Review Article

ERA'S JOURNAL OF MEDICAL RESEARCH VOL.10 NO.1

10.24041/ejmr2023.10

AFLATOXIN B1: A REVIEW ON BIOCHEMICAL PROPERTIES, EXPOSURE, MECHANISMS OF ACTION AND CHRONIC DISEASES CAUSED BY AFLATOXINS

Rana Majeed Hameed, Maher Abbood Mukheef, Hassan H. Khader, Ghizal Fatima*, Subuhi Anwar**

Department of Biochemistry, Department of Biotechnology, Department of Pathology***

College of Medicine, University of Kerbala, Iraq-566001

Era's Lucknow Medical College and Hospital, Era University, Lucknow, U.P., India-226003.

Received on : 14-10-2022

Accepted on : 27-06-2023

Address for correspondence

Dr. Rana Majeed Hameed

Department of Biochemistry

College of Medicine,

University of Kerbala, Iraq-566001.

Email: rana.m@uokerbala.edu.iq

Contact no: +44-7440725302

ABSTRACT

It has been reported that AFB1 is related to renal adverse effects, specially with Uncertain cause chronic kidney disease. It is a phrase that has been employed to refer to CKD that is not caused by any well-known risk factors, such as hypertension, diabetes, or HIV. Across the world, reports of CKDu are becoming more frequent, and in several areas in Central America, eastern Europe, and south Asia, they are reaching epidemic levels. In the first epidemiological investigation, which was conducted in 2007 and sought to uncover potential risk factors of CKDu, it was claimed that the disease was caused by the environment (1). Environmental factors that have been researched as potential causes of CKDu include heavy metal exposure, high seasonal temperatures, pesticide use, mycotoxins, polluted water resources, and snake bites. In order to comprehend and avoid CKDu, it may be useful to highlight common risk factors across various international settings and populations as the underlying aetiologies in most locations have not been adequately defined. 30% and 21%, respectively, of ESRD patients have diabetes and hypertension; however, younger individuals in underdeveloped nations are more likely to have glomerulonephritis and CKD with an unknown aetiology. As a result, the goal of this research was to follow the theoretical research on AFB1 and its part in the aetiology of chronic renal disease, which is yet unknown.

KEYWORDS: Toxin, AFB1, Human Health, Carcinogen.

INTRODUCTION

Considering the issue of food security as well as due to the Financial damages brought on by this, poisoning of agricultural commodities with AF is a severe issue (2). It is estimated that solely corn harvests in the USA lose 52 million dollars annually (3).

Aflatoxin exposure varies in severity and duration according to the health disorders it causes. Numerous health problems, including cancer, hepatocellular carcinoma, liver cirrhosis, infertility, aflatoxicosis, immunodeficiency, anemia, stunting, nephropathy, underweight in humans, and nutritional interference, can be brought on by aflatoxins poisoning (4). Also, recent research suggests that populations that use maize as a main dietary source may be at risk for neural tube problems due to the B aflatoxins (5). According to Darwish WS (4), ochratoxins, zearalenone, deoxynevalenol, and beauvericin are the next most prevalent mycotoxins in Africa after aflatoxins (43.75%), fumonisin (21.87%), and ochratoxins (12.5%). In samples gathered from a number of African nations, comprising Benin, Ghana, Mali, Togo, and Bourkina Faso, as well as Lesotho, Sudan, Zambia, Uganda, Kenya, Egypt, Tunisia, Tanzania, Morocco, South Africa, and Nigeria, they found high levels of aflatoxin. In small-scale studies in sub-Saharan Africa, exposure to aflatoxin while pregnancy has been linked to poor birth outcomes. The SHINE (Sanitation Hygiene Infant Nutrition Efficacy) experiment is a significant, a community-based, cluster-randomized study conducted in Zimbabwe with the goal of examining the impacts of a combination of diets and cleanliness treatments on the development and the potential role of aflatoxin exposure (6).

In addition to their presence in food and consuming agricultural products, aflatoxin might be discovered in biological samples. In fact, monitoring aflatoxin exposure is crucial in humans and animals by looking for indicators for Aflatoxin in bodily fluids like blood and urine (7).

Since the damage to human health of the estimated

aflatoxin exposure affects 4.5 billion people on a continuous basis can be viewed as being extremely high (8). The liver, which is often in charge of detoxifying chemicals and toxins, is where aflatoxin has its most severe effects on people. During severe aflatoxicosis, Hepatocellular damage and death are caused by the AFB1-epoxide's interactions with different cellular macromolecules. Aflatoxin exposure in humans and animals resulted in substantial bile duct growth and considerable necrosis of parenchymal cells in liver tissue samples (9).

Experiments conducted in China and African nations with high rates of hepatitis B infection and widespread dietary aflatoxin exposure have provided evidence of aflatoxin's detrimental impact on human health. Blood tests have revealed that a relatively high percentage of West Africans are aflatoxin-exposed, suggesting that exposure to aflatoxins in West Africa is common and likely begins in utero. About 98% of participants in a research conducted in Nigeria, Guinea Conakry, the Gambia and Senegal tested positive for aflatoxin indicators (10).

According to reports, B aflatoxin causes liver and kidney cancers in rats, and there may be a connection to an increase in esophageal cancer. Animal products such visceral organs, milk, and meat contain mycotoxins and their metabolites and eggs as well as plant-derived meals, contaminated air, and dust are all risk factors, have been shown to cause human exposure to mycotoxins. This has led to the recent recognition of aflatoxins as a significant sanitary issue (11).

According to reports, Aflatoxins are quickly absorbed in the digestive system after ingestion (because to their low molecular weight) by an unidentified passive mechanism. After 15 minutes, metabolites of aflatoxins are subsequently detected in the blood, and as soon as 12 hours after feeding, they are detected in milk (12). Aflatoxins are hepato-carcinogenic and can lead to aflatoxicosis in episodes of poisoning, especially when combined with prolonged viral hepatitis B infection. Moreover, exposure to aflatoxin in Gambian children has been linked to a lower amount of salivary IgA. (13).

Mycotoxin exposure happens in regions of the world inappropriate storage practices and food handling are common. starvation is an issue, and there are few restrictions in place to safeguard the population who are exposed. A. flavus-contaminated food products are a common way for people to become infected with AFB1. Both humans and animals exposed to AFB1 develop liver cancer. It also causes acute hepatotoxicity. Hemorrhage, Hepatocellular necrosis in the periportal region with bile duct injury are the hallmarks of both acute and chronic hepatotoxicity from AFB1 (14).

AFLATOXINB1

AflatoxinB1 circulate in human bloodstream with concentration 10-30 ng /liter of blood ,Also transferred to woman milk (AFM1) with concentration ranged from 16-1990 ng / liter of milk (15) (16). Consuming contaminated food is the major method of contact to AFB1 (17). Yet, individuals exposed to the environment have reported using the dermal and inhalation channels (18).

Child malnutrition, Reye syndrome, toxic hepatitis, liver fibrosis, and immunodeficiency are a few of the negative impacts on human health associated with exposure to AFB1 (19). (20). Together with infection with the hepatitis B virus, AFB1 is a substantial health risk for hepatocellular cancer (21). Aflatoxin exposure during infancy can also affect a child's ability to grow (22).

In epidemiological research examining how exposure to mycotoxin is related and disease risk, biomarkers of exposure to AFB1 were crucial (23). Aflatoxin binds to and disrupts the enzymes and substrates necessary for the transcription, translation, and beginning of protein synthesis. They engage in interactions with purines and purine nucleosides, creating adduct with proteins, DNA, and RNA that hinder protein synthesis. Aflatoxin also prevents the production of RNA by interfering with RNA polymerase activity that is DNA-dependent and causes endoplasmic reticulum degranulation. Moreover, increased liver and renal necrosis may be the cause of the decreased protein levels in bodily tissues such the heart, liver, kidney, and skeletal muscle (24). AFB1 is a potent immunosuppressive, teratogenic, mutagenic, and carcinogen that has the potential to impair normal protein synthesis processes and block multiple metabolic systems, harming various organs, including the kidney, liver, and heart (25). Aflatoxins have been documented to have an impact on a variety of body organs, including the heart, skeletal muscles, lungs, brain, liver, kidneys, testicles, and numerous exocrine and endocrine organs (26).

The decreased amount AFB1 harms the liver, as seen by a decrease in total protein, because protein synthesis is impaired, as well as on the kidney where aflatoxins are known to suppress Activity of DNA-dependent RNA polymerase, RNA production and endoplasmic reticulum degranulation (25). According to reports, AFB1 causes liver pallor, discoloration, enlargement, In broiler chickens given aflatoxin, the liver parenchyma was congested, hepatocytes'

cytoplasmic vacuolation or fatty modifications, necrosis, and necrosis of the newly developed biliary system were all present as well as mononuclear and heterophilic cell infiltration (27).

According to research on animals, under typical conditions, 50% of the oral dose of AFB1 is promptly absorbed in the duodenum and delivered to the liver via the portal system. The liver and kidneys, to a lesser extent, have high concentrations of AFB1. Furthermore, free AFB1 or water-soluble metabolites may be discovered in the mesenteric venous blood (28).

Evaluating AFB1 occupational exposure and performing risk assessments as a result assessment can both benefit from the use of internal dosage biomarkers. These indicators can be found in bodily fluids such milk, urine, serum plasma, and faeces, and they may comprise metabolites or free aflatoxins. However, it must be remembered that such assessments may provide data about aflatoxin intake as well as the extent of particular absorption (affected by several factors, such as the specific work performed and each person's distinct metabolic rates) and digestion itself (29).

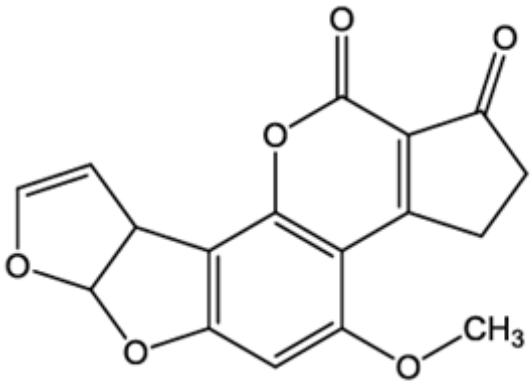
Rapid covalent reactions occur between AFB1 activated form and macromolecules such proteins, cellular DNA, RNA, and other types of ribonucleic acids. The soluble component of liver homogenates contains a NADPH-dependent cytoplasmic enzyme can also be used to reduce AFB1 and produce aflatoxicol (AFL). As seen in various species, These AFB1 biotransformation metabolites may all remain as residues in the liver. These residues are regarded as indicators of dietary toxin exposure (30).

They have garnered more attention than other mycotoxins because AFB1 showed the strongest carcinogenic effects in both people and animals. Many developing nations, like Saudi Arabia, have tried to lessen the toxicity of aflatoxins by enacting regulations that govern exposure and set limitations on how much of these poisons can be present in food and animal feed. Nonetheless, it is recognized that achieving absolute safety is exceedingly difficult. In naturally contaminated food, Of the 17 chemicals, AFB1 is the most pervasive, dangerous, and carcinogenic AFs that have been identified so far (31).

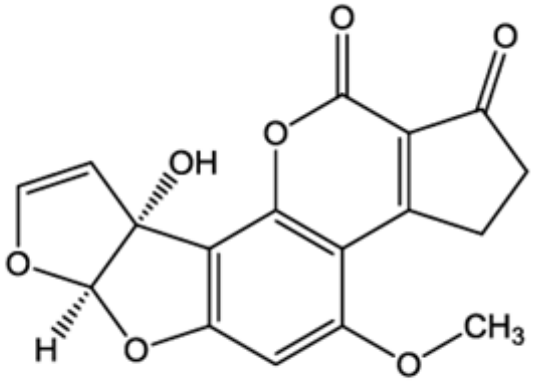
PHYSIOCHEMICAL PROPERTIES OF AFB1

AflatoxinB1 ($C_{17}H_{12}0_6$, MW $_{312}$) is crystalline compound, is 10–20 mg/litre moderately polar solvents including methanol, chloroform, and water, as well as and dimethylsulfoxide. AFB1 fluoresces when exposed to UV light. AFB1's crystalline form is stable at temperatures of 100Co in the absence of light, especially UV radiation. According to its chemical makeup, AFB1 is a fused dihydrofurofuran moiety on a desirable alternative coumarin structure (14).

One of AFB1's hydroxylated metabolites, aflatoxin M1 (C17H1207, MW 328), is secreted in urine and discovered in the milk of mammals that eaten AFB1. When subjected to UV light, AFB1 exhibits the designation B is due to the large amount of fluorescence emission in the blue region and the joining of a lactone ring from the coumarin structure with a cyclopentenone ring (Figure 2).(32)



Aflatoxin B1 (AFB1)



Aflatoxin M1 (AFM1)

Figure 2 shows the chemical compositions of aflatoxin B1 and aflatoxin M1 (32).

The chemical makeup of both poisons is similar; they are easily soluble in polar organic solvents but only minimally soluble in water and nonpolar solvents (33). They possess significant thermal stability that keeps them from being thermally damaged during the production of food, even at high temperatures (>100 Co). This represents a significant barrier to reducing food contamination with aflatoxin, especially in dairy products like milk as pasteurization and other heat

treatments by themselves have shown to be ineffective (34).

They become unstable in UV light when there is oxygen present and at severe p H levels (3 or >10). In an alkaline environment, the lactone ring opens, which results in the destruction of aflatoxin; however, in an acidic environment, this process is reversible. At high temperatures, ammoniation opens the lactone ring, resulting in the irreversible decarboxylation of aflatoxins. (35).

AFLATOXIN INGESTION, DISTRIBUTION, METABOLISM, EXCRETION, AND MODES OF ACTION

Because of their chemical makeup, most mycotoxins are chemicals that are highly liposoluble and absorbable from the exposure site, including the respiratory and gastrointestinal tracts, entering the bloodstream, from which point they might expand throughout the body and reach other organs including the liver and kidneys (36).

As aflatoxins enter the body, they are taken up by cell membranes and eventually reach the bloodstream. The liver, which is the main organ for xenobiotic processing, receives them through the blood to a variety of tissues. Aflatoxins are mostly processed a reactive epoxide intermediate is produced by the liver, or the less dangerous aflatoxin M1 (37). P450s are widely distributed in nature, which means that every organism contains them. Plant poisons, environmental carcinogens, and a wide range of anticancer medications are just a few examples of the exogenous

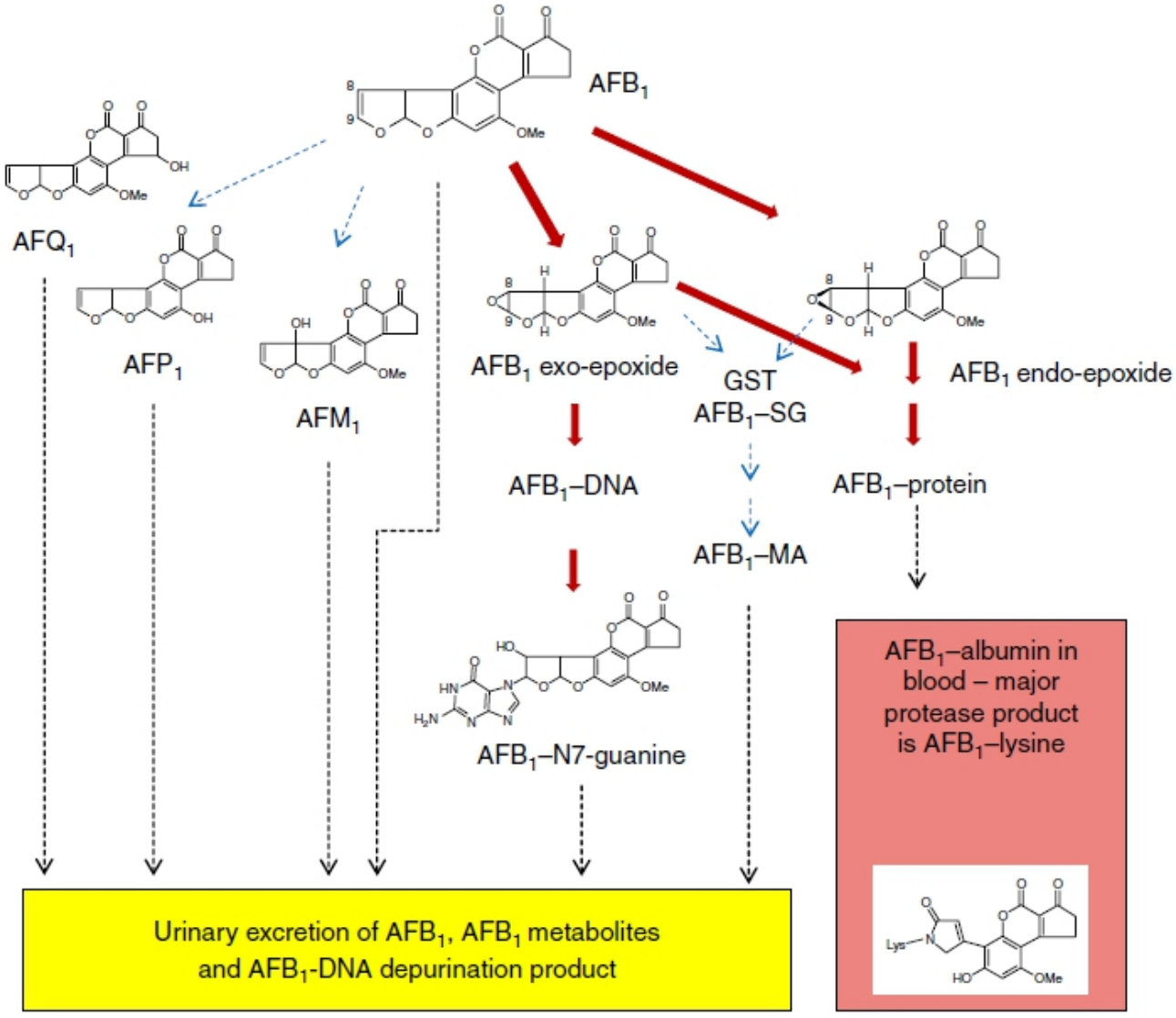


Fig. 3 : Biomarkers and the Metabolism of Aflatoxin B1. Mercapturic Acid, Glutathione, Glutathione S-transferase, GST, Routes Through the Blood or Excretion that are Connected to or Unrelated to Epoxide Toxicity (41).

and endogenous substances that are subject to oxidative metabolism by P450 enzymes that metabolise xenobiotics. First and foremost, P450 enzymes in the human liver are in charge of activating the electrophilic AFB1-8,9-epoxide from AFB1. AFB1 can be activated to produce mutagenic metabolites and derivatives related to DNA by five distinct P450s from the human liver, such as 1A2, 2A6, 2B7, 3A3, and 3A4 (14).

A reactive form of aflatoxin called aflatoxin-8, 9-epoxide binds to DNA and albumin in blood serum to generate DNA-damaging adducts, is produced by the cytochrome P450 (CYP450) microsomal enzymes in humans and sensitive animal species. Aflatoxin is transformed into aflatoxin-8,9-epoxide by a variety of CYP450 enzyme isoforms in the liver. This reactive oxygen species can attach to proteins to induce acute toxicity (aflatoxicosis) or to DNA to trigger liver cancer. (37).

The primary CYP enzymes involved in the metabolism of human AFB1 in the liver are CYP3A4, CYP3A5, and CYP1A2, whereas lipoxygenases and prostaglandin H synthase appear to be important in its biotransformation in the lung (38, 39). There are numerous pathways in AFB1's metabolism, including some of which are shown in figure 3. Additional processes include odealkylation to AFP1, hydroxylation to AFM1 and AFQ1, and ketoreduction to AFL. The metabolites of aflatoxin B1, including AFM1, AFQ1, and AFP1, as well as AFB1-N7-guanine, the DNA adduct's depurination product, can be used as biomarkers to determine whether a person has been exposed to this mycotoxin. Moreover, the blood adduct of AFB1 and albumin or AFB1 and lysin (40) are helpful biomarkers of exposure.

Because immune-mediated mechanisms include constantly proliferating and differentiating cells, the immune system is vulnerable to aflatoxin. Chronic aflatoxin exposure has been shown to directly depress immunological function in both humans and animals, particularly in cell-mediated responses, as seen in (Figure 4). (42).

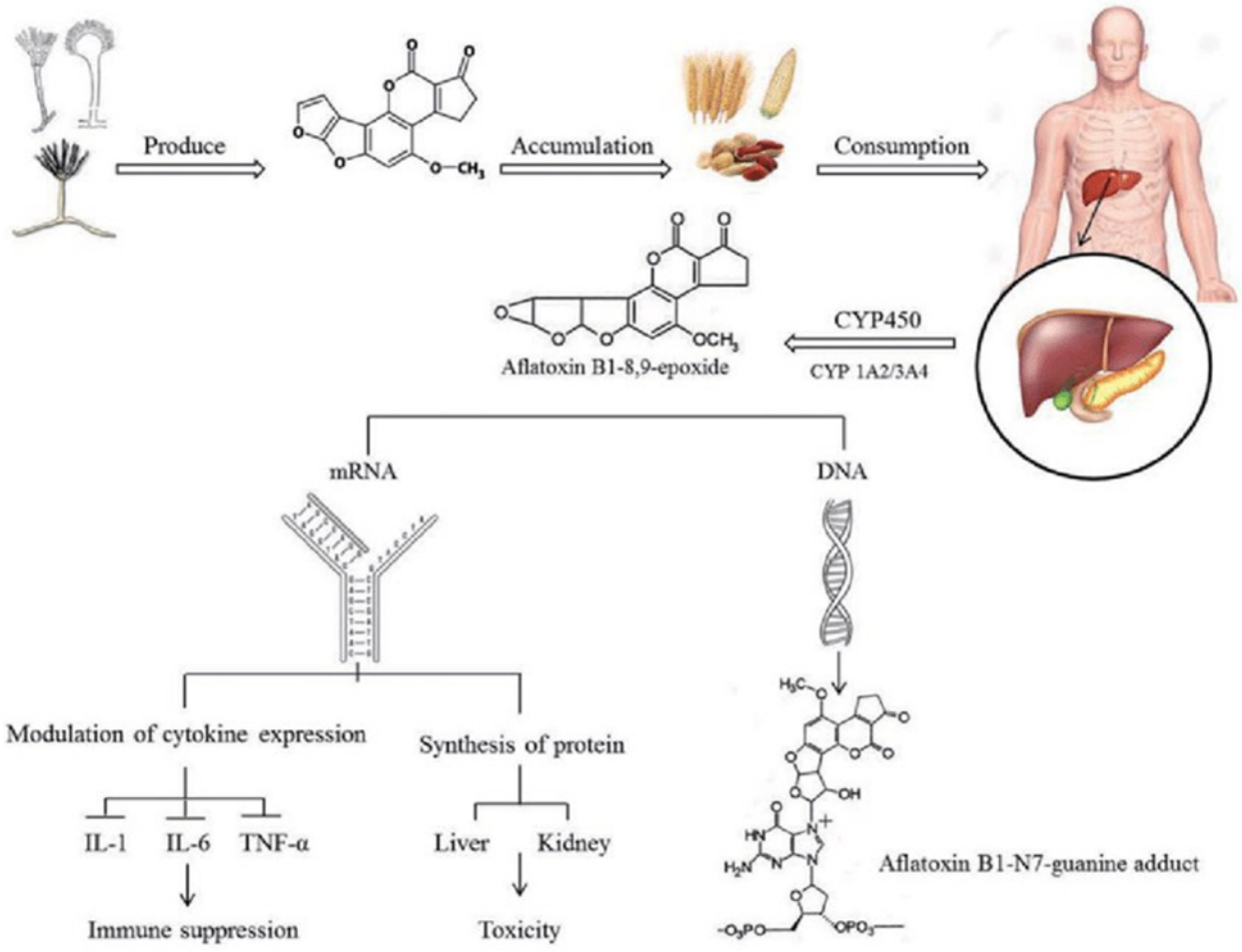


Fig. 4: Aflatoxin B1's Toxicological Life Cycle (42).

AFB1 is metabolised by CYP3A4, a distinct isoform of P450, to AFB1-endo-epoxide, a less hazardous product that can be eliminated in a variety of ways and cannot bind to nucleic acids. Exo- and endo-epoxides can both quickly hydrolyze without enzymes to form by reacting with serum albumin's lysine's -amino group, AFB1-8,9 dihydrodiol is produced. (43).

AFB1 attaches to DNA as well, altering its structural properties and resulting in gene alterations as well as adjustments to cell cycle control points and telomere length (44). The genetic blueprint that controls cell growth is corrupted by the liver cells' AFB1 binding to DNA at the guanine base, which results in the development of tumours (44). Apoptosis (increased cell death) and ATP production disruption are caused by mutation-induced harm to mit-DNA and mitochondrial membrane adduction (45). By interfering with the various control points that control the growth and proliferation of the cell cycle, Reactive aflatoxin-8, 9-epoxide can affect the mitotic (M) phase, growth (G1 and G2), and DNA synthesis phase (S phase) of the cell cycle, which can all have an impact on cell dysregulation and the emergence of cancer (46). according to Figure 5.

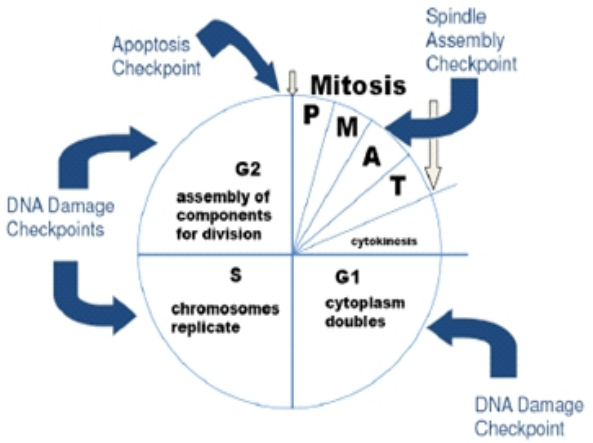


Fig. 5: A Number of Cell Cycle Check Points, A Number of Cell Cycle Phases, Including G1 and G2 Gaps (Growth Phase), P-Prophase, M-Metaphase, A-Anaphase, T-Telophase, and S-Synthetic DNA Phase, Can be harmed by the Binding of Aflatoxins and AF-8,9-epoxide. (47).

According to published research, AFB1 can cross the human placenta and be digested by in-country enzymes. Depending on where the placenta is in its development, the placenta has varying concentrations of P450 enzymes. The tissue-specific lipoxygenase, however, has the ability to epoxidize AFB1 to ALF (48). The epoxide can also be detoxified enzymatically by conjugating to glutathione by the action of glutathione Stransferase (49).

GSH serves as an antioxidant and performs a variety of tasks related to membrane preservation and stability, Lowered oxidative stress variables associated with lipid peroxidation and high levels of reactive oxygen species (ROS) they produce similar to how it aids in the liver's ability to remove aflatoxins and other chemicals (50). (51).

Increased GSH depletion causes metabolic processes to become uncoupled, which compromises cell membranes and causes lipid peroxidation. It also results in unusually high amounts of ROS, which are detected in aflatoxin-affected cells. This lowering intensifies the harm caused by the 8, 9 epoxides to vital biological components (DNA, lipids, and proteins). Nevertheless, the AFB1-8, 9-epoxide metabolite's reaction with DNA to produce adducts has the most harmful side effects (52). The adduct causes gene alterations that result in liver malignancies, notably hepatocellular carcinomas, and is comparatively resistant to DNA repair mechanisms (50).

AFM1 contamination of human milk is a serious problem due to these drugs' ability to penetrate the human placenta and accumulate there; infant exposure to them might start during pregnancy. (53). A recent epidemiological investigation, however, found Breast milk contains AFB1, AFB2, AFG1 and AFG2 in Egyptian women (54). According to reports, the biliary pathway is used to eliminate AFB1 and AFM1 the most, followed by the urine pathway. Furthermore, AFB1 was detected in two calves' kidney and urine at varied amounts after being given 0.8 mg and 1.8 mg/kg body weight, respectively (55). The two AFs' and their metabolites' specific mechanism of toxicity is still unknown.

CARCINOGENICITY OF AFB1

AFB1 is classified by the World Health Organization (WHO) as a class 1 carcinogen. (56). AFB1 may also contribute to clinically diagnosed cases of gastrointestinal cancer in Asians and Africans, according to a number of epidemiological studies (57).

Aflatoxin B1 has been identified as the mycotoxin that causes cancer the most among the other mycotoxins. It has been demonstrated that aflatoxin B1 may penetrate cell membranes and bind to DNA, where it causes permanent changes. (58).

AFB1 is converted by liver p450 enzymes to aflatoxin-8, 9-exo-epoxide. Particularly the p53 tumour suppressor gene is susceptible to the extremely reactive exo-ability of epoxides to interact with proteins, DNA, and RNA to produce derivatives (59).

When AFB1 binds to DNA, it forms the most

significant promutagenic adduct, 8, 9 dihydro-8-(N7 guanyl)-9-hydroxy. AFB1-N7-Gua can then be converted into an AFB1-formamidopyrimidine (AFB1-FABY) adduct, which can result in mutations that change guanine (G) into thymine (T) (60). According to figure 6.

Moreover, these adducts may cause the p53 tumour suppressor genes codon 249 to change from arginine to serine, rendering the gene inoperable and promoting the development of cancer (61). In addition to the hepatotoxicity of AFB1 that was previously discussed, other negative effects on different organs, such as the kidney (62).

aflatoxin that is primarily ingested by humans and animals. Other forms of aflatoxin exposure include ingestion of aflatoxins that are transferred milk and milk derivatives, such as cheese and powdered milk, are produced from feed. (b) by inhaling aflatoxins, particularly AFB1, from contaminated meals in factories and enterprises (26).

In human groups who are more likely to acquire hepatocellular carcinoma, several epidemiological investigations examined urinary aflatoxin M1, aflatoxinserum aflatoxin-albumin/lysin adduct, N7-guanine, and as indicators of AFB1 exposure (65) (23).

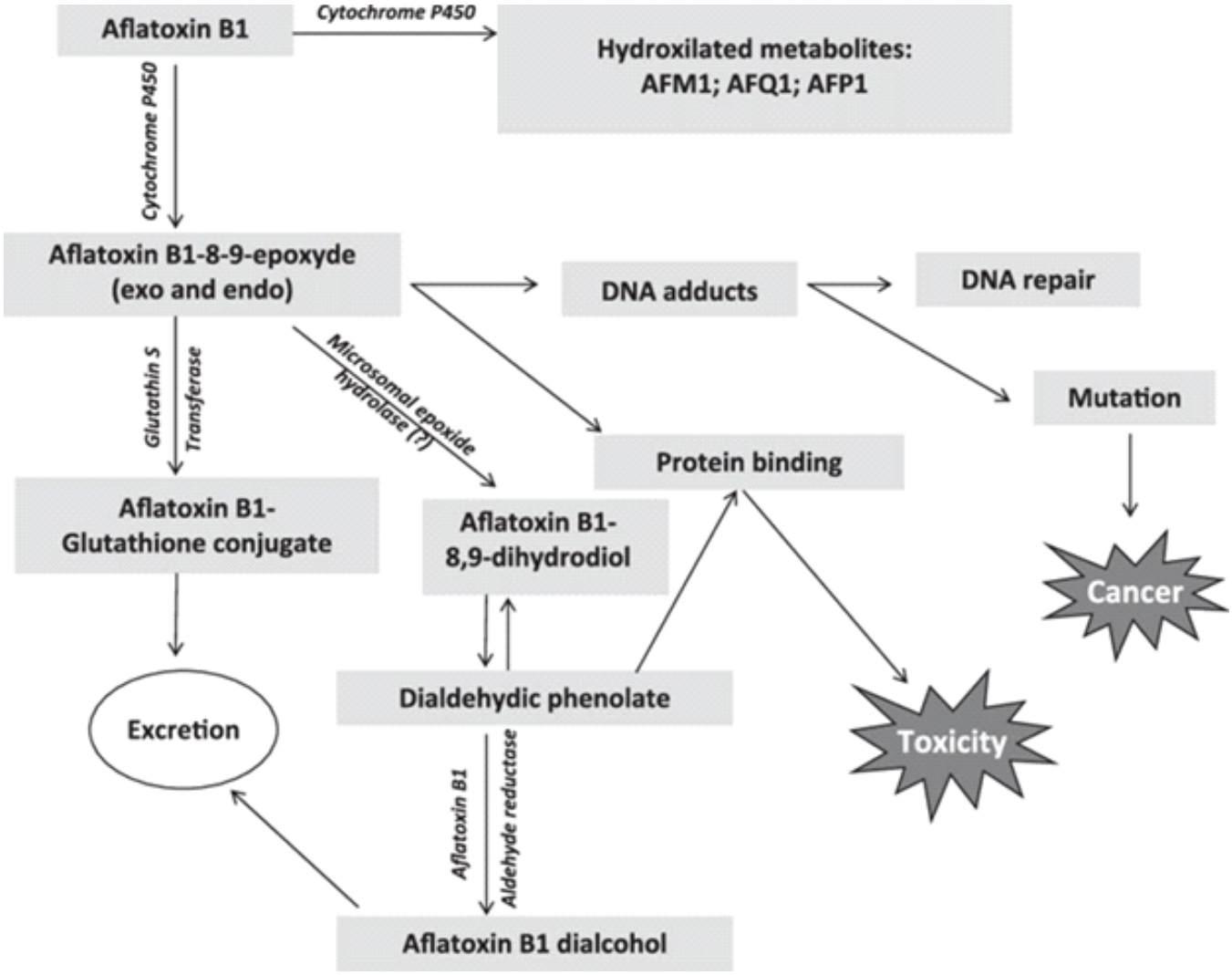


Fig. 6: Pathways of Aflatoxin B1biotransformation (63).

Human exposure to AFB1

Flavonoids are extremely liposoluble substances that are quickly absorbed from the exposure site into the blood stream, typically via the respiratory tract and digestive system. AFM1 is the predominant form of

CHRONIC CONDITIONS ASSOCIATED WITH AFLATOXIN

The most prevalent and serious chronic condition brought on by lifetime exposure to modest levels of aflatoxins is cancer. Despite the fact that eating

aflatoxins has historically associated with primary liver cancer, including HCC and bile duct hyperplasia (66). These mycotoxins have also been linked to the development of cancer in a number of organs, including the viscera, bone, kidney, pancreas, and bladder (67).

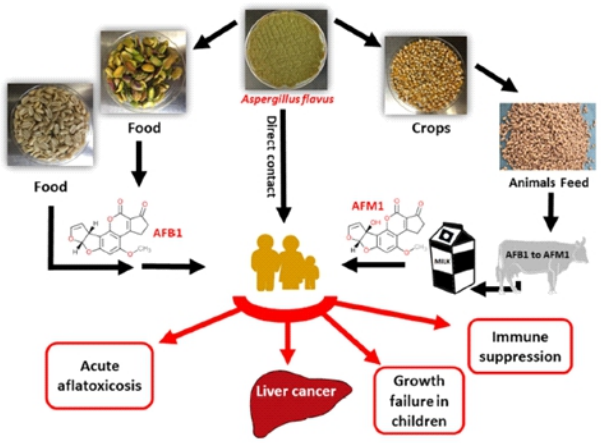


Figure 7- AFB1 and AFM1's main Contamination/exposure Routes, Harmful Human Health Consequences, and other Information Are Summarised in a Schematic Presentation. (64).

It was predicted that only Aflatoxin B1 alone causes 25,200 to 155,000 cases annually (68), approximately 40% of those incidents taking place in sub-Saharan Africa (8). due to the fact that one-third of all liver cancer cases found on the African continent are attributable to aflatoxin (69). China, which has the highest liver cancer frequency in the world on a global scale, has the majority of its liver cancer cases in its southern region, where exposure to dietary aflatoxins and HB chronic infections is widespread and most frequent. (66).

Adverse renal consequences are linked to AFB1 exposure in animal studies. The exposed animals had significantly lower levels of total proteins and higher amounts of urea and creatinine (70). Treatment of poultry with food contaminated with AFB1 can cause renal tubular epithelial cells to degenerate, tubular blood sinus congestion, a substantially greater kidney/body the weight index, a lower glomerular filtration rate, a decrease in renal tubular reabsorption and glucose function, an increase in sodium and potassium excretion, among other things. (71).

In postmortem kidney specimens from Nigerian youngsters, substantial percentages of aflatoxins and other mycotoxins (aflatoxin 60%) were found (72) , and ochratoxin levels were 61.29% and 93.5%, respectively, in the urine of CKD patients from Sri Lanka. (73). The kidney is vulnerable to a variety of toxic chemicals because of how much blood it receives, how much blood flows in at rest (20–25%), and how much circulating toxins get to the kidneys (74).

Due to their heavy activity, the kidneys also require a lot of oxygen and nutrients; as a result, they filter about one-third of the blood that enters them, and 98–99% of the salt and water is reabsorbed. Before being eliminated in the urine, aflatoxins, especially AFB1 and its metabolites, cause nephrotoxicity in several areas of the nephrone (24).

According to reports, increased renal necrosis is what causes the protein content to decrease as a result of aflatoxin exposure (75). In experimental animals, AFB1 has been shown to generate kidney tumours, while in 80% of hamsters, a combination of Hepatic and renal tumours were discovered to be caused by AFB and AFG. (76).

In the proximal renal tubules, Furthermore, megalocytosis and kidney abnormalities were seen - like characteristics. AFB1-exposed African birds were reported to experience congestion and parenchyma haemorrhageaberrant glomerular epithelial cell growth, fatty and hemorrhagic kidney syndrome, glomerular basement membrane thickness, aberrant glomerular epithelial cell growth, and degenerative changes in renal tubular cells (27). Other animals' glomerular filtration rates, glucose uptake, tubular transport of organic anions and electrolytes, as well as the kidney alkaline phosphatases, pyruvate and glutamate-oxaloacetate transaminases, and were all found to be affected by aflatoxins, their metabolites, and the ROS they produced. AFB1 led to the loss of microvilli, chromatin aggregation, and mitochondrial degeneration in cultured kidney cell lines. (27).

There are a number of mycotoxins that have been suggested as nephritis causes. A study of the mycotoxin levels in urine from 31 CKDu patients found that fumonisins (19.4%), ochratoxins (93.5%), and aflatoxins (61.3%) were present (77).

These indications point to AFB1's potential accumulation in human kidneys and Despite the fact that no research has looked at the connection in human populations, AFB1 exposure and impaired kidney function, there may be a link to chronic kidney disease in individuals (72).

Information on exposure over the course of two to three months is provided by AFB1-albumin adducts (78). The Lys product is the sole protein adduct of AFB1 that has been described. The production of this substance may boost AFB1's acute toxicity and carcinogenic potential. Adducts have been discovered in cord blood (79) and peripheral blood (80).

METHODS OF DETECTION SERUM AFLATOXIN B1

For the purpose of finding mycotoxins, it's critical to design quick, accurate, and repeatable assays. Several academics are interested in the precise and quick qualitative and quantitative examination for mycotoxins. There have been established various analytical techniques with varying sensitivity and accuracy that can be utilised for various objectives. Enzyme immunoassays, Techniques including high-performance liquid chromatography (FD), TLC, and HPLC with UV or fluorescence detection are widely used to assess mycotoxins (EIAs). Mycotoxins can now be evaluated both qualitatively and quantitatively using recently developed techniques like liquid chromatography-mass spectrometry (LC-MS) and gas chromatography-mass spectrometry (GC-MS). (81). The most popular quantitative techniques for studying and the methods for analyzing High performance liquid chromatography (HPLC), thin layer chromatography (TLC), and liquid chromatography (LC) are all methods used to analyze aflatoxins (82). These methods have excellent sensitivity but frequently call for experienced operators, thorough sample preparation, and pricey machinery (83).

TLC, or thin-layer chromatography, is a method that can be used to separate, assess the purity of, and pinpoint organic molecules. One of the most popular separation methods in aflatoxin analysis is TLC, also known as simple chromatography or planar chromatography. In normal-phase TLC, a stationary phase, such as cellulose, silica, or alumina, is immobilised on a glass or plastic plate while the mobile phase is a solvent. The sample, which may be a liquid or one that has been dispersed in a spot of the solvent is positioned on the stationary phase.. By running standards beside the unidentified spot, a sample's composition can be determined. The solvent then travels up the plate through capillary action after being positioned vertically in a tank with one edge of the plate in it. The plate is withdrawn from the tank once the solvent has reached the other edge, and the separated spots are seen using UV, fluorescence, MS, or other methods because the components have various partitioning behaviours (81).

Indicators of normal biological or pathological processes that may be objectively examined and assessed are called biomarkers, poisonous reactions to a hazardous agent or pharmacologic reactions to a therapeutic intervention. The three categorised biomarker types are susceptibility, response, and exposure (84).

Mycotoxin biomarkers are components of mycotoxins or the consequences of their relationship to target molecules, such as protein or DNA adducts and glucuronide conjugates, that can be identified in bodily fluids or tissues and linked to ingested mycotoxins (85).

Biomarkers track cellular, biological, or molecular alterations in bodily tissues, cells, or fluids to detect disease or chemical exposure. The identification of specific biomarkers may aid in the identification, diagnosis, and treatment of people who a.re afflicted and at risk but still asymptomatic since biomarkers are used to monitor or suggest biological processes. Environmental agent biomarker development should be based on detailed understanding of metabolism, byproduct generation, and overall mechanism of action (28). AFM1, a hydroxylated metabolite of AFB1 that is found in breast milk and indicates exposure over the previous 24 hours, and aflatoxin-albumin adduct (AF-alb) in plasma or serum are the biomarkers for aflatoxin exposure. AF-alb has a half-life of 2 months and allows the assessment of more chronic exposure to aflatoxin. (86). Using HPLC-fluorescence or LC-MS/MS to measure the serum proteolytic digests' AFB1-lysine aflatoxin-lysine adduct is an alternative approach for determining aflatoxin exposure utilising the AF-albumin adduct (87).

All of these techniques may be used to investigate the indirect assessment of AFs adducts, such as the serum AFB1-lysine adduct, which may be a good indicator of the long-term effects of aflatoxin exposure. Also, it may be a good idea to use these techniques to examine gene expression, which can provide light on the processes of aflatoxicosis and lessen its impact on renal damage, particularly in cases of unknown aetiology. The final step in food detection is the development of nanomaterials technologies that can precisely identify the contents and specific components (AFB1 adduct).

REFERENCE

1. Nanayakkara S, Senevirathna STMLD, Harada KH, et al. Systematic evaluation of exposure to trace elements and minerals in patients with chronic kidney disease of uncertain etiology (CKDu) in Sri Lanka. J Trace Elem Med Biol. 2019 Jul;54:206-213.
2. Kumar P, Mahato DK, Kamle M, Mohanta TK, Kang SG. Aflatoxins: A Global Concern for Food Safety, Human Health and Their Management. Front Microbiol. 2017 Jan 17;7:2170.
3. Mitchell NJ, Bowers E, Hurburgh C, Wu F. Potential economic losses to the US corn industry from aflatoxin contamination. Food Addit

Contam Part A Chem Anal Control Expo Risk Assess. 2016;33(3):540-50.

4. Darwish WS, Ikenaka Y, Nakayama SM, Ishizuka M. An overview on mycotoxin contamination of foods in Africa. J Vet Med Sci. 2014 Jun;76(6):789-97.
5. Wild CP, Gong YY. Mycotoxins and human disease: a largely ignored global health issue. Carcinogenesis. 2010 Jan;31(1):71-82.
6. Smith LE, Mbuya MNN, Prendergast AJ, Turner PC, Ruboko S, Humphrey JH, Nelson RJ, Chigumira A, Kembo G, Stoltzfus RJ. Determinants of recent aflatoxin exposure among pregnant women in rural Zimbabwe. Mol Nutr Food Res. 2017 Sep;61(9).
7. Sulaiman SH, Jamaluddin R, Sabran MR. Association between Urinary Aflatoxin (AFM_1) and Dietary Intake among Adults in Hulu Langat District, Selangor, Malaysia. Nutrients. 2018 Apr 7;10(4):460.
8. Williams JH, Phillips TD, Jolly PE, Stiles JK, Jolly CM, Aggarwal D. Human aflatoxicosis in developing countries: a review of toxicology, exposure, potential health consequences, and interventions. Am J Clin Nutr. 2004 Nov;80(5):1106-22.
9. Jolly PE, Shuaib FM, Jiang Y, Preko P, Baidoo J, Stiles JK, Wang JS, Phillips TD, Williams JH. Association of high viral load and abnormal liver function with high aflatoxin B1-albumin adduct levels in HIV-positive Ghanaians: preliminary observations. Food Addit Contam Part A Chem Anal Control Expo Risk Assess. 2011 Sep;28(9):1224-34.
10. Sowley E. Aflatoxins: A silent threat in developing countries. African Journal of Biotechnology. 2016; 15. 1864-1870.
11. Jarvis BB. Chemistry and toxicology of molds isolated from water-damaged buildings. Adv Exp Med Biol. 2002;504:43-52.
12. Moschini, Ricardo & Sisterna, Marina & Carmona, Marcelo. Modelling of wheat black point incidence based on meteorological variables in the southern Argentinean Pampas region. Australian Journal of Agricultural Research -(2006). AUST J AGR RES. 57.
13. Turner PC, Moore SE, Hall AJ, Prentice AM, Wild CP. Modification of immune function through exposure to dietary aflatoxin in Gambian children. Environ Health Perspect. 2003 Feb;111(2):217-20.
14. Kensler TW, Roebuck BD, Wogan GN, Groopman JD. Aflatoxin: a 50-year odyssey of mechanistic and translational toxicology. Toxicol Sci. 2011 Mar;120 Suppl 1(Suppl 1):S28-48.
15. Dharumadurai D., Shanmugapriya S., Thajuddin N., Annamalai P. (2011). Aflatoxins and Aflatoxicosis in Human and Animals.
16. Magan N., Olsen M. (Eds.). Mycotoxins in food: detection and control. s.l. : Woodhead Publishing, 2004.
17. Iqbal SZ, Asi MR, Hanif U, Zuber M, Jinap S. The presence of aflatoxins and ochratoxin A in rice and rice products; and evaluation of dietary intake. Food Chem. 2016 Nov 1;210:135-40.
18. Malik A, Ali S, Shahid M, Bhargava R. Occupational exposure to Aspergillus and aflatoxins among food-grain workers in India. Int J Occup Environ Health. 2014 Jul-Sep;20(3):189-93.
19. Chu YJ, Yang HI, Wu HC, et al. Aflatoxin B1 exposure increases the risk of hepatocellular carcinoma associated with hepatitis C virus infection or alcohol consumption. Eur J Cancer. 2018 May;94:37-46.
20. McMillan A, Renaud JB, Burgess KMN. et al. Aflatoxin exposure in Nigerian children with severe acute malnutrition. Food Chem Toxicol. 2018 Jan;111:356-362.
21. Sun Z, Chen T, Thorgeirsson SS, et al. Dramatic reduction of liver cancer incidence in young adults: 28 year follow-up of etiological interventions in an endemic area of China. Carcinogenesis. 2013 Aug;34(8):1800-5.
22. Turner PC. The molecular epidemiology of chronic aflatoxin driven impaired child growth. Scientifica (Cairo). 2013;2013:152879.
23. Turner PC, Flannery B, Isitt C, et al. The role of biomarkers in evaluating human health concerns from fungal contaminants in food. Nutr Res Rev. 2012 Jun;25(1):162-79.
24. Sharma V., Sharma C., Paliwal R. et al. (2011). Ameliorative Effects of Curcuma Longa and Curcumin onAflatoxin B1 Induced Serological and Biochemical Changes In Kidney of Male Mice. Asian Journal of Biochemical and Pharmaceutical Research. 2. 338-351.
25. Mohammed A.M., Metwally N.S. Antiaflatoxicogenic activities of some aqeous plant extracts against AFB1 induced renal and cardiac damage. Journal of Pharmacology and Toxicology, 2009; 4, 1-16.

26. Bbosa G., Kitya D., Lubega A. et al. Review of the Biological and Health Effects of Aflatoxins on Body Organs and Body Systems. 2013 10.5772/51201.
27. Hussain Z. Khan M., Hassan Z. Development, Dairy & Production, Poultry & Singh, Toba. . Production of aflatoxins from Aspergillus flavus and acute aflatoxicosis in young broiler chicks. Pakistan Journal of Agricultural Sciences. 2008 45.
28. Jager A., Ramalho F., Zambelli L. Biomarkers of Aflatoxin Exposure and Its Relationship with the Hepatocellular Carcinoma..
29. Viegas S, Veiga L, Figueiredo P, et al. Assessment of workers' exposure to aflatoxin B1 in a Portuguese waste industry. Ann Occup Hyg. 2015 Mar;59(2):173-81.
30. Ramalho LNZ, Porta LD, Rosim RE, et al. Aflatoxin B1 residues in human livers and their relationship with markers of hepatic carcinogenesis in São Paulo, Brazil. Toxicol Rep. 2018 Jul 25;5:777-784.
31. Wu F, Guclu H. Aflatoxin regulations in a network of global maize trade. PLoS One. 2012;7(9):e45151.
32. Marchese S, Polo A, Ariano A, et al. Aflatoxin B1 and M1: Biological Properties and Their Involvement in Cancer Development. Toxins (Basel). 2018 May 24;10(6):214.
33. MdQuadri S.H., Niranjan M.S., Chaluvaraju K.C. at al. An overview on chemistry,toxicity, analysis and control of aflatoxins. Int. J. Chem. Life Sci, 2013Vol. 2, pp. 1071–1078.
34. Jard G, Liboz T, Mathieu F, et al. Review of mycotoxin reduction in food and feed: from prevention in the field to detoxification by adsorption or transformation. Food Addit Contam Part A Chem Anal Control Expo Risk Assess. 2011 Nov;28(11):1590-609.
35. Kumar V. V. Aflatoxins: Properties, toxicity and detoxification. International Journal of Nutrition & Food Science, 2018 Vol. 6.
36. Ahmed Adam MA, Tabana YM, Musa KB, et al. Effects of different mycotoxins on humans, cell genome and their involvement in cancer (Review). Oncol Rep. 2017 Mar;37(3):1321-1336.
37. Wu F, Khlangwiset P. Health economic impacts and cost-effectiveness of aflatoxin-reduction strategies in Africa: case studies in biocontrol and post-harvest interventions. Food Addit Contam Part A Chem Anal Control Expo Risk Assess. 2010 Apr;27(4):496-509.
38. Wild CP, Turner PC. The toxicology of aflatoxins as a basis for public health decisions. Mutagenesis. 2002 Nov;17(6):471-81.
39. Dohnal V, Wu Q, Kuča K. Metabolism of aflatoxins: key enzymes and interindividual as well as interspecies differences. Arch Toxicol. 2014 Sep;88(9):1635-44.
40. Groopman JD, Egner PA, Schulze KJ, et al. Aflatoxin exposure during the first 1000 days of life in rural South Asia assessed by aflatoxin B_1-lysine albumin biomarkers. Food Chem Toxicol. 2014 Dec;74:184-189.
41. Turner PC, Flannery B, Isitt C, et al. The role of biomarkers in evaluating human health concerns from fungal contaminants in food. Nutr Res Rev. 2012 Jun;25(1):162-79.
42. Benkerroum N. Chronic and Acute Toxicities of Aflatoxins: Mechanisms of Action. Int J Environ Res Public Health. 2020 Jan 8;17(2):423.
43. Wild CP, Gong YY. Mycotoxins and human disease: a largely ignored global health issue. Carcinogenesis. 2010 Jan;31(1):71-82.
44. Vermeulen K, Berneman ZN, Van Bockstaele DR. Cell cycle and apoptosis. Cell Prolif. 2003 Jun;36(3):165-175.
45. Neurotoxicity of Mycotoxins. http://www.drthrasher.org/page189.html, (Accessed on 10th June 2012). Thrasher, J. D., & Crawley, S. L. 2012.
46. Ezekiel C., Alabi O. Anokwuru C., Oginni, O. Studies on dietary aflatoxin-induced genotoxicity using two in vivo bioassays. Archives of Applied Science Research. 3. 2011; 97-106.
47. Bbosa G., Kitya D., Lubega A., et al. (2013). Review of the Biological and Health Effects of Aflatoxins on Body Organs and Body Systems. 10.5772/51201.
48. Mantle PG, Faucet-Marquis V, Manderville RA, et al. Structures of covalent adducts between DNA and ochratoxin a: a new factor in debate about genotoxicity and human risk assessment. Chem Res Toxicol. 2010 Jan;23(1):89-98.
49. Kuilman ME, Maas RF, Fink-Gremmels J. Cytochrome P450-mediated metabolism and cytotoxicity of aflatoxin B(1) in bovine hepatocytes. Toxicol In Vitro. 2000 Aug;14(4):321-7.
50. Halliwell B. Oxidative stress and cancer: have we

moved forward? Biochem J. 2007 Jan 1;401(1):1-11.

51. Verma R. J.Aflatoxin Cause DNA Damage. International Journal of Human Genetics, 2003; Vol. 4, pp. 231-236.
52. Zhang X, Zhang QY, Liu D, et al. Expression of cytochrome p450 and other biotransformation genes in fetal and adult human nasal mucosa. Drug Metab Dispos. 2005 Oct;33(10):1423-8.
53. Galvano F, Pietri A, Bertuzzi T, et al. Maternal dietary habits and mycotoxin occurrence in human mature milk. Mol Nutr Food Res. 2008 Apr;52(4):496-501.
54. Polychronaki N, West RM, Turner PC, et al. A longitudinal assessment of aflatoxin M1 excretion in breast milk of selected Egyptian mothers. Food Chem Toxicol. 2007 Jul;45(7):1210-1215.
55. Polychronaki N, Wild CP, Mykkänen H, et al. Urinary biomarkers of aflatoxin exposure in young children from Egypt and Guinea. Food Chem Toxicol. 2008 Feb;46(2):519-26.
56. Thrasher JD, Crawley S. The biocontaminants and complexity of damp indoor spaces: more than what meets the eyes. Toxicol Ind Health. 2009 Oct-Nov;25(9-10):583-615.
57. M. A. Abdel-Wahhab, A. Ibrahim, A. A. El-Nekeety. et al. Meyer extractcounteracts the oxidative stress in rats fed multi-mycotoxinscontaminated. "Panax ginseng C.A. 3, 2012, Comunicata Scientiae,, Vol. 3, pp. 143-153.
58. Forouharmehr A, Harkinezhad T, Qasemi-Panahi B. Effect of Aflatoxin B1 on Growth of Bovine Mammary Epithelial Cells in 3D and Monolayer Culture System. Adv Pharm Bull. 2013;3(1):143-6.
59. Qi LN, Bai T, Chen ZS, et al. The p53 mutation spectrum in hepatocellular carcinoma from Guangxi, China : role of chronic hepatitis B virus infection and aflatoxin B1 exposure. Liver Int. 2015 Mar;35(3):999-1009.
60. Dai Y, Huang K, Zhang B, et al. Aflatoxin B1-induced epigenetic alterations: An overview. Food Chem Toxicol. 2017 Nov;109(Pt 1):683-689.
61. Aflatoxins as a cause of hepatocellular carcinoma. Kew, M.C. 3, 2013, Journal of Gastrointestinal & Liver Diseases, Vol. 22, pp. 305-310.
62. Vitamin E supplementation ameliorates aflatoxin B1-induced nephrotoxicity in rats. Abdel-Hamid, A.A., Firgany Ael, D.,. 2015, Acta Histochem, Vol. 117, pp. , 767-779.
63. Overview on aflatoxins and oxidative stress. Marin, D. E., & Taranu, I. 3-4, 2012, Toxin Reviews, Vol. 31, pp. 32–43.
64. Controlling aflatoxin contamination and propagation of Aspergillus flavus by a soy-fermenting Aspergillus oryzae strain. Alshannaq, A. F., Gibbons, J. G., Lee, M.-K., Han, K.-H., Hong, S.-B., & Yu, J.-H. 1, 2018, Scientific Reports, Vol. 8.
65. Present and futuredirections of translational research on aflatoxin and hepatocellularcarcinoma: a review. Wogan GN, Kensler TW, Groopman JD. 2012, Food Addit Contam Part A Chem Anal Control Expo Risk Assess, Vol. 29, pp. 249–257.
66. Epidemiology and natural history of hepatocellular carcinoma. McGlynn, K.A. and London, W.T. 2005, Best Pract. Res., Vol. 19, pp. 3–23.
67. Harmful effect and control strategies of aflatoxin B1 produced by Aspergillus flavus and Aspergillus parasiticus strains on poultry: Review. Fouad, M.A., et al. 2019, Toxins (Basel), Vol. 11, p. 176.
68. Global burden of aflatoxin-induced hepatocellular carcinoma: Arisk assessment. Liu, Y. and Wu, F. 2010, Environ. Health Perspect, Vol. 118, pp. 818–824.
69. World Health Organization estimates of the global and regional disease burden of four foodborne chemical toxins,2010: A data synthesis. Gibb, H., et al. 2015, F1000Reserch, Vol. 4, p. 1393.
70. Protective effect of curcumin against experimentally induced aflatoxicosis on the renal cortex of adult male albino rats: a histological and immunohistochemical study. AM, El-Mahalaway. 2015, Int J Clin Exp Pathol , Vol. 8, pp. 6019–6030.
71. Evaluation of toxicological impacts on Sprague–Dawley rat by successively low dose of aflatoxin B1. Wei, W., et al. 14, 2014, J. Sci. Food Agric, Vol. 94, pp. 3017-3022.
72. Determination of environmental exposure to microcystin and aflatoxin as a risk for renal function based on 5493 rural people in Southwest China. Lin, H., Liu, W., Zeng, H., Pu, C., Zhang,

R., Qiu, Z., ... & Yang, X. 10, 2016, Environmental science & technology, Vol. 50, pp. 5346-5356.

73. Mycotoxin detection in urine samples from patients with chronic kidney disease of uncertain etiology in Sri Lanka. Desalegn, B., et al. 1, 2011, Bull. Environ. Contam. Toxicol, Vol. 87, pp. 6-10.
74. Is indoor mold contamination a threat to health? Harriet, A. M. 2, 2003, Journal of Environmental Health,, Vol. 62, pp. 0022-0892.
75. Experimental aflatoxin B1 toxicosis in young rabbits- A clinical and patho-anatomical study. Lakkawar, A. W., Chattopadhyay, S. K., & Johri, T. S. 2004, Slovenian Veterinary Research, Vol. 41, pp. 73-81.
76. Review of the biological and health effects of aflatoxins on body organs and body systems. Bbosa, G. S., Kitya, D., Lubega, A., Ogwal-Okeng, J., Anokbonggo, W. W., & Kyegombe, D. B. 2013, Aflatoxins-recent advances and future prospects, Vol. 12, pp. 239-265.
77. Mycotoxin detection in urine samples from patients with chronickidney disease of uncertain etiology in Sri Lanka. Desalegn, B., Nanayakkara, S., Harada, K. H., Hitomi, T.,Chandrajith, R., Karunaratne, U., et al. 1, 2011, Bulletin of Environmental Contamination and Toxicology,, Vol. 87, p. 6.
78. Aflatoxin B1 exposure, hepatitis B virus infection and hepatocellular carcinoma in Taiwan. Wu H., Wang Q., Yang H. et al. 3, 2009, Cancer Epidemiology Biomarkers and Prevention., Vol. 18, pp. 846-853.
79. TP53 R249S mutations,exposure to aflatoxin and occurrence of hepatocellular carcinoma in a cohort of chronic hepatitis B virus carriers from Quidong, China. Szymanska K., Chen J., Cui Y., Gong Y. et al. 5, 2009, Cancer Epidemiology Biomarkers and Prevention., Vol. 18, pp. 1638-1643.
80. Aflatoxin exposure in utero causes growth faltering in Gambian infants. Turner P., Collinson A., Cheung Y., Gong. Y et al. 2007, International Journal of Epidemiology, Vol. 36, pp. 1119-1125.
81. Qualitative and quantitative analysis of mycotoxins. Rahmani, A., Jinap, S., & Soleimany, F. 3, 2009, Comprehensive Reviews in Food Science and Food Safety, Vol. 8, pp. 202-251.
82. Matrix-free analysis of aflatoxins in pistachio nuts using parallel factor modeling of liquid chromatography diodearraydetection data. Vosough, M., Bayat, M., and Salemi, A. 1, 2010, Analytica chimica acta, Vol. 663, pp. 11–18.
83. Rapid detection of food-borne contaminants using an array biosensor. Sapsford, K., Ngundi, M., Moore, M., Lassman, M., Shriver-Lake, L., Taitt, C., and Ligler,F. 2, 2009, Sensors and Actuators B: Chemical, Vol. 113, pp. 599–607.
84. Mycotoxin Biomarkers of Exposure A Comprehensive Review. Vidal, A., et al. 2018, Compr. Rev. Food Sci. Food Saf., Vol. 17, pp. 1127–1155.
85. The role of mycotoxins in the human exposome: Application of mycotoxin biomarkers in exposome-health studies. Marín, S., et al. 2018, Food Chem. Toxicol., Vol. 121, pp. 504–518.
86. Aflatoxin Exposure and Associated Human Health Effects, a Review of Epidemiological Studies. Gong, Y. Y., Watson, S., & Routledge, M. N. 1, 2016, Food Safety, Vol. 4, pp. 14–27. doi:10.14252/foodsafetyfscj.2015026 (https://doi.org/10.14252/foodsafetyfscj.2015026).
87. Quantitative analysis and chronic dosimetry of the aflatoxin B1 plasma albumin adduct Lys-AFB1 in rats by isotope dilution mass spectrometry. Scholl PF, McCoy L, Kensler TW, Groopman JD. 2006, Chem Res Toxicol, Vol. 19, pp. 44-49.

Orcid ID:

Rana Majeed Hameed - https://orcid.org/0000-0002-3567-5425

Maher Abbood Mukheef - https://orcid.org/0000-0002-8787-4522

Hassan H. Khader - https://orcid.org/0000-0003-0462-5983

Ghizal Fatima - https://orcid.org/0000-0001-8516-655X

Subuhi Anwar - https://orcid.org/0000-0002-0505-1494

How to cite this article:

Anwar S., Yadav D. Developmental Delay in Children Associated with Screen Time. Era J. Med. Res. 2023; 10(1): 61-73.