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REVIEW

Harmful effect of toxins on poultry

Hassan Nima Habib[a], Alfred Solaka Karomy[a], Qutaiba Jassim Gheni[a], Wessam Monther Mohammed Saleh[b]

[a]Department of Animal Production, College of Agriculture, University of Basrah, Iraq.
[b]Department of Internal and Preventive Medicine, College of Veterinary Medicine, University of Basrah, Iraq.

ABSTRACT Toxins are a primary concern in the poultry industry, as major economic losses occur annually due to contamination of bird food with aflatoxins. At the same time, there is an expansion in the poultry industry, be it broilers or laying, and this expansion coincided with a turbulent increase in the percentage of contamination of poultry feed, which led researchers and workers in this field to look for unconventional feed, to get rid of this contamination. Therefore, it is urgent to know aflatoxin (its causes and effects). This review aimed to provide a general introduction to aflatoxin, its causes, chemical structure, metabolism and impact on DNA, as well as its economic effects, as well as the direct and indirect effect of aflatoxins on genes and gene expression. The necessary strategies have been revised to reduce aflatoxins or to reduce their negative effects. In conclusion, the effect of aflatoxin on the poultry industry is significant and very dangerous, and more detailed studies are needed to reduce its effect.

KEYWORDS aflatoxin; negative effects; poultry industry; poultry feed

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Efeito nocivo das toxinas nas aves domésticas

RESUMO As toxinas são uma preocupação primordial na indústria avícola, pois grandes perdas econômicas ocorrem anualmente devido à contaminação dos alimentos das aves com aflatoxinas. Ao mesmo tempo, há uma expansão na indústria avícola, seja de frangos de corte ou poedeiras e, essa expansão, coincidiu com um aumento turbulento na porcentagem de contaminação dos alimentos para aves, o que levou pesquisadores e trabalhadores nesse campo a procurar alimentos não convencionais para se livrar dessa contaminação. Portanto, é urgente conhecer a aflatoxina (suas causas e efeitos). Esta revisão teve como objetivo fornecer uma introdução geral à aflatoxina, suas causas, estrutura química, metabolismo e impacto no DNA, bem como seus efeitos econômicos, assim como o efeito direto e indireto das aflatoxinas nos genes e na expressão gênica. As estratégias necessárias foram revisadas para reduzir as aflatoxinas ou reduzir seus efeitos negativos. Em conclusão, o efeito da aflatoxina na indústria avícola é significativo e muito perigoso, e são necessários estudos mais detalhados para reduzir seu efeito.

PALAVRAS-CHAVE: aflatoxina, alimentos para aves, avicultura, efeitos negativos

Introduction

Aflatoxins (AFs) and ochratoxins are the most common pollutants in poultry feed, Cereal kernels are appropriate for the expansion of Aspergillus species (Fareed et al 2014). Aflatoxin is mainly produced from Aspergillus flavus and A. parasiticus, moreover, aflatoxin B1 (AFB1) is more toxic than other aflatoxins such as B1, B2, G1, G2, and M1 (Babu *et al.,* 2014). If poultry consumes feed containing aflatoxins, they can be exposed to aflatoxicosis (table 1), which can lead to significant economic losses in poultry projects, Aflatoxin has a negative impact on the poultry production industry by directly affecting important productive and physiological traits such as the efficiency of food conversion, weight gain,

CONTATO Hassan Nima Habib – hassan.nima@uobasrah.edu.iq

feed consumption as well as disease resistance, due to reduced immune response (Fareed et al 2014). Aflatoxins are generally very toxic, teratogenic and carcinogenic, they can be agents of human hepatocellular carcinoma (Marchese *et al* 2018). Toxic effects of aflatoxin B1 (AFB1) in animals are varied due to differences in susceptibility (Sarma et al 2017), The effect may be different within the same breed, possibly because of the genetic variations of individuals in genes responsible for stress resistance (Habib et al 2017; Habib et al 2018). On the other hand, aflatoxins generally affect the growth of farm animals. The dietary levels of aflatoxin (table 2) generally resisted are =50 ppb in chicks, =100 ppb in adult chicken (Dhama et al 2007).

Table 1 Minimum aflatoxins concentrations with minor effects in poultry.
Minimum dietary contamination level (ppb) to cause.

Species	100% Lethality	Gross Hepatic Lesions	Impaired Production
Chicken	NR (>4000)	800 [1]	800 [1]
Duck	1000 [2]	500 [2]	500 [2]
Goose	4000 [2]	500 [2]	700 [3]
Pheasant	4000 [2]	500 [2]	1000 [2]
Quail (Bobwhite)	ND	ND	700 [3]
Turkey	800 [1]	400 [1]	400 [1]

Source: Monson et al (2015)

Mycotoxins are by-products of filamentous fungi because of their intake by animals, there are a vast diversity of toxins, created by numerous fungi, relying on the type of product, geographical place, and climatologic conditions. Cereal plants may be polluted by mycotoxins in two ways: fungi growing as pathogens on plants or growing saprophytically on stored plants (Glenn 2007). Mycotoxins are possible intimidation to human health. Joint FAO/WHO experts commissions are providing an assessment of relative health hazards connected with specific approach maximum limits for specific toxins. Feeding polluted materials to animals, specially single-stomached animals (Who 1979), decline feed intake, the efficiency of feed utilization, decrease body weight gain, increased disease happening (due to immune –repression) and reduced reproductive capability (Morgavi and Riley 2007), all this will lead to very significant economic losses (Wu 2006).

As well as the biological activity of Mycotoxins, the toxic metabolites which created via toxigenic fungi mainly, pertinence to *Aspergillus*, *Fusarium* and *Penicillium* species, that foray crops in the farm and may expand on foods through store under proper conditions of humidity and temperature (Shamsudeen et al 2013).

The Organization of Food and Agriculture evaluated around 25% of animal fodder and human foods are polluted by mycotoxins, powerful pains have been made to purify them using the chemical and physical adsorbents, despite all that the success achieved so far is limited (Huwig et al 2001; Yiannikouris and Jouany 2002; Shetty and Jespersen 2006). Mycotoxins adversely impact the health and output of animals and poultry (Zain 2011; Katole et al 2013), some countries like India, the industry of poultry was affected because of the pollution of various agricultural leeches or wide mycotoxin exposure, which leads to heavily affected the economy caused by their immunosuppressive effects among the influenced birds. Among the more than 350 mycotoxins that have been specified in nature trichothecenes, ochratoxins (OT), fumonisins (F), citrinins (CIT) and aflatoxins (AF) are the extremely popular and significant in poultry (Patil et al 2014).

The growth of *Aspergillus* and toxic production

There are some factors that directly affect the growth and production of fungi. They need a temperature between 24-35 °C for growth the production of aflatoxin (Williams et al 2004), the production of aflatoxins also depends on soil quality, different drought conditions, and on the products themselves (Brown et al 2001; Bankole and Mabekoje 2004), increasing rain during the harvest period clearly increases the moisture of the product, which increases the possibility of damaging the protective shell of the product by insects, making it vulnerable to the colonization of fungi and production of toxins during the storage period (Hell et al 2000; Hawkins et al 2005; Turner et al 2005; Ono et al 2010).

Table 2 Comparative acute toxicity of a single oral dose of aflatoxin.

Species	Age	Oral LD_{50} (mg/kg Body weight) [1]
Baboon	A	2.0–2.2
Cat	A	0.6
Chicken	E	0.3–5.0
Chicken	Y	6.5–18.0
Dog	A	0.5–1.0
Duck	E	0.5–1.0
Duck	N	0.3–0.6
Guinea Pig	Y	1.4–2.0
Hamster	Y	10.2–12.8
Macaque (Cynomolgus)	A	2.2
Macaque (Rhesus)	A	7.8–8.0
Mouse	N	1.5
Mouse	Y	7.3–9.0
Rabbit	Y	0.3–0.5
Rat	N	0.6–1.0
Rat	Y	5.5–7.4
Rat	A	6.3–18.0
Sheep	A	2.0
Swine	Y	0.6
Trout	Y	0.5
Turkey	Y	1.4–3.2

Source: Monson et al (2015)

The effect of mycotoxins on economic

The bad economic effects of mycotoxins on farmers and consumers of agricultural, animal products and society were ultimate. Grain producers and grain farmers will be affected by reduced farm operations, grain storage, and testing costs, respectively. In addition, grain farmers must continue at high prices with the loss of agricultural production. On the other hand, consumers of agricultural products have suffered irreversible complications arising from the use of infected products as well. Finally, society as a final customer must pay exorbitant costs for increased organization and research, lower exports and higher imports and treatments. Currently, these costs are present at every level of grain production and accurate cost estimation is impossible (Umaya 2011).

Aflatoxicosis

Aflatoxin is one of the most spread and economically important mycotoxins that can affect the poultry. In the United States, the total yearly wastage due to aflatoxins in corn is nearly $163 million (Ghimpeţeanu et al 2012). The yearly market wastage in corn unacceptable for food is about $31 million, whereas the wastage through corn unacceptable for feed and during livestock losses is evaluated at $132 million. The cost of research and monitoring activities are between $500 million and $1.5 billion a year to manage mycotoxin-producing fungi (Abbas 2005). Aflatoxin came from the word Aspergillus by using the first letter and the word flavus by using the first three letters. The structure of aflatoxins (AFs) are about of furocoumarin derivatives with particular fluorescence beneath ultraviolet light. Count on the colour of the fluorescence, AFs are split into aflatoxin B1 and B2 (AFB1, AFB2) for blue fluorescence, and G1 and G2 (AFG1, AFG2) for green fluorescence. Aflatoxin M1 and M2 (AFM1, AFM2), renowned as milk-AFs, are the metabolites of AFB1 and AFB2. The other metabolites of AFB1 are aflatoxin Q1 (AFQ1) and aflatoxin. Aflatoxin is considered the most thoughtful mycotoxin, because of its poisoning to both animals and people and their high carcinogenic power. Out of AFs group, AFB1 is the most toxic and is categorized as a human carcinogen (Talebi et al 2011).

Causes of aflatoxin

Crops mature down cozy and humid weather in tropical or semitropical lands are mostly more prone to aflatoxin pollution than those in temperate regions. Groundnuts and groundnut meal are by far the two agricultural commodities that seem to have the highest danger of aflatoxin pollution (Dhanasekaran et al 2011). However, these wares are important, as substrates, fungal growth and aflatoxin pollution are the results of interactions through the fungus, the steward and the climate. The suitable mingling of these factors determines the invasion and habitation of the substrate, the kind and amount of aflatoxin created. (Guevara-Gonzalez 2011). Water stress, high-temperature stress and insect harm of the steward implant are large specific factors in mold invasion and toxin production. Similarly, specific crop growth stages, poor fertility, high crop consistency, and herb concurrence have been linked with increased mold growth and toxin production (Jayalakshmi and Jyothi 2012). The humidity content of the substrate and temperature are the master agents organize fungal evolution and toxin formation. The humidity content of 18% for starchy cereal grains and 9-10% for oil-rich walnut and seeds has been established for the maximum production of the toxin (Dhanasekaran et al 2011). Further, the floor, optimum and maximum temperatures for aflatoxin production have been notified to be 120-270 °C and 400-420 °C respectively. Recurrent, pollution of corn and other commodities with high levels of aflatoxins has been an earnestly trouble all over the world resulting in significant economic damages to farmers and a validity hazard to farm animals and humans as well (Battilani et al 2016).

Causes of aflatoxin

From the chemical point of view, aflatoxins are formed from a high-oxygenated heterocyclic component (composition furanocoumarins), they have a B furn-fused coumarin nucleus (Table 3), the B aflatoxin has an acyclic cyclopentane shape. M and G collections are the outcomes of B group hydroxylation and Kenton ring, respectively (Gourama and Bullerman 1995).

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Table 3 Physical and chemical important properties of the Aflatoxin (Abedi and Talebi 2015)

Aflatoxin	Molecular formula	Molecular weight	Melting point	UV absorption max UV(ε (L mol^{-1}cm^{-1})) metanol	
				265 nm	360-362 nm
B_1	$C_{17}H_{12}O_6$	312	268-269	12400	21800
B_2	$C_{17}H_{14}O_6$	314	286-289	12100	24000
G_1	$C_{17}H_{12}O_7$	328	244-246	9600	17700
G_2	$C_{17}H_{14}O_7$	330	237-240	8200	17100

Source: Abedi and Talebi (2015)

On the other hand, the B1 aflatoxin has 312 molecular weight and $C_{17}H_{12}O_6$ formula, shown comparatively acute blue fluorescence versus UV, aflatoxin disintegrates into colourless crystals at temperatures of 268-269 °C (James 1997). Meanwhile, Yunus et al (2011) refers that the aflatoxins are furanocoumarin complex and contain B1, B2, G1, G2, M1 as well as M2 (Figure 1).

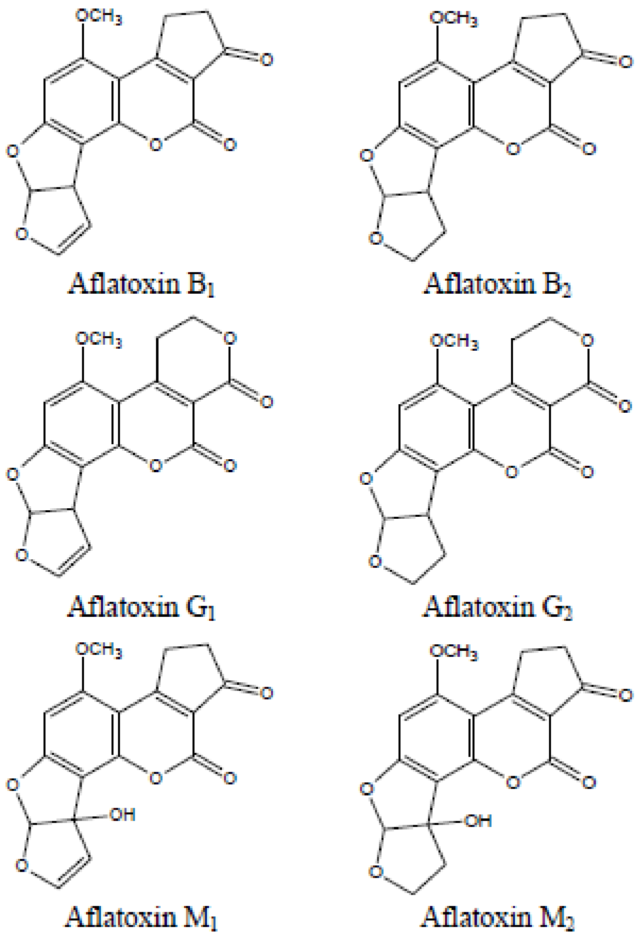

Figure 1 Structure of aflatoxins.
Source: Yunus et al (2011)

Metabolism and mechanisms of action to the aflatoxin B1

The absorption from the gastrointestinal tract should be complete since very small doses, even in the presence of food, can cause toxicity. After the absorption, the highest concentration of the toxin is found in the liver (Mintzlaff et al 1974). Upon reaching the liver, aflatoxin B1 exposure to metabolism by the enzymes of microsomal to several metabolites through hydration, demethylation, epoxidation, and hydroxylation. Therefore, hydroxylation of AFB1 at C4 or C22 output, AFM1 and AFQ1, respectively. Hydration of the C2 – C3 double bond outcome in the formulation of AFB2a, which is quickly formed in certain avian types (Patterson and Roberts 1970). AFP1 produces of O-demethylation whilst the AFB1 – epoxide is formed by consists of at the 2,3 dual ligament.

Aflatoxicol is the only metabolite of AFB1 created by a dissolvable cytoplasmic reductase enzyme regulation. The toxic impacts of aflatoxin B1, targeting the liver. As a result, the metabolism of proteins, carbohydrates and, lipids in the liver is seriously impaired by AFB1. The toxin inhibits RNA polymerase and subsequent protein synthesis at a faster rate in ducks than in rats probably because of faster liver metabolism of AFB1 in ducks than in rats (Smith, 1965). In day-old chicks, AFB1 reduces the activity of liver UDP glucose-glycogen transglucosylase resulting in depletion of hepatic glycogen stores (Shankaran et al 1970). On the other hand, there is lipid accumulation in the liver of chickens and ducklings exposed to aflatoxin (Carnaghan et al 1966). With regard to its toxic effects on liver microsomal enzymes, AFB1 is known to decrease microsomal glucose-6-phosphatase activity (Shankaran et al 1970) whereas stimulation of microsomal enzyme activity by inducers seems to be unaffected by AFB1 (Kato et al., 1970). Indeed, pre-treatment of toxins catalyzes its metabolism in mice when it is examined in the laboratory (Schabort and Steyn 1969).

There are four metabolic pathways to aflatoxin B1, which means that there is a great diversity in its metabolism (Wu et al 2009), even within the same species of animal and depending on many factors, including the animal's age and its physiological status, but the implicit mechanism has to be the metabolizing enzymes in species (Dohnal et al 2014). The first stage of metabolism is to convert the original molecules into hydrophilic components by using major enzymatic hydrolytic and Oxidation-reduction reactions (Dohnal et al 2014), while the second stage is distinguished conjugation of the original molecule or its metabolites with nucleophile molecules, perhaps the main path to detoxification is pairing with glutathione (Dohnal et al 2014). The main metabolic track and the clef metabolizing enzymes of aflatoxin B1 in humans and animals has been shown in Figure 2.

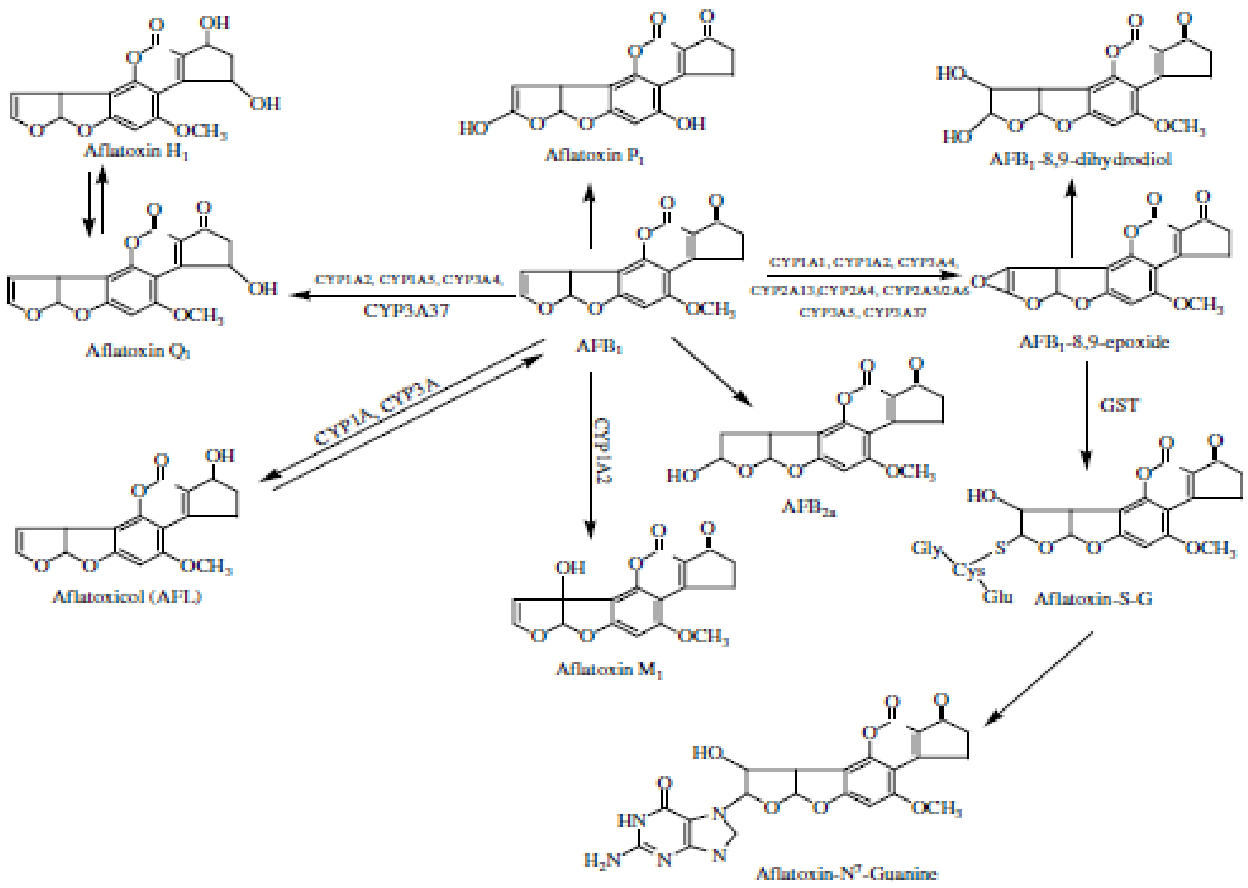

Figure 2 The main metabolic track and the clef metabolizing enzymes of aflatoxin B1 in humans and animals.
Source: Dohnal et al (2014)

The effect of aflatoxins on poultry feeding

The Avian species are unevenly sensible to chronic aflatoxicosis (Arafa et al 1981), it is ingested through feed contaminated with mycotoxins (Fraga et al 2007). Ducklings and Turkey poultry are more sensible (Lozano and Diaz, 2006). Aflatoxins have reduced immunity extremely and raise the capability of birds to many intended factors (Dalvi 1986). The bird's productive performance, likewise greatly influenced (Yaroshenko et al 2003). In poultry, aflatoxicosis is showed as idle, anorexia, low feed exhaustion, and growth average, opisthotonus, diarrhea, convexity back and cramps of neck muscles then death with legs extended to the back (Borisova et al 1990). Birds are liable to contagions and flop to prompt protective antibodies. In layers, there is a deterioration in the production of eggs and reduced hatchability, because of immunosuppressive harms of thymus and bursa of Fabricius (Jand and Sharma 2005)

Mottled liver and the bile duct is enlarged widely, whereas chronic exposure to aflatoxins may lead to low death-rate low growth average, haggard firm liver and haggard magnify kidneys (Asuzu and Shetty 1986). The myocardium exposed to congestion, catarrhal sore of intestines, insufflation of pericardial sac and hemorrhage in the pancreas and serous membranes (Espada et al 1992). Total pathological lesions include enlarged liver with pale necrotic lesions and swollen bitterness (Jand and Sharma 2005). In chronic cases, cirrhosis is more pronounced and birds may develop two gelatin under the skin. Microscopic lesions include degenerative and necrotic changes in the liver with the drain of lymphocyte cells and polymorphic and bile duct is enlarged (Espada et al 1992). The cumulation of fat in the liver is clearly observed in the birds that died from aflatoxicosis (Fukal et al 1988), while the capillary basement membrane in kidneys was thick, spread hemorrhages, tumescent and multiple tubules in the parenchyma (Glahn et al 1991).

The clinical sign and lesions in turkeys involve ataxia, diarrhea, winding feathers, opisthotonus, cramps, tumescent feet, generalized edema, and keratoconjunctivitis (Fazal et al 1980).

In poultry, the immune system is extremely affected through the aflatoxicosis, the liver turns into orange-colored and edematous in sharp cases, however, in chronic cases, the liver turns into pale and astringent (Quist et al 2000).

Often in poultry, symptoms are limited to enlarged kidneys (Figure 3), catarrhal intestinal inflammation, heart congestion, viscera, and subcutaneous hemorrhage, as well as spots on the liver (Figure 4) (Giambrone et al 1985), while, Uchida et al (1988) indicated that in ducks and duckling, the aflatoxicosis increase the hepatotoxicity in birds suffered from duck hepatitis virus.

Perhaps the most dangerous thing that can be caused by aflatoxins is what Abedi and Talebi (2015) mentioned about the molecular changes that caused by aflatoxins like the changes in gene expression modalities. This led researchers to find effective solutions to get rid of aflatoxins such as adding charcoal and lyophilized yeast to the feed (Jayasri et al 2017) and the seabuckthorn leaves (Ghabru et al 2018) to reduce the effect of aflatoxin toxicity, while some studies have used some mineral elements in the feed that are effective antioxidants such as zinc and selenium and others to reduce the effects of aflatoxins (Mughal et al 2017; Fouad et al 2019), or use curcumin as a possible factor to protect from aflatoxins (Li et al 2019). Some studies have used propionic as an antibiotic to reduce the effects of aflatoxin (Abed et al 2018; Hernandez-Patlan et al 2019), however, some studies indicated that the use of some locally produced mycotoxins has reduced the effect of aflatoxins (Saleemi et al 2020), on the other hand, Surai (2020) pointed out that vitagene modification by nutritional wherewithals like betaine, silymarin, carnitine, and taurine, can contribute to improving the productive performance of poultry and reducing the effects of aflatoxins.

De Oliveira et al (2018) indicate that there is an importance to study the mycotoxins in the poultry production industry to prevent its harmful effects on the industry greatly. Perhaps the interest in cereals greatly from the period of harvesting and manufacturing until consumption is one of the most important key points to reduce the effects of aflatoxins.

As for Wang and Hogan (2019), they indicate that the harmful effect of toxins on broiler chicken extends to the later stages of growth, causing many health problems resulting from reduced feed intake and others, therefore, contaminated feed should be avoided at all stages of bird growth.

Some studies such as Nabi et al (2018) have linked the commercially available binders toxins to reducing the effects of aflatoxins.

Solis-Cruz et al (2019) indicate that the aflatoxins bring out sharp toxic effects on the productive parameters and the immune system although there are many ways to face these effects, there are no perfect strategies to exclude impacts.

Ghimpeţeanu et al (2012), indicate that the aflatoxins may be the cause of cancer, poisoning and enlarged liver, aqueous degeneration and changes in the level of fat, peripheral fibrosis, and bile duct enlargement. Therefore, in order to reduce the effects of these toxins on the poultry industry, it is very important to develop global plans to prevent the spread of these mycotoxins by using modern analytical techniques and developing a new concept related to the maximum level of toxins in poultry feed.

Figure 3 Marked enlargement and pale kidneys in poultry.
Source: Kumar et al (2014)

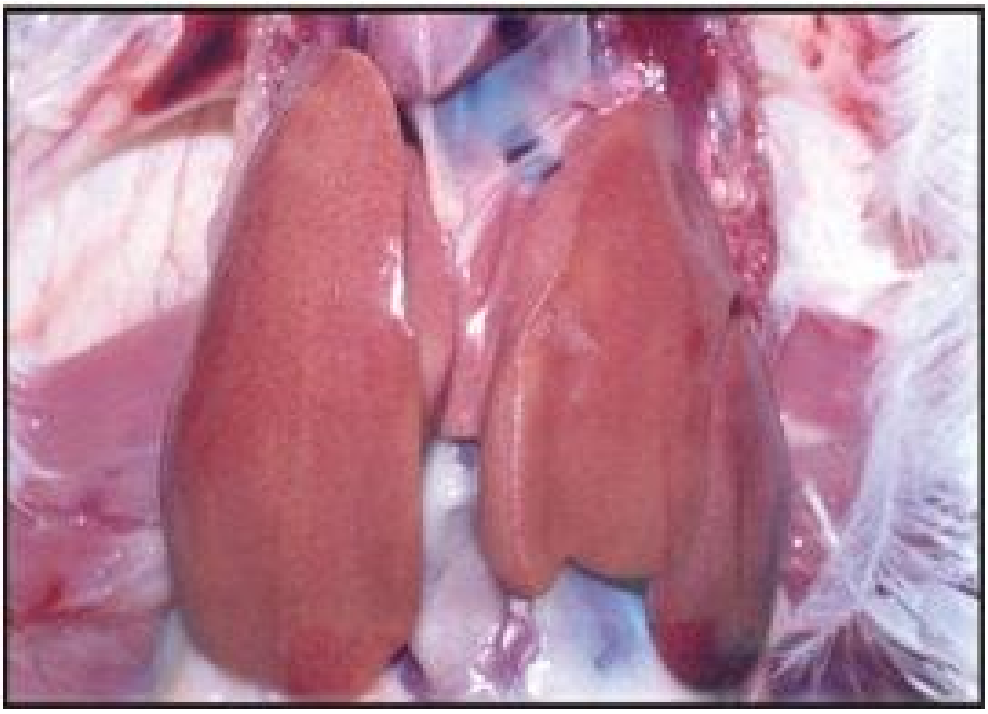

Figure 4 Markedly enlarged and pale liver in poultry.
Source: Kumar et al (2014)

The interaction of aflatoxin with DNA

Studies have indicated that the effect of aflatoxins lies in their ability to form a complex with both DNA and RNA or protein which may cause great damage to the genetic material or lead to the occurrence of genetic mutations, which may have a very bad impact on the organism (Verma 2004; Abedi and Talebi 2015), while Abbès et al (2016) indicated that the aflatoxins cause damage in DNA, raise in caspase activity and effect on the natural mRNA levels of cytokines, and the effect may reach the DNA of the fetuses, causing damage (Gülbahçe et al 2018).

Rawal et al (2010) indicate that the aflatoxin was absorbed in the small intestine. While it is metabolized firstly in the liver and activated by cytochrome P450 (CYP) enzymes, the toxicity of the resulting reactive compound and its direct effect on the DNA, RNA, proteins and other cellular molecules.

Monson et al (2014) and Reed et al (2018) indicated that there was a significant correlation between exposition to aflatoxins and expression of metabolic genes in the first and second phase of metabolic as well as other genes significant in the cellular arrangement (Figure 5).

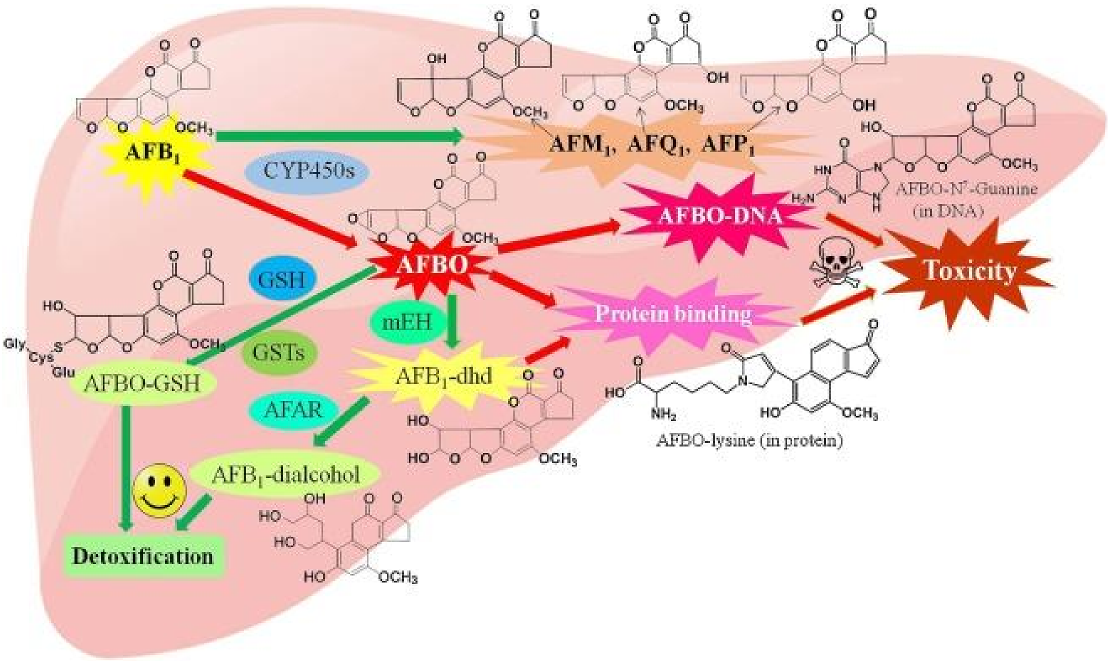

Figure 5 The metabolism lane of aflatoxins.
Source: Deng et al (2018)

Final Considerations

Toxins pose a great danger to the poultry industry, and its effect may be not only on birds but also on consumers of poultry products. Therefore, this topic needs more detailed studies.

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