corn, peanuts, and cottonseed, which are commonly used as poultry feed ingredients. Usually, fungi contaminate crops during pre-harvest and postharvest and their presence can persist and proliferate in poultry feedstuffs during storage and handling, whilst producing several toxic secondary metabolites including aflatoxin- B_1 (AFB_1), B_2 (AFB_2), G_1 (AFG_1), and G_2 (AFG_2) (Pitt and Miller, 2017). Among these metabolites, AFB_1 is of utmost relevance in poultry health as it is considered the most toxic and abundant (De Ruyck et al., 2015). Aflatoxin toxicity in poultry occurs at <1 mg/kg with the primary target being the liver while the functionalities of the immune, digestive and hematopoietic systems are also compromised (Yasir Allah et al., 2018; Nadeem and Hadeel, 2022). The detrimental effects of aflatoxins in poultry feed include lowered growth performance, meat and egg quality, antioxidant status, reproductive performance, immune functions and increased mortality, which can result in economic losses for poultry producers. Some of these adverse impacts are discussed.

Feed Digestion and Growth Performance

Aflatoxins are widely recognized for their detrimental impact on the growth performance of poultry species. Extensive research has shed light on the effects of aflatoxins on the growth performance and feed utilization in poultry. It is well-established that dietary aflatoxin reduces the quality and nutritional value of poultry feed, leading to decreased feed intake, feed efficiency, growth rate, and increased mortality (Raju and Devegowda, 2000; Dersjant-Li et al., 2003; Yunus et al., 2011; He et al., 2014; Fouad et al., 2019; Mohseni Soltani et al., 2019). Notably, studies have reported significant reductions of 21% and 10% in body weight of broiler chickens fed diets containing 300 μg/kg and 0.8 mg/kg of AFB_1, respectively (Raju and Devegowda, 2002, Tedesco et al., 2004). However, it is worth mentioning that (Agboola et al., 2015) did not observe any effects of aflatoxins on the feed conversion ratio (FCR) of chickens, this is due to the effectiveness of antibiotics and probiotics which were used as mycotoxin binders to relegate the adverse effects of aflatoxins.

Generally, the negative impacts of aflatoxins on the growth performance of poultry birds are directed primarily through their effect on the production and secretion of enzymes required for the breakdown of ingested feed, as well as the absorption and utilization of nutrients. Studies have indicated that the presence of aflatoxin in poultry diets diminished the activity of digestive enzymes, leading to a decrease in the apparent digestibility of crude protein and energy and increase in fecal excretion of protein, suggesting that aflatoxins may interfere with the bird's ability to absorb and utilize dietary protein (Han et al., 2008). Such reduction in enzyme activity is often associated with pancreatic damage, as the pancreas is responsible for secreting the digestive enzymes required for feed breakdown in the intestine and the release of nutrients to support poultry growth and development (Fouad et al., 2019). Furthermore, AFB_1 can be greatly taken up by the small intestine resulting in abnormal intestinal development, health and functionality. Previous studies have demonstrated that AFB_1 can lower villus height, crypt depth, and height to depth ratio (H/D) ratio in various species of poultry (Jahanian et al., 2016; Jahanian et al., 2017), with evidences of decreased absorptive cells, weakened cell integrity, lesions, and increased apoptosis in the jejunum of broilers (Peng et al., 2014, Zheng et al., 2017; Fang et al., 2018; Fouad et al., 2019). Consequently, these factors contribute to reduced weight gain and feed efficiency. Aflatoxins have been found to impair the growth rate in poultry by binding their metabolites to deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) of cells, thereby limiting protein synthesis (Peles et al., 2019).

The extent of aflatoxin's impact on poultry largely depends on various factors, including dosage and level of exposure, duration of exposure, as well as the species and age of the birds. Young birds tend to be more susceptible to the toxic effects of aflatoxins compared to older birds. Moreover, exposure to aflatoxins during the early weeks of life can have long-lasting effects on the growth and development of young birds (Fouad et al., 2019). This increased vulnerability in young birds can be attributed to their underdeveloped livers, which hinder the detoxification process of aflatoxin metabolites. For example, when chicks were fed a diet containing 1,600 μg of AFB_1 for 7 d, it resulted in deposition of 1.63, 0.49, and 0.41 μg/kg of AFB_1 in the muscle tissues at 14, 21, and 28 days of age, respectively. This clearly indicates that younger chicks accumulate more AFB_1 compared to older birds (Hussain et al., 2010). Conversely, aflatoxicosis has been reported in breeder hens, broilers, quail, white Pekin ducks, and turkeys when exposed to approximately 3,000, 2,000, 1,500, and 500 μg AFB_1/ kg diet, respectively (Stanley et al., 2004; Rauber et al., 2007; Chen et al., 2014; Shannon et al., 2017; Sakamoto et al., 2018; Fouad et al., 2019). This varying species' susceptibility to aflatoxicosis was shown to be due to their varying inherent capabilities of converting AFB_1 to the more toxic AFB_1-8 9-epoxide, and consequently, AFBO, which adduces to the DNA-causing lesions (Gülbahçe Mutlu et al., 2018). These findings highlight the importance of key considerations including the age and species of poultry in developing and implementing strategies for the effective control and management of aflatoxin exposure in poultry production.

Liver and Kidney Dysfunctions and Damages

Following absorption from the gastrointestinal tract (**GIT**), aflatoxin is enzymatically converted (by cytochrome P450 enzymes) to its metabolically active and toxic form, exo-AFB_1-8, 9-epoxide (**AFBO**) (Rawal and Coulombe, 2011). The liver is thus, the chief organ of bioaccumulation and metabolic breakdown of aflatoxins in the body and is therefore, responsible for the protection of the body against its toxic effects. However, the rate of aflatoxins removal is slower compared to other mycotoxins, especially trichothecenes (Eaton and Gallagher, 1994; Siloto et al., 2013). Prolonged exposure to aflatoxin can cause morphological and histological changes in the liver, potentially leading to liver damage and dysfunction in poultry (Yunus et al., 2011). Generally, aflatoxicosis in poultry species has been associated with increased risks of hepatotoxicity, cirrhosis, and liver cancer. Other notable adverse effect of AFB_1 in poultry include increased deposition of fat in the liver leading to imbalance in lipid metabolism, increase in liver weight and represses secretions of liver enzymes as well as increased apoptosis of the liver cells (Tejada-Castañeda et al., 2008).

The detrimental effects of AFB_1 in liver metabolism can be seen in the high fluctuations in the levels of several hepatocytes-derived enzymes and biochemical metabolites. Therefore, the blood levels of these compounds have been used as key indicators in the assessment of aflatoxin contamination in poultry. Aspartate aminotransferase (**AST**) and alanine aminotransferase (**ALT**) are 2 key enzymes involved in protein metabolism in the liver and thus, can reflect the integrity and functionality of hepatocytes (Jiang et al., 2014). Studies have shown marked elevations in the plasma levels of ALT and AST in poultry birds suggesting varying degrees of liver damages (Gómez-Espinosa et al., 2017, Muhammad et al., 2018). Furthermore, the plasma levels of cholesterol, albumin, triglyceride, total protein, and globulin were found to decrease in poultry fed diets contaminated with aflatoxins (Şehu et al., 2005; Bailey et al., 2006; Tejada-Castañeda et al., 2008; Gholami-Ahangaran et al., 2016; Gómez-Espinosa et al., 2017; Rajput et al., 2017). Equally, (Mahmood et al., 2017) also reported that the toxic metabolites of aflatoxins in the liver may inhibit protein synthesis, leading to anorexia. These changes suggest diminished protein and lipid synthesis, which could account for the reduced weight gain and overall productivity of poultry fed aflatoxin contaminated diets.

On the other hand, the kidney which is also involved in the detoxification and maintaining homeostasis also plays a critical role in the metabolism of aflatoxins in poultry. Studies have demonstrated that the kidney accumulates more AFB_1 than the liver in poultry, hence, it is equally, largely susceptible to cellular damages and dysfunctionality resulting from toxicity. For instance, when chicks were fed diets containing 2,500 μg AFB_1/kg generated from *A. parasiticus* (NRRL 2,999) for their first 21 d, the kidney was observed to accumulate twice as much AFB_1 as the liver (Neeff et al., 2013). A more recent study showed that broiler chicks fed with 40 μg/kg of *A. flavus* (NRRL 3,357) accumulated about 4 times more AFB_1 in the kidney than liver (Liu et al., 2018). This exposes the kidney to oxidative damage from the AFB_1 compared to the liver. AFB_1 exposure to birds resulted in an increase in kidney size, apoptotic cells and metabolic dysfunctions as indicated by the heightened blood levels of creatinine and uric acids (Liang et al., 2015, Gómez-Espinosa et al., 2017). Further, the impact of aflatoxins on the kidney is experienced by the lowered production of 1, 25-dihydroxyxalciferol, calcium, and phosphorus in the blood (Gholami-Ahangaran et al., 2016; Fouad et al., 2019). Consequently, this can adversely affect bone mineralization, tibial bone quality, and eggshell quality (Fouad et al., 2019).

Immune Status and Oxidative Stress

Antibody and Vaccinal Immunity. Aflatoxins have well-established detrimental effects on the immune systems of poultry species. Aflatoxins are known to suppress the production of immunoglobulins, namely, Immunoglobulin A (**IgA**), Immunoglobulin G (**IgG**), and Immunoglobulins M (**IgM**), which increases the susceptibility of birds to bacterial, viral, and parasitic infections, ultimately impacting their overall health and survival (Azzam and Gabal, 1998; Yunus et al., 2009). Studies on broilers chickens fed diets containing 40 μg AFB_1/kg from *A. flavus* and 1,000 μg AFB_1/kg from *A. flavus* demonstrated significant reductions in the production of IgA, IgG, and IgM, as well as alterations in the T and B lymphocytes ratios (Rajput et al., 2017; Liu et al., 2018).

Aflatoxins may exert a non-specific effect on protein synthesis by inhibiting the activities of RNA polymerase, leading to decreased immunoglobulin production (Surai and Dvorska, 2005; Yunus et al., 2011; Bhatti et al., 2017). The lowered levels of serum proteins, specifically IgA, IgG, and IgM, result in a considerable suppression of acquired immunity from vaccination programs in certain disease models (Yunus et al., 2011; Bhatti et al., 2017). Therefore, even at low levels, AFB_1 can have adverse effects on the effectiveness of vaccines, potentially increasing the occurrence of diseases such as Marek's disease, infections bursal disease (**IBD**), congenitally acquired *salmonellosis*, and duodenal and cecal coccidiosis, even in flocks that have been properly vaccinated against these agents (Oswald et al., 2005).

Furthermore, feeding birds with diets containing 0.5 to 1 mg AFB_1/kg revealed additional adverse effects, including dysfunction of the spleen, T and B lymphocytes, and degeneration of the bursa of Fabricius (Richard et al., 1973; Yuan et al., 2016; Lakkawar et al., 2017). These effects lead to the suppression of interferon production and the cellular immune response (Celik et al., 2000, Yuan et al., 2016). Antibody titers against sheep red blood cells, Newcastle disease virus, and avian influenza (**H5N1**) were found to be decreased in poultry diets contaminated with AFB_1 (He et al., 2013; Manafi, 2018).

Lymphoid Organ Alterations

The absolute and relative weights of immune organs in birds have been used as indicators of immune status, given their association with general immune functions (Fouad et al., 2019). However, exposure of poultry birds to AFB_1 can have adverse effects on the relative weights of immune organs such as the spleen, thymus, and bursa of Fabricius. The specific effects of aflatoxin on organ weights may vary depending on the organ and the level of exposure in birds, and they can also cause various histological changes in the tissues, potentially affecting their functionalities (Liu et al., 2018).

Aflatoxins have been observed to decrease the relative weight of the bursa by reducing the diameter of lymphoid follicles and the number of lymphocytes (Yuan et al., 2016; Bhatti et al., 2017).The reduction in organ weights induced by AFB_1 may be attributed to its impact on suppressing cellular antioxidants, elevating malondialdehyde (**MDA**) levels, and subsequently leading to oxidative damage, cellular necrosis, and apoptosis in these organs (Yuan et al., 2016; Peng et al., 2017).

Lipid Peroxidation and Oxidative Stress

The effects of aflatoxins on lipid metabolism and oxidative damage in birds have been well-documented. Research indicates that aflatoxins can disrupt the synthesis, absorption, and transport of lipids within the body. The active metabolite of aflatoxins, AFBO, increases the levels of lipid peroxides in the liver, leading to lipid peroxidation. This process hampers enzyme activities, compromises cellular membrane integrity, and triggers oxidative stress and apoptosis (Fouad et al., 2019, Wang et al., 2019).

Oxidative damage occurs when the production of reactive oxygen species (**ROS**) and free radicals by aflatoxins exceeds the antioxidant capacity (both enzymatic and non-enzymatic) of cells. Studies have shown that aflatoxins elevate the levels of MDA and conjugated dienes, which are indicators of oxidative damage. Additionally, aflatoxins decrease the activities of important enzymatic antioxidants such as glutathione peroxidase (**GPx**), superoxide dismutase (**SOD**), and catalase (**CAT**) (Gowda et al., 2008; Balogh et al., 2019). The decreased synthesis of proteins following exposure to aflatoxins may contribute to the decline in enzyme activities. This reduction in antioxidant enzyme activities further intensifies the toxicity induced by aflatoxins. Several studies have reported increased generation of cellular ROS and down-regulation of genes involved in the expression of antioxidant enzymes, including GPx, SOD, and CAT, in chickens fed diets containing aflatoxins (Gowda et al., 2008, Yarru et al., 2009).

Reproductive Performance and Egg Quality and Public Safety

Reproductive Performance. The reproduction systems of both male and female poultry are vulnerable to the negative impacts of AFB_1, which can lead to suppressed fertility and reproduction. Birds exposed to AFB_1 exhibit lowered feed intake and feed efficiency, resulting in reduced availability of energy and nutrients needed for growth, development, and normal functioning of reproductive tissues. This can also cause delayed sexual maturation in birds (Ortatatli et al., 2002). Aflatoxins, such as AFB_1, have been shown to negatively affect various aspects of reproduction in poultry, including hormone production, development of reproductive tissues, and gamete production, thereby positively influencing reproductivity. Studies have demonstrated that aflatoxicosis causes significant decreases in testicular weights and plasma levels of androgens in mature and immature White Leghorns, ducks and Japanese quails (Doerr and Ottinger, 1980, Eraslan et al., 2006). Additionally, poults chicks fed a diet containing AFB_1 took about 3 to 7 wk longer to reach sexual maturity compared to those on an AFB_1-free diet (Pandey and Chauhan, 2007). Exposure to AFB_1 has also been shown to cause a reduction in the size of seminiferous tubules, leading to suppressed spermatogenesis in mature rooster cocks and increased production of abnormal spermatozoa (Ortatatli et al., 2002). These changes directly impact the reproduction efficiency and hatchability of eggs, which can have significant economic implications for the poultry industry.

Similarly, female poultry exposed to AFB_1 experience negative effects on reproduction. In laying chicken and quail hens, AFB_1 has been found to reduce ovarian weights, hinder folliculogenesis, and delay sexual maturity (Doerr and Ottinger, 1980; Wolzak et al., 1986). At 18 d of inoculation, administering AFB_1 to eggs at a dosage of 0.04 g/kg suppressed tibial weight and length, as well as embryo weight, resulting in decreased hatching weight and length and increased yolk sac weight (Oznurlu et al., 2012; Yin et al., 2017). Furthermore, including AFB_1 in hens' diets increases the deposition of AFB_1 in eggs, resulting in high embryonic mortality, diminished hatchability, and low chick quality (Khan et al., 2014). In embryos, AFB_1 can bind with DNA, inducing mutations by altering certain bases in the promoter sequences of growth hormone-regulated gene 1 (Gülbahçe Mutlu et al., 2018). This may explain the observed low hatchability, high percentage of defective embryos, and elevated embryonic mortality found in eggs from layer breeder hens fed AFB_1-contaminated diets for 3 wk (Khan et al., 2014).

Egg Quality and Public Safety Concerns. The exposure of birds to diets containing AFB_1 also leads to lowered eggshell thickness, reduced yolk color score, and increased concentration of AFB_1 in eggs and meat (Pandey and Chauhan, 2007; Manafi, 2018). The occurrence of these toxins in poultry products poses a significant public health risk as they can be easily transferred into meat and egg products and therefore, may serve as a point of exposure to humans who consume these products. When consumed, AFB_1 can cause several health challenges in humans including liver toxicity, cancer, and lowered immune functions. Thus, the need to ensure the quality and safety of poultry products cannot be over-emphasized. Deposition of AFB_1 in eggs can occur rapidly, with considerable levels detected in layer breeder hens as early as 5 d after consuming AFB_1-contaminated feed (Ul-Hassan et al., 2012). Consequently, various countries have established allowable levels of poultry feeds and feed ingredients to address these concerns as it practically difficult to produce feeds and feed ingredients free from aflatoxin. However, high levels of aflatoxin in maize and groundnut warrant limiting their use in feed to minimum required levels after proper testing for its levels. For example, in China, the allowable levels are set at 10 μg AFB_1/kg, European Union at 20 μg AFB_1/kg, United States 20 μg AFB_1/kg, in Brazil at 50 μg AFB_1/kg, in South Africa at 10 μg AFB_1/kg, while Indian regulatory limit is 30 μg AFB_1/kg (He et al., 2013; Andrea Molina et al. 2017; Feng et al., 2017; Abbasi et al., 2018). However, even at such low dietary levels, adverse effects on reproductive development and fertility in poultry have been reported.

The resulting lowered reproductive efficiencies, poor hatchability, and chick quality amount to huge economic losses for poultry farmers. Also, the issue of food safety and quality can affect the marketability of poultry products, thereby compromising the profitability of production. This has implications for the safety, quality, and marketability of these products, potentially resulting in economic losses. Overall, the issue of aflatoxin in poultry production is significant and hence requires the development and implementation of comprehensive and appropriate measures for adequately addressing aflatoxin mitigation.

Therefore, to mitigate the effects of aflatoxins on poultry health and performance, it is crucial to monitor and mitigate feed contaminations and exposure of poultry to aflatoxins. Good storage practices and proper handling of feed can help reduce the risk of aflatoxins contamination. Furthermore, regular monitoring of poultry health and performance can help with the early identification of potential issues and allow for timely intervention.

PHYTOGENIC COMPOUNDS AND THEIR POTENTIAL APPLICATION IN POULTRY NUTRITION

Phytogenics refer to a group of plant-based compounds derived from herbs (thyme, oregano, and rosemary), spices (turmeric, cumin, and black pepper) and various other plant parts. They are rich in nutrients and bioactive compounds, including essential oils, eugenol, capsaicin, polyphenols, flavonoids, alkaloids, and saponins (Pannee et al., 2014; Rajput et al., 2017). Therefore, they are widely considered for use in animal nutrition as natural feed additives to optimize animal health, performance and overall productivity (Huang and Lee, 2018; Armanini et al., 2021). Phytogenics feed additives (**PFA**) possess several beneficial properties that have made them increasingly essential in animal nutrition and as potential replacements for antibiotics use. They are known to demonstrate antimicrobial, antioxidant, and immunomodulatory activities, which contribute to their modulation of gut health and functions, improved efficiency of nutrient utilization, improvement of growth and a reduction in the negative environmental impacts of poultry production (Abdelli et al., 2021).

Numerous studies have demonstrated the positive effects of PFA on the antioxidant capacities of birds, offering them protection against the damaging effects of lipid peroxidation (Siani et al., 2013; Lin et al., 2015; Lee et al., 2017; Huang and Lee, 2018). Evidence shows that PFA can provide antioxidant support along the gut lining, maintaining a balance between the generation of free radicals and their neutralization (Oladeji et al., 2019). The antioxidant properties of phytogenic compounds are attributed to the presence of hydroxyl groups that act as hydrogen donors effectively delaying the production of harmful radicals during lipid oxidation (Marchese et al., 2017). Examples include the essential oil from *Minthostachys verticillata* which is rich in polyphenolic compounds and has been shown to suppress the formation of DNA adducts and conjugation with glutathione, protecting against AFB_1-induced damage (Escobar et al., 2019). The inclusion of 250 mg/kg diet of grape seed proanthocyanidin extract has also demonstrated the ability to enhance antioxidant enzyme activity and reduce lipid peroxidation, thereby mitigating the negative impact on the liver (Rajput et al., 2017). Similarly, *Urtica diocia* seed extract administered at 300 mL/ kg of diet also showed lowered lipid peroxidation in the live and kidney with overall growth improvement (Uyar et al., 2016).

Also, PFA possess immunomodulatory activities implying that they can modulate immune response by stimulating immune cells and promoting cytokines promotion (Yunus et al., 2011; Kim et al., 2013). This therefore translates into improved immune functions and increased resistance to disease challenges. Published reports demonstrate that the inclusion of turmeric in broiler diets can increase the level of immunoglobulins (IgA, IgG, and IgM) and reduce the ratio of monocytes, thereby enhancing specific immunity against pathogens (Li et al., 2011, Akhavan-Salamat and Ghasemi, 2016). Similarly, thyme essential oil supplementation improved cutaneous basophil hypersensitivity and reduced the stress indicator H/L ratio (Jahanian and Rasouli, 2015). Also, the inclusion of cinnamon at 0.4% and 0.8% in boiler chicken diets increased hemoglobin concentration and lymphocyte proportion in the blood (Najafi and Taherpour, 2014).

Furthermore, phytogenic compounds can be used as natural growth promoters in poultry nutrition due to their positive effects on the proliferation and promotion of beneficial gut bacteria (Li et al., 2012). This improvement in gut microbiota enhances digestion, nutrient absorption, and strengthens the gut barrier function, thereby reducing the entry of harmful bacteria and toxins into the body. Green tea leaf and pomegranate rind extracts have been shown to increase the levels of lactic acid-producing bacteria in the gut, which positively regulate the composition of intestinal microflora, promote intestinal immunity, and contribute to overall intestinal health (Chen et al., 2020). Phytogenic compounds such as oregano and thyme essential oils administered at 0.6 mL/L have also been found to inhibit the growth of *E.coli* while improving the growth performance of broilers (Burt and Reinders, 2003). Generally, phytogenics exert a broad-spectrum antimicrobial action throughout the gastrointestinal tract, enhancing nutrient utilization, gastrointestinal histomorphology, and host immunity (Ganguly, 2013). Therefore, the use of PFA in poultry nutrition provides a valuable tool for ameliorating the negative effects of stress factors such as aflatoxins in poultry production, while improving the overall health and performance of birds.

PHYTOGENICS AND MITIGATION OF AFLATOXICOSIS IN POULTRY

Aflatoxin contamination can have significant adverse impacts in poultry including lowered gut health and functionality, lowered efficiency of feed utilization, increased inflammation, and immune dysfunction (Rajput et al., 2017; Manafi, 2018). The need to address these challenges of mycotoxins has resulted in the development and application of several decontamination approaches such as physical, chemical, and biological tools (Juodeikiene et al., 2012; Hojnik et al., 2017; Gacem et al., 2020; Piotrowska, 2021; Nahle et al., 2022). Chemical mitigation tools which aim at converting mycotoxins into less toxic metabolites have resulted in peroxidation, ammonization, and ozonation processes that present toxicity concerns with adverse effects on the palatability and quantity of the poultry products (Abdulhameed et al., 2022). Therefore, PFA have emerged as a valuable option for the prevention and mitigation of the issues of aflatoxicosis and similar conditions due to their numerous beneficial properties in addition to their being sustainable, biodegradable and can further lower greenhouse emissions from poultry production (Rajput et al., 2017; Gacem et al., 2020; Meng et al., 2020). Additionally, their potential to serve as alternatives to antibiotics use in poultry has attracted attention to this area of study. The amelioration of PFA against aflatoxins in poultry production can be achieved through various physiological mechanisms discussed below.

Antioxidant Mechanisms of Phytogenics in Mitigating Aflatoxicosis

Recent investigations have implicated oxidative stress as a key mechanism for inducing the toxic effects of several mycotoxins, including aflatoxins. Exposure to aflatoxins can stimulate the generation of ROS molecules and oxidative stress which are the major causes of cancer and mutations in animals (Liu and Wang, 2016). The antioxidant activity of phytogenic compounds is attributed to their ability to scavenge free radicals and ROS generated during metabolic reactions in cells, particularly in response to aflatoxin exposure (Basiouni et al., 2023).

Free radicals are highly reactive and unstable molecules that possess an unpaired electron in their outer shell (Lee et al., 2017). They can cause oxidative damage to cells and tissues by reacting with cellular components such as proteins, lipids, and DNA (Na and Surh, 2008). Phytogenic compounds function by donating an electron to free radicals, neutralizing them, and reducing oxidative stress. The mechanism by which phytogenic compounds mitigate aflatoxicosis through free radical scavenging involves hydrogen atom transfer and single electron transfer processes (Reis et al., 2019). Phenolic and carotenoids compounds such as flavonoids, phenolic acids, β-carotene, and lycopene, donate a hydrogen atom and electron to free radicals, thereby neutralizing them and reducing their reactivity (Reis et al., 2019). Phytogenic compounds also scavenge free radicals through chelation, where they bind to metals ions like iron and copper that catalyze free radical formation. For example, flavonoids found in green tea can chelate iron and copper ions, reducing their ability to generate free radicals and damage cells (Weinreb et al., 2009). Binding to these metal ions reduces free radical formation and quenches their excited state, thereby reducing aflatoxin toxicity in poultry (Paraskeuas et al., 2017).

Moreover, phytogenic compounds enhance the activity of antioxidant enzymes, including GPx, SOD, and CAT, which further alleviate oxidative stress during aflatoxicosis. They activate specific genes responsible for antioxidant enzyme production. For instance, the polyphenols in green tea have shown to increase the expression of genes involved in aflatoxin detoxification (Damaziak et al., 2018). Phytogenic bioactive compounds also regulate signaling pathways associated with antioxidant enzyme production and activity. Citrus fruit flavonoids, for example, activate the Nrf2 pathway, a key regulator of antioxidant enzymes (Kuralkar and Kuralkar, 2021). Dietary flavonoids in phytogenics, such as those found in *Camellia sinensis*, upregulate the expression of GPx, an important enzyme involved in aflatoxin detoxification (Reygaert, 2014). This effect enhances the liver's ability to neutralize and eliminate these toxins, thereby reducing aflatoxin exposure and its impact on affected birds. Additionally, essential oils, phenols, flavonoids, and tannins present in phytogenic compounds protect the polyunsaturated fatty acids in cell membranes by preventing free radicals from attacking them, thereby reducing lipid peroxidation in affected tissues and cells (Makhuvele et al., 2020).

Through their scavenging ability, modulation of gene expression, enhancement of enzyme activities, regulation of signaling pathways, metal chelation, and possibly, altering aflatoxin metabolism, phytogenic compounds play a crucial role in enhancing the efficiency of the antioxidant defense system in poultry exposed to aflatoxins.

Immunomodulatory Mechanisms of Phytogenics in Mitigating Aflatoxicosis

Phytogenic substances have been found to possess immunomodulatory effects, which aid in mitigating the negative impacts of aflatoxins on poultry, thereby enhancing poultry health and productivity. These natural bioactive compounds derived from plants play a crucial role in modulating the animal's immune system through the modulation of cytokine production, regulation of immune cell proliferation, and anti-inflammatory activity (Huang and Lee, 2018). Cytokines are signaling molecules that play vital roles in immune regulation and inflammation. Phytogenic substances modulate cytokine production by regulating transcription factors that bind to specific regions of DNA, controlling gene expression (Akira et al., 2006). Nuclear factor-kappa B (NF_kB) and activator protein-1 (**AP-1**) are 2 important transcription factors involved cytokine productions. Phytogenics such as *Curcuma longa, Thymus*, and *Cinnamomum* are known to inhibit NF_kB and AP-1, thereby suppressing the production of pro-inflammatory cytokines such as interleukin-1β (**IL-1β**), interleukin-6 (**IL-6**), and tumor necrosis factor-alpha (**TNF-α**) (Li and Verma, 2002; Akhavan-Salamat and Ghasemi, 2016).

Another mechanism by which phytogenics modulate cytokine production is through the regulation of mitogen-activated protein kinases (**MAPKs**). MAPKs are a family of protein kinases that regulate various cellular processes, including cytokine production. Phytochemicals such as epigallocatechin gallate (**EGCG**), genistein, and resveratrol are the active constituents in phytogenics that are known to inhibit MAPKs, thereby suppressing the production of pro-inflammatory cytokines (Byeon et al., 2012, Yu et al., 2012). Additionally, plant bioactive compounds regulate the activity of enzymes involved in cytokine synthesis. Cyclooxygenase-2 (**COX-2**) and inducible nitric oxide synthase (**iNOS**) are 2 enzymes that are involved in the synthesis of pro-inflammatory cytokines (Harizi and Gualde, 2006). The use of dietary green tea, curcumin, and resveratrol in poultry diets is known to inhibit COX-2 and iNOS, thereby suppressing the production of pro-inflammatory cytokines (Huang and Lee, 2018).Thus, the modulation of cytokine production by phytochemicals involves the regulation of transcription factors, MAPKs, enzymes involved in cytokines synthesis, and direct interaction with cytokines and their receptors.

Phytogenics also exhibit immunomodulatory properties by mitigating immune cell proliferation through the regulation of the immune cell activity. Studies have shown that phytogenics modulate the activity of immune cells such as T cells, B cells, macrophage, and dendritic cells (Medzhitov and Janeway, 1997, Ramasamy et al., 2014). For instance, the use of turmeric as a phytogenic feed additive increased T cell proliferation and activity, as well as enhanced the production of cytokines due to the presence of bioactive compound *curcumin* found in turmeric (Nouzarian et al., 2011). This plays a critical role in the immune response by recognizing and eliminating foreign antigens and activating macrophages, responsible for engulfing and digesting foreign substances, including bacteria, viruses and toxins.

Additionally, the anti-inflammatory properties of phytogenics help to reduce inflammation and modulate immune response by inhibiting the activity of COX enzymes, which are responsible for the production of prostaglandins, a group of lipid mediators that promote inflammation (Pannee et al., 2014). For example, cinnamaldehyde, the major bioactive compound in cinnamon have been reported to suppress lipopolysaccharide (LPS)-induced activation of NF_kB and interferon regulatory factor 3, resulting in decreased expression of the toll-like receptor (4)TLR4 target genes, COX-2 and interferon-beta (IFN-β) (Youn et al., 2008).

Therefore, phytogenics can be used as natural additives to modulate the immune response and regulate the expression of inflammatory mediators in poultry affected with aflatoxicosis. By influencing cytokine production, immune cell proliferation, and inflammatory pathways, phytogenic substances contribute to the overall enhancement of poultry health and productivity.

CHALLENGES AND CONSIDERATIONS FOR THE USE OF PHYTOGENICS IN POULTRY PRODUCTION

In poultry production, phytogenic feed additives have shown promising effects on growth, feed efficiency, and overall health improvement. However, their utilization is accompanied by certain challenges that need to be addressed. These challenges include the variability in manufacturing methods, potential synergistic effects, effective dose, toxicity of plant substances, risk of allergic reactions, and presence of anti-nutritional factors. For instance, the minimum inhibitory concentration of most phytogenics is higher than the level considered feasible (Yang et al., 2015) . Phytogenic compounds such as essential oils (EOs), can be challenging to use as feed additives due to their volatile and reactive nature, which can result in varying concentrations in final products. Again, their effectiveness can be influenced by various conditions during feed production practices and storage, thereby resulting in variable biological activity (Stevanović et al., 2018).

Phytogenic feed additives are classified as feed additives and are subject to regulatory oversight in most developing countries including Sub-Saharan Africa which involves the systematic regulation, surveillance and control measures implemented by the authorities to safeguard animal health, food safety and environmental integrity. As a result, the regulatory landscape for these products can be complex and varies across different countries and regions. Further, interactions between phytogenic additives and other feed additives or medications can impact their efficacy and safety. It is crucial to ensure compatibility between phytogenic products and other components in poultry diets to avoid negative adverse effects. The combination of different phytogenic compounds, such as EOs, can result in synergistic interactions that may have a negative impact on the animal. These effects result from the complex interaction between the different forms of bioactive compounds such as ketones, phenols, aldehydes, ethers or esters found in phytogenics (Bassolé and Juliani, 2012).

Another concern is the variability in the composition and efficacy of phytogenic feed additives. The active components in these additives can significantly vary depending on factors such as plant species, growing conditions, and the extraction method used (Abdelli et al., 2021). This variability makes it challenging to predict the precise effects of phytogenic products on poultry performance, thus impacting this effectiveness. Some PFAs are known to be readily absorbed in the upper gastrointestinal tract, which means that most of them will not reach the lower gastrointestinal where they are expected to exert their major functions. For instance, the benefits of supplementing broiler diet with a mixture of encapsulated essential oils were higher than the tested PFAs in powdered, non-protected form (Hafeez et al., 2016).

While phytogenics offer potential benefits for poultry, it is essential to address concerns regarding the toxicity of plant substances, interactions with other feed additives, composition variability, and the potential for allergic reactions (Yang et al., 2015). Therefore, it is necessary to carefully evaluate the risks and benefits of phytogenic products to ensure their safe and effective use in poultry production.

CONCLUSIONS AND APPLICATIONS

This review underscores the significance of aflatoxin contamination in poultry production and explores the potential of phytogenic compounds in mitigating aflatoxicosis. Phytogenics, with their inherent antioxidant and immunomodulatory properties, have demonstrated the ability to counteract some of the detrimental effects of aflatoxins on poultry health and production.

1. The antioxidant mechanisms of phytogenics effectively combat aflatoxin-induced oxidative stress, inflammation, and immune dysfunctions, ultimately improving gut health, feed efficiency, and overall productivity in poultry.
2. Phytogenics show great potentials, but some challenges and considerations must be addressed for their effective utilization in poultry production. Issues like the standardization of phytogenic preparations, understanding their interactions with other feed additives, ensuring consistent efficacy, and assessing cost-effectiveness are key concerns that must be addressed.
3. Further research is required to optimize the use of phytogenics in poultry nutrition and to fully harness their potential in mitigating aflatoxicosis. By overcoming these challenges and expanding our knowledge, phytogenics can be used as invaluable tools for the promotion of poultry health, welfare, and sustainable production practices.
4. Furthermore, continued investigation and advancement in this field will enhance poultry nutrition and also contribute to the

development of safer and more environmental friendly alternatives to antibiotics.

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DISCLOSURES

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