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AFLATOXINS AND THEIR EFFECTS ON THE BIOLOGICAL SYSTEM

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ABSTRACT
Aflatoxins are mostly toxic secondary fungal metabolites which are derived from some certain strains of fungi such as species of *Aspergillus*, specifically *Aspergillus flavus*, *Aspergillus parasiticus* and they are quickly absorbed by blood cells in the human body if consumed in any aflatoxin contaminated food. It can also lead to serious threats to both human and animal health hazards by causing various diseases. Aflatoxin breaks down DNA and cause genomic damage during cell division, leading to cancer even death where these breakdown products accumulate in the liver. Aflatoxin B_1 which is mostly found in nature is known to have contaminate most important foods such as wheat, maize, rice, groundnuts, dried fruit, pearl millet, tree nuts (almonds, pecans, walnuts), black pepper, coriander, turmeric, zinger cocoa beans etc. This review discusses Aflatoxins and its Effect on Biological System. The consumption of aflatoxins causes diseases known as aflatoxicoses. Chronic aflatoxicosis leads to cancer, immune suppression and other, slow pathological conditions, whereas acute aflatoxicosis leads to death. Liver is the main target organ and liver damage occurred when poultry, fish, rodents and non human primates are fed with the food is contaminated with aflatoxin B_1. In conclusion, this review work have provided the fact that Aflatoxins (mainly aflatoxin B_1) are responsible for liver cancer which are spread by contamination of *Aspergillus* spp. that mostly occur by *Aspergillus flavus*. Though, several techniques have been established and can be employed for the effective control and safety of food and its management worldwide.

KEYWORDS: *Aspergillus flavus*, *Aspergillus parasiticus*, Aflatoxin, Aflatoxicosis.

INTRODUCTION
Aflatoxins (a type of Mycotoxins) are a group of approximately 20 related fungal metabolites produced in cereals, maize grains, peanuts and animal feed which the fungi; *Aspergillus flavus* and *Aspergillus parasiticus* mainly produce.[1] In 1960, aflatoxins were first discovered during mass deaths of turkeys in England due to liver disease. The aflatoxins contain a coumarin nucleus linked to a bifuran and either a pentanone (AFB_1 and the dihydro derivative AFB_2) or a six-membered lactone (AFG_1 and its corresponding derivative AFG_2).[2] These four compounds are separated by the color of their fluorescence under long-wave ultraviolet illumination (B = blue; G = green). Of the four, B_1 is found in highest concentrations followed by G_1 and G_2.[3] *Aspergillus flavus* and *Aspergillus parasiticus* are mold fungus possessing network of hyphae called mycelium, which secretes various enzymes that break down the complex food materials and absorb micronutrients to fuel the additional fungal growth.[4] The colonies of *Aspergillus flavus* grow rapidly and the diameter reach about 6-7 cm in 10-14 days. Both fungi have a worldwide distribution and normally occur as saprophytes in soil and other decaying organic matters.[5] They readily colonize on many important crops such as corn, cotton seed, peanuts and tree nuts. Thus, they contaminate a wide variety of agricultural products in the field and storage areas.[6] *A. flavus, A. parasiticus, A. nomius, A. tamarii and A. bombycis* are the only molds that have so far been reported to produce aflatoxins.[7] However, the *Aspergillus flavus* strains range from nontoxic to those that produce aflatoxins B_1 and B_2, (AFB_1 and AFB_2): whereas *A. parasiticus* produces aflatoxins B_1, B_2, G_1, and G_2 (AFB_1, AFB_2, AFG_1, and AFG_2). *A. parasiticus* tends to be more stable in producing aflatoxins than *A. flavus.*[8]

Classifications of aflatoxins
Aflatoxin consists of a group of 20 fungal metabolites. Out of them only B_1, B_2, G_1, G_2, M_1 and M_2 are usually found in foods, where "B" and "G" referring to the blue and green fluorescent colors produced on thin layer chromatography plates under UV light, while the subscript numbers 1 and 2 indicate major and minor compounds, respectively. M_1, M_2 is the metabolites of B_1, B_2 found in human and animal milk. Aflatoxin B_1 and B_2 are produced by *A. flavus* and *A. parasiticus*. Aflatoxin G_1 & G_2 are produced by *A.parasiticus.*[1,9,10] Aflatoxins are dihydrofuran or tetrahydrafurano moieties, polycyclic structure, fused to a coumarin ring

and attached to a bifuran system. The presence of lactone ring makes aflatoxins unstable to alkaline hydrolysis. Nevertheless, aflatoxins are stable at high temperature with little damage occurring during cooking or pasteurization, in the presence of oxygen unstable to UV light, extreme pH values and oxidizing agents.[11]

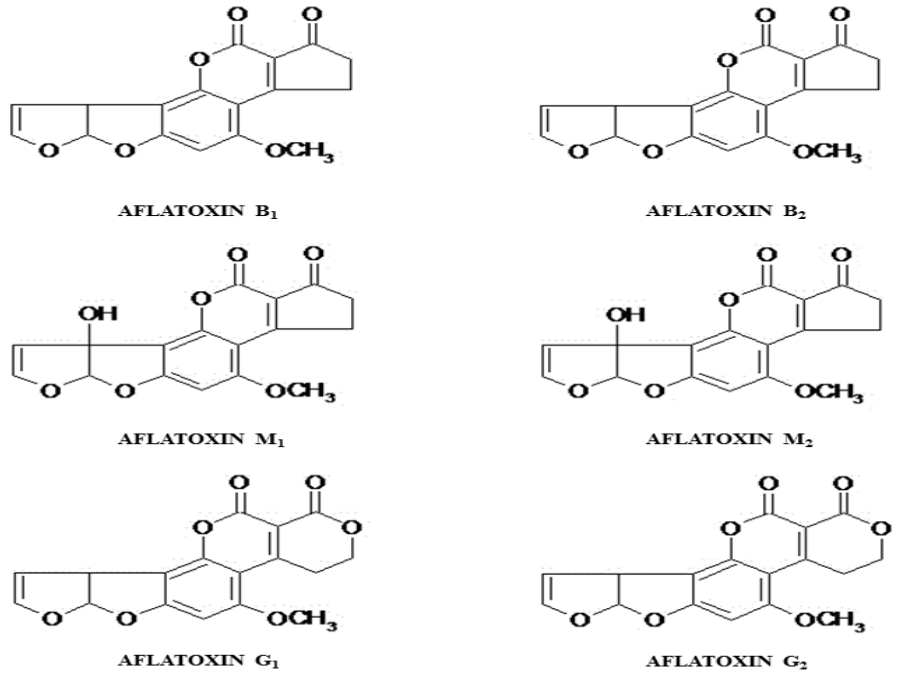

Figure 1: Structures of Aflatoxins.

Physical and Chemical Properties of Aflatoxins

Aflatoxins are colourless to pale yellow crystals that exhibit fluorescence under UV light. They are slightly soluble in water (10-20µg/ml) and freely soluble in moderately polar solvents such as chloroform, menthol and dimethyl sulfoxide. They are unstable in UV light in presence of oxygen, unstable in extreme pH (<3 or >10). Under alkaline conditions the lactone ring opens and the aflatoxins are destroyed, but this reaction is reversible on acidification. Ammoniation results in the opening of lactone ring at high temperature; causes decarboxylation of aflatoxins and this reaction is irreversible (Physical and chemical properties of aflatoxins).[12]

Aflatoxin Poisoning

The consumption of aflatoxins causes diseases that are known as aflatoxicoses. Chronic aflatoxicosis leads to cancer, immune suppression and other, slow pathological conditions. It also means that it has been caused by long-term exposure to low to moderate levels of aflatoxin, whereas acute aflatoxicosis is caused by the short-term exposure to high levels of aflatoxin, which leads to death. Liver is the main target organ and liver damage occurred when poultry, fish, rodents and non-human primates are fed with the food is contaminated with aflatoxin B_1. As the liver is a lipophilic organ, it stores and concentrates all compounds carried by blood stream, i.e. drugs, contaminants, mycotoxins etc., in the hepatocytes and with a long exposure time, may transform themselves into a cancer cell line.[13]

Acute Aflatoxicosis

Acute aflatoxicosis in animals was first documented in 1960, after more than 100,000 turkeys died following an outbreak in the United Kingdom.[9] Acute aflatoxicosis is associated with extremely high doses of aflatoxin, is characterized by hemorrhaging, acute liver damage, edema, and high mortality rates in humans. Acute aflatoxicosis is associated with sporadic outbreaks of the consumption of highly contaminated foods. Early symptoms of acute, high level exposure to aflatoxin include diminished appetite, malaise, and low fever; later symptoms, which include vomiting, abdominal pain, and hepatitis, can signal potentially fatal liver failure.[14]

Chronic Aflatoxicosis

Chronic aflatoxicosis is associated with long-term exposure to low to moderate levels of aflatoxin in the food supply. It is estimated that more than 5 billion people in developing countries worldwide are at risk of chronic aflatoxin exposure through contaminated foods, chronic low-level exposure to aflatoxin, particularly aflatoxin B_1[15,16], is associated with an increased risk of developing hepatocellular carcinoma, or liver cancer, as well as impaired immune function and malnutrition and stunted growth in children.[9,17] Hepatocellular carcinoma, as a result of chronic aflatoxin exposure, presents most often in persons with a chronic hepatitis B virus and/or chronic hepatitis C virus infections[18,19,20], this indicates that exposure to aflatoxin and hepatitis B infection, key risk factors for liver cancer, are particularly prevalent in developing nations in which

people subsist largely on grains.[20]

Aflatoxins and Dietary Antioxidants

In maintaining the structural and functional integrity of the cells, antioxidants can stabilize the reactive oxygen species (ROS), also increasing the capacity of the immune system to respond to the antigens.[21] Among the antioxidants, selenium, carotenoids, vitamins A, C and E are the most important. These antioxidants could be administered as diet supplements, because it was shown that their dietary deficiency could lead to alterations of different organs functions, tumor progression, infections, and inflammation and alteration of the general health status.[22,23,24] The balance between the antioxidants and the pro-oxidant causes the regulation of different metabolic pathways that allows the maintainace of immunocompetence and the protection in stress conditions. Nutritional stress factors have a negative impact on this balance antioxidant/pro-oxidant. In consideration, aflatoxins could be considered to belong to the most important dietary stress factors.[25]

Supplementation of Dietary Antioxidant in Aflatoxicosis

Among vitamins, vitamin E rapidly reacts with the peroxide radicals in order to form tocopheroxyl, a form of stable radicals, capable to generate α-tocopherol through the reaction with the ascorbate.[26] In AFB_1 intoxicated rats, dietary vitamin E protects the membrane directly against damage induced by lipid peroxidation, and indirectly the hepatic microsomal monooxygenase activities. Genotoxic effects of AFB_1 are decreased by dietary vitamin E through the alteration of the activities of hepatic microsomal cytochrome P-450 activities.[27] Also, in mice testis, vitamin E pretreatment significantly ameliorates the aflatoxin induced lipid peroxidation, which could be due to higher enzymatic and non enzymatic antioxidants in the testis as compared with those given aflatoxin alone.[28] The capacity of α-tocopherol to reduce the concentration of ROS following AFB_1 exposure was associated with a reduction in the AFB_1 metabolism.[29] In rats, vitamin E, but also other antioxidants (ascorbic acid, selenium, etc.) could have a protective effect in the AFB_1 liver induced cancer.[30] On the other hand, vitamin E increases the activity of biomarkers associated with the oxidative stress[31] and was not able to reduce the formation of high adduct concentration (AFB-AD).[32] In addition, vitamin E has no beneficial effects on the toxicity associated with the aflatoxin intoxication, but aflatoxin was able to reduce the concentrations of serum retinol and tocopherol[33]. In some cases, completion of vitamins A and E meliorate aflatoxin induce changes and inhibited aflatoxin induced carcinogenesis through anti mutagenic effect.[28,34,35] Lycopene and beta-carotene are effective in restraining the in vitro toxicity induced by AFB_1 on human hepatocytes by decreasing apoptosis and the level of AFB-AD.[31] These carotenoids also inhibited AFB_1-induced mutations in pro apoptotic proteins p53 tumor suppressor gene and inhibited the metabolism of AFB_1.[36] In cultured human lymphocytes, vitamins A, C, and E could actually inhibit AFB_1-induced sister chromatid exchange and exhibited protective effects by inhibiting AFB_1-induced ROS generation.[37] In woodchuck hepatocytes, vitamin C decreases the AFB_1-related lipid peroxidation and inhibits the AFB-AD formation32. In consideration, vitamin C guards the animals from acute toxicity of AFB_1 by activating AFB_1-epoxide hydroxylase, aldehyde reductase, and CYP3A enzymes located in the enterocytes.[38]

Aflatoxin Management And Control Approach

Some resistance associated with protein of maize kernel endosperm are regulated by specific gene were identified by peptide sequencing and among them a stress related peroxiredoxin antioxidant (PER_1) was significantly induced upon *Aspergillus flavus* infection. Biotechnological approaches of genetic control and factors associated that affect biosynthesis of aflatoxin and have been reviewed for aflatoxin management strategies.[39] Genomic technology based research is advanced for identification of the genes and its duty is for the production and modification of the aflatoxin biosynthesis process.[40,41] If a definite pattern of diet including apiaceous vegetables, such as carrots, parsnips, celery, parsley etc. can be maintained that are chemo-preventive and may reduce the carcinogenic effects of aflatoxin in humans.[42]

CONCLUSION

Aflatoxins (mainly aflatoxin B_1) are responsible for liver cancer and can spread by contamination of *Aspergillus* spp. that mostly occur by *Aspergillus flavus*. Antioxidants (vitamins, polyphenolic acids, terpenoids, flavonoids and vegetable pigments) are a good alternative for the reduction of toxicological effects of aflatoxin in biological system. In developing countries, excessive level of aflatoxins contamination in food requires major concern. Several techniques like physical, chemical, biological, and genetic engineering have been developed and employed for the mitigation of aflatoxin, effective control, safety of food and its management worldwide.

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