MYCOTOXINS AND MYCOTOXICOSIS

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ABSTRACT: Mycotoxins, toxic metabolites of filamentous fungi, are small organic molecules implicated in several human and animal health issues. A wide range of filamentous fungi is involved in the production of mycotoxins under suitable environmental conditions. Mycotoxins are usually ingested with food or drinking material and the implications are known as mycotoxicosis. Mycotoxicosis is responsible for lowered weight gain, immune suppressions, hepatic disorders and impairment of other body organs. Main actions include mutagenicity, carcinogenicity and cytolysis. These toxins are among major cause of vaccination failures and stunted growth in human beings. The toxins are highly stable and resistant to environmental influences. The only way is the proper storage conditions of food products by avoiding fungal contamination especially which are mycotoxins producers.

Keywords: Fungi, mycotoxins, mycotoxicosis, immune suppression and health.

INTRODUCTION

Mycotoxins are secondary metabolites of fungi (Bennett and Klich, 2003). These are normally produced in stationary phase or late lag phase and not growing phase. More than 100 fungal species produce mycotoxins and the most common for toxin production are *Aspergillus*, *Penicillium* and *Fusarium* (Pitt, 2000). Molds grow on many food stuffs as nuts, cereals, spices and dried fruits and produce toxins. Most mycotoxins can persist food processing and are stable chemically (Berbegal *et al.*, 2019). Approximately, 400 mycotoxins are produced by fungi and the most common which cause disease in human and animal are fumonisins, ochratoxin, zearalenone, aflatoxin and trichothecenes (Abbas, 2019). Mycotoxins exposure can occur through airborne particles inhalation which may contain toxins that include components of mold and through ingestion. Mycotoxin contaminated food cause serious health problem in animals and humans such as nephrotoxic, carcinogenic and immunosuppressive (Tittlemier *et al.*, 2019). Some mycotoxins are harmful to other microorganisms (Berthiller *et al.*, 2013). Mycotoxicosis is the name used for toxicity associated with exposure to mycotoxins. Mycotoxins have the potential for bitter and long-lasting health effects through infiltration, skin contact and respiration. They inhibit protein synthesis, damage macrophage systems, inhibit the clearance of lung tissue, and increase bacterial endotoxin sensitivity. Symptoms of mycotoxicosis depend on the type of mycotoxin; focus and duration of exposure; and the age, health, and sex of the person exposed. It is possible that vitamin deficiency, caloric deficiency, alcohol abuse, and infectious disease can all have startling effects on mycotoxins (Bennett and Klich, 2003).

Fungi: Saprophytic fungi can easily grow on wide range of feed material produce mycotoxins. *Aspergillus*, *Penecillium*, *Alternaria*, *Fusarium*, *Cladosporium*, *Helminthosporium* and *Claviceps* are common toxigenic molds. *Fusarium*, *Stachybotrys*, *Trichoderma*, *Trichothecium*, *Memnoniella*, *Phomopsis* and *Myrothecium* are Trichothecenes producers. Ochratoxins are toxic metabolites of *Aspergillus ochraceus*, *Aspergillus carbonarius* and *Penicillium verrucosum*. Fumonisins are toxic secondary metabolites of some *Fusarium* species (Speijers and Speijers, 2004). *Fusarium verticillioides*, *Fusarium graminearum*, *Fusarium proliferatum. Fusarium equiseti* ,*Fusarium culmorum*, *Fusarium crookwellense*, are normally known for production Zearalenone (Goswami and Kistler, 2005; Serrano *et al.*, 2013).

TYPES OF MYCOTOXINS

Aflatoxins: Aflatoxins are mainly produced by *Aspergillus parasiticus* and *A. flavus* (Klich, 2007). These fungi usually effect cereal crops that include corn, wheat (Pakfetrat *et al.*, 2019), cotton, walnut and peanuts and cause serious problems in human and animals such as nephrotoxicity, immune toxicity and hepatotoxicity. The major aflatoxins are B1, G1, G2 and B2 (Yu *et al.*, 2004).

These aflatoxins display the strength of toxicity, mutagenicity and carcinogenicity (Kasoju *et al.*, 2020). Aflatoxin B1 has the most lethal effect on human and animal it has the high level of carcinogenicity and it can penetrate the membrane of the cell and change the genome when it attaches to the DNA to become stable (Goldblatt, 2012).

Ochratoxin: Ochratoxin A (OTA) is a mycotoxin produced by strains of *Aspergillus* like *A. ochraceus*, *A. niger* and rarely by *A. carbonarius*. *Penicillium verrucosum* and *P. nordicum* have been reported to produce OTA as well (Amézqueta *et al.*, 2009). OTA is a carcinogenic mycotoxin and mostly found in citrus food (Battilani and Pietri, 2002). This mycotoxin exhibits nephrotoxic effects like the degeneration of the convoluted tubule of nephron, renal interstitial fibrosis, decrease in thickness of basal membrane and glomerular hyalinization, anemia and proteinuria. OTA displays teratogenic, genotoxic and carcinogenic effects (Wu *et al.*, 2019). OTA is a potent immune suppressor and immunomodulatory, giving rise to effects like the size reduction of thymus, spleen and lymph nodes, depression of antibody response, changes in immune cells number and function. OTA is toxic for embryos and it leaves residues in several tissues and animal products (O'Brien and Dietrich, 2005).

Citrinin: *Citrinin* is produced by several strains of *Penicillium* and *Aspergillus*, reason for which it often occurs with Ochratoxin A. Other citrinin producing *Penicillium spp.* are *P. lividum*, *P. implicatum*, *P. citreoviride*, *P. viridicatum* and others. Some *Monascus* strains are known to produce citrinin as well (Nguyen *et al.*, 2007). Originally, citrinin was characterized as an antibacterial having activities against *Bacillus subtilis* and several *Micrococcus strains.* (Huang *et al.*, 2019). Toxic effects were extensively studied on model animals like mice, swine and poultry, with the kidney identified as being the main target organ. These effects include enlargement and degeneration of proximal tubules. In addition, citrinin exerts a depressive action on the central nervous system. Dietary exposure to citrinin has been reported to impair liver metabolism, increase water consumption, provoke diarrhea and alter intestinal villi morphology. Furthermore, citrinin has teratogenic and carcinogenic proprieties (Shimizu *et al.*, 2005).

Ergot Alkaloids: Ergot alkaloids are produced by certain fungi belonging to the genus *Claviceps* including *C. purpurea*, *C. paspali* and *C. fusiformis*. True ergots are sclerotia, or compact masses of hardened fungal mycelium containing nutrients reserves (Panaccione and Coyle, 2005). Sclerotia appear like fruit bodies and replace the seed of some cereals. The fungal spores are carried by the wind and upon germination on cereal or grass heads, form hyphae, which can penetrate and destroy the seeds, replacing them with a sclerotium. The fungus uses the nutrients from the plant for the development of the sclerotia and the production of the ergot alkaloids (Poole *et al.*, 2019). Pharmacological effects of ergots are due to their structural similarity to neurotransmitters such as noradrenaline, dopamine and serotonin. Some ergots show high affinity to the serotonin receptor and can cause serotonine syndrome that leads to neuropathological changes in the convulsive ergotism. Other toxic effects of ergot alkaloids include digestive disorders like vomiting, diarrhea, feed refusal, reduced weight gain and abortion (Schardl *et al.*, 2006).

Patulin: The mycotoxin patulin is produced by *Penicillium patulum*. To date there are other known Penicillium and Aspergillus strains that are able to produce patulin like *P. crustosum*, *P. expansum*, *P. roqueforti*, etc. Patulin is mainly associated with damaged and rotting fruits. This mycotoxin is commonly found in apples when affected by 'brown rot' but also in pears, peaches, grapes, apricots, olives and low acid fruit juices (Li *et al.*, 2019). Patulin was believed to be carcinogenic, although recent studies invalidated this option (Ramalingam *et al.*, 2019).This mycotoxin exerts nephrotoxic and immunotoxic effects. Patulin produces gastrointestinal symptoms like gastric ulcers, intestinal hemorrhages, lesions in the duodenum and alteration of intestinal barrier function (Puel *et al.*, 2010). It is destroyed by the fermentation process and is therefore unavailable for apple drinks, such as cider. Although patulin has not been shown to be carcinogenic, it is reported to harm the immune system in animals (Liu *et al.*, 2019).

Trichothecenes: Trichothecenes are formally produced by these species i.e *Fusarium, Cephalosporium and Trichoderma.* Trichothecenes inhibit the protein synthesis. The inhibition occurs at ribosomes at all three stages of the synthesis of protein. At the stage of initiation, it inhibits the association of tRNA to the start codon or the enzyme involved in protein synthesis which is peptidyl transferase (Eriksen and Pettersson, 2004).

Zearalinone: *Fusarium graminearum* and *Fusarium cerealis* produce zearalenone found in cereal crops (Llorent-Martinez *et al.*, 2019). It affects the reproductive function of animals because of its estrogen like effect. It also reduces the immune function and cause damage to kidney and liver which leads to immunotoxicity and cytotoxicity. Zearalenone when bind to the estrogen receptor and activate the estrogen response element and induce a variety of estrogen effects and it will affect the animal reproductive system. The ZEA can bind to the Endoplasmic reticulum in cytoplasm and cause lipid peroxidation which then produces a variety of cytotoxic effects (Liu *et al.*, 2019).

Fumonisins: Fumonisin B1 is nephrotoxic and hepatotoxic. It is a major member of toxin, termed as fumonisins, which are produced by several species of fungi such as Fusarium molds and *Fusarium verticillioides* which occur in wheat, cereals and corn. Fumonisin B1 has structure similarity with sphingolipid component. Normally the amino group of Sphingosine (So) and Sphinganine (Sa) usually form an amide bond with fatty acid carboxyl to produce a ceramide. Fumonisin B1 cause the inhibition of the ceramide which will decrease sphingosine and increase sphinganine and result in the accumulation of 1-phosphate metabolite and decrease sphingolipids production (Liu *et al.*, 2019).

Sources of mycotoxins: There are various routes by which animals and human expose to mycotoxins. The routes are ingestion, inhalation, through skin and parental. The aflatoxin producing feed contaminant produces aflatoxins in feed. Then aflatoxins are ingested by animals and birds. The animals produce milk having AFM_1 in it. Similarly, birds ingest aflatoxins secrete metabolites in eggs and meat (Schothorst and van Egmond, 2004)**.** Human gets exposure to aflatoxins via two means either by direct ingestion of aflatoxin contaminated food or by intake or ingestion of eggs, milk and meat containing metabolites of aflatoxins.

Buildings are another source of mycotoxins and people living or working in areas with mold increase their chances of adverse health effects. Molds growing in buildings and have the ability to grow at a certain water activity requirement. Some of the mycotoxins are produced by *Stachybotrys, Alternaria*, *Penicillium* and *Aspergillus* (Abbas, 2019). *Stachybotrys chartarum* carries a higher load of mycotoxins as compared to other molds grown in indoor environment (Marin *et al.*, 2013). The infestation of *S. chartarum* in buildings containing gypsum board, as well as on ceiling tiles, is very common and has recently become a more recognized problem. When gypsum board has been repeatedly introduced to moisture, *S. chartarum* grows readily on its cellulose face. This stresses the importance of moisture controls and ventilation within residential homes and other buildings (Moretti *et al.*, 2019). Common exposures to airborne mycotoxins in the built indoor environment are below the CoNTC, however agricultural environments have potential to produce levels greater than the CoNTC (van Egmond *et al.*, 2007).

Mycotoxins can be found in food chain, it could be by being used as livestock feed or by being directly taken by humans. In 2004 in Kenya, one twenty five people died and nearly two hundreds others were treated after consuming maize contaminated by aflatoxin (Gruber-Dorninger *et al.*, 2019). Due to food shortages at the time, farmers may have been harvesting maize earlier than normal to prevent thefts from their fields, so that the grain had not fully matured and was more susceptible to infection (Greco *et al.*, 2019). Mycotoxins in animal fodder, particularly silage, can decrease the performance of farm animals and potentially kill them. Several mycotoxins reduce milk yield when ingested by dairy cattle. The contamination of medicinal plants by mycotoxins can contribute to human health problems and therefore symbolizes a special risk (Munkvold, 2003).

Mycotoxicosis: Mycotoxicosis is a scientific term used to elaborate a chain of toxic conditions triggered by the consumption of mycotoxins via contaminated feed (Munkvold *et al.*, 2019). It is poisoning caused due to the ingestion of the fungal secondary metabolites. Mycotoxins produce their toxic effects in several ways, including impairment of metabolic, nutritional or endocrine functions. Many mycotoxins damage the liver, reduce average daily feed intake, growth and feed efficiency. Some are teratogenic or carcinogenic. The effect of mycotoxins may vary with the amount ingested, the time over which it is consumed, and the age of exposure (Alhamoud *et al.*, 2019). Mycotoxins are the small molecules; hence they cross the biological membrane and diffuse into the tissues, organs and cells. They can cause injury to the cell membrane so that cytolysis occurs.

As the feed material consumed through the oral route, digestive system is affected as the mycotoxins moved through the digestive tract (Murphy *et al.*, 2006). The gastrointestinal tract is the very first target for these toxicants as well as it acts as the first physiological obstacle against food contaminants. As food touched the intestinal wall, mycotoxins absorbed through the intestinal wall. It causes gradual decrease in the intestinal wall thickness as the sloughing of the cells occur resulting in the malabsorption of the nutrients. As the mycotoxins enter in the blood, it causes destruction of the leukocytes, important in innate immunity. Not only WBC's mycotoxins causes destruction of the neutrophils, leukocytes and monocytes. Hence leukopenia results in the immunosuppression. Through blood mycotoxins can reached to various organs of the body. The liver is an important organ that play role in the detoxification of the poison and chemicals. It metabolize the mycotoxins results in the minor change in the structure but the liver cells are also vulnerable to the toxins. Mycotoxins can also cross the placenta to cause destruction of the zygote resulting in miscarriage. In embryonic life, damage due to mycotoxins produced teratogenic effect such as anatomical deformity or stunted growth (Hussein and Brasel, 2001). In humans, aflatoxin is majorly counted as a causative agent of liver cancer.in humans and animals it may lead to necrosis which ultimately ends up to hepatocellular carcinoma (Zain, 2011). Aflatoxin B1 is primarily metabolized in liver (Subramanian, 2002).

Mycotoxins decrease the feed consumption of birds, decrease in weight gain. It not only reduced the egg

production but also decrease the egg weight. It causes changes in liver and increases the amount of fat in liver. Weight of each organ inside the body of birds is also affected. Aflatoxins disturb the metabolic activity of body as toxic metabolites bind with different enzymes involve in metabolism. As results digestion of various nutrients is lowered. If birds ingest the feed contaminated with aflatoxins, it will change the protein profile of bird's serum. Liver is the most effected organ in body by aflatoxins. Histopathological analysis revealed the congestion of hepatic sinusoids and necrosis and focal hemorrhagic lesions in liver. Mycotoxins have been considered less toxic to ruminants. However, aflatoxins affect the productivity of these animals if they ingest aflatoxins for longer period (Cattle, goat, sheep and deer). In cattle severity of negative effects of aflatoxins depends upon the concentration of toxins ingested by these animals. However, exposed cattle have less production with low quality of milk and weak immune system. Aflatoxins also disturb the rumen metabolism by slowing down the motility of rumen. Previously sheep were considered the most resistant specie (Olaniyi and Akinyele, 2019). Ochratoxicosis occurs less frequently in poultry than aflatoxicosis but is more lethal based on its acute toxicity, it is nephrotoxic. Ochratoxins are rapidly excreted in bile and urine. Environmental conditions favoring ochratoxin production are similar to those for aflatoxicosis. It is mostly prevalent in Ducks quail, turkey, chickens. Ducks are seven times more sensitive than chickens. Fumonisin was reported as the causative agents of esophageal cancer. Fumonisins acts as powerful competitive inhibitor of ceramide-synthase, which is a key enzyme in sphingo-lipid biosynthesis. That's why they lead to disruption in sphingo-lipid metabolism in multiple cells and tissues. The main effect of trichothenes toxin is gastro-enteric (Sudakin, 2003), but also affecting the nervous and circulatory system. These mycotoxins inhibit the protein synthesis which results in disruption of DNA and RNA synthesis. Contact with this mycotoxin produces a toxic effect which consist of an excessive necrosis of the skin and mucous membrane (Berthiller *et al.*, 2005). The main sign of zearalenone toxicity is estrogenic as the active part of zearalenone is similar to estrogen (Rogowska *et al.*, 2019). It inhibit the follicle development and ovulation by reducing the follicle stimulating hormone concentration as this mycotoxin adopt a similar configuration to that of 17-beta estradiol and other natural estrogens that bind to the estrogen receptors (Rai *et al.*, 2019).

Mitigation: Mycotoxins are highly resistant to constipation or broken down in digestion, and therefore remain in the food chain in meat and dairy products (González-Jartín *et al.*, 2019). Even heat treatments, such as cooking and ice, do not destroy certain mycotoxins (Patience *et al.*, 2014).

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