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MYCOTOXINS - A GLOBAL ONE HEALTH CONCERN: A REVIEW

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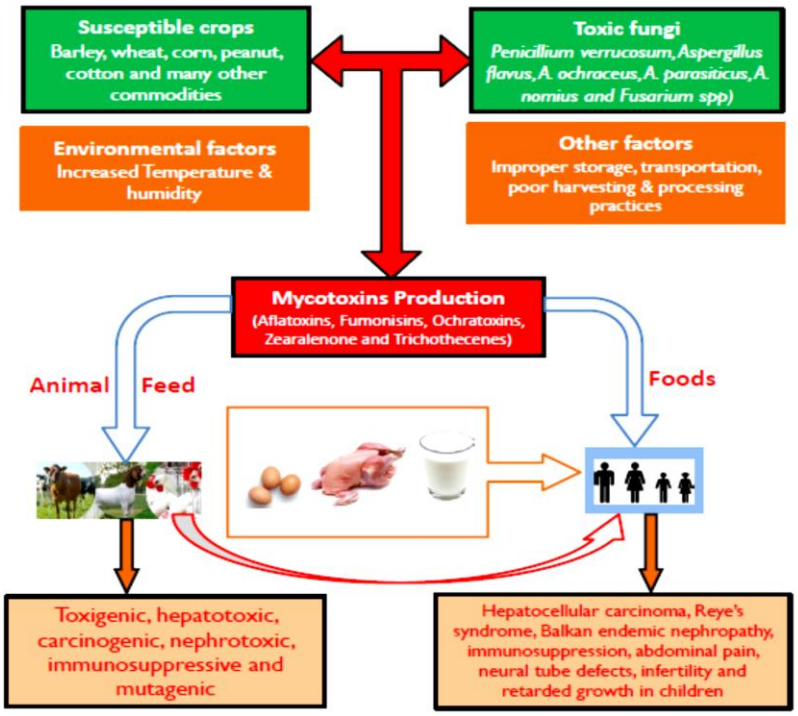
ABSTRACT



Fungal contamination of crops and production of toxic secondary metabolites (mycotoxins) are the inevitable issues throughout the world, mainly in the developing countries. These toxins associated with adverse effects on animals, humans and crops, result in health issues and economic losses. The major mycotoxins that have agro-economic importance are aflatoxins, fumonisins, ochratoxins, zearalenone and trichothecenes. These toxins are produced by different types of molds that contaminate crops under favorable conditions and become the part of animal and human diet. Several studies have described their hepatotoxic, nephrotoxic, carcinogenic, immunosuppressive, toxigenic and mutagenic characteristics, and most mycotoxins represent a considerable risk to animal and human life. Compound stomach animals show some resistance against mycotoxicosis as compared to monogastric animals due to capability of rumen microbiota to degrade mycotoxins. The adverse effects of mycotoxins in humans include hepatocellular

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carcinoma, Reye's syndrome, Balkan endemic nephropathy (BEN), immunosuppression, abdominal pain, neural tube defects, infertility and retarded growth in children. This review describes different types of mycotoxins and their adverse effects on animal species and humans by keeping in mind the One-Health aspect.

Keywords: Mycotoxins, Molds, Pathology, Humans, Animals.

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INTRODUCTION

Mycotoxins are the fungal metabolites, produced in cereal crops, and exerting serious threats to human and animal health. These are highly toxic and unavoidable food contaminants (Amaike and Keller 2011). In developing countries there are five groups of mycotoxins, that occur quite often in food: aflatoxins, deoxynivalenol, ochratoxins, zearalenone, and fumonisins; and they are produced by various fungal species like *Penicillium verrucosum, Aspergillus flavus, Aspergillus ochraceus, Aspergillus parasiticus, Aspergillus nomius* and *Fusarium spp.* (Vila-Donat et al. 2018). These fungal species infect barley, wheat, corn, peanut, cotton and many other commodities (Abdallah et al. 2017), and produced immunotoxicity, hepatotoxicity, nephrotoxicity and teratogenicity like complications in animals and humans (Amaike and Keller 2011). The fungal proliferation and mycotoxins production occur when there is high environmental temperature and moisture (Saleemi et al. 2020, Saleemi et al. 2017, Naseem et al. 2018). Other factors that contribute the risk of production are improper storage, transportation, poor harvesting and processing practices (Uegaki and Tsunoda 2018). Due to economic losses in respect of animal productivity, trade and human health, it attracts worldwide attention. Now the world is facing the food safety issue and regarding this problem, a number of studies have been conducted to solve this issue by addressing the consumers about food safety aspects (Martins et al. 2017). The United States Food and Drug Administration (USFDA) implemented a diagnostic laboratory in 1985, to check the contamination of feed with mycotoxins to ensure toxin free diet. Food and Agriculture Organization (FAO) and World Health Organization (WHO) also play an important role to prevent this contamination through awareness sessions to consumers. It is not possible to destroy the mycotoxins through cooking. The only way to get mycotoxin free products is through advanced techniques in food processing like Hazard Analysis of Critical Control Points (HACCP) and good manufacturing practices (GMP) (Maldonado-Siman et al. 2014). Whenever mycotoxins are produced in crops, they directly create negative impact on animal health and directly or indirectly produce serious health issues in humans. Mycotoxicosis occurs in humans through contaminated plant origin food and animal products (milk, cheese and meat) (Hanvi et al. 2019). This review demonstrates the negative effects of mycotoxins on animals and humans and identifies the impact of mycotoxins on environment. This review also highlights the current status of mycotoxins contamination in feed from a global perspective, regulation of mycotoxins in human food and animal feed, current methods for analysis of mycotoxins in food commodities, and mycotoxins control strategies.

1. Effects of Mycotoxins on Animals Health

There are different types of mycotoxins that produced various pathological and immunological effects on animal species.

1.1. *Aflatoxins*

Aflatoxins are poisonous substances produced by certain species of *Aspergillus* (*flavus, parasiticus, nomius, arachidicola, bombycis, pseudotamarii, minisclerotigenes, rambellii*), but they are mainly produced by *Aspergillus flavus and Aspergillus parasiticus* that are found all over the world, and pose serious health issues in animals (Haque et al. 2020). On the basis of fluorescence under ultra-violet light, aflatoxins are designated as B1, B2 (emits blue fluorescence) and G1, G2 (emits green fluorescence). Liver is the primary target in aflatoxin B1 (AFB1) susceptible animal species.

Cytochrome P450 (CYP) enzymes, which are expressed in liver, showed a strong correlation in metabolic activation of AFB1. This CYP convert aflatoxin to reactive 8,9-epoxide which is capable to bind DNA and protein. AFB1-DNA adducts induce transversion of G to T in tumor suppressor gene p53, which is associated with liver cancer (Zhao et al. 2020).

The early sign and symptoms in aflatoxicosis are pyrexia, anorexia, and malaise and as the disease progress, the animal is suffering from abdominal pain, vomiting and hepatomegaly. Acute aflatoxicosis is rare (Etzel 2014, AL-Ruwaili et al. 2018), but in chronic stage it has carcinogenic as well as immunosuppressive effects (Qian et al. 2014). AFB1 inhibits the expression of IL-4 that has anti-inflammatory activity and increases the release of IFN-γ and TNF-α from natural killer (NK) cells that accelerates inflammatory process. The immunosuppression activity of aflatoxin- B1 (AFB1) is because of decreasing the capacity of antigen presenting cells (APC) of dendritic cell (Mehrzad et al. 2014). AFB1 is more carcinogenic than others (Pukkasorn and Ratphitagsanti 2018). When animal is

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fed with AFB1 and AFB2 contaminated feed, these toxins are further metabolized through hydroxylation and excreted as M1 and M2 in the urine, feces, milk and lesser extent to meat (Bennett and Klich 2003).

Both animals and humans are prone to toxic and carcinogenic effect of aflatoxin. The acute toxicity leads to sudden death (Etzel 2014). In chronicity, there is immunosuppression, development of neoplasm and various other pathological conditions. AFB1 cause necrosis and degeneration of hepatic parenchyma in birds, fish, non-human primates and rodents. The severity of aflatoxicosis depends upon many factors like breed, specie, age, feed and health status of the animals (Cullen and Newberne1994).

1.1.1. *Poultry*: Broilers are more resistant to aflatoxicosis than other species of poultry birds (Arafa et al. 1981). AFB1 is called as silent killer because it is unavoidable contaminant and its prolonged contamination leads to adverse toxicopathological effects. Acute Aflatoxin toxicity lead to decreased feed intake, reduced feed conversion ratio, altered normal behavior, immunosuppression, hepatomegaly, nephritis, altered hematological parameters, and overall reduced performance (Saleemi et al. 2020, Saleemi et al. 2017) (Table 1). While chronic aflatoxicosis has been associated with increased blood urea nitrogen, decreased level of total protein, triglyceride in serum of broiler birds (Grenier and Applegate 2013). In 1960's researchers found that aflatoxicosis lead to fatty infiltration, proliferation of connective tissue and pinpoint hemorrhages in various organs of affected chickens (Newberne and Butler 1969). In 1984, Chen and his colleagues found that AFB1 and AFB2 residues present in all tissues of the affected birds. The highest concentration present in gizzard, liver and kidney. The presence of toxin residues in liver and kidney associated with their metabolism and detoxification activity.

1.1.2. *Cattle*: Aflatoxins have both acute and chronic toxicity in animals, and produce quite different effects: acute liver damage, liver cirrhosis, induction of tumors and teratogenicity and other genetic effects. Aflatoxicosis is primarily a hepatic disease (Bennet and Klich, 2003). Aflatoxicosis produces clinical signs in animals like gastrointestinal disturbances, negative effect on reproductivity, decreased milk production, immunosuppression, anemia, and liver diseases (Table 1). Nursing animals are more prone to aflatoxicosis due to the conversion of AFB1 to its metabolites AFM1 excreted by dairy animal in milk (Robens and Richard 1992). Many studies have been conducted about the carcinogenic effect of AFB1, AFM1 and AFG1 in different species. However, it is identified through experimental trial on different species that only AFB1 has carcigenocity property in different species of domestic and laboratory animals. AF also produced coagulation defects by impairing the function of factors VII, IX, X and prothrombin. Liver function test (LFT) reveled high level of bilirubin in serum, increased level of liver specific enzymes (SGPT, SGOT, SAP, LDH, and GGT). Urinalysis was also showed abnormal findings like hematuria, proteinuria, glycosuria and ketonuria (Hussein and Brasel 2001).

Aflatoxin has negative effect on feed consumption, rumen metabolism, production and immunity. The feeding of aflatoxin contaminated feed significantly reduced the growth rate (Choudhary et al. 1998). Lymphocytic blastogenesis and mitogen induced stimulation are suppressed by AFB1 (Bodine et al. 1984). In another study, AFB1 contamination of feed (200- 800 µg/kg) caused significant rumen hypomotility as the dose increases (Cook et al. 1986). Aflatoxins not only affect the milk yield but it also affects its quality. In another study, ten Holstein Friesian cows were given AFB1 through rumen cannula at the dose of 13 mg per animal per day, the milk yield was significantly decreased in a dose dependent manner and also the AFM1 level in milk was ranged from 1.05 to 10.58 ng/l (Veldman et al. 1992). In 1961, first case of aflatoxicosis was reported in calves, had been feeding with aflatoxin contaminated feed (groundnut) for six weeks. Gross lesions include proliferation of fibrous tissue in liver, biliary hyperplasia and vaso-occlusive disease. Another case has showed icterus, centrilobular necrosis and proliferation of connective tissue in hepatic parenchyma (Newberne and Butler 1969).

1.1.3. *Sheep*: Sheep are more resistant to mycotoxins (Miller and Wilson 1994). In a study, AF contaminated feed (2.5 mg/kg) leads to hepatotoxicity, nephritis, altered mineral metabolism and decrease plasma mineral concentration (Ramos et al. 1996) (Table 1). Another study with same dose causes increased concentration of fibrinogen (Fernández et al. 1997).

1.1.4. *Horses*: In horses, Asquith (1991) found that, AFB1 contaminated feed (58.4 µg/kg) revealed hepatomegaly, nephritis, hyperplasia of bile duct (Table 1). The major clinical signs of aflatoxicosis were depression, jaundice, lameness and death. In other cases, equine aflatoxicosis characterized as subcutaneous hemorrhage, enteric lesion, kidney damage, liver necrosis and myocardial lesions (Vesonder et al. 1991).

1.1.5. *Rats and mice*: In a case study of rats and mice, aflatoxicosis is associated with the hepatocellular carcinomas, pulmonary tumors, hepatic tumors formation (Gelderblom and Snyman 1991). Rats are extensively used as a model for human aflatoxicosis, regarding carcinogenic effects of AF (Table 1).

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1.1.6. *Dogs*: The mycotoxicosis is severe in pets and lead to death. In 1952, a case of hepatitis was reported in dog that was due to consumption of moldy feed. After aflatoxin discovery, it was found that hepatitis in dog was due to AFB1 that lead to death. Another study of aflatoxicosis in dogs was associated with anorexia, depression and weakness (Devegowda and Castaldo 2000).

1.2. *Ochratoxins*: *Aspergillus* and *Penicillium* genera of molds produced ochratoxin-A (OTA). *Aspergillus ochraceous*, *A. sclerotiorum*, *A. melleus*, *A. sulphureus*, *P. verrucossum* are the major species that produced OTA (Tao et al. 2018). Many food items like cereals, nuts, cocoa beans, cassava flour, peanuts, dried fruits, poultry eggs and milk are naturally contaminated by OTA (Weidenbörner 2001). It has been reported that in cocoa beans there is 50% and in the cocoa powder 22% OTA contamination was found in natural conditions (Tafuri et al. 2004). The toxicological effects of OTA are different in different poultry species. But it is nephrotoxic in all animal species and is most likely toxic to humans. OTA also considered as hepatotoxic, neurotoxic, immune suppressant, teratogen, and a carcinogen (Table 1). It is reported that OTA induces oxidative stress to human kidney-2 cells which regulated the translocation of transcription factors aryl hydrocarbon receptor (AhR) and pregnane X receptor (PXR). Activation of Ahr and PXR by OTA leads to immunosuppression, renal damage and cancer by regulating cytochrome enzymes (CYP1A1 and CYP1A2) (Zhao et al. 2020).

1.2.1. *Poultry*: First few outbreaks of ochratoxicosis have been reported in laying hens, broiler chicken and in turkey birds. In turkey, the clinical signs were decreased feed intake, poor FCR and increased mortality rate. Pathological lesions were nephritis and mild hepatitis. In broilers, reduction in growth rate, poor FCR, nephrotoxicity and air-sacculitis were observed (Table 1). In laying hens, decreased egg production along with nephritis (Hamilton et al. 1982). The necropsy findings in case ochratoxicosis were inflamed and pale-yellow kidneys, liver become yellowish and friable. The microscopic lesions include vacuolar degeneration and megaleucocytosis of liver cells, biliary epithelium hyperplasia and hypertrophy of proximal convoluted tubular epithelial cells of kidney (Santin et al. 2002).

Kumar et al. (2004) reported that OTA is more nephrotoxic than hepatotoxic for broilers. OTA also infect other body organs associated with atrophy of the spleen, thymus and bursa along with lymphocytic depletion. It was also reported the negative effects of OTA on bird's performance, hematological, biochemical and immune system in laying hens. The immunosuppressive effect of OTA in poultry birds include, reduction in the weight of immunological organs (bursa and spleen), decreased number of antibodies (IgA, IgG and IgM) bearing immune cells and response to phytohemagglutinin (PHAP) is also reduced (Hassan et al. 2012). OTA decreases the hematological parameters (RBCs count, WBCs count, PCV, HB) and also lead to the development of anemia in in White Leghorn Cockerels. OTA decreases the serum total proteins but increases the serum alanine transferase enzyme, urea and creatinine (Ahmad et al. 2012). The toxico-pathological effects of OTA includes, development of neoplasm in liver and kidney, hepatomegaly, nephrotoxicity, degenerative changes in liver and kidney, brain becomes edematous, bone marrow has fatty changes, hemorrhages in muscles, depletion of lymphoid organs in Plymouth chicks. Clinically, body weight, FCR is decreased and the relative weight of both liver and kidney is significantly higher due to OTA. High proteinuria due to OTA toxicity also indicate severe glomerulonephritis. OTA also increased the susceptibility of birds to other diseases due to its immunosuppressive effect and produced severe clinico-patholgical effects along with *Eimeria tenella* infection, fowl typhoid, *Salmonella gallinarum* and *E. coli* infection (Gupta et al. 2008).

1.2.2. *Cattle*: There was no serious health issue of OTA in the cattle fed with naturally contaminated feed of OTA. In a study, barley contamination with OTA (390–540 µg/kg) and AFB1 (12–13 µg/kg) did not cause significant toxic-pathological effect in calves (12 weeks old) (Patterson et al. 1981). Cattle can degrade OTA up to 12 mg/kg body weight (Hult et al. 1980). Oral administration of 11-25 mg OTA/kg body weight causes death of the calves. The lethal dose of OTA is more than 13 mg/kg of body weight for cattle through oral route (Ribelin et al. 1978). In dairy cattle OTA contaminated feed (48µg/kg) cause feed refusal, decreased milk production and retained fetal membrane but in beef cattle no signs and symptoms were observed. However, when cattle are in either dry period or near to parturition are more susceptible to OTA (Fink-Gremmels 2008).

1.2.3. *Sheep and Goats:* Ochratoxicosis has been rarely occurred in small ruminant species (sheep and goats). But if there is prolong ingestion of OTA contaminated diet, then it produces adverse health effects (Xiao et al. 1991).

1.2.4. *Dogs and cats:* In dogs and cats, OTA primarily affects kidneys. OTA at the dose of 0.2 -3 mg/kg produces clinical signs like vomiting, anorexia, increase thirst, polyuria, ataxia and death. Pathological lesions include tubular epithelial degeneration, hemorrhagic enteritis of large intestine and necrosis of lymphoid organs (thymus, spleen, lymph nodes and lymph nodes) (Zain 2011).

1.3. *Zearalenone*

Fusarium molds (*F. graminearum*, *F. culmorum*, *F. crookwellense*) affect wheat, oat, sorghum and barley and produced Zearalenone (ZEN). ZEN is mainly produced by *Fusarium graminearum*. It has estrogenic activity in farm

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animals (cattle and sheep). Because of its structural similarity to estradiol, zearalenone and its metabolites (α-zearalenol and β- zearalenol) bind to estrogen receptor and produce a variety of reproductive problems. (McCormick et al. 2011).

1.3.1. *Pigs:* In boars, ZEN associated with feminization, decreased libido, reduced serum testosterone level, decreased weight of the testes, and altered spermatogenesis (Diekman and Green 1992) (Table 1). In pigs, ZEN toxicity lead to vulvovaginitis, embryonic mortality, anestrus, decreased LH and P4 secretion, delayed post- weaning estrus, induced degeneration of germinal epithelium (Etienne and Dourmad 1994). Another study concluded that due to ZEN toxicity, reduced conception rate and litter size, enlargement of vulva, uterus and ovaries in piglets (Vanyi et al. 1994)

1.3.2. *Cattle*: In cattle, ZEN toxicity lead to decreased milk production, infertility, increased serum concentration of estrogen (D'mello et al. 1999) and decreased conception rate.

1.3.3. *Rats and mice*: In rats, reduced testosterone levels in serum and sperm counts were observed (Kaliamurthy et al. 1997), while in mice persistent estrous and sterility (Ito and Ohtsubo 1994), genotoxicity and hepatocellular carcinoma were found in ZEN toxicity (Pfohl-Leszkowicz et al. 1995).

1.4. *Trichothecenes*

There are two types of trichothecenes toxins, and they are produced by *Fusarium culmorum*, *F. graminearum*, *F. sporotrichioides and F. poae*. Diacetoxyscirpenol (DAS) and T-2 toxins have carbonyl group at 8th carbon position and they belong to group A trichothecene (Yan et al. 2020), while group B includes deoxynivalenol (DON), and nivalenol (NIV). DON and NIV have no carbonyl group at the same position. (Schwarzer et al. 2009). Type A trichothecenes have been found to be more toxic than type B members.

Early toxicological studies reported that trichothecenes prevent peptide bond formation of 60S ribosomal subunit resulting in inhibition of eukaryotic protein synthesis. Trichothecenes were later shown to inhibit mitochondrial protein synthesis and interact with protein sulfhydryl groups. The harmful effects of trichothecene were eventually due to production of oxidative stress due to generation of free radicals (McCormick et al. 2011).

1.4.1. *Poultry*: In broiler birds, DON contaminated feed causes increased relative weight of heart, muscular stomach (gizzard) and lymphoid organ (bursa) (Kubena et al. 1995). NIV contamination reduced feed intake and FCR in broiler. Gross lesions include decreased liver size and erosions in the gizzard (Prelusky 1997). T-2 and DAS adversely affect the poultry birds. A study showed that at the dose of 4-16 mg/kg, both T-2 and DAS toxins cause decrease in gain of body weight, reduced feed intake, formation of ulcers and plaques in the bucal cavity of 7-day old broiler chicks (Zain 2011).

1.4.2. *Cattle*: In cattle, DAS cause decreased feed intake, GIT lesions, reduced milk production and diarrhea (Galhardo et al. 1997) (Table 1). In cattle, T-2 toxin cause immunosuppression by reducing the lymphoproliferative response against phytohemagglutinin, neutrophil activity and lymphocytic blastogenesis. T-2 also has negative affect on IgA, IgG and IgM serum concentration (Mann et al. 1984). This T-2 toxin also causes infertility in bovine and necrosis of immune organs and abortion in last trimester (Placinta et al. 1999). At the dose of 10-50 mg/kg contamination of feed, sloughing of ruminal papilla and formation of abomasal ulcers was found (Gholampour Azizi et al. 2014). Other than T-2 toxin, no adverse effects of other trichothecenes (DON, DAS) have been found in cattle (Dicostanzo et al. 1996).

1.4.3. *Rats*: In rats, 5-25 µg/kg T-2 contamination of feed for extended periods (up to 16 week) results decreased feed intake, gastric ulcers and depression of thymus. It also disturbed the lipid metabolism by increasing the level of triglyceride, phosphatidyl choline, free cholesterol and total phospholipids (Kang et al. 2020). In rats, symptoms of acute T-2 toxicity caused lethargy, decreased body temperature, reduced feed intake, increased leukocytes, tachycardia, hypotension and death (Wannemacher Jr 1991).

1.4.4. *Dogs and Cats*: The level of DON toxin in the dog feed should be below than 0.5 mg/kg to avoid toxicological effect on animal health. Intravenous injection of T-2 toxin at the dose of 2 mg/kg in cats resulted in death due to hypovolemic shock and also cause leukopenia (Devegowda and Castaldo 2000).

1.5. *Fumonisins*

Fusarium verticillioides and *Fusarium proliferatum* are highly toxic because of their carcinogenic metabolites (Fumonisin B1 and Fumonisin B2) (Feijo et al. 2018). Fumonisin B1 is more toxic than Fumonisin B2 due to its neoplastic activity in rats and also causes equine leukoencephalomalacia (Onami et al. 2018). Fumonisin inhibit sphinganine-N-acetyl transferase enzyme, involved in sphingolipid metabolism resulting in increased sphinganine and sphingosine along with a decrease in sphingolipid complex, which is commonly accepted mechanism for fumonisins toxicity in most species

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(McCormick et al. 2011). It has been reported that fumonisins toxin affects different organs like gut, brain, liver and lungs in poultry, calves, pigs and horses.

1.5.1. *Poultry*: In chicken embryo it causes high mortality in birds, pathological lesions on liver and other internal organs, enlarged beaks and edema of the brain (Javed et al. 1993), hemorrhages in subcutaneous and in hepatic parenchyma (Zacharias et al. 1996). In broiler birds, dose-dependent clinical manifestations are decreased weight gain and increased mortality (Javed et al. 1993), while in layer birds it cause diarrhea (Prathapkumar et al. 1997).

1.5.2. *Horses*: In horses, equine leuko-encephalomalacia, anorexia, incoordination, lungs and brain become edematous (Fazekas and Bajmocy 1996), liquefactive necrosis of white matter, lesions in the cerebral cortex, hypersensitivity and death (Schumacher et al. 1995) (Table 1).

1.5.3. Sheep: In ovine, at the dose of (11.1–45.5 mg/kg of body weight), fumonisins produced inflammation of liver and kidney (Edrington et al. 1995).

1.5.4. *Cattle*: In bovine, Fusarium mycotoxins influence the reproductive functions of cattle by affecting granulosa cells proliferation and steroid production (Albonico et al. 2016) (Table 1).

2. Effects of Mycotoxins on Human Health

Mycotoxicosis occurs in humans due to consumption of fungal contaminated food and it can be acute or chronic depending upon the duration of disease (James et al. 2007). Prior to the discovery and implementation of modern milling practices, Fusarium species have been implicated in several human outbreaks of mycotoxicosis. In 1932-1947 Russian peoples were suffered in alimentary toxic-aleukia, characterized by hyperemia of mucus membrane, pain in esophagus, inflamed larynx, difficulty in respiration, GIT inflammation and ataxia. This was due to ingestion of *F. sporitrichoides* and *F. poae* contaminated cereal grains (Lewis et al. 2005).

2.1. *Aflatoxins*

Aflatoxicosis in human mainly affects the liver and cause hepatitis and jaundice leading to death. In Kenya, India and Malaysia repetitive cases of aflatoxicosis of same nature (hepatitis) were observed in different years (Shephard 2004). AFB1 has linked to liver cancer in association with hepatitis B virus and also known as human carcinogen (WHO and IARC 1993). There are many cases reported about AFB1 association with hepatocellular carcinoma synergistically with HBV infection (Shephard 2004). This is due to prolong exposure of low dose of AFB1. In china, about 250,000 people were died due to liver cancer and later on investigation revealed that the contributing factor of HBV infection was the ingestion of AFB1 (Wild et al. 1992). In developing countries, there are some conditions that favor the occurrence of acute aflatoxicosis in humans like inadequate food supply, lack of infrastructure for the aflatoxin control, and also environment conditions that support fungal growth (Zhang et al. 2020).

Aflatoxins residues have been found in Reye's syndrome affected children and were thought to be a contributing factor to this disease. Reye's syndrome, characterized by encephalopathy, deterioration and enlargement of visceral organs (liver and kidney), and edema of cerebral part of brain (Blunden et al. 1991).
A recent study reported a strong association between circulating AFB1-lysine adducts and gall bladder cancer (GBC) in humans. (Singh and Kapoor 2018) (Table 1).

2.2. *Ochratoxins*

Ochratoxin-A cause nephropathy and renal neoplasm in animals but less characterized health effects on human health. A study concluded that OTA contaminated feed associated with human diseases like chronic interstitial nephropathy (CIN), Balkan endemic nephropathy (BEN) and other renal anomalies, but the mechanism have not been completely studied (Bui-Klimke and Wu 2015) (Table 1).

2.3. *Fumonisins*

In India due to consumption of fumonisins contaminated sorghum and maize lead to food poisoning associated with abdominal pain, borborygmi and diarrhea. IARC classified the fumonisin B1 to Group 2B carcinogen in humans (IARC and WHO 2002). In some regions of North China and South Africa, fumonisins toxicity have also been implicated in reduced folic acid uptake and produced developmental defects of neural tube in rural people that consumed infected maize (Marasas et al. 2004) (Table 1). In China, fumonisins toxicity have also been linked to esophageal cancer due to ingestion of fumonisins contaminated feed (Rogowska et al. 2019).

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Table 1: Pathological Effects of mycotoxins on animals and humans

Mycotoxins	Fungus	Effected crops	Pathological effects in animals	Health effects in humans
Aflatoxins	*Aspergillus flavus, A. parasiticus A. nomius*	Cereal grains, peanuts, corn, cotton, soy	**Poultry**: Hepatomegaly, nephritis, immune-suppression genotoxicity, oncogenicity, and overall reduced performance (Saleemi et al. 2017, Bhatti et al. 2017, Hameed et al. 2017, Khan et al. 2017a, Naseem et al. 2018). **Cattle**: Hepatitis, gastrointestinal disturbances, negative effect on reproductivity, decreased milk production, immunosuppression and anemia (Robens and Richard 1992). **Sheep**: hepatotoxicity and nephritis (Ramos et al. 1996). **Horses**: Subcutaneous hemorrhage, enteric lesions, kidney damage, liver necrosis, nephritis, hyperplasia of bile duct and myocardial lesions (Vesonder et al. 1991). **Rats and mice**: Hepatocellular carcinomas and pulmonary tumors (Gelderblom and Snyman 1991). **Dogs**: Hepatitis, anorexia, depression and weakness (Devegowda and Castaldo 2000).	Hepatocellular carcinoma, Reye's syndrome Immunosuppression, GBC, retarded growth and development in Childs (Singh and Kapoor 2018, Turner et al. 2003, Shephard 2004, Jiang et al. 2005).
Ochratoxin A	*Aspergillus occhraceous, Penicillium verrucosum, Aspergillus clavatus*	Oat, wheat, corn, barely and others	**Poultry**: Nephritis, Hepatomegaly, genotoxicity and immunosuppression (Khatoon et al. 2017, Khan et al. 2017b). **Cattle**: Feed refusal, decreased milk production and retained fetal membrane (Fink-Gremmels 2008). **Dogs and cats**: Vomiting, anorexia, increase thirst, polyuria, ataxia and death. Lesions include nephritis, hemorrhagic enteritis of large intestine and necrosis of lymphoid organs (thymus, spleen, lymph nodes and lymph nodes) (Zain 2011).	Balkan endemic nephropathy (BEN), Chronic interstitial nephropathy (CIN) (Bui-Klimke and Wu 2015).
Trichothecenes	*Fusarium graminearum F.sporotrichioides F. culmorum F. acuminatum F. poae, F. roseum F. tricinctum*	Wheat, barley, oats, rice, corn	**Poultry**: Decrease in gain of body weight, reduced feed intake and FCR, formation of ulcers and plaques in the bucal cavity of 7-day old broiler chicks (Zain 2011) **Cattle**: Hematoxicity, feed refusal, gastrointestinal disturbances, immunosuppression (Galhardo et al. 1997, Prelusky 1997, Kang et al. 2020) **Rats**: Decreased feed intake, lethargy, decreased body temperature, gastric ulcers, depression of thymus, increased leukocytes, tachycardia, hypotension and death (Wannemacher Jr 1991). **Dogs and cats**: Death due to hypovolemic shock (Devegowda and Castaldo 2000).	Induce lipid peroxidation, decreases the levels of antioxidant enzymes, and ultimately lead to apoptosis (Qinghua et al. 2017).
Fumonisins B1, B2, B3	*Fusarium proliferatum F. moniliforme.*	Wheat, barley, oats, rice, corn	**Poultry**: Pathological lesions on liver and other internal organs, enlarged beaks and edema of the brain, haemorrhages in subcutaneous and in hepatic parenchyma (Zacharias et al. 1996, Javed et al. 1993). **Cattle**: Influence the reproductive functions of cattle by affecting granulosa cells proliferation and steroid production (Albonico et al. 2016). **Horses**: Equine leukoencephalomalacia, necrosis of brain, liquefactive necrosis of white matter, lesions in the cereberal cortex, hypersensitivity and death (Schumacher et al. 1995). **Sheep**: Inflammation of liver and kidney (Onami et al. 2018).	Esophageal tumors, abdominal pain, neural tube defects (Rogowska et al. 2019).
Zearalenone	*Fusarium graminearum, F. crookwellense F. culmorum,*	Wheat, barley, oats, rice, corn	**Pigs**: Hyperestroginisim, Feminization and decreased libido in male, while anestrus, vulvovaginitis, abortion and prolapse in female (Etienne and Dourmad 1994, Vanyi et al. 1994). **Cattle**: Decreased milk production, infertility, decreased conception rate (D'mello et al. 1999). **Rats and mice**: In rats, reduced testosterone levels in serum and sperm counts were observed, while in mice persistent estrous and sterility, genotoxicity and hepatocellular carcinoma (Ito and Ohtsubo 1994, Pfohl-Leszkowicz et al. 1995, Kaliamurthy et al. 1997).	Toxic to the development of gametogenesis and embryo in human and animals (Yang et al. 2018). Premature puberty in children, May cause infertility (Massart and Saggese 2010).

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2.4. *Trichothecenes and ZEN*

Trichothecenes also used as biological agent. In 1975-1981 T-2 toxin has been used as germ warfare in 'yellow rain' against the population of Democratic Republic (Peraica et al. 1999). Similar biological warfare agents such as DAS, nivalenol, DON and ZEN were found in affected areas of Combodia, isolated from aquatic source and leaves. (Peraica et al. 1999). Both Zearalenone (ZEN) and deoxynivalenol (DON) toxicity have been reported in USA, Australia and Japan resulting in gastrointestinal illness like nausea, vomition and diarrhea. Zearalenone has also been toxic to the development of gametogenesis and embryo in human and animals (Yang et al. 2018) (Table 1).

3. Role of Mycotoxins Contaminated Environment in One-Health Aspect

Air pollution has been receiving increased attention globally. One such pollutant is mold, not only in outdoor but also in indoor environment having excessive amount of moisture. Mycotoxicosis is multi-disciplinary issue involving environmentalist, medical and veterinary practitioners, agricultural engineer, plant pathologist, analytical chemist and agronomist. Mycotoxicosis arises in industrialized and developing countries when social, environmental and economic conditions coupled with meteorological conditions (temperature and humidity) which favor the growth of molds (Capcarova et al. 2016).

The occurrence of mycotoxins and contamination of agricultural products tend to vary year to year relies on environmental and handling conditions. Many studies describe the adverse effects of fungus-contaminated environment, especially fusarium on the respiratory and cutaneous systems. Ochratoxins (A, B, and C) and trichothecenes (T-2) are major class of mycotoxins, found in food and water damaged buildings, and has been known to cause serious health issues in humans (Hope and Hope 2012). It has been reported that trichothecenes can be released at ~300-fold the concentration of spores, that commonly detected in the air of contaminated buildings and caused multisystemic effects in exposed persons (Ratnaseelan et al. 2018).

Climate change has significant effects on food security such as infection of toxigenic fungi and contamination with mycotoxins. Acclimatization of mycotoxigenic fungi and production of mycotoxins, especially AFB1 appears to be unaffected by climate change, leads to continuous contamination of animal feed and human food, resulting serious health issues in animals and human (Medina et al. 2017).

4. Current Status of Mycotoxins Contamination in Feed from a Global Perspective

Mycotoxins contamination in animal feed is a serious concern because of their adverse effects not only in animals but also in human due to usage of animal products (Hussein and Brasel 2001). Therefore, monitoring of mycotoxins contamination in feed is a prerequisite to overcome this problem globally (Kabak et al. 2006). Recently, a study was conducted to determine mycotoxins contamination in feed on a large scale by collecting samples from 100 countries. 74,821 samples of wheat, Barley, maize and soybean were analyzed from 2008 to 2017. Prevalence of mycotoxins in these samples was; DON (64%), fumonisin (60%), ZEN (45%), AFB1 (23%), T-2 (19%) and OTA (15%). Meanwhile, co-contamination of DON, ZEN and fumonisins as well as AFB1 and fumonisins were found in a large fraction of samples (64%). However, as a notable exception, maximum level of AFB1 (20 µg/kg) were detected in 41.1%, 38.5% and 20% samples collected from South Asia, Sub-Saharan Africa and Southeast Asia, respectively (Gruber-Dorninger et al. 2019).

Each feed showed a distinct pattern of mycotoxin occurrence. Maize mainly contaminated with fumonisins and often contained ZEN, DON and AFB1. Barley and wheat showed high prevalence of DON and frequently contained T-2 and ZEN. Soyabean was highly contaminated ZEN, DON, T-2 and AFB1 (Gruber-Dorninger et al. 2019). These results revealed strong association of certain fungal pathogens with these crops (Blacutt et al. 2018, Miller 2008).

5. Regulation of Mycotoxins in Human Food and Animal Feed

Many countries are well aware of the importance of mycotoxins and have developed regulations governing acceptable concentration of mycotoxins in human food and animal feed, guided by food regulating bodies such as the Food and Agriculture Organization (FAO), World Health Organization (WHO) and European Union (EU). The acceptable limits of certain mycotoxins in different food and feed are discussed in Table 2.

6. Current Methods for Analysis of Mycotoxins in Food

There are many techniques have been developed for analysis of mycotoxins in animal feed and food to ensure food security and related health issue in animals and human. Among these techniques, the most common methods currently used are described below.

6.1. *Chromatographic Techniques*

Chromatographic techniques are highly selective and accurate for quantitative analysis of mycotoxins in contaminated feed. High-performance liquid chromatography (HPLC), Gas chromatography (GC), liquid

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chromatography-tandem mass spectrometry (LC-MS/MS) and Thin-layer chromatography (TLC) are widely used chromatographic techniques for mycotoxins quantification (Alshannaq and Yu 2017). Among them, HPLC is most

Table 2: Acceptable level of mycotoxins in various commodities

Mycotoxins	Acceptable level in different products	References
Aflatoxins	• Animal feed 0-50 ppb (average 20 ppb) • Cereals, peanuts, and dried fruits 2 ppb for AFB1 and 4 ppb for AF B1+B2+G1+G2	FAO (2004) Bhat et al. (2010)
Aflatoxin M1	• Milk 0.05 ppb	European Commission (2006) Ismail et al. (2016)
Ochratoxin A	• Poultry feed 100 ppb • Cereal and cereal products 250 ppb	European Commission (2006)
Fumonisins	• Maize and maize product 60 ppm • Feed stuff for equids 5 ppm • Breeding ruminants, breeding poultry 30-50 ppm • Feed stuff for poultry, calves, lambs, kids 20 ppm • Human food 2-4 ppm	US Food and Drug Administration (2001) European Commission (2006) Azizi and Rouhi (2013)
Zearalenone	• Cereal products 2000 ppb • Maize by-products 3000 ppb • Feed for sheep, goats, calves, dairy cattle 500 ppb • Human food 250 ppb	Wu et al. (2016)
Deoxynivalenol	• Cereals and cereal products 8000 ppb • Feed stuffs for calves, lambs and kids 2000 ppb	European Commission (2006)

commonly used to detect AF, OTA, fumonisins, DON, ZEN in contaminated feed. LC-MS/MS has been used to detect multiple toxins simultaneously in different commodities. TLC is simple, economical and rapid screening chromatography technique to determine mycotoxins contamination, but it is not commonly used due to lack of automation. GC only used for volatile mycotoxins (trichothecenes and patulin) detection, also limits its commercial use (Roseanu et al. 2010).

6.2. *Enzyme linked immuno-sorbent assay (ELISA)*

ELISA is an important immunological detection method for the detection of mycotoxins. ELISA test is based on the detection of specific mycotoxin structure through specific antibody. Different types of ELISA kits are used for toxins determination such as direct, indirect and competitive ELISA. The most commonly used ELISA for mycotoxin analysis is direct and competitive ELISA. This requires microtitration plate for the reaction of Ag and Ab with an incubation period of 1-2 hours. At present, kinetic phase Ab-Ag binding-based ELISA kits are also available having incubation period in minutes (Zheng et al. 2006).

6.3. *Lateral Flow Immunoassay (LFIA)*

LFIA is rapid, cost effective, one step qualitative detection test of a specific mycotoxin, based on the principle of ELISA. A multiplex LFIA has ability to provide both qualitative and quantitative analysis of AFB1, OTA and ZEN in contaminated grains (Haque et al. 2020).

6.4. *Fluorescence polarization immunoassay (FP)*

FP is a competitive homogenous assay that rapidly determines mycotoxins contamination without separation and washing requirements. The detection of mycotoxins based on the rate of fluorophore in the solution. If a sample has highly contaminated, then added antibodies bind to toxin molecules and less toxin molecules are available for fluorophore binding. As a result, tumbling motion of free-floating fluorophore increased, leading to more polarization. FP kits are available for detection of aflatoxins, DON, ZEN and fumonisins (Zhang et al. 2017).

6.5. *Biosensor methods*

Biosensor methods have been used as quantitative technology to determine mycotoxins contamination in food samples. They are highly sensitive, robust, cost effective, portable, high-throughput technology that allows rapid and real-time detection of mycotoxins in contaminated feed stuff (Haque et al. 2020). Biosensor technology based on the immobilization of antibodies on various nanomaterials like graphite, carbon nanotubes, nanoparticles and quantum dots. These nanomaterials are coupled with biomolecules such as enzymes, antibodies, bio or artificial receptors, nucleic acids, DNA/RNA aptamers for detection of food mycotoxins (Rovina et al. 2019).

7. Control Measures

Various methods are adopted to control the development of pathogenic fungus and production of mycotoxins in feed.

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7.1. *Biological control*

Bacteria, yeasts and a-toxigenic fungi have been evaluated as potential biocontrol agents of mycotoxigenic fungi and their toxins (Bacon et al. 2001). Microorganisms like lactic acid bacteria namely, bifidobacteria, lactobacillus and propionibacteria are used to control the mycotoxins in contaminated feed and animal body through their excellent binding capacity to AFB1. These lactic acid bacteria also prevent growth of molds in food products by producing hydrolytic enzymes such as maltase, saccharase and β-galactosidases that decompose carbohydrates in addition to increasing host's enzyme activity (Yiannikouris and Jouany 2002). *Nocardia corynebacteroides* showed a promising degradation of aflatoxins B, G and M1 in various food products, without showing any toxic by-products (Tejada-Castañeda et al. 2008). Recently, it has been reported that *Bacillus licheniformis* CRF1 and *Pseudomonas aeruginosa* showed degradation of aflatoxins, while *P.putida* DSM 29T and KT2442 were able to degrade OTA (Haque et al. 2020). In another report, *Bacillus subtilis* ANSB01G was useful to reduce ZEN in naturally contaminated agricultural commodities (lei et al. 2014). In case of trichothecenes, microbial degradation has been elucidated by different pathways like de-epioxidation, glucosylation, oxygenation and epimerization. A commercial product has been developed having *Eubacterium* sp. Strain BBSH 797 to detoxify trichothecenes in animal feed (Čolović et al. 2019). A Gram-positive bacterium *Eggerthella* has been isolated from chicken intestines, capable of detoxifying trichothecenes (T-2, DON) with high de-epoxidation efficiency (Gao et al. 2018). Certain bacteria deoxify mycotoxin in contaminated feed to non- toxic metabolites using specific enzymes. This approach has been capitalized by *Corynebacterium rubrum* to metabolize mycotoxin in contaminated feed (Nakazato et al. 1990).

Biologically we can also control mycotoxins by harvesting non-pathogenic mold that can compete in development with toxigenic strains of mold under field conditions. This will reduce the growth of mycotoxin fungi (Cleveland et al. 2003). *In vitro* studies about aflatoxins degradation have been investigated in numerous cases. It has been reported that aflatoxin contamination was controlled up to 95.9% by growing the a-toxigenic species of *A. parasiticus* and *A. flavus* (Zain 2011). Certain fungi and yeast have been shown the ability to degrade different mycotoxins. The cell wall of *Saccharomyces cerevisiae* is a good source of glucomannans (mycotoxin binders) and its dose about 500 g is enough to reduce 58% of AFM1 content in the milk of dairy cow that have been fed with 0.05% AFB1 on dry matter basis (Withlow and Hagler Jr 1999). Similarly, Fusarium has also been controlled by harvesting competitive a-toxigenic fungi (Fouad and Ruan 2019). It was observed that the black yeast, *Exophiala spinifera* has capability to degrade fumonisin B1 through deamination of its toxic amines (Čolović et al. 2019).

It has been reported that, it is possible to inhibit the *in vitro* production of OTA by yeasts through competitive exclusion using different species of yeasts (*Hanseniaspora uvarum*, *Pichia kluyveri* and *Pichia anomala*). *Trichoderma* also control the growth and development of toxigenic fungi through different mechanism like fungistasis, rhizosphere modification, competition for space and nutrients, antibiosis, mycoparasitism, and the stimulation of plant-defense mechanisms (Benítez et al. 2004). Moreover, a feeding trial was tested using a new strain to degrade OTA, called *Trichosporon mycotoxinivorants.* Dietary inclusion of this yeast ameliorates the OTA induced immunosuppression in broiler chicks (Čolović et al. 2019). *In vitro* study revealed that *T. mycotoxinivorants* is a principal transformation product of ZEN. Due to biotransformation of ZEN in its metabolites, estrogen activity of ZEN was diminished and ultimately no interaction of ZEN was observed with human estrogen receptor (Vekiru et al. 2010).

7.2. *Physical methods*

Thermal degradation and inactivation by radiation have been applied for mycotoxins decontamination. Mycotoxins are generally heat resistant under conventional cooking temperature (80-121 °C). Mycotoxins degradations by heat treatment depends on many factors including type and concentration of mycotoxins, pH and moisture level in the feed, binding strength between mycotoxins and feed constituents, heating temperature, degree of heat penetration and processing time. Different approaches of thermal degradation were used to reduce the mycotoxins level in food commodities. Crumbling, pelleting and extrusion are commonly used processes for feed preparation. Although these processes significantly reduce toxins level but does not lead to complete removal of mycotoxins (Čolović et al. 2019). Kabak studied the outcomes of different extrusion parameters on mycotoxins reduction. He concluded that application of extrusion with high temperature (>150 °C) significantly reduces ZEN and fumonisins, while moderate reduction of aflatoxins and DON (Kabak 2009). Extrusion in combination with glucose at 160 °C or higher, leads to significant reduction of fumonisisns. For example, greatest degree of Fumonisin B1 reduction (75-85%) was observed when corn grits undergo extrusion process with 10% added glucose. This applied extrusion resulted in the formation of fewer toxic metabolites (Čolović et al. 2019).

Ionizing radiation has also been used to detoxify mycotoxins in storage condition. Usually X-rays and γ-rays have been extensively investigated for mycotoxins degradations. The inactivation of mycotoxins through irradiation depends on radiation dose, and type of agricultural products and toxins. It has been reported that γ-rays degrade AFB1 up to 100% in peanut meal at the dose of 10 kg by forming free radicals. Aflatoxins are also sensitive to UV-

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radiations. This has been proven that UV-radiation at 365 nm for 20 min degrading 56.2% AFM1 from aflatoxin-contaminated milk, while 30 min UV-treatment leads to 45.7% degradation of AFB1 from dried figs (Shantha and Sreenivasa Murthy 1977, Altug et al. 1990).

The other physical methods are cleaning, manual sorting, washing, winnowing, crushing and dehulling of cereal grains are helpful to reduce the mycotoxins (aflatoxins and fumonisins) level significantly (Fandohan et al. 2005). In cleaning process, dust, hair, husks and shallow particles are separated from contaminated grain. During sorting, clean product is separated from contaminated cereals, while washing with sodium carbonate solution can reduce the level of mycotoxins from contaminated grains. Mycotoxins contamination also reduced through sanitation measures like destruction or removal of residue of previously harvested crop (Hell et al. 2000). Proper drying and storage are the critical features that will significantly reduce the proliferation of fungus and production of toxins. If there is proper drying and moisture level reduces to 12- 15% then there is no growth of fungus. It was reported that if the level of moisture content in groundnuts is about 6% then it can be stored for 6 months without adding toxin binder (Awuah and Ellis 2002).

7.3. *Chemical methods*

Different types of chemicals are available like hydrogen peroxide, ozone, caustic soda, ammonia, bisulphites, formaldehyde and chlorinated agents. They have the ability to degrade mycotoxins present in the feed. But these techniques are expensive, less efficient and many of them produce adverse effect on animal and humans health (Scott 1998). Amphotericin B and itraconazole are fungicidal especially used against *A. flavus* and *A. parasiticus* that produce aflatoxins (Ni and Streett 2005). Prochloraz, azoxystrobin, cyproconazole, propiconazole, tebuconazole and epoxyconazole are used to reduce fumonisins contamination (Haidukowski et al. 2005).

Electrochemically produced ozone has been shown protection against AFB1 by chemically oxidizing different functional groups of AFB1 in contaminated corn. Similarly, it has also proved deactivating agent against OTA contaminated cereal. Hydrogen peroxide also reported to degrade ZEN in contaminated grains up to 84% through oxidation process (Čolović et al. 2019). In many countries, ammonia gas treatment (ammoniation) has been used to detoxify aflatoxins and ochratoxins. Ammoniation efficacy varies on certain type of mycotoxins. Application of ammonium hydroxide (caustic soda) in lab animals against fumonisins did not produce any promising results in lowering toxicity. In developed countries, ammoniation has been successfully used to detoxify AFB1 contaminated maize by transformation of AFB1 to aflatoxin D1, which is far less toxic. Nevertheless, this method effect food quality due to presence excessive ammonia level in the food (Agriopoulou et al. 2020). Reducing agent such as sodium bisulfite has ability to destruct AFB1 and trichothecenes by forming sulphonate derivatives. Besides AFB1 and trichothecenes, bisulfite decreased the level of DON by converting into deoxynivalenol-sulfonate and overcome the depressive impacts of DON in certain animal species (Hathout and Aly 2014).

The use of feed additives has been used in contaminated diet to minimize the adverse effects of mycotoxins on the animal such as *Saccharomyces cerevisiae yeast.* Bentonite clay also used to absorb mycotoxins and remove them from gastrointestinal tract. Silymarin (bioactive extract of *Silybum marianum*) has used to ameliorate the pathological effects of mycotoxins by acting as antioxidant and stimulant for liver regeneration (Saleemi et al. 2020).

Conclusion: Mycotoxicosis is a global issue regarding food safety. FAO and WHO expert committee analyzed the risk assessment of mycotoxins toxicity and declared that it is the big issue in developing countries as they may cause severe and irrevocable health issues in animals and humans. Meanwhile, we cannot exclude the impact of environmental and biological factors on occurrence and predominance of mycotoxigenic fungi in stored agricultural commodities. It is known that once there is contamination of feed or food, almost nothing can be done to remove mycotoxins. The basic and efficient measure in the reduction of fungal contamination at storage facilities of susceptible crops is to control environment by manipulation of ecological factors. This will minimize the entrance of fungal-derived mycotoxins in feed and food chain and ultimately curtail their adverse effects on animal and human health. We can tackle the inadequacies of this global one-health issue by involving multi-discipline professionals and concerned authorities to play their vital role in assessment and mitigation of risk factors, identification of research gaps, promotion of basic and applied research, public awareness and capacity buildings.

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