Mycotoxins

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Mycotoxins

- Mycotoxin is a convenient generic term describing the toxic
- secondary metabolites produced by fungi. “Myco” means fungal (mold) and “toxin” represents poison .
- They encompass a considerable variety of low molecular weight compounds with diverse chemical structures and biological activities.

- In considering the effects of mycotoxins on animals, it is important to distinguish between “mycotoxicoses” and “mycosis:”.

Mycotoxins

- Mycotoxicoses is used to describe the action of mycotoxin(s) and is frequently mediated through a number of organs, notably the liver, kidney, lungs, and the nervous, endocrine, and immune systems.

Mycotoxins

- Mycosis" refers to a generalized invasion of living tissue(s) by growing fungi.
- Due to their diverse chemical structures, mycotoxins may exhibit a number of biological effects, including both acute and chronic toxic effects as well as carcinogenic, mutagenic, genotoxic, and immunotoxic effects.

Historical reports of Mycotoxins

- Modern mycotoxicology was not developed until the discovery of aflatoxins in the early 1960s as the causative agent in the
- peanut meal causing the "Turkey X" disease that killed more than 10,000 turkeys fed with the contaminated meal.
- Because aflatoxins are a series of highly potent carcinogens produced by commonly occurring *Aspergillus flavus* and *A. parasiticus*, research has focused new attention on mycotoxins .

Mycotoxins

- In the last 40 years, many new mycotoxins have been identified and characterized, and their biosynthetic origin in various fungi elucidated. It has been estimated that at least 25% of the world's agricultural product is contaminated with mycotoxins and certain diseases have been linked to ingestion of food contaminated with mycotoxins.

Classification of mycotoxins

- Mycotoxins may be classified as a polyketides, terpenes and nitrogen containing metabolites based on their bio origin.
- Classification of mycotoxins according to site of action in the human body:-

Classification of mycotoxins

- 1-hepatotoxins: Aflatoxicoses
- 2-Nephrotoxins: Ochratoxins which is a potent nephrotoxin was first isolated from Aspergillus ochraceous in south Africa.
- 3-Reproductive system toxins: Zearalenon.

Classification of mycotoxins

- 4-Muscular tissue toxins : Ergot alkaloids.
- 5- Teratotoxins and carcinogenic toxins: Sterigmatocystin, it's a precursor in the biosynthesis of aflatoxins.

Classification of mycotoxins

- PRODUCTION OF MYCOTOXINS BY TOXICOGENIC
- Invasion by fungi and production of mycotoxins in commodities can occur under favorable conditions in the field, at harvest, and during processing,
- transportation and storage.

Aflatoxins

- At least 16 structurally related toxins in this group are produced by *Asparagillus flavus* and
- *A. ochraceous* has also been *A. parasiticus* found to produce aflatoxins.
- Although liver cancer may be attributable to exposure to aflatoxin in parts in Africa ,the formation of an epoxide could well be key to both acute and chronic toxicity and those animals and human which fail to produce it are relatively resistant to both.

Aflatoxins

- the epoxide will react with DNA and then react with the protein and cause sever toxicity(DNA adduct).
- Several studies have demonstrated that very young children may be exposed to aflatoxins even before they are weaned because mothers consuming aflatoxin in their food may secret aflatoxin M1 in their milk .

Aflatoxins

- *Other significant members of the aflatoxin family, such as M1 and M2, are metabolites of AFB1 and AFB2, respectively, and originally isolated from bovine milk.
- Aflatoxins are mutagenic, teratogenic, and hepatocarcinogenic.
- Aflatoxin B1 is one of the most potent naturally occurring carcinogen, extensive research was primarily done on this toxin. The main target organ of AF is the liver.
- AFB1 also affects other organs and tissues including the lungs and the entire respiratory system.

Aflatoxins

- Toxic effect
- AFM1, a hydroxylated metabolite of AFB1, is about 10 times less toxic than AFB1; but its presence in milk is of concern for human health.
- Pathogenesis: Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide and the major risk factors include chronic infections with the hepatitis B (HBV) or C (HCV) virus, and exposure to dietary aflatoxin B1(AFB1)

Aflatoxins

- Contamination of foods occurs during growth and as a result of storage in deficient or inappropriate facilities. These toxins cause serious public health hazards, including the

Aflatoxins

- causation of hepatocellular carcinoma by aflatoxin B1. Exposure begins in vitero and is life-long. The innocuous parent molecule of the fungus is converted by members of the cytochrome p450 family into mutagenic and carcinogenic intermediates. Aflatoxin-B1 is converted into aflatoxin B1-8,9 exo-epoxide, which is in turn converted into 8,9dihydroxy-8-(N7) guanyl-9-hydroxy aflatoxin B1 adduct. This adduct is metabolized into aflatoxin B1 formaminopyrimidine adduct.

Aflatoxins

- These adducts are mutagenic and carcinogenic. In addition, an arginine to serine mutation at codon 249 of the p53 tumor suppressor gene is produced, abrogating the function of the tumor suppressor gene, and contributing to hepatocarcinogenesis. Aflatoxin B1 acts synergistically with hepatitis B virus in causing hepatocellular carcinoma.

Aflatoxins

- A number of interactions between the two carcinogens may be responsible for this action, including integration of hepatitis B virus x gene and its consequences, as well as interference with nucleotide excision repair, activation of p21waf1/cip1, generation of DNA mutations, and altered methylation of genes. But much remains to be learnt about the precise pathogenic mechanisms responsible for aflatoxin B1-induced hepatocellular carcinoma as well as the interaction between the toxin and hepatitis B virus in causing the tumor.

Ochratoxin A

- Ochratoxin A, the most toxic member of this group of mycotoxins, has been found to be a potent nephrotoxin causing kidney damage as well as liver necrosis and enteritis in human (a debilitating disease in man known as Belkan endemic nephropathy) and many animal species
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Ochratoxins

- The OA inhibits carboxypeptidase A, renal phosphoenolpyruvate carboxykinase, phenylalanine tRNA synthetase, and phenylalanine hydroxylase activity.
- Formation of free radicals has been considered as one of the mechanisms for the carcinogenic/toxic effects of OA.

Ochratoxins

- PathOgenesis of Ochratoxins
- Exposure to the mycotoxin ochratoxin A (OTA) causes nephropathy in domestic animals and rodents and renal tumors in rodents and poultry. Humans are exposed to OTA by consuming foods made with contaminated cereal grains and other commodities. Management of human health risks due to OTA exposure depends, in part, on establishing a mode of action (MOA) for OTA carcinogenesis.
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Ochratoxins

- OTA-induced renal damage but no tumors were observed in the strains of mice [53 heterozygous (p53+/−) and p53 homozygous (p53+/+)], indicating that p53 heterozygosity conferred little additional sensitivity to OTA. Renal changes included dose-dependent increases in cellular proliferation, apoptosis, karyomegaly, and tubular degeneration in proximal tubules, which were consistent with ochratoxicosis.

Fumonisins

- Fumonisins (Fm) are a group of toxic metabolites produced primarily by *F. verticillioides, F. proliferatum* and other related species readily colonize corn all over the world. Also *F. anthophilum, F. nupiforme, and F. nygamai* are capable of producing Fms.

Fumonisins

- In 1970, an outbreak of leukoenchephalomalacia (ELEM) in horses in South Africa was associated with the contamination of corn with the fungus Fusarium verticillioides. It is one of the most prevalent seed-borne fungi associated with corn. Another study was done on the possible role of fungal toxins in the etiology of human esophageal cancer in a region in South Africa. The diet of the people living in this area was homegrown corn and F. verticillioides was the most prevalent fungus in the corn consumed by the people with high incidence of esophageal cancer.

Fumonisins

- More than 11 structurally related Fms (B1, B2, B3, B4, C1, C4, A1, A2, etc.), have been found since the discovery of FmB1.

- Pathogenesis: Fumonisin B1 (FB1) is a mycotoxin that commonly occurs in maize. FB1 causes a variety of toxic effects in different animal species and has been implicated as a contributing factor of esophageal cancers in humans.

Fumonisins

- Fumonisins are a group of naturally occurring compounds produced by the fungus Fusarium moniliforme. They are believed to be the etiologic agent of several animal diseases associated with consumption of corn-based feeds including porcine pulmonary edema. Recently it was shown in vitro that fumonisins are specific inhibitors of sphingosine and sphinganine N- acyltransferases. Inhibition of these enzymes in cultured cells results in the accumulation of free long chain sphingoid

Fumonisins

- bases, specifically sphingosine and sphinganine, and the depletion of complex sphingolipids.
- edema only occurred at 175 ppm, while histologic liver damage was present at ≥23 ppm, and serum liver enzymes were significantly elevated at ≥101 ppm.

Fumonisins

- Fumonisin B1 is hepatotoxic and nephrotoxic in all animal species tested. The earliest histological change to appear in either the liver or kidney of fumonisin-treated animals is increased apoptosis followed by regenerative cell proliferation. While the acute toxicity of fumonisin is low, it is the known cause of two diseases which occur in domestic animals with rapid onset: equine leukoencephalomalacia and porcine pulmonary oedema syndrome. Both of these diseases involve disturbed sphingolipid metabolism and cardiovascular dysfunction.

Trichothecenes (TCTCs)

- Several species of Fusarium infect corn, wheat, barley, and rice.
- Under favorable conditions, they elaborate a number of different types of mycotoxins
- (TCTCs) are generally classified as macrocyclic (Type C) or nonmacrocyclic (Types A and B). Although more than 100 TCTCs have been identified, only a few frequently found in foods and feeds are potentially hazardous to human and animal health.

Trichothecenes (TCTCs)

- Trichothecenes (TCTCs)
- Other fungal genera elaborate TCTCs are: Myrothecium, Trichoderma, Trichothecium, Cephalosporium, Verticimonosporium, and Stachybotrys.

Trichothecenes (TCTCs)

- Fusaria toxins:
- A)T-2 toxin, a highly toxic type A TCTC, is produced by F. tricinctum, F. sporotrichioides.
- Unlike most mycotoxins, which are usually synthesized near 25C, the optimal temperature for T-2 toxin production is around 15°C

Trichothecenes (TCTCs)

- B) Deoxynivalenol (DON)
- The DON is a major type B TCTC mycotoxin produced by F. graminearum (major) and other related fungi such as F. culmorum and F. crookwellense. Because DON causes feed refusal and emesis in swine, the name "vomitoxin" is also used for this mycotoxin

Pencillium mycotoxins

- Penicillia produce many mycotoxins with diverse toxic effects. Cyclochlorotine, luteoskyrin (LS), and rugulosin (RS) have long been considered to be possibly involved in the yellow rice disease during the Second World War. They are hepatotoxins. Several other mycotoxins, including patulin (PT) penicillic acid (PA) citrinin (CT), cyclopiazonic acid , which are produced primarily by several species of Penicillia .PT and PA are produced by many species in the genera *Aspergillus* and *Penicillium*.

Removal or Elimination of Mycotoxins.

- Since most of the mycotoxin burden in contaminated commodities is localized to a relatively small number or seeds or kernels removal of these contaminated seeds/kernels is effective in detoxifying the commodity.
- Methods currently used include:
- (a) physical separation by:

Removal or Elimination of Mycotoxins.

- identification and removal of damaged seed;
- mechanical or electronic sorting;
- flotation and density separation of damaged or contaminated seed;
- physical screening and subsequent removal of damaged kernels by air blowing;
- washing with water
- use of specific gravity methods

Removal or Elimination of Mycotoxins.

- Avoiding Human Exposure
- Role of Rigorous Monitoring Programs
- While it is impossible to remove mycotoxins completely from foods and feeds, effective measures to decrease the risk of exposure depend on a rigorous program of monitoring mycotoxins in foods and feeds. Consequently, governments in many countries have set limits for permissible levels or tolerance levels for a number of mycotoxins in foods and feeds.
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Removal or Elimination of Mycotoxins.

- Over 50 countries of the world have developed such guidelines. For example, levels varying from zero tolerance to 50 ppb have been set for total AFs.
- A tolerance level of 1 ppm for DON in grains for human consumption has been set by a number of countries, including the United States. The FmB1 levels established by FDA in 2000 are limited to 5, 20, 60 100, 30, and 10 ppm, in corn and corn by-products to be used for horse and rabbit, catfish and swine, and mink, poultry,
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