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An Overview of Mycotoxins in Human Health with Emphasis on Development and Progression of Liver Cancer

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Abstract

Contamination of food and feed by mycotoxins has become serious problem worldwide. Contamination of human food with mycotoxin at different stages of food chain has also been observed. *Aspergillus, Alternaria, Claviceps, Fusarium, Penicillium and Stachybotrys* constitute some of the most important genera of mycotoxins. Amongst them, in recent times due to the genotoxic substance aflatoxin B1 being produced by *Aspergillus flavus and Aspergillus parasiticus,* food contamination by it has been an area of major concern from the point of view of human health as it is a potent hepatocarcinogenic substance. Along with *Aspergillus* other mycotoxins are nephrotoxic, nephrocarcinogenic and also affect the reproductive system. Case studies from the last two decade suggest that people living and working in damp and moldy area has greater chances of developing asthma, bronchitis, skin diseases and other health disorder.

Keywords: Aflatoxin; Fungi; Hepatocellular carcinoma; Mycotoxin

Introduction

Mycotoxins are a structurally diverse group of small molecular weight compounds, which are chiefly produced by the secondary metabolism of fungi, or molds, under suitable temperature and humidity conditions. It is produced on different type of food stuff and is directly and indirectly hazardous for both human and animal's health. Fungi are extremely adaptable organisms and are able to metabolize a large variety of substrates over a wide range of environmental conditions and they produce mycotoxins only under aerobic condition [1]. It has been estimated that 25% of the world's crops are affected by moulds or fungal growth [2]. Mycotoxins have toxic effects on both human and animals health which is called mycotoxicosis and the level of toxicity of different mycotoxins depends on the quantity of toxins, age of animals, time of exposure and also vary with species to species. Mycotoxins are generally found in arid, humid region and temperate region and have been reported to contaminate human food with its toxic secondary metabolites at various stages in the food chain and their continued exposure has been reported to cause diseases in both human and animal [3]. Prolonged storage of crops in hot and humid conditions has been observed to promote growth of the afltoxin-producing fungi and accumulation of the toxin [4,5]. Some of the most important genera of mycotoxicogenic fungi (*Aspergillus, Alternaria, Claviceps, Fusarium, Penicillium* and *Stachybotrys)* have been reported to arise on human food and animal feed components such as corn, sorghum, wheat, barley, peanuts, and other legumes and oil seeds. A wide range of commodities can be contaminated with mycotoxins both at pre- and post-harvest stage [6] (Table 1).

Mycotoxin Exposure and Detection

Exposure to mycotoxins can occur in human and other animals through contamination of cereal grains, other seeds with untraced fungi. There are basically five broad groups of mycotoxins namely aflatoxin, vomitoxin, ochratoxin A, fumonisin and zearalenone. Frequently contamination of aflatoxins has been observed in maize, dry fruits, peanuts etc. In case of ochratoxin a contamination has been reported in wine coffee and cereals, whereas with fumonisin traces have been reported in maize and maize made products. Mycotoxins have exhibited high mutagenic, carcinogenic and teratogenic effect on animals and human after exposure and are thus hazardous. Amongst them notably, aflatoxin is highly dangerous due to its potent carcinogenic and mutagenic property; the hydroxylated metabolite aflatoxin B1 and aflatoxin M1 is excreted into milk from 1 to 6% of dietary intake [7]. To detect mycotoxin contamination several chromatographic methods has been employed notable being HPLC to detect the concentration of mycotoxins in plasma. Another successful approach has been to use DNA adducts to determine exposure to aflatoxin B1 [8] and

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Table 1: Human diseases caused by mycotoxins contamination.

Disease	Symptoms	Mycotoxin source	Fungus
Akakabio-byo (red mold disease)	Headache, vomiting, diarrhea	Wheat, barley, oats, rice	*Fusarium* sp
Alimentary toxic aleukia	Nausea, vomiting, diarrhea, blisters, rashes and irritation on skin, bleeding, leukopenia	Cereal grains (toxic bread)	*Fusarium* sp
Balkan nephropathy	Slowly progressive disease, weakness, lassitude, lumber pain, pale and copper-brown skin, discoloration of palms and sole with terminal renal failure	Cereal grains	*Penicillium* sp
Cardiac beriberi	Febrile sense, progressive dyspnea, edema, irregular heartbeats	Rice	*Aspergillus* sp *Penicillium* sp
Celery harvester's disease	Allergy, skin irritation	Celery (Pink rot)	*Sclerontinia* sp
Ergotism	Convulsive and gangrenous symptoms	Rye, cereal grains	*Claviceps purpurea*
Hepatocarcinoma	Pain in upper right belly, heaviness, swelling, loss of appetite, weight loss, nausea, vomiting, yellow skin and eyes.	Cereal grains, peanuts	*Aspergillus flavus* *Aspergillus parasiticus*
Kwashiorkor	Loss of muscle mass, pot belly, regular infections, inflamed skin.	Cereal grains	*Aspergillus flavus* *Aspergillus parasiticus* *Aspergillus flavus* *Aspergillus parasiticus* *Aspergillus flavus* *Aspergillus parasiticus*
Neural tube defects	Bladder and bowel dysfunction, developmental delay and hearing impairment, associated motor and sensory problems.	Maize	*Fusarium verticillioides* *Fusarium proliferatum*
Oesophageal tumors	Dysphagia, weight loss, epigastric pain, persistent cough	Corn	*Fusarium verticilloides* *Fusarium proliferatum*
Onyalai	Haemorrhage from ruptured bullae, gastrointestinal bleeding, haemorrhagic bullae in oronasopharynx	Millet	*Phoma sorghina*
Reye's syndrome	Sudden vomiting, loss of interest, confusion, slurred speech, sleepiness	Cereal grains (grain dust)	*Aspergillus* sp
Stachybotryotoxicosis	Fatigue and weakness, headache, morning stiffness, joint pain, unusual skin sensation, short breath, sinus, chronic cough.	Cereal grains (grain dust)	*Stachybotrys atra*

ochratoxin A [9,10].

Mycotoxins and Human Disease

Mycotoxins are responsible for many type of acute and chronic disease in human and other species. Beardall and Miller have given a very detailed account of human illnesses that have been associated with mycotoxin ingestion [11]. Aflatoxin B1which is toxic metabolite of *Aspergillus flavus* and *Aspergillus parasiticus* has exhibited both chronic and acute genotoxic and carcinogenic properties and is the most potent natural carcinogen reported [13]. In dairy cattle, another problem arises from the transformation of AFB1 and AFB2 into hydroxylated metabolites, aflatoxin M1 and M2 (AFM1 and AFM2), which are found in milk and milk products obtained from livestock that have ingested contaminated feed [12]. Aflatoxin B1 is the most potent natural carcinogen known and is usually the major aflatoxin produced by toxigenic strains [13]. Mycotoxins have teratogenic, acute, chronic, mutagenic hemorrhagic, hepatotoxic, nephrotoxic and neurotoxic types of toxicity and in humans they have been reported to damge liver and kidney and if left untreated can progressively lead to death. Their toxicity is mainly due to interruption of protein synthesis and DNA replication, necrosis, lung infection and decreased immunity and can also exhibit mutagenic and teratogenic effects. Long term exposure to mycotoxin has been reported to cause brain damage, induction of cancer in liver and death [14]. With respect to reproductive health, although it has been hypothesized that aflatoxins have adverse effects on birth outcomes but so far there is no critical summary of the literature on the subject [15].

Mycotoxins and Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is one of the most common cancers world-wide and there is an attaining geographic variation in incidence. More than 80% of all HCC cases has been reported to occur in developing countries, and approximately 55% of all cases from China (especially in the southeast areas such as Guangxi) [16]. Due to very poor prognosis resulting from metastasis and reoccurrence, HCC is the third leading cause of cancer related deaths in the world [17]. After a long four decades of study, including experimental data and epidemiological studies in human populations, aflatoxin B1 (AFB1) has been classified as carcinogenic to humans by the International Agency for Research on Cancer [18]. Historically, several epidemiological studies conducted in Asia and Africa have shown an association between high aflatoxin exposure, estimated by sampling foodstuffs or by dietary questionnaires, and increased incidence of HCC [18]. Although chronic HBV infection is the major risk factor for HCC, other environmental exposures such as drinking alcohol, tobacco smoking and aflatoxins in particular have also been suggested to increase the risk [19]. Numerous studies have demonstrated that a linear correlation exists between serum AFB1 dietary exposure and the risk of HCC development [20]. Aflatoxins are metabolized by hepatic enzymes and in the process generate reactive epoxide species that are able to form a covalent bond with guanine [21] (Figure 1). Another mycotoxin, Ochratoxin A has been reported to be teratogenic in rat, hamster and chick embryo, and is an inhibitor of hepatic mitochondrial transport systems and causes damage to liver and has been reported to be excreted in milk of animals contaminated with it [22,23].

Effect of Mycotoxin on Organ other than Liver

Review of literature suggests that although hepatotoxicity and to some extent renal toxicity has been the focus of researchers globally but it also affects other organs directly like brain and they have been classified under a separate class known as neuromycotoxins and includes tremorgens, trichothecenes, citreoviridin, patulin, fumonisin. Infact study suggests that the primary site of trichothecene action is the brain [24] and the primary clinical symptoms are eye pain, nausea, muscle tremor, vomiting, dyspnea, weakness, etc. Neurophysiological effects of mold exposure have been reported

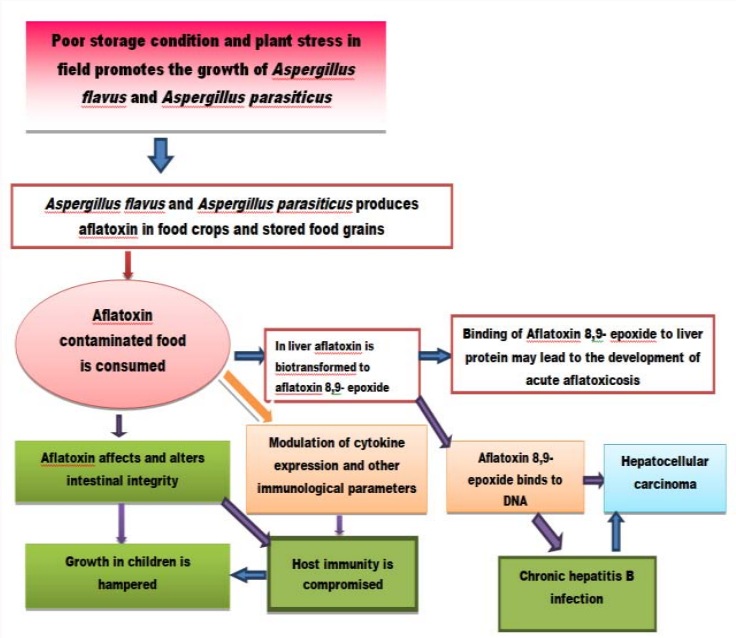

Figure 1: Mechanisms of action of aflatoxin and the development of hepatocellular carcinoma.

in children as compared with controls [25]. Exposure to aflatoxin differs from species to species and has been reported to decrease reproductive rate, cause embryo death, teratogenicity and tumors. Zearalenone which is a non steroid esterogenic mycotoxin is insoluble in water and is also heat-stable and persists in both animal feeds and is also present in foodstuffs and foods. At lower dose, zearalenone has been reported to effect female estrogen hormone and increase the maturity time of mammary gland whereas at higher doses interferes with conception and is secreted in the milk thus affecting the viability of newborn animals [26,27]. Another mycotoxin, Ochratoxin A, apart from its teratogenic property and liver carcinogenicity has also been reported to cause nephrotoxicity and damage gut and lymphoid tissue particularly at higher doses [22].

Prophylactic Measures to Prevent Mycotoxicity and HCC

Depending on the environmental and substrate conditions, various mycotoxins may occur simultaneously or singly and their contamination always has adverse effects on the health of human and animals [28]. To prevent the adverse effect, first approach is the elimination of mycotoxin exposure especially of hazardous ones like aflatoxin, which is known to cause hepatocellular carcinoma. To prevent and decrease the incidences of liver cancer, vaccination can be promoted to improve immunity. Apart from this, it has also been demonstrated in animal studies and in some human studies that oltipraz is an effective agent in blocking aflatoxin adducts formation and thereby prevents the development and progression of cancer. Mechanism is speculated to be via induction of aflatoxin detoxifying enzymes [21]. Pre-clinical studies and cancer prevention trials that use biomarkers as intermediate endpoints to assess the efficacy of promising chemopreventive agents has shown that several agents can provide some level of protection against aflatoxin-induced liver cancer in experimental systems [29,30]. Since mycotoxins are known to pass through animals and human by contaminated food stuff and dietary product, primary prevention of mycotoxin exposure can be checked by increasing standardization storage, handling of crops and food stuffs both pre and post harvesting stage.

Control of Moulds and Mycotoxins in Animal Feeds

Moulds and mycotoxin contamination in animal food and feed can be easily attained by keeping moisture under control, maintenance of temperature unfavourable to their growth and cleaning of equipment's. Thus, aeration of grain bins is important to reduce moisture migration and keep the feedstuff dry [27]. Binding agents such as bentonite, alumino silicates, spent canola oil; bleaching clays and alfalfa fiber have been used in feeds containing mycotoxins to prevent intestinal absorption of the toxins [31]. Other substances which have antimycotics properties can be used like cinnamon, cinnamon oil, clove and clove oil [32]. Various physical and chemical strategies have also been developed to help prevent mycotoxin contamination, including physical separation, extraction with sorbents, and adsorption [33]. Some of the common methods that have been employed to analyze mycotoxins are thin layer chromatography, high performance liquid chromatography with UV or fluorescence detection, liquid chromatography-mass spectrometry and gas chromatography-mass spectrometry. Ultraviolet light can also be employed to screen aflatoxin contamination and is cheap and cost effective [34].

Conclusion

Economic impact of mycotoxins on both human and animal health is very large in both developing as well as developed countries. Globally all the countries are suffering from huge economic losses due to mycotoxin contamination of food stuffs. Further, it also increases the propensity of hepatitis B and C induced HCC and can also have adverse effect on other human organs. Attempts should be made to find means to lower fumonisins, aflatoxin and mycotoxin contamination as a whole to an acceptable level for a better happier and healthier world.

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