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AFLATOXINS: MEDICAL SIGNIFICANCE, VULNERABLE POPULATION GROUPS AND POSSIBLE PREVENTIVE MEASURES

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Aflatoxins are widely distributed in nature as common contaminants of a number of staple foods, including maize, oilseeds, spices, groundnuts, tree nuts, rice, milk and dried fruit. Although the aflatoxin parent molecule is harmless, it is converted by members of the cytochrome p450 superfamily into electrophilic intermediates that are toxic, mutagenic, teratogenic and carcinogenic.

The aim of this manuscript is the examination of aflatoxin relevance observed from a clinical standpoint, its influence on public health, critical groups and the measures for prevention of food contamination by this toxine. The data used in the research are obtained from books and relevant literature by means of PubMed browser. Acute hepatitis is the manifestation of acute aflatoxicosis while chronic exposure to it can lead to malnutrition, suppressed immune response and hepatocellular carcinoma. Reye syndrome and kwashiorkor are considered to be pediatric forms of aflatoxicosis. Children and individuals with viral hepatits B infection are especially susceptibile to aflatoxin effects. Aflatoxin contamination depends on the genotype of the crop planted, soil type, climate of the region, weather conditions, timing of harvest, insect activity, and the way of drying of the crop before storage. Control of aflatoxin contamination could be achieved by implementation of adequate screening methods, agricultural strategies and biological methods.

The most important preventive measures include realization of aflatoxin regulatory programs, proper information to the farmers, traders and other important groups, and vaccination against hepatits B virus. Promotion of multidisciplinary approach and better funding in further researches will help in designing effective and novel strategies to eliminate aflatoxin contamination for a safer, nutritious and sustainable food and feed supply and public health improvement. *Acta Medica Medianae 2017;56(2) :51-56.*

Key words: *aflatoxin contamination, public health, prevention*

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Introduction

There is approximately 250 known species of genus Aspergilli which belong to the class of imperfect filamentous fungi. Many of them produce beneficial secondary metabolites, such as antibiotics and other pharmaceuticals (1). However, they can product many secondary metabolites which are not always beneficial and some of them are even toxic and/or carcinogenic. These metabolites called mycotoxins, are structurally very diverse chemical compounds with diverse toxic effects and a variety of biological activities (2). Within the genus Aspergillus, the following species have a greater economic impact: Aspergillus flavus, Aspergillus parasiticus and Aspergillus nominus which produce aflatoxins. These toxins can be produced under certain environmental conditions and in a variety of substrates, and are common contaminants of a number of staple foods, including maize, oilseeds, spices, groundnuts, tree nuts, rice, milk and dried fruit (3). They are widely distributed in nature and although the aflatoxin parent molecule is harmless, it is converted into electrophilic intermediates that are toxic, mutagenic, teratogenic and carcinogenic and may cause serious health hazards to animals and humans (4-6).

The aim of this manuscript is the examination of relevance of aflatoxin, observed from a clinical standpoint, its influence on public health, critical groups and the measures for prevention of food contamination by this toxine. The data used in the research are obtained from books and relevant literature by means of PubMed browser.

Medical significance of aflatoxins

The four major aflatoxins are aflatoxin B1, B2, G1 and G2. Aflatoxin B1 and aflatoxin B2 are typically produced by toxigenic strains of Aspergillus flavus, whereas most strains of Aspergillus parasiticus produce all of the aflatoxins. Damage of the liver which is the primary target organ has been documented in rodents, birds, fish, poultry, and nonhuman primates after the ingestion of aflatoxin B1, the most toxic and abundant member of the family.

Acute hepatitis is the manifestation of acute aflatoxicosis in humans (7). After consumption of maize that was heavily contaminated with aflatoxin, in India in 1974, 100 people died of hepatitis and aflatoxin B1 was detected in high concentration in their livers (8, 9). It has been hypothesized that Reye syndrome, marked by encephalopathy and fatty degeneration of the viscera, and kwashiorkor, a severe malnutrition disease, are forms of pediatric aflatoxicosis. Although aflatoxins have been found in the livers of children with kwashiorkor and in Reye syndrome patients, a strong cause-and-effect relationship between these disease conditions and aflatoxin exposure has not been established (7).

Chronic exposure to aflatoxins can lead to malnutrition, suppressed immune response, proliferation of the bile duct, centrilobular necrosis and fatty infiltration of the liver and hepatic lesions. Firstly, it has been experimentally shown that such an exposure produce cancer in many animal species and further researches correlated increased aflatoxin ingestion with increased risk of hepatocellular carcinoma (HCC) in humans (7). When Aflatoxin B1 contribution to the pathogenesis of HCC was definitely proven, World Health Organization classified it as a "group A" carcinogen (10, 11).

It has been considered that mechanism of aflatoxin-induced carcinogenesis involves tumor promotion or progression. There is evidence that aflatoxin takes part in the activation of protooncogenes and in mutations of the tumor suppressor gene p53. Aflatoxin exposure and p53 mutations have been tightly linked in epidemiologic studies in Africa and China (12).The p53 gene encodes a transcription factor which is involved in cell cycle regulation. This gene is commonly mutated in liver cancers in humans (13). In animal models, cytochrome P450 monooxygenase in the liver modifies aflatoxin B1 into a more toxic and carcinogenic by-product during detoxification (14, 15). The epoxide form of aflatoxin binds to guanine residues in DNA, forms guanyl-N7 adducts, and induces mutations. At the third base of codon 249, a G to T transversion is a mutation hot spot of the p53 tumor suppressor gene (16). It is generally believed that this is the mechanism for initiating hepatocarcinoma formation (17-19).

There is also a suggestion that aflatoxin is connected with various chromosomal aberrations, unscheduled DNA synthesis and chromosomal strand breaks in human cells (17, 20).

Environmental influence and sensitive population groups

A wide range of commodities such as cereals, oilseeds, tree nuts, spices, dried fruit, milk and meat can be contaminated by aflatoxins. The foods which are most susceptibile to contamination and consumed in the greatest amounts are maize and groundnuts. These groceries are the major staple food source in developing countries located in the tropical regions. Individuals who live in these regions are in the greater risk of aflatoxin exposure because of the poverty and lack of food diversity. Growth of Aspergillus fungi and level of aflatoxin contamination in food depends on many factors. Any stage of food production is susceptible to contamination, from pre-harvest to storage (3, 21).

Aflatoxin contamination is affected by the genotype of the crop planted, soil type, climate of the region, minimum and maximum daily temperatures, and daily net evaporation. Other important factors are also stress or damage to the crop due to drought, poor timing of harvest, insect activity, heavy rains at harvest and post-harvest, and inadequate drying of the crop before storage which can be contributed by unfavourable humidity, temperature, and aeration values (3).

Lower body weights and immature neurologic and immune systems in children can lead to illness and complications that might not affect adults. Children reaction to environmental toxins may not be proportional to their state of development.

To analyse the influence of aflatoxin exposure on growth in humans two separate epidemiologic studies in West Africa were conducted by Gong et al (22, 23). The resuls showed a conspicuous association between the exposure to aflatoxin in children with both acute and chronic malnutrition states. It has also been shown that aflatoxin exposure is an important factor in modulating the rate of recovery from kwashiorkor in children, but the exact mechanism is not completely explained yet (24, 25).

In endemic areas, pregnant women are often exposed to aflatoxin contaminated food. Research is needed to better understand the effects of aflatoxin exposure in utero and early childhood. This knowledge is fundamental in identification and design of preventive strategies (12).

Individuals with chronic hepatitis B virus infection exposed to aflatoxin are at up to 30 times greater risk for liver cancer development than individuals exposed to aflatoxin alone (26, 27). Aflatoxin and hepatitis B virus as two HCC risk factors are mainly characteristic of poor nations worldwide (27,28). The synergistic effect of aflatoxin also appears to be present in hepatitis C virus induced liver cancer, but the quantitative relationship in inducing HCC is not yet established (27, 29).

Preventive measures and intervention strategies

Control of aflatoxin contamination

Potential medical and economic impact of aflatoxins clearly implicate the need for elimination or at least minimization of its presence in food and feedstuff. This includes monitoring, managing and controlling their levels in agricultural products from preharvest to post-harvest and from farm to market. The first step in this strategy is legal regulations which include mandatory statutory procedures in order to ensure food safety.

Screening

Numerous analytical techniques have been developed in order to detect aflatoxin levels in food samples which should reduce the risk of its consumption in animals and humans. Those metods include high pressure liquid chromatography (HPLC), thin layer chromatography (TLC), gas chromatography (GC), rapid immuno-assay (RIA) and serum assay (ELISA) (30-32). Various agricultural commodities can also be tested with commercial test kits.

Agricultural strategies

Interventions in agricultural production for reducing aflatoxin levels in food are the methods which can be used either in pre-harvest or in post harvest period (33).

Appropriate practices on pre-harvested crops such as proper irrigation and pest management can reduce aflatoxin contamination. Crops should be chosen according to its resistance to drought, disease, and pests and advantage should be given to the strains of that crop which are genetically more resistant to the growth of the fungus and the production of aflatoxins. Infected debris from the previous harvest may cause infection of the current crop, so its elimination can also prevent contamination. (3).

Post harvest fungal growth and aflatoxin contamination can be caused by inadequate drying of crops especially in the countries with hot and wet climates (34, 35). Contamination can be reduced by sorting and disposing of visibly moldy or damaged kernels before storage as well as moisture, insect, and rodent control during storage (3, 36, 37). Aflatoxin contamination of maize depends on storage time, facilities used for storage, and the form of maize stored (3,38). Another strategy in corn and peanuts include detoxification of aflatoxin contaminated grains (39). Thorough drying and proper storage of groundnuts as simple and inexpensive measures can also have significant influence on aflatoxin levels, as shown in a community-based intervention study in Africa (37).

Biological Control

Germplasm is any living tissue (seed, leaf or another plant part) from which new plant can be grown. Their genetic diversity gives plant breeders the sustained ability to develop high quality varieties that can resist constantly evolving pests and diseases. Unfortunately, no highly resistant varieties or germplasm lines have been identified so far for the major crops such as cotton, corn, and peanut. Some low to medium resistant lines in corn are under testing and development (40, 41). Progress has been made in identifying the genes in corn that shows resistance to aflatoxin producing fungus (42).

Aflatoxin contamination could be controlled to a considerable degree by the introduction of germplasms which are resistant either to fungal invasion or toxin production or both. Along with naturally resistant germplasms, a novel pool of germplasms that demonstrate the desired characteristics can be identified, which could be very important for the success of the current marker-assistance breeding programs. Resisting levels of existing germplasms could be enhanced by the identification of specific biochemical factors linked to the resistance against Aspergillus flavus. Application of nonaflatoxigenic, biocompetitive, native Aspergillus flavus strains to outcompete toxigenic isolates in the fields could also manage aflatoxin contamination (43).

Information spreading

Numerous information have been gathered about aflatoxin contamination during growing, harvesting and storage of crops, as well as the health hazards of aflatoxin exposure. However, this information rarely gets to traders, farmers, and all those who need to be informed. If the value of different interventions and useful information is disseminated in a proper way, much could be done for safer storage, handling and transportation practices of agricultural commodities (44). In Kenya in 2005, for example, people who were informed about maize drying and storage had lower serum aflatoxin levels than those who did not receive this information (3).

Vaccination against hepatitis B virus

The risk of HCC in individuals exposed to aflatoxins is increased exponentially if those individuals also have hepatits B virus infection. Hepatitis B vaccination in infancy has been shown to be safe and effective (28, 45). It has no impact on aflatoxin levels alone, but prevents the synergistic impact of hepatitis B virus and aflatoxin in inducing liver cancer (46). This is particularly important for developing countries where both the incidence of hepatitis B virus and exposure to aflatoxins are high (28, 47).

Conclusions

Aflatoxin contamination of food and feed supply and its influence on human health, especially HCC development, are serious global public health issues. Elimination or at least minimization of aflatoxin presense in food and feedstuff could be achieved through proper monitoring, managing and controlling its levels in agricultural products from preharvest to post-harvest period. Human diet modulated by substances which reduce or prevent aflatoxin toxicity would have a great potential in reducing the incidence of aflatoxin induced HCC in endemic areas (12). Aflatoxin regulatory programs are already in place in most countries although

not all information are still spreaded in the proper way. Promotion of multidisciplinary approa- ches and better funding of further researches will help in designing effective and novel strategies to eliminate aflatoxin contamination for a safer, nutri-tious and sustainable food and feed supply and public health improvement.

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AFLATOKSINI: MEDICINSKI ZNAČAJ, RIZIČNE GRUPE I MOGUĆE PREVENTIVNE MERE

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Aflatoksini su široko rasprostranjeni u prirodi kao česti kontaminanti brojnih osnovnih životnih namirnica uključujući kukuruz, razne žitarice, začine, kikiriki, orahe, pirinač, mleko i sušeno voće. Iako je molekul aflatoksina bezopasan, njegov metabolit nastao pod dejstvom citohroma p450 ima toksični, mutageni, teratogeni i kancerogeni efekat.

Cilj ovog rada bio je sagledavanje kliničkog značaja aflatoksina, njegovog uticaja na javno zdravlje, rizičnih grupa, kao i preventivnih mera kojima bi se izbegla kontaminacija namirnica ovim toksinom. Korišćeni su podaci iz knjiga i referentne literature obezbeđene primenom PubMed pretraživača. Manifestacija akutne aflatoksikoze je akutni hepatitis, dok hronično izlaganje može da dovede do razvoja malnutricije, supresije imunskog odgovora i hepatocelularnog karcinoma. Rejev sindrom i kvašiorkor se smatraju pedijatrijskim formama aflatoksikoze. Deca i osobe inficirane virusom hepatitisa B su posebno osetljivi na aflatoksin. Kontaminacija aflatoksinima zavisi od genotipa zasađenih biljaka, tipa zemljišta, klime, vremenskih uslova, termina žetve, aktivnosti insekata i načina sušenja biljaka pre skladištenja. Kontrola kontaminacije aflatoksinima se može postići uvođenjem adekvatnih metoda skrininga, efiksnijim strategijama u poljoprivrednoj proizvodnji i biološkim metodama.

Najvažnije preventivne mere podrazumevaju sprovođenje regulatornih programa za aflatoksine, širenje korisnih informacija farmerima, trgovcima i svima koji mogu da imaju korist ili daju doprinos kao i vakcinacija protiv hepatits B virusa. Primena multidisciplinarnog pristupa i adekvatno finansiranje budućih istraživanja mogu pomoći u dizajniranju novih i efektivnih strategija za eliminisanje kontaminacije aflatoksinima u cilju proizvodnje sigurnije, hranjlivije i održivije hrane i poboljšanja javnog zdravlja. *Acta Medica Medianae 2017;56(2):51-56.*

Ključne reči: *: aflatoksin, kontaminacija, javno zdravlje, prevencija*