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Review Article

MYCOTOXINS: A CRITICAL REVIEW ON OCCURRENCE AND SIGNIFICANCE

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ABSTRACT

The contamination of foods and feed with mycotoxins is a commonly known problem. Intense investigations have been conducted by studying the existence of the various mycotoxins to find out how they affect human and animal food chains. Several mycotoxins reported to date are cosmopolitan in distribution and incur severe health-associated risks (including cancer and neurological disorders). Hence, creating awareness among consumers regarding mycotoxins is of great importance for food safety. In this review, the focus is on the types and occurrence of various types of mycotoxins in food and feed associated with risks to humans and livestock as well as their significance. This review is meant to be informative not only for health-conscious consumers but also for experts in the field to pave the way for future research to fill the existing gaps in our knowledge with regard to mycotoxins and food safety.

Keywords: Mycotoxin, Mycotoxicoses, Contamination, Aflatoxin, Trichothecene, Fumonisin, *Aspergillus*, *Fusarium*, *Penicillium*, Secondary metabolites.

INTRODUCTION

Mycotoxins are secondary metabolites of fungi. Fungi normally grow between 10 and 40°C, over a pH range of 4 to 8, and at water activity (aw) levels above 0.70 (sometimes can grow on a very dry surface also) [1]. The growth conditions of a specific fungal species might vary in the field compared to post harvest stages. Even though swift growth of a particular mold can occur on a substrate, it is not a prerequisite that the mold should produce a mycotoxin. This fact indicates that the production of mycotoxin from a particular species depends entirely on the availability of optimum conditions.

The most common mycotoxins are aflatoxins, ochratoxin A, fumonisins, deoxynivalenol, T-2 toxin and zearalenone. Some mycotoxins or mycotoxin derivatives have found use as antibiotics, growth promotants, and other kinds of drugs; still others have been implicated as chemical warfare agent due to their pharmacological activity. Many foods and feeds including corn, wheat, barley, rice, oats, nuts, milk, cheese, peanuts and cottonseed can become contaminated with mycotoxins since they can form in commodities before harvest, during the time between harvesting and drying, and in storage. The poisoning by mycotoxin is referred to as mycotoxicoses. A wide range of adverse and toxic effects in animals are produced by mycotoxin in addition to being food borne hazards to humans.

Many species of bacteria, fungi and yeasts have been shown to enzymatically degrade mycotoxins. However, question remains on the toxicity of products of enzymatic degradation and undesired effects of fermentation with non-native microorganisms on quality of food.

TYPES OF MYCOTOXIN

Mycotoxins have been reported to be carcinogenic, tremorogenic, haemorrhagic, teratogenic, and dermatitis to a wide range of organisms and to cause hepatic carcinoma in humans [2]. More than a 100 species of filamentous fungi are known to cause toxic responses under naturally occurring conditions by producing mycotoxins. Mycotoxins can enter the human and animal food chains by direct contamination when the food has been contaminated by toxigenic fungi while growing or after harvest, or indirect contamination, for example in milk from cows fed with contaminated food [3]. More than 300 mycotoxins are known, of which about 20 are serious contaminants of crops used in human foods and animal feeds. Mycotoxin contamination of foods and feeds depends highly on environmental conditions that lead to mould growth and toxin production [4].

Aflatoxin

Aflatoxins B1, B2, G1 and G2 are produced by three molds of the *Aspergillus* species: *A. flavus* (A+fla+toxin), *A. parasiticus* and A. *nomius* and various species of *Penicillium*, *Rhizopus*, *Mucor* and *Streptomyces*, which contaminate plants and plant products [5].

Aflatoxins in milk: Feed-borne aflatoxin appears in milk as the metabolite, Aflatoxin M1 (AFM1). AFM1 has been categorized as a possible human carcinogen by the International Agency for Research on Cancer, IARC [6]. Alvito et al. used the multiplex method for the aflatoxins to determine these toxins in baby food in Portugal [7]. Out of 27 samples that were analyzed, AFM1 could be determined in 2 samples of cereal-based food and in 2 samples of milk powder-based infant formulae, with AFM1 contents ranging from 17-41 ng/kg. Compared to Aflatoxin B1 (AFB1), AFM1 is rather less carcinogenic and mutagenic; however, it has been reported to exhibit a high level of genotoxic activity in animals (The Joint FAO/WHO Expert Committee on Food Additives) [8].

Milk contamination by AFM1 might occur in 2 ways, directly due to intake of contaminated feeds by animals that might pass into the milk, or indirectly following contamination of milk and milk products with fungi [9, 10, 11]. However, it should be noted that Aflatoxin M1 is a metabolite of Aflatoxin B1, and therefore the possibilities of any direct carryover of AFM1 from feed to milk could be ruled out.

Aflatoxins in raw drugs: Several reports are available on aflatoxins contaminating raw drugs of plant origin. The potential of producing aflatoxins (AFB1) by some 20 strains of *Aspergillus flavus* contaminating raw drugs has been reported by Chourasia [12] who reported levels ranging between 0.09 and 0.88 µg/mL of the culture filtrate. Roy and others also detected aflatoxin contamination by analyzing common drug plants. Out of 15 samples analyzed, 14 were positive for aflatoxins ranging between 0.09 µg/g in *Acacia catechu* and 1.20 µg/g in *Piper nigrum* [13].

Aflatoxins in eggs: Egg consumption as a rich source of protein is well known. Reports available on contamination in eggs by Aflatoxin are scarce [14, 15, 16]. Hens fed with contaminated feeds with more than 3300 mg/kg of AFB1 over a period of 28 d were reported to produce contaminated eggs [17]. Also, reports are available on the presence of Aflatoxin residues transmitted into eggs [18]. However, since 1974, a limit of 20 µg AFB1/kg of layer feed has been set by the European communities.

Significance: Aflatoxins are of economic and health importance because of their ability to contaminate human food and animal feeds, in particular cereals, nuts and oilseeds [19]. The economic impact of aflatoxins is derived directly from crop and livestock losses due to aflatoxins and directly from the cost of regulatory programs designed to reduce risks to human and animal health [20]. The Food and Agricultural Organisation (FAO) estimates that 25% of the world's crops are affected by mycotoxins, of which the most notorious are aflatoxins. Aflatoxin losses to livestock and poultry

producers from aflatoxin-contaminated feeds include death and more subtle effects of immune system suppression, reduced growth rates, and losses in feed efficiency [21]. Other adverse economic effects of aflatoxins include lower yields for food and fibre crop [22].

Aflatoxin reduces the immune system, increasing the chances of infection and targets the liver causing reduced liver function and death. Symptoms which can be seen include reduced feed intake, reduced milk production and increased somatic cell counts. In 1974, many human fatalities occurred in India, when unseasonal rains and a scarcity of food prompted the consumption of heavily Aflatoxin-contaminated maize.

The chronic effects, caused by the consumption of low dietary levels (parts per billion) of the aflatoxins, on the health and productivity of domestic animals are well established. For example, in cattle, pigs and poultry; reduced weight gain [23], reduced milk yield in cows; and reduced feed conversion in pigs and poultry has been reported. Low levels of Aflatoxin have been associated with an increased susceptibility to disease in poultry; pigs and cattle as well as vaccine failures have also been reported. If similar immunosuppressive effects are manifested in humans, it is possible that the aflatoxins (and other mycotoxins) could be significantly enhancing the incidence of human disease in developing countries.

Ochratoxin-A (OTA)

Ochratoxin-A (OTA; molecular weight 403.8) is the 2nd most important mycotoxin produced by the fungi *Aspergillus ochraceus* and *Penicillium verrucosum*. Isolates of *Aspergillus niger* as well as *A. carbonarius* are capable of producing OTA [24]. OTA generally appears during storage of fresh produce (in cereals, coffee, cocoa, dried fruit, spices, and also in pork) and occasionally in the field on grapes. It may also be present in some of the internal organs (particularly blood and kidneys) of animals that have been fed on contaminated feeds. In temperate climates OTA is produced by *Penicillium verrucosum*, while a number of *Aspergillus* spp. (*A. ochraceous*, *A. niger*, *A. sulphureus*, *A. sclerotiorum*, and *A. melleus*) are known to be responsible for its production in tropical and pan-tropical regions of the world. *Petromyces alliaceus* from onion isolated by Moss has shown it to be a good OTA producer under laboratory conditions [25]. OTA has also been shown to be biosynthesized by *Aspergillus carbonarius* in apple and grape juice [26].

OTA in milk: Contaminations of human milk by OTA are common in the temperate and cool areas of the world, including Italy [27], Switzerland [28], Germany [29], and France [30]. OTA contamination in milk from tropical/ hot regions has also been reported in India [31], Egypt [32], and Brazil [33]. In Norway [34], the relationship between OTA contamination of human milk and dietary intake was examined and it was concluded that the risk of OTA was related to dietary intakes (cereals, processed meat products, cheese, cakes, cookies, and juices).

OTA in wine, coffee, tea, cocoa, and herbs: OTA are more common in red wines than in rose and white wines. Impact of geographical effects on the occurrence of OTA in red wines has been reported in Germany [35]; Italy [36]; Greece [37]; Portuguese wines [38]; and in Chilean vineyards [39]. The occurrence and the concerns pertaining to OTA in grapes and wine have been extensively reviewed [40, 41, 42].

Significance: Ochratoxin A (OTA) is a nephrotoxic, hepatotoxic and teratogenic mycotoxin produced by storage molds (mainly by species of *Aspergillus* and *Penicillium*) on a variety of commodities. Exposure to low concentrations of this toxin causes morphological and functional changes in kidney and liver of several domestic and experimental animals. The toxin has also been found in human sera from people living in areas where Balkan endemic nephropathy occurs, and it is suggested to be a possible determinant of this fatal human disease [43].

Although there is currently inadequate evidence in humans for the carcinogenicity of Ochratoxin A, there is sufficient evidence in experimental animals. Ochratoxin A has been found in significant quantities in pig meat, as a result of its transfer from feeding stuffs.

Fusariotoxins (*Fusarium* toxins)

Fungi belonging to the genus *Fusarium* are associated with the production of Fusariotoxins. There are 2 types of toxins produced by these fungi, namely, metabolites that have properties similar to the hormone estrogen such as ZEN (F-2 toxin) and other ones that are the nonestrogenic trichothecenes. There are several synonyms related to Fusariotoxins poisoning: fusario - mycotoxicosis, trichothecenes mycotoxicosis, T-2 toxicosis, vomitoxicosis and ZEN toxicosis.

a. **Fumonisins**

Fumonisins (synonym: Macrofusine, molecular weight 721.8) are the most recently isolated mycotoxins (first discovered in 1988) that are known to possess high cancer-inducing properties [44]. This toxin was originally isolated from *Fusarium moniliforme* (present name: *F. verticillioides* Sheldon.) and from *Fusarium proliferatum*, a common fungal contaminant of corn (maize) throughout the world [45]. Of late, 6 different types of fumonisins (FA1, FA2, FB1, FB2, FB3, and FB4) have been reported, wherein the "A" series is the amides and the "B" series possesses a free amine [46]. Reports are available on the presence of fumonisins in several agricultural products like corn, corn flour, dried milled maize fractions, dried figs, herbal tea, medicinal plants, bovine milk, and others [47,48,49,50,51] indicating high risks to public health.

Some of the *Fusarium* species (*F. avenaceum*, *F. poae*, and *F. tricinctum*) are also known to produce the mycotoxins beauvericin (BEA) and enniatins (ENNs) [52, 53] which are the cyclic hexadepsipeptides consisting of alternating hydroxyl-acid and N-methyl amino acid residues. These 2 types of toxins have been isolated from grains obtained from Scandinavia [54]. Jestoi has reported the occurrence of BEA contamination in cereals obtained from other locations [55].

Significance: The fumonisins are a group of mycotoxins which have been characterized comparatively recently [56]. To date, only the fumonisins FB1 and FB2 appear to be toxicologically significant. The occurrence of FB1 in cereals, primarily maize, has been associated with serious outbreaks of leukoencephalomalacia (LEM) in horses and pulmonary oedema in pigs. LEM is characterised by liquefactive necrotic lesions of the white matter of the cerebral hemispheres and has been reported in many countries, including the USA, Argentina, Brazil, Egypt, South Africa and China. FB1 is also toxic to the central nervous system, liver, pancreas, kidney and lung in a number of animal species. FB2 is hepatotoxic in rats.

The incidence of *F. moniliforme* in domestically - produced maize has been correlated with human oesophageal cancer rates in the Transkei, southern Africa and in China. The levels of fumonisins in domestically-produced maize have been reported as similar to those levels which produced LEM and hepatotoxicity in animals.

b. **Zearalenone**

ZEN (molecular weight: 318.4) and zearalenol are estrogenic resorcylic acid lactones compounds produced by *Fusarium* species [57]. Among the human population, children are the most affected due to consumption of ZEN-contaminated foods (mainly cereals and cereal-based food products). Co-occurrence with other *Fusarium* toxins like deoxynivalenol, nivalenol and fumonisin is often observed and depends on several factors like genotype, climatic condition and harvest season and storage condition. Nevertheless, available data indicate that maize has the highest risk of contamination while wheat, oats and soybean have been found to be contaminated occasionally [58, 59].

Significance: Zearalenone is responsible for many outbreaks of oestrogenic syndromes amongst farm animals [60]. The occurrence of zearalenone in maize has been responsible for outbreaks of hyperestrogenism in animals, particularly pigs, characterized by vulvar and mammary swelling, uterine hypertrophy and infertility. There is limited evidence in experimental animals and inadequate evidence in humans for the carcinogenicity of zearalenone. It is not transmitted from feed to milk to any significant extent.

c. **Vomitoxin** (**DON**)

DON (12, 13-epoxy-3, 4, 15-trihydroxytrichothec-9-en-8-one; molecular weight: 240.26) is commonly known as alpha-methyl phenethylamine, amphetamine deoxynivalenol, 4-deoxynivalenol (DON), or as RD-toxin. Vomitoxin is commonly encountered in food products and feeds prepared from contaminated corn and wheat [61]. DON has been reported in most parts of the world [62]. Vomitoxin is considered to be highly stable and can survive various food processing methods (such as milling, powdering). DON and its metabolite de-epoxy-DON have also been reported to be present in low amounts in eggs [63, 64] and in beer at low levels [65]. Recently, low levels of deoxynivalenol (2.6 to 17.9 ng/g) and its metabolite de-epoxy-DON (2.4 to 23.7 ng/g) have been reported in 20 home-produced egg samples collected in Belgium [66].

Significance: Consumption of vomitoxin-contaminated products has been correlated with reduced milk production in dairy cattle, vomiting in swine, inhibition of reproductive performance and immune function in several animal species, along with induction of apoptosis in mice [67, 68]. Maximum tolerated levels in the range of 500 to 1000 µg/kg (0.05 to 0.1 ppm) for DON in most other food products have also been set [69]. In humans, the effects of DON on health are not completely understood. However, some toxicity information after consumption of DON-contaminated cereals, grains, and other products has been reported [70].

d. **Trichothecenes**

Trichothecenes are sesquiterpenoid mycotoxins that accumulate in kernels of infected spikelets rendering the grain unsuitable for human or animal consumption [71]. Similar to ZEN and vomitoxin, trichothecenes are also produced by *Fusarium* species. Trichothecenes are also known to be produced by other fungal genera like *Trichoderma*, *Trichothecium*, *Myrothecium* and *Stachybotrys.* Trichothecenes are usually found to be contaminants of cereals and their derivatives [72].

Nearly 160 trichothecenes have been identified and are classified into 4 groups depending on their chemical structure. The major ones are T-2 and HT-2 toxins (group A) and nivalenol (NIV) (group B).

Significance: The trichothecenes cause the greatest problems to animal health. General signs of TCs toxicity in animals include weight loss, decreased feed conversion, feed refusal, vomiting, bloody diarrhea, severe dermatitis, hemorrhage, decreased egg production, abortion and death. Clinical effects produced by TCs can be grouped into four clinical categories: (1) feed refusal, (2) dermal necrosis, (3) gastroenteric effects, (4) coagulopathy [73].

(i) **T-2 toxin**: T-2 toxin was first isolated from the mould *Fusarium tricinctum (F. sporotrichoides*) [74]. It belongs to non-macrocyclic type A trichothecenes. *F. sporotrichioides*, the major producer of T-2 toxin, occurs mainly in temperate to cold areas and is associated with cereals which have been allowed to overwinter in the field.

Significance: T-2 mycotoxin, a highly toxic trichothecene that, together with some closely related compounds, has been the causative agent of a number of illnesses in humans and domestic animals. During the 1970s and 1980s, the trichothecene mycotoxins gained some notoriety as putative biological warfare agents when they were implicated in “yellow rain” attacks in Southeast Asia [75].

T-2 toxin poisoning occurred in Kashmir, India, in 1987 and was attributed to the consumption of bread made from moldy flour. The major symptom was abdominal pain together with inflammation of the throat, diarrhea, bloody stools and vomiting. T-2 toxin has been implicated with the occurrence of haemorrhagic toxicoses (mouldy maize toxicoses) in farm animals. The most significant effect of T-2 toxin and other trichothecenes, may be the immunosuppressive activity, which has been clearly demonstrated in experimental animals. The effect of T-2 toxin on the immune system is probably linked to the inhibitory effect of this toxin on the biosynthesis of macromolecules. There is limited evidence that T-2 toxin may be carcinogenic in animals.

Alternaria toxins

Mycotoxins produced by fungi belonging to *Alternaria* species are referred to as Alternaria toxins. They commonly occur during the pre- and postharvest stages of fruits and vegetables. The most important toxin-producing species is *Alternaria alternata*, which usually contaminates cereals, sunflower seeds, rapeseed, olives, and fruits. The other fungal species producing these toxins include *A. alternata*, *A. dauci*, *A. cucumerina*, *A. solani* and *A. tenuissima*.

Some *Alternaria* species are well known for the production of toxic secondary metabolites, some of which are powerful mycotoxins that have been implicated in the development of cancer in mammals [76]. Among these metabolites with mammalian toxicity are alternariol (AOH), alternariol monomethyl ether (AME) [77]. The toxins AOH and AME have been detected in sorghum [79] sunflower seeds [79], barley, wheat, oats [80], olives, tomatoes, mandarin oranges, peppers, and melons.

Significance: *Alternaria* toxins have been implicated in animal and in human health disorders. Recently it has been reported that AOH and AME posses cytotoxic, genotoxic and mutagenic properties *in vitro* [81], and there is also some evidence of carcinogenic properties [82], *Alternaria* spp. were also detected in cereal samples in which *Fusarium* spp. were implicated as the likely cause for the outbreak of alimentary toxic aleukia in Russia.

Claviceps purpurea/ergot toxins

Sclerotia of fungi belonging to the genus *Claviceps* produce ergot alkaloids. A sclerotium is a dark-colored, hard mycelial mass that establishes itself on the seed or kernel of the plant. Usually, wild grass species are considered to favor the cross-contamination of *C. purpurea* onto the cultivated grass. Apart from *Claviceps*, ergot alkaloids are also produced as secondary metabolites by fungal species belonging to *Penicillium*, *Aspergillus*, and *Rhizopus*. The legal limit of ergot is 0.3 per cent by weight for rye or wheat and 0.1 per cent for barley, oats, or triticale.

Significance: Ergot reduces yield because seeds or kernels are replaced by sclerotia. The disease is of greater significance because of the toxic alkaloids produced by the fungus. Grain is classified as "ergoty" if it exceeds this level and is of lower value. When infected rye (a staple for humans in European countries with cold wet climates) was ground and used to produce bread, non-lethal levels of ergot poisoning caused severe hallucinations or intense burning pain (St Anthony's fire) and gangrene of feet, hands, and whole limbs, due to the vasoconstrictive action of the ergot alkaloids [83]. The pharmacological activities of the fungus are due to components that include lysergic acid diethylamide (LSD) [84].

Patulin

Agronomic practices employed during fruit cultivation and juice making have been reported to significantly influence the occurrence and production of patulin and citrinin. Patulin (molecular weight: 145.1) is a mycotoxin that forms the smallest group of toxic metabolites referred to as polyketides, and is reported to be produced by fungi belonging to *Aspergillus* spp., *Penicillium expansum*, and *Paecilomyces* and *Byssochlamys* spp. (*Byssochlamys nivea*, *B. fulva*) [85].

Significance: Patulin has also become important to apple processors as a method for monitoring the quality of apple juices and concentrates. The presence of high amounts of patulin indicates that moldy apples were used in the production of the juices. Patulin is being considered as a “possible toxin” in Europe and New Zealand and is regarded as the most dangerous mycotoxin in fruits, particularly apples, pears, and their products [86]. Patulin is mainly associated with surface-injured fruits, which renders them vulnerable to fungal infection, mainly by *Penicillium* spp [87].

Citrinin

Citrinin (molecular weight: 250.25) is the secondary metabolite produced by *Penicillium expansum* and some of the *Aspergillus* and *Monascus* spp [88]. Citrinin often occurs as a common contaminant of food and feed (fruits, barley, maize, cheese, dietary supplements) [89]. Barley, as well as other cereals employed for producing beer has been reported to be a good substrate for the growth of many toxigenic fungi capable of producing Citrinin [90].

Significance: *Paenibacillus polymyxa*, a Gram-positive low-G1C spore-forming soil bacterium, belongs to the plant growth-promoting rhizobacteria. The swarming motility of *P. polymyxa* strain E681 was greatly induced by a secondary metabolite, citrinin, produced by *Penicillium citrinum* KCTC6549 in a dose-dependent manner at concentrations of 2.5–15.0 mgmL_1 on tryptic soy agar plates containing 1.0% (w/v) agar [91].

Cyclopiazonic acid

Cyclopiazonic acid (α-CPA; Fig 11) (molecular weight: 336.4) is a toxic secondary metabolite that was originally isolated from *Penicillium cyclopium* and later on from other fungal species like: *P. griseofulvum*, *Aspergillus flavus*, *A. versicolor* and *A. tamarii*. Chemically, it is an indole tetramic acid that targets the liver, kidneys and gastrointestinal tract in animals [92]. The significance of CPA is obscure; however, it is reported to naturally occur in peanuts, corn, and in cheese.

Besides colonizing various grains and seeds [93], these molds can grow on any food substrates, such as cheese and meat products [94]. Therefore CPA can contaminate a number of agriculture commodities, animal feeds and food sources.

Significance: It has been shown to be toxic in several animal species including swine, chickens, turkeys, guinea pigs, rats, and dogs. Toxic evidence in animals, depending upon the species, includes gastrointestinal changes of necrosis and inflammation, hepatitis, kidney lesions and in coordination due to effects on muscle tissue. The importance of this compound in immunosuppression has been studied with little significance on this system

CONCLUSIONS

The occurrence of mycotoxins in the food chain is an unavoidable and serious problem the world is facing as it continues to present threat to food safety. Apart from practicing good sanitary measures, awareness has to be created to indicate the toxic effects associated with mycotoxin poisonings in humans and livestock. Wide gaps still exist on the toxicological effects of feeding animals mycotoxin-contaminated feeds. Research in this field is a necessity as there is every possibility that the toxins will enter the human food chain. Intensive screening of microbes may lead to detection of efficient and applicable microorganisms. Based on the available reports of mycotoxin-degrading microorganisms in digestive tract of animals, the activity of these microorganisms may be increased and they may be used *in vivo* for degradation of mycotoxins in food. With the application of molecular biology techniques, the potential mycotoxin degrading microbial strains can be engineered to significantly improve the quality and safety of foods from mycotoxins contamination to protect consumer's health. Finally a most useful practical technology should be developed from economical point of view.

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