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REVIEW ARTICLE **OPEN ACCESS**

Emerging fusarium mycotoxins and their toxicological effects on mammals

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ABSTRACT

Mycotoxins are secondary metabolites produced by fungi that have harmful effects on humans, animals and crops, resulting in sickness and financial losses. Mycotoxins are produced by fusarium fungi in a wide range of species. Fusarium is especially common in areas where cereals are grown and thus, any substantial amount of mycotoxins in major dietary sources, animal feed, can be carried over in the food chain and cause serious health problems in humans or livestock. Commonly produced fusaria toxins are zearalenone, fumonisins, moniliformins, trichothecenes, deoxynivalenol and fusaric acid. Adaptation and accumulation to mycotoxins in higher trophic levels in mammals and other animals elicit complication for survival for the species. These pharmacologically active fungal metabolites usually enter the body by consuming contaminated food that causes metabolic trepidation. This review summarizes the information regarding the toxicological effects of fusaria toxins. These mycotoxins cause acute and chronic illness with carcinogenic, hepatotoxic, teratogenic and immunosuppressive effects in humans. Besides adverse effects on humans and animals these toxins are harmful to crops. Mycotoxins are highly stable compounds and therefore, there is an urgent need to develop natural biocontrol and rapid screening strategies to minimize the harmful effect of the fungi.

Keywords: *Mycotoxins, fusarium, toxicogenic properties, mammals*

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INTRODUCTION

Among prokaryotic and eukaryotic species that nature produces, fungi play a very important and unexplored role. Fungi are the members of subkingdom Thallophyta which lack chlorophyll and have well-defined nuclei [1]. In some species, they have an assimilative body that might be amoeboid or unicellular and also they lack vascular tissues. They are made up of multicellular branching filaments called hyphae that reproduce asexually *via* spores [2]. Fungi being heterotrophs and widespread occurrence make them a challenge and a risk for human life. Fungi digest and generate a wide array of simple to very intricate organic compounds during their lifespan. The precise characteristic of fungi is to produce toxins apart from displaying certain biological activities. Mycotoxins are of relatively low-molecular-weight and non-volatile affecting vertebrates in various ways. All the fungi may be categorized by temperature, Mesophiles (e.g., *Penicillium chrysogenum*, *P. expansum*, *P. cyclopium, Aspergillus Versicolor, A. flavus, A. nidulans, A. fumigatus),* Thermophiles (e.g., *Byssochlamys*, *Aspergillusfumigatus*), Thermotolerants (e.g., *Aspergillus niger*) *and Cryophiles (e.g., Cladosporium, Alternaria)* or by the humidity, Hygrophiles (e.g., *Cladosporium*, *Fusarium*, *Mucorales*) and Xerophiles (e.g., *Aspergillus restrictus*, *A. glaucus*, *A.* Versicolor) [3].

Mycotoxins, which are mostly acquired by *Aspergillus, Penicillium, Fusarium, Alternaria* and *Claviceps* produce a variety of chemical substances resulting from the secondary metabolism of these moulds [4]. Aspergillus produces aflatoxin B1, resulting in food contamination, thereby deteriorating human health and causing liver cancer [5]. The different strains of mycotoxins have convincingly changed over the years and are dependent on various factors such as storage and environmental circumstances and crop type [6]. Different mycotoxins remain stable throughout normal food processing and can be found in food products and other processed commodities [7]. The financial disaster and deteriorating stamina issues in humans and other animals due to mycotoxin contamination are mammoth. For that reason, a rapid screening approach will form a significant device for the safeguard of humans and animals and early detection economical loss will be minimized. Mycotoxicosis resulting from contaminated food will jeopardize the aforesaid prevalence if no preventative measures are taken. Fusarium species are the most important toxigenic fungus ubiquitous in cereals and various products for human and animal use,

resulting in a significant economic setback i n agriculture [8]. Fusariums are believed to be field fungi but few species can develop in stored grain mainly under low temperature and moisture [7]. The toxigenic rate of various species of fusarium have been elucidated and of these, 35 have been characterized to raise mycotoxins, of which zearalenone, trichothecenes, moniliformin and fumonisins were abundantly found [6]. Fusaric acid and deoxynivalenol are the other influential fusarium mycotoxins which also prove their toxigenic effects (Table 1). Fusarium mycotoxins have been found globally, although there are regional divergences in their relative importance, for example; the toxigenic rate of fumonisins is higher in the southern hemisphere than in the northern and similarly, the toxicity of type B trichothecenes is more noteworthy in North America and Europe than type A trichothecenes [9].

Table 1: Malfunctioning caused by different toxins produced by fusarium

Toxin	Fungal genus	Disorder	Source	Model	Reference
Trichothecenes	Fusarium	Protein synthesis inhibitor	Cereal grains	Eukaryotes	[10]
Fumonisins	Fusarium	Leukoencephalomalacia	Maize	Horse	[11]
Zearalanone	Fusarium	Vulvo-vaginitis	Maize, Sorghum	Pig	[12]
Moniliformin	Fusarium	Keshan disease	Corn, Wheat Kernels	Human	[13]
Deoxynivalenol	Fusarium	Feed refusal	Oats, Barley	Pig, Mice, Rat	[14]
Fusaric acid	Fusarium	Subacute ruminal acidosis (SARA)	Grains	Cow	[15]

TOXICOLOGICALLY IMPORTANT FUSARIUM MYCOTOXINS

Trichothecenes are the most common and well-known group of fusarium mycotoxins. These mycotoxins are classified as 12,13-epoxy-trichothecenes because they are tricyclic sesquiterpenes with a double bond at C-9, 10 and an epoxy ring at C-12, 13 (Figure 1). Regurgitation and feed refusal are the hallmark symptoms of trichothecene intake. The common symptoms of trichothecenes are bruise of the mucous membrane in the gastrointestinal tract leading to protracted haemorrhage and toxicity related to haematology [9]. The larger ribosomal subunit (60S) is required for protein synthesis because it catalyses the creation of peptide bonds and trichothecenes block this vital process (protein synthesis) by attaching to the peptidyl transferase [10]. In vitro and in vivo studies have shown that these mycotoxins cause programmed cell death in various organs [16]. Trichothecenes also impede DNA and RNA synthesis and this inhibition has only been mentioned at concentrations comparable to or greater than those required to suppress protein synthesis [17]. However, minor amounts of trichothecene toxicants are seen 24 hours after oral or intravenous exposure and are knocked out promptly without any aggregation in any tissues. After intravenous injection, the predominant secretion route in pigs is urine. However, a significant fraction of toxin is eliminated in the faeces after oral exposure [18]. Interconversion of acetylation and de-acetylation reactions is an important phenomenon while experiencing the diverse metabolic reactions of trichothecenes leading to hydrolysis of side-chain groups, for example, conversion of acetylated toxin fusarenon-X, 3-acetyl DON, T-2 toxin to the de-acetylated form NIV, DON, HT-2 respectively.

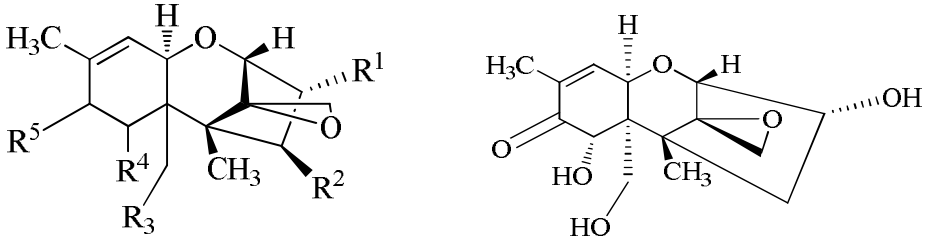

Figure 1. Structure of Trichothecene and Deoxynivalenol (DON)

Fumonisins are a prominent group of toxins since they cause a variety of ailments in humans and domestic animals [11, 19]. Fungi like *Fusarium verticillioides*, *Fusarium proliferatum* and some related species produce a significant group of mycotoxins, Fumonisins (B1 and B2) (Figure 2) [20]. An elevated level of the presence of fumonisins, along with moniliformin in animal feed, has vital health entailments and the known changes encompass equine leukoencephalomalacia in horses commonly known as moldy corn poisoning, porcine pulmonary oedema (PPE) in pigs, immunodepressive consequences in turkey and decrease of vitamin A in chicks resulting in cyanosis, death and hydrothorax in pigs [11, 21]. In various countries, human oesophageal cancer has been correlated to fumonisin B1 and fumonisins promote hepatocarcinogenesis in rat hepatocytes because they impede protein synthesis, ceramide synthetase and chromosomal aberration [22, 23]. Fumonisin's toxicity inhibits the enzyme synthase, which is required

for the acylation of different fatty acids. The resulting increase of fatty acids in the plasma, serum or urine inturn can be used as a biomarker for calculating the toxigenic rate of fumonisins in animals after dietary exposure [24].

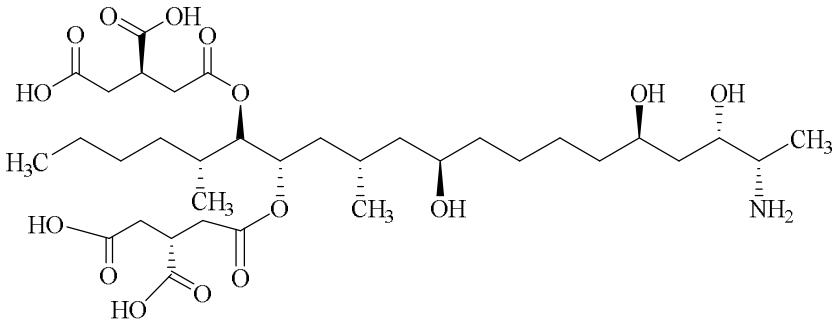

Figure 2. Structure of Fumonisin (FB1)

Zearalenone (ZEN) is a mycotoxin generated by a variety of fusaria species, including *F. graminearum*, *F. culmorum*, *F. equiseti*, and *F. poae* that has a high affinity for estrogen receptors (Figure 3) [25]. The concentration of ZEN more than 20 ng/g in feed causes vaginal prolapse, sterility, vulval oedema, overgrowth of mammary glands in females, and the development of female characters in males [26]. When the concentration of ZEN in a porcine's food exceeds 50 ng/g, it produces pseudopregnancy, which leads to infertility [27]. Although ZEN's LD50 value of 210 g/kg b.w. indicates that it has low relative toxicity and has emerged as a disrupter of the mammalian endocrine system, with evidence of genotoxicity in mice [28]. ZEN may affect the uterus by altering the structure of uterine tissues, resulting in a decrease in LH and progesterone [29]. ZEN may also reduce serum testosterone, testicular weight and spermatogenesis in male pigs, producing female characteristics and decreasing sexual drive. ZEN is also linked to infertility, hyperestrogenism and decreased milk production in cows, with conception rates dropping from 87 to 62 percent [30].

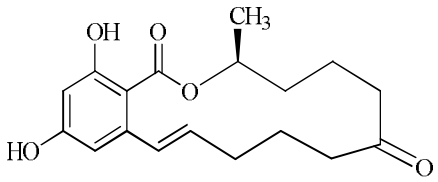

Figure 3. Structure of Zearalanone (ZON)

A variety of fusarium species produce moniliformin (MON) [1-hydroxycyclobut-1-ene-3, 4-dione] (Figure 4). Keshan disease, which is more or less regarded as cardiomyopathy, is most prevalent in China due to MON [31]. Due to moniliformin, the most prominent symptoms depicted in domestic fowls are increased muscular weakness, respiratory problems, unconsciousness and ultimately death [32]. Broilers, turkeys and ducklings have shown high mortality and other pathological problems such as hydropericardium and myocardial paleness [33]. Moniliformin inhibited the pyruvate dehydrogenase complex, gluconeogenesis and chromosomal abnormalities in chicken and rat hepatocytes [34]. By interrupting pyruvate incorporation into the tricarboxylic acid cycle, MON also inhibits oxidation of the TCA intermediate α-ketoglutarate and pyruvate dehydrogenase [32]. MON suppresses transketolase and aldose reductase by arbitrating with carbohydrate metabolism and increasing oxidative damage in myoblasts and it also inhibits glutathione peroxidase and glutathione reductase [35, 36]. Likewise, MON contaminated feed may have some immunosuppressive effects by diluting the feasibility of blood lymphocytes of broiler chickens [37]. Muscular dystrophy, myocardial infarction, pulmonary trauma and some histological alterations in various organs such as the kidneys, lungs and pancreas are the most common signs of acute moniliformin toxicity, followed by unconsciousness and death [38].

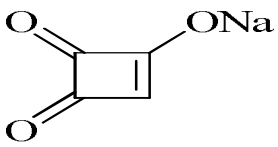

Figure 4. Structure of Moniliformin

Fusaric acid (FA), also known as 5-butyl picolinic acid, is a well-known mycotoxin generated by numerous fusarium species (e.g. *Fusarium oxysporum*). By promoting the wilting process, fusaric acid plays an important role in plant pathogenicity [39]. FA has a pyridine ring and a butyl side chain, allowing it to easily penetrate cell membranes (Figure 5) [40]. The inclusion of nitrogen and oxygen in the pyridine ring and carboxylic acid group, respectively, may boost FA's toxicological effects when chelating with specific ions such as zinc, magnesium, calcium and iron [41]. While gaining resistance against intruding microorganisms and retaliation to extraneous infective agents, numerous signalling pathways are triggered off in the cells of the immune system, which shows a defense mechanism against various environmental exposures such as bacteria, parasites, fungi, viruses and other malfunctions [42]. Primarily there is commencement of mitogen-activated protein kinase (MAPK) activity which guides numerous immune responses varying from trauma and cell death/survival [43]. Distortion in mitochondrial membrane potential and inhibition of ATP synthesis in plants due to FA is well recognized [44]. Fusaric acid also inhibits protein synthesis, nucleic acid synthesis and dopamine-hydroxylase action [45]. In zebrafish and rats, FA induces teratogenic effects by the impediment of lysyl oxidase (a copper-dependent enzyme) and decreased level of nor-adrenaline in various organs like brain, heart, spleen and adrenal gland [46].

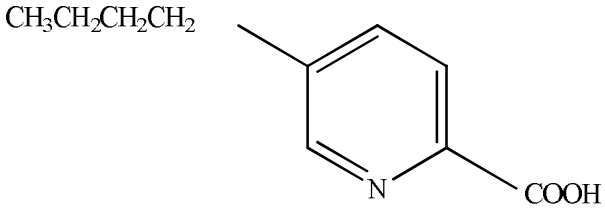

Figure 5. Structure of Fusaric acid

METABOLIC IMPORTANCE OF FUSARIUM MYCOTOXINS

There are signs of adverse effects in animals due to the metabolism of mycotoxins. The microbial conversion of deoxynivalenol (DON) in the gut of animals and its microbial transformation, type and relative toxicity of the metabolites generated have all been thoroughly documented in pigs, with the caecum, colon and rectum showing the most microbial transformation [47]. Various metabolites of ZEN, such as α-zearalenol and β-zearalenol have been discovered in sheep and increased levels of these metabolites may be removed via urine as glucuronides by grazing sheep [48]. α-zearalanol, also known as zeranol, is found in the urine of ruminants and equines and investigations have revealed that zeranol may be produced in these animals due to the metabolism of ZEN and other compounds found naturally in fusarium-infected pastures [48].

ADVERSE EFFECTS OF FUSARIUM MYCOTOXINS ON NON-RUMINANTS

The disorders induced by various mycotoxins can be classified as acute or chronic, resulting in a toxic response that leads to cancer and other irreversible consequences [48]. Pigs, for example, have been proven to be extremely vulnerable to T-2 toxin, DON and ZEN and almost all fusarium mycotoxins have demonstrated unequal reactions in monogastrics. Poultry also is badly overblown by both T-2 and DON but are very resistant to the oestrogenic effects of ZEN [49]. Mycotoxins produced by fusarium have been found to impact chickens and because of the chemicals in the diet and the variances between and within species, the range of mycotoxicosis differs in animal species. Besides decreased intake of feed and subsequent body weight, ulceration and plaque formation in the oral cavity were noticed due to T-2 toxin or DAS (4 or 16 mg/kg of feed) in 7-day-old chicks. When hens (67-69 weeks old) and roosters (25-27 weeks old) were fed DAS at 65 and 10 mg/kg of feed, respectively, the rate of fertility was raised in hens (67-69 weeks old) and lowered in roosters (25-27 weeks old) [50]. Alimentary toxic aleukia was caused by the infestation of cereal grains with several fusarium species such as *F. sporitrichoides* and *F. poae*, with side effects including esophageal pain, asphyxiation, laryngitis, diarrhoea and dizziness [51]. Similar toxic effects were shown by both DON and ZEN in scabby grain and the symptoms included sickness, vomiting and diarrhea [52]. Fumonisin B1 was connected to a disease outbreak in India with symptoms including acute stomach discomfort and diarrhea [53].

ADVERSE EFFECTS OF FUSARIUM MYCOTOXINS ON RUMINANTS

Although ruminants sensitivity to negative effects of mycotoxins is less well understood than that of non-ruminants, there is an influence on reproduction, growth and productivity when ruminants consume mycotoxin-contaminated feed for extended period [54]. When calves are given T-2 toxin, immunosuppression is induced, resulting in lower serum IgM, IgG and IgA concentrations and lymphoid

tissue necrosis (Figure 6) [55]. T-2 toxin-contaminated feed has also resulted in bovine sterility and miscarriage in the third trimester of pregnancy [6]. Calves fed T-2 toxin at 10-50 mg/kg of feed developed stomach ulcers [56]. Similarly, high dietary amounts of ZEN (12 mg/kg of feed) for an extended period (10 days) may significantly affect sheep sexual function by lowering fertility and ovulation rates [55]. In lambs, increased fumonisin doses (11.1–45.5 mg/kg body weight) have been shown to cause severe and lethal nephrotoxicity and hepatotoxicity [57].

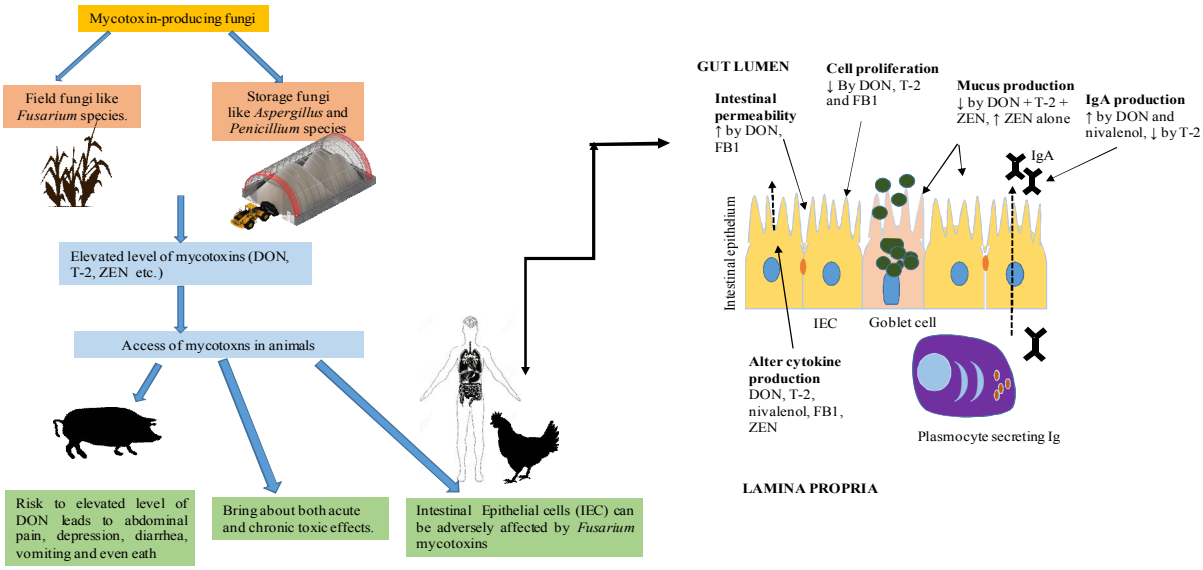

Figure 6. The increased production ofmycotoxins produced by various fungi (like field fungi and storage fungi) enters the animal world (both ruminants and non-ruminants) thereby altering the intestinal epithelium. Nonetheless, fusarium mycotoxins affect a wide range of intestinal defence processes, including cell proliferation, mucus layer, epithelial integrity, immunoglobulins (Ig) and cytokine production.

CONCLUSION

The fusarium mycotoxins found in animal feeds and forages are trichothecenes, zearalenone and fumonisins. These mycotoxins have been implicated in cases of mycotoxicosis in animals when present in adequate amounts. Trichothecenes are responsible for several diseases such as regurgitation of food, showing negative response while feeding and abrasions in the mouth of pigs. Fumonisins are convincingly related to swelling of lungs in porcine and moldy corn poisoning in horses. Fusarium mycotoxins are also suspected of being implicated in sheep weight loss, a high death rate in poultry and inflammation in the duodenum and proximal region of the jejunum in horses. Moreover, fundamental causes of immunotoxicity and teratogenicity must be considered while assessing risk management from these mycotoxins. In addition, synergistic connections between DON and fusaric acid, DON and FB1 and DON and DAS in young sheep have been observed. Similarly, the synergistic effect of FB1 and DON or T-2 toxin in poultry for many serological constituents is commendable. Ultimately, the deep-rooted goal should be to decrease the use of contaminated cereal grains and their products by using those varieties of plants that will overcome the pathogenic effect to some degree.

ABBREVIATIONS

DAS: Diacetoxyscirpenol
DON: Deoxynivalenol
ELEM: Equine leukoencephalomalacia
FB1: Fumonisin B1
MON Moniliformin
NIV: Nivalenol
NOAEL: No Observed Adverse Effect Level
PPE: Porcine pulmonary edema
SCFA: Short chain fatty acids
SARA: Subacute ruminal acidosis
ZEN: Zearalenone

AUTHOR CONTRIBUTION

RAN prepared the initial draft for the manuscript. RKK and JDA collaborated on the paper's structure and arguments and made important edits and signed off on the final version of the manuscript.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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