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AFLATOXINS AND AFLATOXICOSIS, A NEW OR FORGOTTEN OLD CHALLENGE IN THE BACKGROUND OF CLIMATE CHANGE IN THE 20TH-21ST CENTURIES

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რეზიუმე

აფლატოქსინები ბუნებრივად წარმოქმნილი მიკოტოქსინებია, რომლებიც წარმოიქმნება ასპერგილუსის სოკოს მრავალი სახეობის, განსაკუთრებით Aspergillus flavus და Aflatoxins parasiticus მიერ. აფლატოქსინები ტოქსიკური და ყველაზე ცნობილი კანცეროგენული ნივთიერებებია. ორგანიზმში მოხვედრის შემდეგ, აფლატოქსინები ღვიძლში მეტაბოლიზდება რეაქტიულ შუალედურ აფლატოქსინ M, ეპოქსიდამდე. აფლატოქსინების წარმოქმნაზე გავლენას ახდენს კლიმატური ცვლილებები (ტემპერატურა და ტენიანობა - ყველაზე ცუდი თბილი და სველი გარემოა); ასე რომ, დაბინძურების ხარისხი იცვლება გეოგრაფიული მდებარეობის, სასოფლო-სამეურნეო, აგროტექნიკური პრაქტიკისა და ასევე არაქისის (და სხვა.) მგრძნობელობის მიხედვით სოკოების მიმართ, მოსავლის აღებამდე, შენახვისა და/ან გადამუშავების პერიოდში. აფლატოქსინებს უფრო დიდი ყურადღება ექცევა, ვიდრე ნებისმიერ სხვა მიკოტოქსინს, რადგან მათ აშკარად აქვთ ძლიერი კანცეროგენული ეფექტი ლაბორატორიულ ვირთხებში და მათი შხამიანი ეფექტი ადამიანებზე.

კვლევებმა აჩვენა, რომ B ჰეპატიტის ვირუსით (HBV) ერთდროული ინფექცია აფლატოქსინის ზემოქმედების დროს ზრდის ჰეპატოცელულარული კარცინომის (HCC) რისკს. აფლატოქსინი ასოცირდება როგორც ტოქსიკურობასთან, ასევე კანცეროგენურობასთან ადამიანებში და ცხოველებში. მწვავე აფლატოქსიკოზი იწვევს სიკვდილს, მაშინ, როცა ქრონიკული აფლატოქსიკოზი იწვევს უფრო გახანგრძლივებულ პათოლოგიურ ცვლილებებს, მათ შორის კიბოს და იმუნოსუპრესიას.

Introduction to Aspergillus and Aflatoxin B1 (AFB1)

Aflatoxins are mycotoxins produced by many species of fungi of the genus Aspergillus. Among them, it is worth noting *Aspergillus flavus, A.parasiticus, A.fumigatus, A.niger, A.nidulans*. Many carcinogenic substances are also found among aflatoxins. When they get into the body, they undergo metabolism into an intermediate reactive product called epoxide - M. Epoxide [8,9]. Representatives of the genus Aspergillus producing aflatoxins are widespread in nature. They often colonize grain before harvesting and/or during storage (housing). Wheat crops are particularly frequently contaminated with Aspergillus fungi during long-term storage under high humidity conditions or when damaged under

stressful conditions such as drought [1,17]. They cause rotting of plants, hay, non-seed crops, their microbial contamination, and under favorable conditions for their growth (humidity at least 7% and high temperature) burrow into all organic substrates. The crops of wheat, corn, rice, millet, soybean, chickpeas, sunflower, cotton, pepper, nuts are most often damaged. Aflatoxins can be detected in the milk of animals fed food contaminated with Aspergillus fungi. It's worth noting that peanut butter always contains small amounts of aflatoxin [12].

Aspergillus are yellow colored (flavus) mold fungi. The temperature optimum for their growth is 23-26°C. Colonies are usually velvety and pigmented. It grows especially well in the tropics and subtropics (in high humidity conditions) [1,18]. As diets become more diverse and complex, both animals and humans are increasingly exposed to aflatoxin B1 (AFB1), a food contaminant with various toxic effects. This study investigated AFB1's impact on the intestinal barrier. In vitro, porcine jejunal epithelial cells (IPEC-J2) were treated with AFB1 concentrations ranging from 10 to 60 mg/L, showing decreased cell viability at concentrations above 30 mg/L. AFB1 also downregulated tight junction proteins and increased Caspase-3 and Bax/Bcl-2 ratios, indicating cytotoxicity. In vivo, Kunming mice were either untreated, given 1% dimethyl sulfoxide, or AFB1 (0.3 mg/kg body weight) for 28 days. AFB1 exposure significantly affected intestinal parameters such as villus height to crypt depth ratio, intestinal wall thickness, number of intestinal villi, and the expression levels of various proteins including ZO-1, Claudin-3, Occludin, MUC2, and Caspase-3. Both in vitro and in vivo results suggest that AFB1 adversely affects the intestinal function, potentially impacting animal health [25].

Epidemiology and Historical Context of Aflatoxin Discovery

Aspergillosis patients do not pose a danger to the people around them from an epidemiological point of view. Infection always occurs by inhalation and more rarely by alimentary and contact [3]. The discovery of aflatoxins has a rather dramatic history. In 1960, a disease of strange etiology broke out in birds (especially turkeys) in England, Kenya and Uganda. Acute forms of the disease were characterized by the development of liver necrosis. Over 100,000 turkeys died in three months. In the same year, frequent cases of trout diseases with hepatomas were recorded in the USA. It was discovered that both the turkeys and the trout were fed Brazil peanut (groundnut) meal. The lowest fungus *Aspergillus flavus* lived in peanut flour, which under optimal conditions (high humidity and temperature) produces a strong hepatotropic toxin (aflatoxin) [13].

Impact of Climate Change on Aflatoxin Production and Aspergillus Flavus Development

Climate change is expected to have a major effect on aflatoxin generation and Aspergillus flavus development because of elevated CO2 levels, changed precipitation patterns, and rising temperatures [22]. The combined effects of high CO2, water activity, and temperature have a considerable impact on aflatoxin B1 production and mycotoxin biosynthesis [23]. Given the severe health impacts of aflatoxin exposure, anticipatory actions and multimodal solutions are sorely needed to combat food and feed contamination in the context of climate change [24]. Studies have shown a clear correlation between aflatoxin formation under different environmental conditions and the expression of important regulatory and structural genes [23]. These results emphasize the necessity of mitigation and adaptive techniques to control aflatoxin contamination in food as climate change advances.

Types and Sources of Aflatoxins

At least 13 different aflatoxins are found in nature. Among them, B1 is the most toxic and is produced by *Aspergillus flavus* and *Aspergillus parasiticus*. Aflatoxin G1 and G2 are produced only by Aspergillus. The main representatives of aflatoxins are B1, B2, G1 and G2. Aflatoxin M1 and M2 were

originally detected in the milk of cattle fed milled grain. These toxins are produced by a series of processes in the liver of animals. In addition, aflatoxin M1 is a result of *Aspergillus parasiticus* fermentation.

- Aflatoxin B1 and B2 are produced during the fermentation of *Aspergillus flavus* and *Aspergillus parasiticus.*
- Aflatoxin G1 and G2 are produced by Aspergillus.
- Aflatoxin M1 is produced in the liver of humans and animals during the metabolism of aflatoxin B1 and passes into milk.
- Aflatoxin M2 is produced in the liver of domestic animals during the metabolism of aflatoxin B2 and passes into milk [19]

Toxic Effects of Aflatoxins in Animals

Certain doses of aflatoxins induce liver tumors in rats, ducks, chicks, trout and monkeys. Intoxication caused by aspergillosis in animals proceeds acutely, with rapid progression of symptoms: convulsions, paresis, hemorrhages, necrosis, diffuse periportal fibrosis, impaired liver and kidney function (necrosis of these organs) and high mortality. As it turned out, aflatoxin is characterized by pronounced hepatotrophy. Along with general severe toxicosis, it can cause cirrhosis, as well as the development of hepatomas and hepatocellular carcinomas in domestic (turkeys) and experimental (rats) animals, as well as in fish. Adding aflatoxin to the drinking water of rats (a total of 300 μg during the week) caused the development of hepatomas in almost all of them, and in the case of ingestion of 35 μg of the toxin, only 1 rat out of 5 developed a tumor of the mentioned histogenesis. Hepatomas are caused not only by long-term intoxication with small doses of the toxin, but also by single exposure to a large dose [4,5,6].

Sensitivity and Resistance to Aflatoxin

Rats had relatively high sensitivity, mice significantly less. In general, rats are the most well-studied subjects for aflatoxins. The sensitivity of animals decreases with age. Adult male rats are more sensitive than females. Canadian trout were found to be most sensitive to aflatoxin, while catfish were resistant. It is alarming that aflatoxin was found in the milk of cows contaminated with aflatoxin [6,7,12].

Human Cases and Risks of Aflatoxicosis

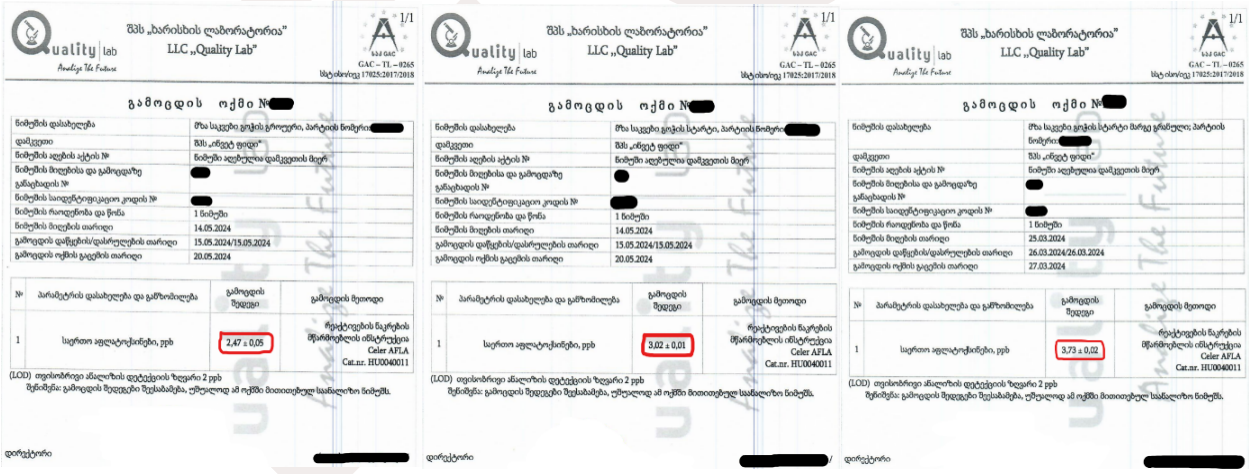
Although the results obtained on different domestic and experimental animals cannot be extrapolated to humans and it raises certain, not very pleasant doubts. it should also be said here that the existing facts do not leave us a reason for optimism. According to some reports, humans have a high resistance to aflatoxin. Despite this, cases of aflatoxicosis have also been reported in humans. In particular, in 1968, 60 people died in the western part of the island of Java, who were fed roasted peanut products; A large number of aborigines in British Guinea died from consuming aflatoxin-contaminated products; In India, where the conditions for the development of *Aspergillus flavus* are very close to ideal, along with cases of aflatoxicosis, cases of liver cirrhosis in children are quite common; In China and so-called Sub-Saharan Africa, 250,000 cases of aflatoxicosis are reported every year, as well as hepatocellular carcinoma and so on [10,14]. Aflatoxin, a metabolic product of the mold Aspergillus, is produced not only in peanut flour, but also in flour of other origins (e.g., bread, corn, etc.), vegetable, oils, milk, etc. Under optimal conditions, the fungus grows on nuts, beans, soybeans, rice, dried food products, etc. For example, since October 2008, the European Commission has decided to limit the import of hazelnuts from Turkey [15]. The situation is exacerbated by the fact that aflatoxin does not break down during heat treatment (including when baking bread, see the table).

Aflatoxins	Molecular formula	Molecular mass	Melting temp.°C
B1	$C_{17}H_{12}O_6$	312	268-269
B2	$C_{17}H_{14}O_6$	314	286-289
G1	$C_{17}H_{12}O_7$	328	244-246
G2	$C_{17}H_{14}O_7$	330	237-240
M1	$C_{17}H_{12}O_7$	328	299
M2	$C_{17}H_{14}O_7$	330	293
B2A	$C_{17}H_{14}O_7$	330	240
G2A	$C_{17}H_{14}O_8$	346	190

Aflatoxin Risks in Georgia

In this regard, a particularly alarming situation could be (or already is) in Georgia, a country once famous for its wheat culture and varieties (Makha, Dolis Puri, Zanduki, Dika, Shavfkha, Tavtukhi, etc.), depending on a number of subjective or objective circumstances, is almost completely switched to importing wheat (rather than wheat flour). When importing, the main thing is the price of the product, which affects the quality of the imported products. Considering the situation in the 90s, we can assume that aflatoxins may have already accumulated in certain (often dangerous) concentrations.

According to today's data, in Georgia, it can be said that the situation will radically change in relation to statistics, because at the beginning of 2024, the National Food Agency established technical regulations regarding the content of unwanted dangerous substances, on the basis of which research has already started since June. Although we currently have serious statistics, it is still an alarming fact that single cases of aflatoxin content in pig feed and raw milk (Nfa.gov.ge) have already been detected in Georgia.

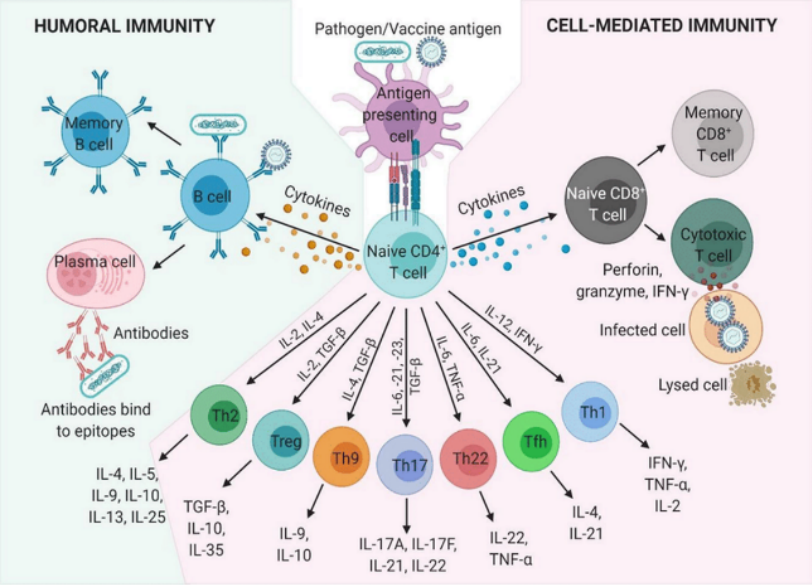


Acute and Chronic Effects of Aflatoxins

High concentrations of aflatoxin cause acute cirrhosis of the liver, which may later progress to cirrhosis and/or acute liver failure, which is manifested by hemorrhage, edema, malabsorption, changes in digestive processes, mental disorders, and coma. No animal species or human is immune to the acute toxic effects of high doses of aflatoxin. In addition, people have relatively high resistance to small doses of aflatoxin, which is why acute aflatoxicosis rarely develops. At high doses, acute aflatoxicosis develops in humans because resistance to high doses is low [16]. Chronic and subclinical forms are not accompanied by such dramatic symptoms as acute aflatoxicosis. Aflatoxicosis especially often affects children, who

suffer from growth and development delays as a result of their influence. Chronic form of aflatoxicosis also causes liver cancer. M1 aflatoxin as a metabolite can cause mutation of the p53 gene, which is an important gene in terms of preventing cell cycle progression when DNA mutations occur. Aflatoxin acts as a DNA mutator not only in the random mutation of DNA, but also has selectivity for mutated p53 DNA, specifically 249 bases (arginin), as a result of which this toxin causes liver tumors.

In the case of aflatoxin, the size or number of pores formed by the toxin in the plasma membrane of target cells (hepatocytes) appears to be critical. In the case of large volume pores or their massive formation, the repair of the plasma membrane by the cell becomes impossible, due to which the cell undergoes destruction. In such a case, the development of aflatoxicosis of different severity should take place. In the case of small pores, the process of fusogenicity and hence carcinogenic effects should take place - at the initiation stage, by the formation of precancerous cells. Thus, in the case of different doses of aflatoxin, the cytopathogenic effects of two, and sometimes three buds may develop and, therefore, a different clinical picture. The transformation of a pre carcinogenic cell produced by aflatoxin into a cancer cell can take place both under the influence of the toxin and without its participation. When a precancerous cell is exposed to other complete carcinogens or promoters, the transformation of this cell into a cancerous cell takes place, which is based on changes at the molecular-subcellular level (amplification of genes, translocations of chromosomes, deletions, duplications).



Aflatoxin has shown a controversial effect on the immune system. Numerous studies have looked into how AFB1 suppresses the human immune system. AFB1 dramatically lowered T-cell counts in the intestines and pro-inflammatory cytokine levels in broiler chickens. AFB1 has been shown in several investigations to inhibit the production of the IL-4, IL-6, and IL-10 genes in a variety of immune cells. On the other hand, broiler birds given AFB1 had higher levels of TNF-α, IFN-γ, and IL-6. AFB1 has been shown to lower the levels of TNF-α, IL-6α, and IL-1α in human monocytes. AFB1 has been shown to suppress the production of interferon in infected monkey kidney cells [24].

Parameter	What it does
IL-6	Associated with inflammatory processes
IL-4	An anti-inflammatory cytokine
IL-2	Helping the proliferation of T-helper cells
MHC genes (major histo-compatibility complex)	essential to innate and adaptive immune functions e.g. some MHC molecules such as class I and class II molecules are important for antigen presentation to T lymphocytes

Scientific studies show that regular consumption of vegetables such as carrots, celery, parsnips and parsnips reduce the carcinogenic effects of aflatoxin [2]. Studies have shown that the risk of developing hepatocellular carcinoma increases with simultaneous infection of aflatoxin with hepatitis B virus (mixed infection). When hepatitis B virus (HBV) is involved in the metabolism of aflatoxins by hepatocytes, aflatoxin M1-DNA conjugation is disrupted in the liver over a

long period of time, which increases the possibility of damage to tumor suppressor genes such as p53. The synergistic effect (aflatoxin + HBV) is significantly higher than the separately induced ejects [19]. The synergistic effect (aflatoxin + HBV) is significantly higher than the separately induced effects. Reducing the level of HBV infection by vaccination is an effective and relatively simple approach that may reduce harmful synergistic effects. In this way, the harmful effect of chronic aflatoxin will be reduced. Such a strategy may prove to be highly effective in many regions of the world where both aflatoxin contamination (for example, West Africa and China) and hepatitis B virus infection are high [19].

There are two basic methods of determining aflatoxin levels in humans:

The first method is determination of AFB1- guanine levels in urine. The presence of a breakdown product confirms infection with aflatoxin B1 within 24 hours. This method can only diagnose new infections, as it is based on the duration of existence of this metabolite. AFB1 - guanine levels can fluctuate from day to day depending on dietary intake and thus is not ideal for assessing long-term exposure. Another method used to detect aflatoxin is determination of AFB1 - albumin level in blood serum. This method allows diagnosis of infection several weeks or months ago [14,19]. Possible cellular mechanism of clinical effects developed by aflatoxins: In order to explain the various clinical effects developed by aflatoxin (intoxications of various degrees, tumors), it is possible to use the data of the karyogram (hybridization) theory, according to which anything capable of fusing somatic cells (fusogenic) should be considered as a risk factor for carcinogenesis [24].

Conventional detection methods:

1. Plate counting, which is laborious and time-consuming [33].
2. Counting conidia, but this may not reflect actual damage or potential mycotoxin production since aflatoxins are produced by mycelia [33].

Rapid detection methods:

1. Enzyme-Linked Immunosorbent Assay (ELISA) using polyclonal antisera, monoclonal antibodies, or single-chain variable fragment (scFv) antibodies to detect A.flavus antigens [34].
2. Nanobody-polyclonal antibody sandwich ELISA, which has a detection limit of 1 μg/mL for A. flavus and can detect fungal concentrations below 2 μg/mg in peanut and maize grains [34].
3. Polymerase Chain Reaction (PCR) for detecting aflatoxin-producing A.flavus at the molecular level [32].
4. Visible/Near-Infrared (VNIR) and HyperSpectral Imaging (HSI) techniques combined with chemometric data analysis for identifying aflatoxin B1 on maize kernels [33].
5. Portable Raman spectrometer with colloidal gold nanoparticles for rapid detection of A. flavus and quantification of aflatoxin B1 in grain crops [31]. The choice of detection method depends on factors such as specificity, sensitivity, simplicity, and the ability to analyze a large number of samples. Rapid methods like ELISA and PCR are preferred when considering a large sample size [32]. Conventional methods like plate counting are still used but are more laborious and time-consuming [33].

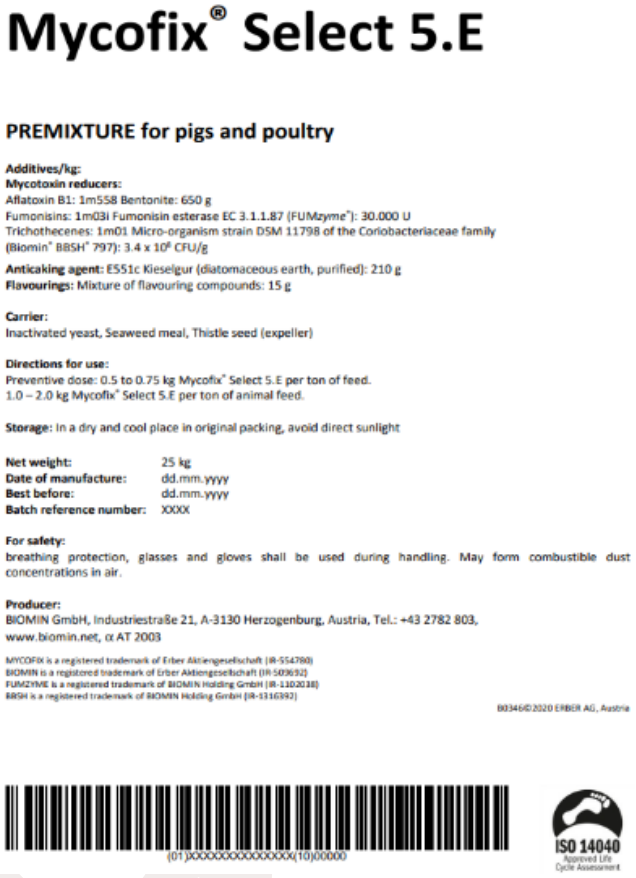
Prevention Methods

Various techniques are used to prevent aflatoxin contamination and the growth of Aspergillus flavus. Breeding for resistance aims to develop maize germplasm resistant to aflatoxin production and fungal growth using diverse screening methods. Biological control methods, like applying Streptomyces yanglinensis 3-10, inhibit fungal growth in the field. Environmental control reduces conditions favorable to A. flavus, such as available water, humidity, and temperature. Good crop management practices,

including timely harvesting, quick drying, and adequate nutrition, are essential for reducing mycotoxin contamination [25,29,30].

Post-harvest management strategies to lower aflatoxin levels during storage include physical separation, specific smoke disinfestation, and food processing techniques. Internal detoxification methods involve chemical and physical treatments, though chemical residues may pose risks. If aflatoxin causes allergic reactions or inflammation, corticosteroids may be used, with antifungal drugs for widespread infections or surgical removal for localized cases. Biological detoxification using specific microbes is a viable approach but requires strict control over microbial performance and safety of the detoxified products [28,29,30].

In summary, in the absence of a treatment approach, prevention is the best solution, both in flora and fauna, and in terms of human exposure not to become the cause of the future pandemic.



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Net weight: 25 kg
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References:

1. Abbas H.K. Aflatoxin and Food Safety.1st Edition, 2019, CRC Press. 616p. ISBN: 978-0367391928.
2. Patrick R. Murray. Medical Microbiology, 9th Edition. 2021, Elsevier. 860p. ISBN: 978-0323673228
3. Anaissie E.J., McGinnis M.R., Pfaller M.A. editors. Clinical mycology, Churchill Livingstone, 2003, 768p. ISBN: 978-0443079375.
4. Bennett J.W., Klich M. Mycotoxins. Clin Microbiol Rev. 2003 Jul; 16 (3):494-516.
5. Chandler F.W., Watts J.C. editors. Pathologic diagnosis of fungal infections, Chicago, 1987, ASCP Press. 303p. ISBN: 978-0891892526.
6. Cohen J., Powderly W.G. editors: Infectious diseases, 2nd Edition, Philadelphia, 2004, Elsevier.
7. Connor D.H. editors. Pathology of infectious diseases. Stamford, Conn. 1997, Appleton & Lange.
8. Fromtling R.A., Rhodes J.C., Dixon D.M.: Taxonomy, classification and morphology of the fungi. Murray P.R. et al./ editors: Manual of clinical microbiology.ed. 8. WASHINGTON. 2003. American Society for Microbiology.
9. Hundler G. 1998. Magical Mushrooms, Mischievous Molds. Princeton, N.J. Princeton University Press.Indoor mold, toxigenic fungi and Stachybotrys chartarum: Infectious disease perspective, Clin Microbiol. Rev. 16:144-172, 2003.
10. Joe S.F., Wong B. Current status of nonculture methods for diagnosis of invasive infectious. Clin. Microbiol. Rev. 15: 465-484, 2002.
11. Kuhn D.M., Ghannoum M.A. Indoor mold, toxigenic fungi and Stachybotrys chartarum: Infectious disease perspective, Clin Microbiol. Rev. 16:144-172, 2003.

12. Mujeeb I. Fungi and fungal infections. In McClatchey K.D., editor: Clinical laboratory medicine, ed. Z. Philadelphia, Lipincott Williams & Wilkins 2002.
13. Murray P.R. editors. Manual of clinical microbiology, ed. 8, Washington D.C., 2003. American Society for Microbiology.
14. Pfaller M.A., McGinnis M.R.: The laboratory and clinical mycology In Anaissie EJ. McGinnis M.R., Pfaller M. A: Clinical mycology, New York, 2003, churchill Livingstone.
15. Reddy S.V., Farid Waliyar (Properties of aflatoxin and its producing fungi) 2002, 1,1.
16. Richard J.L. Mycotoxins and human disease. In Anaissie E.J., McGinnis M.R., Pfaller M.A., editors: Clinical mycology. New York, 2003, Churchill Livingston.
17. Smith T. (June 2005). A Focus on Aflatoxin Contamination- United States National Agricultural Library, Food Safety Research Information Office. Retrieved December 17, 2008.
18. University of Washington, Apiaceous vegetable constituents inhibit human cytochrome- P-450 1Az (hcyp1Az) - mediated mutagenicity of aflatoxin B1, 2006 Sep; 44(9): 1474-84.
19. Williams J.H., Philips T.D., Jilly et al. Human aflatoxicosis in developing countries: a review of toxicology, exposure, potential health consequences and interventions. Am J. Clin. Nutr. 2005; 80;1106-22 (PMID) 15531656.
20. Mutocheluh M, Narkwa PW. Aflatoxin B1: an immunomodulator and cancer agent. In: *IntechOpen eBooks*. ; 2022. doi:10.5772/intechopen.106833
21. Zhang M, Li Q, Wang J, Sun J, Xiang Y, Jin X. Aflatoxin B1 disrupts the intestinal barrier integrity by reducing junction protein and promoting apoptosis in pigs and mice. *Ecotoxicology and Environmental Safety*. 2022;247:114250. doi:10.1016/j.ecoenv.2022.114250
22. Gilbert LA, Horlbeck MA, Adamson B, et al. Genome-Scale CRISPR-Mediated Control of Gene Repression and Activation. Cell. 2014;159(3):647-661. doi:10.1016/j.cell.2014.09.029
23. Medina A, Rodriguez A, Magan N. Effect of climate change on Aspergillus flavus and aflatoxin B1 production. Front Microbiol. 2014;5:348. Published 2014 Jul 22. doi:10.3389/fmicb.2014.00348
24. Battilani P, Toscano P, Van der Fels-Klerx H, et al. Aflatoxin B1 contamination in maize in Europe increases due to climate change. Sci Rep. 2016;6:24328. doi:10.1038/srep24328.
25. Zhang M., Li Q., Wang J. et al. Aflatoxin B1 Disrupts the Intestinal Barrier Integrity by Reducing Junction Protein and Promoting Apoptosis in Pigs and Mice. Ecotoxicol Environ Saf, 2022 Dec 1; 247:114250.
26. Wild C.P., Miller J.D., Groopman J.D. Mycotoxin control in low- and middle-income countries. Lyon (Fr): International Agency for Research on Cancer; 2015.
27. Ashraf B, Ghazy D, Shamel M. Effects of aflatoxin B1 on the submandibular salivary gland of albino rats and possible therapeutic potential of Rosmarinus officinalis: a light and electron microscopic study. *F1000Res*. 2020;9:752. Published 2020 Jul 21. doi:10.12688/f1000research.25196.1
28. Aspergillosis - Diagnosis & treatment - Mayo Clinic. Published January 6, 2022.
29. Hell K, Mutegi C, Fandohan P. Aflatoxin control and prevention strategies in maize for Sub-Saharan Africa. *ResearchGate*. Published online March 4, 2011.
30. Guan Y, Chen J, Nepovimova E, Long M, Wu W, Kuca K. Aflatoxin detoxification using microorganisms and enzymes. *Toxins*. 2021;13(1):46. doi:10.3390/toxins13010046
31. Wang H, Liu M, Zhang Y, et al. Rapid Detection of Aspergillus flavus and Quantitative Determination of Aflatoxin B1 in Grain Crops Using a Portable Raman Spectrometer Combined with Colloidal Au Nanoparticles. Molecules/Molecules Online/Molecules Annual. 2022;27(16):5280. doi:10.3390/molecules27165280.

32. Kumar A, Pathak H, Bhadauria S, Sudan J. Aflatoxin contamination in food crops: causes, detection, and management: a review. Food Production, Processing and Nutrition. 2021;3(1). doi:10.1186/s43014-021-00064-y.
33. Wang T, Li P, Zhang Q, et al. Determination of Aspergillus pathogens in agricultural products by a specific nanobody-polyclonal antibody sandwich ELISA. Scientific Reports. 2017;7(1). doi:10.1038/s41598-017-04195-6.

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AFLATOXINS AND AFLATOXICOSIS, A NEW OR FORGOTTEN OLD CHALLENGE IN THE BACKGROUND OF CLIMATE CHANGE IN THE 20TH-21ST CENTURIES

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SUMMARY

Aflatoxins are naturally occurring mycotoxins that are produced by many species of Aspergillus, a fungus, most notably *Aspergillus flavus* and *Aflatoxins parasiticus*. Aflatoxins are toxic and among the most carcinogenic substances known. After entering the body, aflatoxins are metabolized by the liver to a reactive intermediate, aflatoxin M, an epoxide.

The occurrence of aflatoxins is influenced by the climate changes (temperature and humidity-warm and wet is worst); so, the extent of contamination will vary with geographic location, agricultural and agronomic practices, and the susceptibility of peanuts (etc.) to fungus before they are harvested and during storage and/or processing periods. Aflatoxins have received greater attention than any other mycotoxins because they clearly have a potent carcinogenic effect in laboratory rats and their poisonous effects in humans.

Studies have shown that concurrent infection with the hepatitis B virus (HBV) during aflatoxin exposure increases the risk of hepatocellular carcinoma (HCC).

Aflatoxin is associated with both toxicity and carcinogenicity in human and animal populations. Acute aflatoxicosis results in death, where's chronic aflatoxicosis results in more prolonged pathologic changes including cancer and immunosuppression.

Keywords: Climate change, aflatoxins, global health, Hepatitis B and C, hepatocellular carcinoma