Chapter 12

Review of the Biological and Health Effects of Aflatoxins on Body Organs and Body Systems

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1. Introduction

Aflatoxins are a group of naturally occurring carcinogens that are known to contaminate different human and animal food stuffs. Aflatoxins are poisonous by-products from soil-borne fungus *Aspergillus*, which is responsible for the decomposition of plant materials [1-9]. The occurrence of aflatoxins foods and food products vary with geographic location, agricultural and agronomic practices. The susceptibility of food product to fungal attack occurs during pre-harvest, transportation, storage, and processing of the foods [1, 2, 4, 6, 9, 10]. The problem of aflatoxin contamination of the food products is a common problem in tropical and subtropical regions of the world especially in the developing countries such as the sub-Saharan countries with poor practices and where the environmental conditions of warm temperatures and humidity favors the growth fungi [1, 2, 4, 6, 9, 10]. The various food products contaminated with aflatoxins include cereals like maize, sorghum, pearl millet, rice and wheat; oilseeds such as groundnut, soybean, sunflower and cotton; spices like chillies, black pepper, coriander, turmeric and zinger; tree nuts such as almonds, pistachio, walnuts and coconut; and milk and milk products [11]. The aflatoxins were initially isolated and identified as the causative agent in Turkey X disease that caused necrosis of the liver in 1960 and over 100,000 turkeys died in England and USA and the death was attributed to the consumption of a mould-contaminated peanut meal [2, 6, 9, 12, 13]. Very high concentrations of aflatoxins are most often found in nutritive seeds such as maize, nuts and cereal grains in Africa and rice in China and Southeast Asia [2, 6, 9, 12-14].

Difuranocoumarins	Type of aflatoxin	*Aspergillus specie(s)*
Difurocoumarocyclopentenone series	Aflatoxin B_1 (AFB_1)	*A. flavus, A. arachidicola, A. bombycis, A. minisclerotigenes, A. nomius, A. ochraceoroseus, A. parasiticus, A. pseudotamarii, A. rambellii, Emericella venezuelensis*
	Aflatoxin B_2 (AFB_2)	*A. arachidicola, A. flavus, A. minisclerotigenes, A. nomius, A. parasiticus*
	Aflatoxin B_{2a} (AFB_{2a})	*A. flavus*
	Aflatoxin M_1 (AFM_1)	*A. flavus, A. parasiticus*; metabolite of aflatoxin B_1 in humans and animals and comes from a mother's milk
	Aflatoxin M_2 (AFM_2)	Metabolite of aflatoxin B_2 in milk of cattle fed on contaminated foods
	Aflatoxin M_{2A} (AFM_{2A})	Metabolite of AFM_2
	Aflatoxicol (AFL)	*A. flavus*, metabolite of AFB_1
	Aflatoxicol M_1	Metabolite of AFM_1
Difurocoumarolactone series	Aflatoxin G_1 (AFG_1)	*A. arachidicola, A. flavus, A. minisclerotigenes, A. nomius, A. Parasiticus*
	Aflatoxin G_2 (AFG_2)	*A. arachidicola, A. flavus, A. minisclerotigenes, A. nomius, A. parasiticus*
	Aflatoxin G_{2A} (AFG_{2A})	Metabolite of AFG_2
	Aflatoxin GM_1 (AFG_1)	*A. flavus*
	Aflatoxin GM_2 ($AFGM_2$)	Metabolite of AFG_2
	$AFGM_{2A}$	Metabolite of $AFGM_2$
	Aflatoxin B_3 (AFB_3)	***Aspergillus*** species not defined
	Parasiticol (P)	*A. flavus*
	Aflatrem	*A. flavus, A. minisclerotigenes*
	Aspertoxin	*A. flavus*
	Aflatoxin Q_1 (AFQ_1)	Major metabolite of AFB_1 in in vitro liver preparations of other higher vertebrates

Table 1. Summary of the major aflatoxins produced by the *Aspergillus* species of Moulds

Aflatoxins are a group of approximately 20 related fungal metabolites produced primarily by the fungi *Aspergillus flavus* and *A. parasiticus* [15-18]. Aflatoxins belongs to a group of difuranocoumarins that are classified into two broad groups according to their chemical structure and they include the difurocoumarocyclopentenone series (AFB_1, AFB_2, AFB_{2A}, AFM_1, AFM_2, AFM_{2A} and aflatoxicol) and the difurocoumarolactone series (AFG_1, AFG_2, AFG_{2A}, $AFGM_1$, $AFGM_2$, $AFGM_{2A}$ and AFB_3) [15-19], (Table 1 and figure 1).

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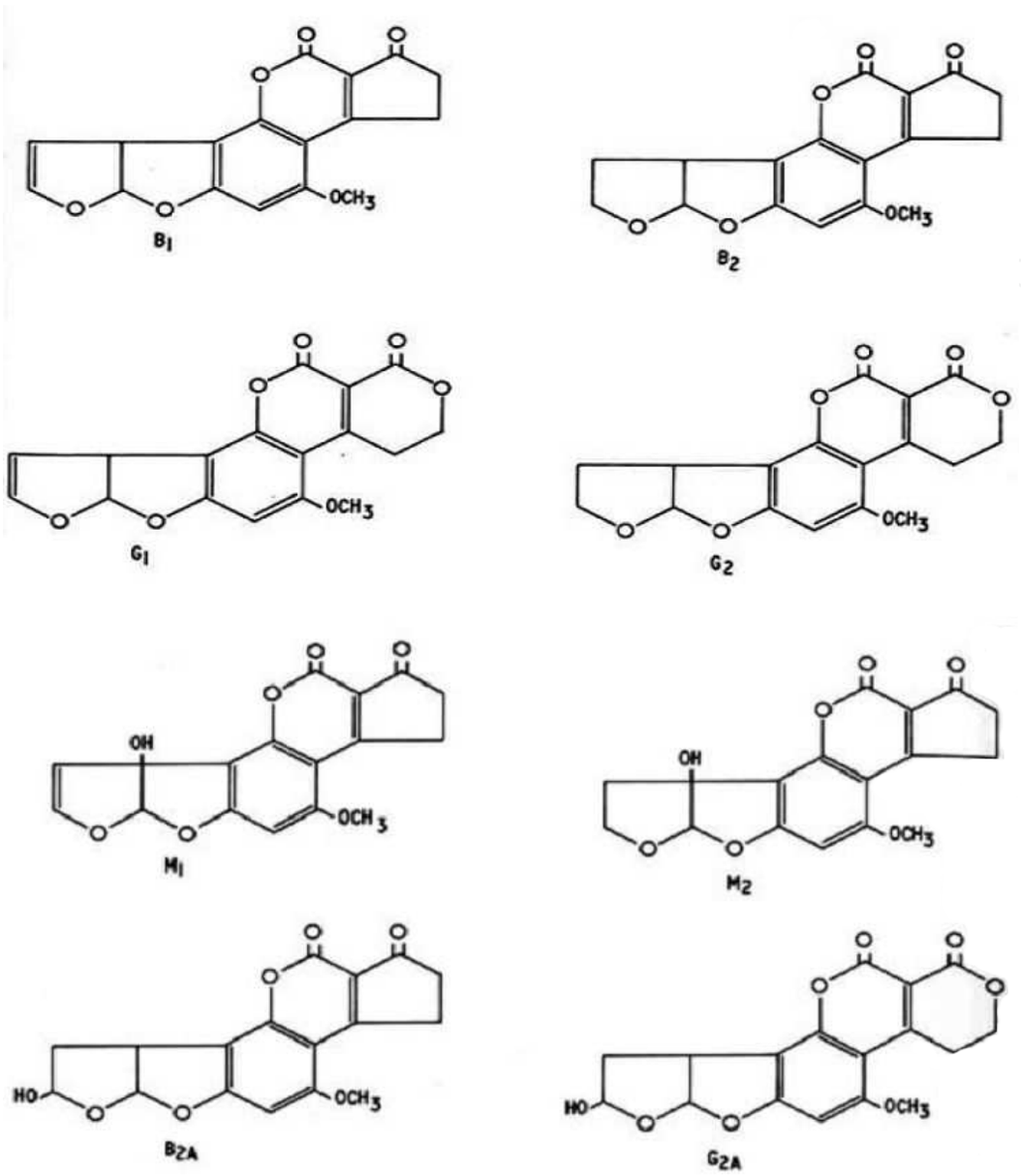

Figure 1. Structures of the major aflatoxins B_1, B_2, G_1, G_2, M_1, M_2, B_{2A} and G_{2A} (Adopted from Reddy, 2012)[16]

The four major naturally known aflatoxins produced by the *Aspergillus* species of mold include AFB_1, AFB_2, AFG_1 and AFG_2 where the "B" and "G" refer to the blue and green fluorescent colors produced under UV light on thin layer chromatography plates, while the subscript numbers 1 and 2 indicate major and minor compounds, respectively. Whereas the B designation of aflatoxins B_1 and B_2 result from the exhibition of blue fluorescence under UV-light, while the G designation refers to the yellow-green fluorescence of the relevant structures under UV-light [2, 6, 9, 12, 13]. The metabolic products of aflatoxins, M_1 and M_2 were first isolated from milk of lactating animals fed on Moldy grains contaminated with aflatoxin hence, the M designation [2, 4]. These toxins have closely similar structures (Figure 1) and form a unique group of highly oxygenated, naturally occurring heterocyclic com-

pounds. Aflatoxins B_2 and G_2 were established as the dihydroxy derivatives of B_1 and G_1, respectively. Whereas, aflatoxin M_1 is 4-hydroxy aflatoxin B_1 and aflatoxin M_2 is 4-dihydroxy aflatoxin B_2. Of the four major aflatoxins (B_1, B_2, G_1 and G_2), G_2 occurs in high quantities though less toxic while AFB_1 is the most toxic of all the aflatoxin. The World Health Organization (WHO) classifies AFB_1 as a class 1 carcinogen [4, 6, 9, 18]. The aflatoxins display potency of toxicity, carcinogenicity, mutagenicity in the order of AFB_1> AFG_1> AFB_2> AFG_2 [15-19]. The extent of toxicity depends on the organ affected especially the liver. The lethal toxicity of aflatoxin B_1 varies in different animals from extremely susceptible (Sheep, Rat, Dog) to resistant species (Monkey, Chicken, Mouse). However, there are no toxicity in humans though epidemiological data from studies in Africa, South Africa, South East Asia and India implicate aflatoxins in the incidence of liver cancer especially the hepatobiliary carcinoma and death of children due to malnutrition, kwashiorkor and marasmus [20, 21]. Aflatoxins have been associated with various diseases like aflatoxicosis and other health problems in humans, livestock and domestic animals globally.

2. Absorption, distribution, metabolism, excretion and mechanisms of action of aflatoxins

Aflatoxins are highly liposoluble compounds and are readily absorbed from the site of exposure usually through the gastrointestinal tract and respiratory tract into blood stream [22, 23]. Human and animals get exposed to aflatoxins by two major routes (a) direct ingestion of aflatoxin-contaminated foods or ingestion of aflatoxins carried over from feed into milk and milk products like cheese and powdered milk as well as other animal tissues mainly as AFM_1 [22](b) by inhalation of dust particles of aflatoxins especially AFB_1 in contaminated foods in industries and factories [24]. After entering the body, the aflatoxins are absorbed across the cell membranes where they reach the blood circulation. They are distributed in blood to different tissues and to the liver, the main organ of metabolism of xenobiotics. Aflatoxins are mainly metabolized by the liver to a reactive epoxide intermediate or hydroxylated to become the less harmful aflatoxin M1 [25, 26]. In humans and susceptible animal species, aflatoxins especially AFB_1 are metabolized by cytochrome P450 (CYP450) microsomal enzymes to aflatoxin-8,9-epoxide, a reactive form that binds to DNA and to albumin in the blood serum, forming adducts and hence causing DNA damage [25, 26]. Various CYP450 enzymes isoforms occur in the liver and they metabolize aflatoxin into a reactive oxygen species (aflatoxin-8,9-epoxide), which may then bind to proteins and cause acute toxicity (aflatoxicosis) or to DNA and induce liver cancer [25, 26]. The predominant human CYP450 isoforms involved in human metabolism of AFB_1 are CYP3A4 and CYP1A2. Both enzymes catalyze the biotransformation of AFB_1 to the highly reactive *exo*-8,9-epoxide of AFB1[27]. CYP 1A2 is also capable of catalyzing the epoxidation of AFB_1 to yield a high proportion of *endo*-epoxide and hydroxylation of AFB1 to form aflatoxin M_1 (AFM_1), which is a poor substrate for epoxidation [27] and less potent than AFB_1 [28]. This is generally considered as the major detoxification metabolic pathway for aflatoxins. The CYP3A4 is the major CYP450 enzyme responsible for activation of AFB_1 into the epoxide form and also form

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AFQ_1, a less toxic detoxification metabolite. The CYP3A5 metabolizes AFB1 mainly to the *exo*-epoxide and some AFQ_1 [29]. However, polymorphism studies with CYP3A5 have indicated that, this enzyme isoform is not expressed by most people especially in Africans [28]. Studies in Gambian children showed that aflatoxin cross the placenta and transported to the fetus and the new born where they can cause detrimental effects [28]. The CYP3A7 is a major CYP450 enzyme isoform in human fetal liver and metabolizes AFB_1 to the 8, 9- epoxide that may cause fetal defects to the developing fetus [30].

The epoxidation of AFB_1 to the exo-8, 9-epoxide is a critical step in the genotoxic pathway of this carcinogen. The binding of AFB1 to DNA and DNA adduction by AFB_1 exo-8,9 epoxide has been reported to cause a functional changes of DNA conformation [31].The epoxide is highly unstable and binds with high affinity to guanine bases in DNA to form afltoxin-N7-guanine [32]. The aflatoxin-N7-guanine has been shown to be capable of forming guanine (purine) to thymine (pyrimidine) transversion mutations in DNA and hence affecting the p53 suppressor gene in the cell cycle [33, 34]. The p53 gene is important in preventing cell cycle progression when there are DNA mutations, or signaling apoptosis. The mutations have been reported to affect some base pair locations more than others especially in the third base of codon 249 of the p53 gene in the region corresponding to the DNA binding domain of the corresponding protein [13, 34]and this appears to be more susceptible to aflatoxin-mediated mutations than nearby bases [35]. AFB1 induces the transversion of base G to base T in the third position of codon 249 and similar mutations have been observed in hepatocellular carcinoma (HCC) in high AFB_1 contaminated food in regions in East Asia and Africa [34, 36, 37].

Epoxide hydrolase and glutathione-S-transferase (GST) are both involved in hepatic detoxification of activated AFB_1, but the GST-catalyzed conjugation of glutathione to AFB_1-8,9-epoxides is thought to play the most important role in preventing epoxide binding to target macromolecules like DNA and various cell proteins [38]. Glutathione pathway is reported to play a vital role in the detoxification of AFB_1 [39, 40]. The AFB_1 8,9 *exo* and *endo*epoxides are conjugated by glutathione to form AFB-mercapturate and the reaction is catalyzed by glutathione S-transferase (GST) [39, 40]. The glutathione-aflatoxin conjugate is transported from the cells with an ATP-dependent multidrug-resistance protein through an accelerated process [39]. Despite a preference for conjugating the more mutagenic AFB_1 exo-epoxide isomer, the relatively low capacity for GST-catalyzed detoxification of bio-activated AFB_1 in lung may be an important factor in the susceptibility of the lung to AFB_1 toxicity [4, 8, 41].The *exo* and *endo* epoxide can also be converted non-enzymatically to AFB_1-8,9-dihydrodiol which in turn can slowly undergo a base-catalysed ring opening reaction to a dialdehyde phenolate ion [27]. AFB_1 dialdehyde can form Schiff bases with lysine residues in serum albumin forming aflatoxin-albumin complex [42]. Also the aflatoxin dialdehyde are reduced to a dialcohol in a NADPH-dependent catalyzed reaction by aflatoxin aldehyde reductase (AFAR) [43]. However the guanine alkylation by aflatoxin B_1 produces *exo*-8,9-epoxide which is the reactive form and a carcinogen to the liver and the reaction is more than 2000 times more efficient in DNA than in aqueous solution [44], (Figure 2).

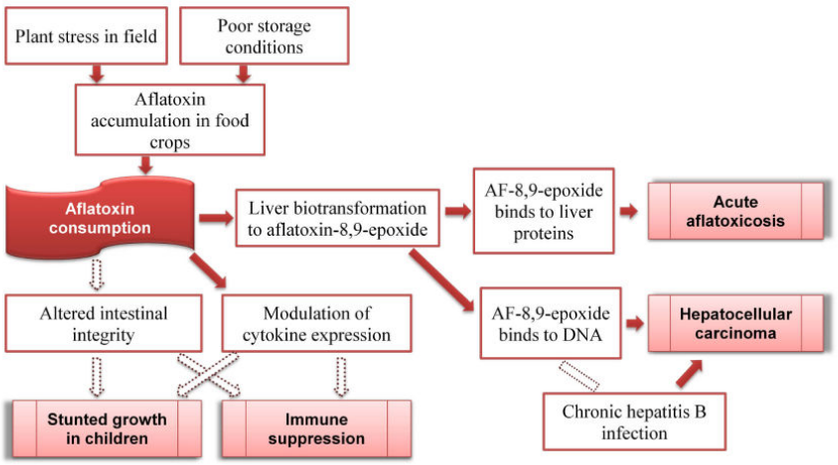

Figure 2. Aflatoxin disease pathways in humans (Adopted from Wu, 2010; Wu, 2011)[10, 26]

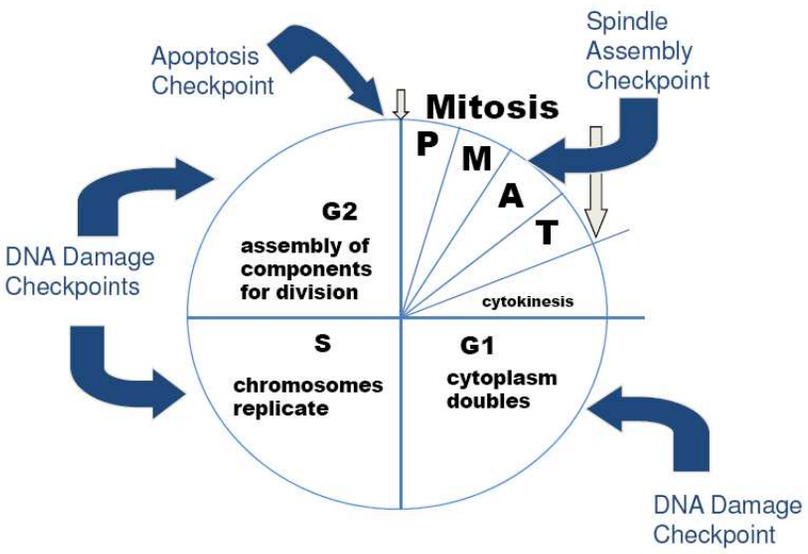

Figure 3. Various check points that can be damaged by binding of aflatoxins and AF-8,9-epoxide causing the deregulation of the cell cycle; P –prophase, M-Metaphase, A- Anaphase, T- Telophase, S- Synthetic DNA phase, G1 and G2 – Gaps (growth phase) [47-49]

2.1. Effect of aflatoxins on mitochondrial DNA

The reactive aflatoxin-8,9-epoxide preferentially binds to mitochondrial DNA (mitDNA) during hepatocarcinogenesis as compared to nuclear DNA that hinder ATP production and FAD/NAD-linked enzymatic functions and this causes the disruption of mitochondrial functions in the various parts of the body that require production of energy in the form of ATP [45]. Aflatoxin damage to mitochondria can lead to mitochondrial diseases and may be responsible for aging mechanisms [45]. It is reported that certain mitochondrial diseases result from the ability of the nucleus to detect energetic deficits in its area. The nucleus attempts to

compensate for the ATP shortages by triggering the replication of any nearby mitochondria but unfortunately, the response promotes replication of the very mitochondria that are causing the local energy deficit hence aggravating the problem [46]. The AFB_1 also binds to DNA and cause structural DNA alterations that lead to gene mutations as well as changes in the length of the telomeres and the check points in the cell cycle [47-49]. The binding of AFB_1 to DNA at the guanine base in liver cells corrupt the genetic code that regulates cell growth, thereby leading to formation of tumors ([45-49]. The damage to mitDNA is caused by adduction and mutations of mitochondrial membranes leading to increased cell death (apoptosis) as well as disruption of energy production (production of ATP) [46, 49, 50]. The reactive aflatoxin-8, 9-epoxide can affect the mitotic (M) phase, growth process (G1 and G2 phase) and DNA synthesis (S phase) in the cell cycle by disrupting the various check points that regulate the cell cycle development and proliferation leading to deregulation of the cell and hence cancer development [47-49], (Figure 3).

However in resistant rodents, their mitDNA is protected from aflatoxins from DNA adducts that effect mitochondrial transcription and translation [46-49]. The mycotoxin alters energy-linked functions of ADP phosphorylation and FAD- and NAD-linked oxidizing substrates and α-ketoglutarate-succinate cytochrome reductases [46-49].

2.2. Effect of aflatoxins on mitochondrial structure

AFB causes ultrastuctural changes in mitochondria [46-49]and also induces mitochondrial directed apoptosis thus reducing their function [20, 29, 48-51]. Also the aflatoxins may affect the telomere length and the various check point in the cell cycle causing further damage to the regulatory processes of the cell cycle [51]. Also the extent of aflatoxin binding to DNA and its damage, the level of different proteins changes from cell cycle and apoptotic pathways such as c-Myc, p53, pRb, Ras, protein kinase A (PKA), protein kinase C (PKC), Bcl-2, NF-kB, CDK, cyclins and CKI contribute to the life or death decision making process that may contribute to the deregulation of the cell proliferation leading to cancer development [34, 48, 49](Figure 3).

2.3. Role of glutathione in detoxification of aflatoxins and their metabolites

However like in hepatic detoxification of aflatoxins and other chemicals, GSH act as antioxidant and has many functions in membrane maintenance and stability as well as in reducing oxidative stress factors and the high reactive oxygen species (ROS) produced from the process of lipid peroxidation [38-41, 46, 52-56]. The increased depletion of GSH leads to abnormally high levels of ROS found in cells affected by aflatoxin due to uncoupling of metabolic processes resulting from the lack of GSH for GSH-peroxidase catalysis of O_2 to H_2O_2 leading to lipid peroxidation and compromised cell membranes. Its reduction further enhances the damage to critical cellular components (DNA, lipids, proteins) by the 8,9 epoxides. However the most serious adverse effects of the AFB1-8,9-epoxide metabolite is that it reacts with amino acids in DNA and forms an adduct [38-41, 46, 52-55]. The adduct are fairly resistant to DNA repair processes and this causes gene mutation that leads to liver cancers especially the hepatocellular carcinomas [38-41, 46, 52-55].

2.4. The role of cytoplasmic reductase in detoxification of AFB_1

Also in the hepatocytes, AFB_1 are converted to other different classes of metabolites by cytoplasmic reductase such as aflatoxicol and by microsomal mixed-function oxidase system to form AFM_1, $AGFQ_1$, AFP_1 and AFB_1 -epoxide (the most toxic and carcinogenic derivative) and these metabolites may be deposited in various body tissues as well as in edible animal products [38-41, 46, 52-55]. These metabolites other than the AFB_1 are less toxic and are conjugated with other molecules that enhance their rapid elimination from the body [22]. The metabolite AFQ_1 has very little cancer-causing potential and they are usually excreted in urine with little effect on the body.

2.5. Effect of aflatoxins on protein synthesis

The aflatoxin binds and interferes with enzymes and substrates that are needed in the initiation, transcription and translation processes involved in protein synthesis. They interacts of with purines and purine nucleosides and impair the process of protein synthesis by forming adducts with DNA, RNA and proteins [57]. Aflatoxin also inhibits RNA synthesis by interacting with the DNA-dependent RNA polymerase activity and thus causes degranulation of endoplasmic reticulum. Also the reduction in protein content in body tissues like in skeletal muscle, heart, liver and kidney could be due to increased liver and kidney necrosis [58]. AFB_1 is a potent mutagenic, carcinogenic, teratogenic, and immunosuppressive and all these may interfere with normal process of protein synthesis as well as inhibition of several metabolic systems thus causing damages to various organs especially the liver, kidney and heart [59, 60].

2.6. Role of aflatoxins in cancer

Aflatoxins especially AFB_1, AFG_1 and AFM_1 are the most toxic, naturally occurring carcinogens known with AFB_1 the most hepatocarcinogenic compound, causing various cancers of the liver and other body organs in humans and animals [4, 14, 45, 61]. Aflatoxin's cancer-causing potential is due to its ability to produce altered forms of DNA adducts. The primary disease associated with aflatoxin intake is hepatocellular carcinoma (HCC, or liver cancer). This disease is the third-leading cause of cancer death globally [4, 45, 61], with about 550,000–600,000 new cases each year. The incidence of liver cancer has been consistently higher in men than in women with a sex ratio ranging from 2 to 3 in most countries [9]. Eighty-three percent of these cancer deaths occur in East Asia and sub-Saharan Africa [62-64]. Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide with extremely poor prognosis. The majority of cases occur in south-east Asia and sub-Saharan Africa where the major risk factors of chronic infection with hepatitis B and C viruses (HBV and HCV) as well as dietary exposure to aflatoxins are a problem [9, 25, 61, 65]. Aflatoxin B_1, the most commonly occurring and potent of the aflatoxins is associated with a specific AGG to AGT amino acid transversion mutation at codon 249 of the p53 gene in human HCC, providing mechanistic support to a causal link between exposure and disease [25, 26, 66, 67]. Liver cancer has an increasing incidence that parallels the rise in chronic hepatitis B (HBV) and hepatitis C (HCV) infection [25, 67, 68]. Chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV) can progress to advanced liver disease, including cirrhosis

and hepatocellular carcinoma (HCC), a form of primary liver cancer [25, 61, 67, 68]. HCC is the third leading cause of cancer-related mortality worldwide [69]. The data show that individuals positive for the hepatitis B virus and exposed to aflatoxin in the diet are about 60 times of risk for developing hepato-biliary carcinoma or liver cancer [26, 66, 67] especially in poor developing countries worldwide [67]. Reports have shown that a number of interactions exist between HBV and aflatoxins in development of hepatocellular carcinoma in humans. They may include the fixation of AFB_1-induced mutations in the presence of liver regeneration and hyperplasia induced by chronic HBV infection, the predisposition of HBV-infected hepatocytes to aflatoxin induced DNA damage, an increase in susceptibility to chronic HBV infection in aflatoxin exposed individuals and oxidative stress exacerbated by co-exposure to aflatoxins and chronic hepatitis infection [61](Figure 4).

In humans, epidemiological studies in Africa, Southeast Asia, USA and other countries of the west where there is a high incidence of hepatocellular carcinoma, have revealed an association between cancer incidence and the aflatoxin content of the diet [5, 6, 70]. Aflatoxin B_1 (AFB_1) is a major risk factor in the pathogenesis of liver cancer in Asia and sub-Saharan Africa [71]. Aflatoxin B_1 is a potent liver carcinogen in a variety of experimental animals. It causes liver tumours in mice, rats, fish, marmosets, tree shrews and monkeys following administration by various routes. Types of cancers described in research animals include hepatocellular carcinoma (rats) colon and kidney (rats), cholangiocellular cancer (hamsters), lung adenomas (mice), and osteogenic sarcoma, adenocarcinoma of the gall bladder and carcinoma of the pancreas (monkeys) [5, 6, 12, 70].

3. Health effects of aflatoxins on human and animals (Aflatoxicosis)

Aflatoxicosis is a condition caused by aflatoxins in both humans and animals. It occurs in two general forms (1) the acute primary aflatoxicosisis produced when moderate to high levels of aflatoxins are consumed. Specific acute episodes of disease may include hemorrhage, acute liver damage, edema, alteration in digestion, absorption and/or metabolism of nutrients, and possibly death [5, 6, 12, 69, 70]. Acute dietary exposure to AFB_1 has been implicated in epidemics of acute hepatic injury [13, 72]. Evidence of acute aflatoxicosis in humans has been reported worldwide especially in the third world countries like Taiwan, Uganda, India, Kenya and many others [7]. (2) The chronic primary aflatoxicosis results from ingestion of low to moderate levels of aflatoxins (USAID, 2012). The effects are usually subclinical and difficult to recognize. Some of the common symptoms are impaired food conversion and slower rates of growth with or without the production of an overt aflatoxin syndrome [9]. The chronic forms of aflatoxicosis include (1) teratogenic effects associated with congenital malformations (2) mutagenic effects where aflatoxins cause changes (mutations) in the genetic code, altering DNA and these changes can be chromosomal breaks, rearrangement of chromosome pieces, gain or loss of entire chromosomes, or changes within a gene (3) the carcinogenic effect in which the carcinogenic mechanisms have been identified such as the genotoxic effect where the electrophilic carcinogens alter genes through interaction with DNA and thus becoming a potential for DNA damage and the genotoxic carcino-

gens that are sometimes effective after a single exposure, can act in a cumulative manner, or act with other genotoxic carcinogens which affect the same organs [50, 60]. Chronic effects of aflatoxin has been reported to impair the normal body immune function by either by reducing phagocytic activity or reduce T cell number and function as observed immunological suppression in animal model. Aflatoxins have also been reported to interfere with nutrition in a dose response relationship between exposure to aflatoxin and rate of growth in infants and children [4, 9, 20, 50, 60]. Aflatoxins also causes nutrient modification like vitamin A or D in animal models and thus making them unavailable for the normal body physiology and hence leads to nutritional deficiencies [7, 20].

The contamination of foods and feeds with aflatoxin can cause serious consequences in human and animal health. It is estimated that more than 5 billion people in developing countries worldwide are at risk of chronic aflatoxin exposure due to consumption of aflatoxin-contaminated foods and of these more than 4 billion people develop aflatoxin related liver cancer especially the hepatocellular carcinoma [64, 69, 73, 74]. Aflatoxin exposure is mainly a problem in poor and developing countries with poor regulatory authorities in food processing and storage as well as with high levels of malnutrition. Aflatoxins have also been linked with kwashiorkor and marasmus in most of the sub-Saharan countries in children [20]. Many people in these countries experience chronic aflatoxicosis associated with long-term exposure to low to moderate levels of aflatoxin in the food supply chain. AFB_1, AFB_2 and AFM have been detected in liver, gall bladder, spleen, heart, muscle and kidney [75]. Aflatoxin B_1 exposure results in both steatosis and accumulation of fat and necrosis or cell death of liver cells. The amount of aflatoxins consumed contributes to the mutagenic, carcinogenic, teratogenic, and immunosuppressive health effects in the body. The adverse effect of aflatoxins in humans ranges from acute hepatic toxicity to chronic disease such as liver cancer, haemorrhages, oedema, and even immediate death. Prolonged consumption of aflatoxins has also been reported to cause impaired immune function and malnutrition and stunted growth in children and a number of disabilities and death [7, 76, 77]. Human studies have reported that aflatoxins cause an increase in circulating alpha tumor necrosing factor, suggesting that these mycotoxins are also immunotoxic in humans. Due to the aflatoxin body immunosuppressant, it has been associated with HIV and tuberculosis [66, 67](Figure 2). Aflatoxins also pose a threat to developing fetuses and they are transferred from mother to infant in breast milk. Aflatoxins have been reported to be associated with a Reye-like Syndrome in Thailand, New Zealand, Czechoslovakia, the United States, Malaysia, Venezuela, and Europe [4, 50, 78].

All species of animals are susceptible to aflatoxicosis and the susceptibility of individual animals to aflatoxicosis varies considerably depending on dose, duration of exposure, species, age, sex and nutrition. AFB_1, AFB_2 and AFM have been detected in liver, gall bladder, spleen, heart, muscle and kidney of growing swine when protein and protein-free portions of the diet were separately fed [75]. Chronic exposure of aflatoxins to animals causes immunosuppression and also interferes with protein metabolism and multiple micronutrients that are critical to health due to adduct formation. These adduct are responsible for mutations, cancer, immunosuppression, lung injury and birth defects [46]. In animals, the aflatoxins cause liver dam-

age, decreased milk production, reduced reproductively and suppressed immunity in animals consuming low dietary concentrations. The aflatoxicosis syndrome in animals may also be characterized by vomiting, abdominal pain, pulmonary oedema, convulsions, coma, and death with cerebral edema and fatty involvement of the liver, kidneys, and heart. In dairy and beef cattle, the signs of acute toxicosis include anorexia, depression, dramatic drop in milk production, weight loss, lethargy, gastrointestinal dysfunctions such as ascitis, icterus, tenesmus, abdominal pain, bloody diarrhoea, decreased feed intake and efficiency; weight loss, jaundice, abortion, hepatoencephalopathy, blindness, walking in circles, ear twitching, frothy mouth, photosensitization, bleeding and death [4, 6, 22, 79]. In poultry, beside inappetance, weight loss, decreased egg production, leg and bone problems, poor pigmentation, fatty liver, kidney dysfunction, bruising and death, suppression to natural immunity and susceptibility to parasitic, bacterial and viral infections can occur [6, 22], (Figure 4).

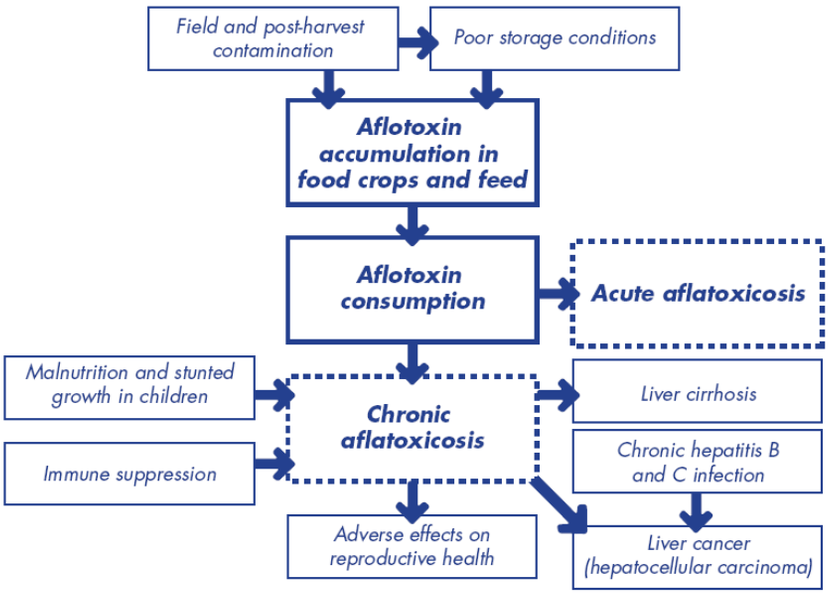

Figure 4. Aflatoxin disease pathways in humans (Adopted from Wu, 2010; USAID, 2012; WHO, 2011; Wu and Tritscher, 2011) [7, 26, 80]

4. Biological effect of aflatoxins on the body organs and body systems

Aflatoxins have been reported to affect the various body organs like the liver, kidneys, lungs, brain, testes and many endocrine and exocrine organs, the heart, skeletal muscles and the different body systems.

4.1. Role of aflatoxins in hepatic injury and other body organs and tissues

Aflatoxins have been reported to cause liver cirrhosis as well as liver cancers [4, 6, 7, 26, 80]. Hepatic injury can be acute or chronic form caused by a variety of toxic agents like aflatox-

ins, chemicals and drugs, trauma and infectious agents [2, 4, 6, 7, 26, 61, 76, 80, 81]. The reduced level of total protein is indicative of the toxic effect of AFB_1 to the liver due to the failure in synthesis of the proteins and kidney in which aflatoxins are known to impair protein biosynthesis by forming adducts with DNA, RNA and proteins, inhibits RNA synthesis, DNA-dependent RNA polymerase activity and causes degranulation of endoplasmic reticulum [58-60]. Acute hepatic injury due to aflatoxin causes a rise in serum enzymes including aspartate aminotransferase, lactate dehydrogenase, glutamate dehyrogenase, gamma-glutamyltransferase and alkaline phosphatase and bilirubin that reflect liver damage as well as other biochemical changes such as proteinura, ketonuria, glycosuria and hematuria [4, 5, 40]. The other frequently used liver enzymes are the alkaline phosphatase (ALP) and Gamma-glutamyltransferase and gamma-glutamyltranspeptidase (GGT and GGTP) that indicate obstruction to the biliary system, either within the liver or in the larger bile channels outside the liver [9, 45, 61]. The presence of jaundice and neurological disorders due to brain damage leading to hepatic encephalopathy are associated with liver failure. Chronic liver failure leads to accumulation of metabolites in circulation such as ammonia and fatty acids that eventually lead to brain damage and hence hepatic encephalopathy [40, 82]. The liver failure makes it unable to detoxify ammonia, the product of protein and amino acid metabolism leading to hyperammonemia that may cross the blood brain barrier leading to increased synthesis of glutamate neurotransmitters henceleading to cytotoxicity of the brain cells and hence the hepatic encephalopathy [82-84]. AFB_1 has been reported to cause pallor discoloration of liver and enlargement of liver and kidneys, congestion of liver parenchyma, cytoplasmic vaculation or fatty change of hepatocytes, necrosis of hepatocytes and newly formed bile ducts, mononuclear and heterophilic cell infiltration are reported in aflatoxin fed broiler chicks [85]. It is also reported that there is a decrease in protein content in skeletal muscle, heart, liver and kidney in aflatoxin-fed animals due to the AFB_1's potent mutagenic, carcinogenic, teratogenic, immunosuppressive and its ability to inhibits several metabolic systems such as protein synthesis thus leading to liver, kidney and heart damage [58-60]. In chicken, the activity of serum or plasma enzymes like the sorbitol dehydrogenase, glutamic dehydrogenase, lactate dehydrogenase, alkaline phosphatase, acid phosphatase, aspartate aminotransferase and alanine aminotransferase were reported to be increased in aflatoxicated chickens [22].

4.2. Effect of aflatoxins on the central nervous system

In the brain or central nervous system, the neurons have a high metabolic rate but little capacity for anaerobic metabolism and subsequently, inadequate oxygen flow to the brain kills the neuronal brain cells within minutes. Some compounds damage neurons or neurotoxic and thus inhibit their function. Mycotoxins especially aflatoxins and its metabolites and other products such as the reactive oxygen species (ROS) like the AFB-8,9-epoxides may interfere with the normal functioning of the nerve cells by forming DNA adducts, protein adducts, oxidative stress factors, mitochondrial directed apoptosis of the nerve cells as well as inhibiting their synthesis of protein, RNA and DNA [40, 44, 47, 50, 52, 54]. Aflatoxins also cause abnormalities in mitochondrial DNA, structure and function, including defective oxidative phosphorylation in the brain cells [29, 49, 50, 54]. The oxidative stress may result in

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damage to critical cellular macromolecules such as DNA, lipids and proteins. Cellular fatty acids are readily oxidized by ROS to produce lipid peroxyl radicals which can subsequently propagate into MDA that may interact with cellular DNA to cause DNA-MDA adduct that may affect energy production in the brain [29, 49, 50, 54]. The role of ROS has been postulated in the development of aging and chronic degenerative diseases, inflammatory diseases and brain cancers [52]. Aflatoxins may also deplete the myelin sheath of the nerves, an important substance that covers the nerves and hence become exposed to insults. Mycotoxins especially aflatoxins have been reported to be toxic to various aspects of brain chemistry and their function [4, 50, 82]. AFB_1 also alters the levels of various biogenic amines (neurotransmitters) and their precursors in rat and mouse brains. Acute AFB_1 treatment in experimental animals has been reported to cause a decrease in regional brain acetylcholinesterase enzymes that may affect the cognitive functions as well as memory and learning of the individual while chronic exposure increases adenohypophyseal acetylcholinesterase [24]. Aflatoxin causes a decrease in dopamine, serotonin and alterations in the levels of the precursor's tyrosine and tryptophan [86-88]. Deficiencies in these neurotransmitter lead to neurological symptoms such as neurocognitive decline and alteration of sleep cycle and symptoms of brain damage like dullness, restlessness, muscle tremor, convulsions, loss of memory, epilepsy, idiocy, loss of muscle coordination, and abnormal sensations [89, 90]. AFB_1 has also been reported to increase the central and peripheral nervous system Na^+/K^+-ATPase, β-glucuronidase and β-galactosidase while inhibiting the Mg^{2+}-ATPse in experimental animals and this also is important in the normal functioning of the glutamate neurotransmitter and their NMDA receptors [24, 53, 91-93]. The liver failure makes it unable to detoxify ammonia, the product of protein and amino acid metabolism leading to hyperammonemia that may cross the blood brain barrier leading to increased synthesis of glutamate neurotransmitters hence leading to cytotoxicity of the brain cells and hence the hepatic encephalopathy [82-84]. Toxic encephalopathy was originally described in children with Reye's syndrome associated with consumption of Aflatoxin B_1 and/or salicylates [78] and subsequently in cases of aflatoxicosis in canines and Chinese children were reported [94]. Aflatoxins also have been linked to Reye's syndrome that is characterized by symptoms of encephalopathy and fatty degeneration of the viscera. It is a pediatric disease characterized by cerebral edema and neuronal degeneration. Toxic encephalopathy due to aflatoxins involves multiple symptoms like loss of balance, recent memory decline, headaches, lightheadedness, spaciness/disorientation, insomnia, loss of coordination [4, 18, 50, 82]. Aflatoxins have been reported to be associated with a Reye-like Syndrome in Thailand, New Zealand, Czechoslovakia, the United States, Malaysia, Venezuela and Europe [4, 9, 24, 50, 78]. Aflatoxins especially AFB_1 have been reported to cause tumors in both the central and peripheral nervous system and several nonepithelial neurogenic tumors like the schwannomas, gliomas, meningiomas and granular cell tumors have been reported [24].

4.3. Effect of aflatoxins on the gastrointestinal tract (GIT)

The gastrointestinal tract (GIT) is the main route of entry of aflatoxins as a result of consumption of aflatoxin-contaminated foods especially AFB_1. It is also the main route of excretion aflatoxin metabolites from the bile. The aflatoxins, metabolites and AF-8,9-epoxides

have been reported to cause intestinal tumors especially the human colon cancers like colon carcinomas and similar results have been reported in experimental animals [24]. Aflatoxins have also been reported to cause serious acute effects on the GIT [95]. Aflatoxins have been implicated as potential factors in the increased incidence of human gastrointestinal and hepatic neoplasms in Africa, Philippines and China [22]. Aflatoxins have been reported to cause digestive system effects such as diarrhea, vomiting, intestinal hemorrhage, and liver necrosis and fibrosis [89]. Aflatoxins have been reported also to damage the integrity of the pancreas. In domestic animals, aflatoxins cause changes in the GIT physiology especially decreased rumen motility and function in cows [24]. In birds, aflatoxins interfere with intestinal morphology, sialic acid production and apparent digestible energy [96].

4.4. Effect of aflatoxins on the respiratory system

Aflatoxins have reported to have serious acute effects on the respiratory systems [95].The respiratory tract is the only organ system with vital functional elements in constant and direct contact with the environment [97]. Many people working in food industries as their occupational setting get exposed to aflatoxins especially AFB_1 when they inhale aflatoxin-contaminated dusts like during grain shelling and processing and have been reported to have a higher incidences of upper respiratory tract and lung cancers [24, 95]. In experimental animals, AFB_1 was reported to induce 100% pulmonary adenomas. In the respiratory tract, aflatoxins may also be converted to active metabolites like in the nasal mucosa [23]. It is also reported that the intranasal administration of AFB_1 lead to formation of tissue-bound metabolites in subtentacular cells, bowman's glands and in neuronal cells in the olfactory mucosa but there is no evidence that AFB_1 may induce tumours in olfactory bulbs [98]. Epoxide hydrolase and glutathione-S-transferase (GST) are both involved in hepatic detoxification of activated AFB_1 but the GST-catalyzed conjugation of glutathione to AFB_1-8,9-epoxides is thought to play more important role in preventing epoxide binding to target macromolecules [23, 89, 99]. However, the low capacity for GST-catalyzed detoxification of bio-activated AFB_1 in lung may be an important factor in the susceptibility of the lung to AFB_1 toxicity ([41]. Nose-only inhalation exposure of rats to AFB_1 aerosols suppressed alveolar macrophage (AM). Intratracheal administration of AFB_1 also suppressed the release of tumor necrosis factor-alpha from AMs and impaired systemic innate and acquired immune defenses as well as suppression of peritoneal macrophage phagocytosis and the primary splenic antibody response thus leading to suppression of respiratory tract defenses system [99].

4.5. Effect of aflatoxins on the cardiovascular system, blood and blood cells

Aflatoxins have reported to have serious acute effects on the cardiovascular systems including vascular fragility and hemorrhaging in tissues [58, 89, 95] as well as heart damage and teratogenic effects [59, 60]. It is reported that there is a decrease in protein content of the muscles of these tissues and organs as well as inhibition of their metabolic processes attributable by the aflatoxin consumption of contaminated foods [59, 60].

4.6. Effect of aflatoxins on the blood and blood cells

The aflatoxins and its metabolites as well as the generated reactive oxygen species(ROS) has been reported to have a deleterious effects on the bone and blood cells as well as induction of cancers on the hemopoietic system in bone marrow and lymphoid organs where blood, blood cells and blood components are produced [52]. The blood system can be damaged by agents that affect blood cell production (bone marrow), the components of blood (platelets, red blood cells, and white blood cells), or the oxygen-carrying capacity of red blood cells or impair blood clotting and their poor growth rates. Oxidative damage by the AFB_1 on human lymphocytes has been reported [100] and significant declines in both the proportion of peripheral blood lymphocytes and in the percentages of ANAE-positive peripheral blood lymphocytes (T-lymphocytes) in a dose dependent manner has been observed [101]. Aflatoxins have been linked to anemia in pregnancy [7, 102] and alterations in erythrocytes during induced chronic aflatoxicosis in rabbit also have been reported [103, 104]. Aflatoxin causes hematopietic suppression and anemia, decrease in total erythrocytes, packed-cell volume and hemoglobin [16] as well as toxicity to red blood cells [103]. Aflatoxin is known to produce hemolytic anemia by decreasing the circulating mature erythrocytes [104]and consequently the spleen appear congested because of an unusually high concentration of inorganic iron and debris from the circulation [103, 104]. In birds, AFB_1 is reported to causes hematological changes [105]. Aflatoxicosis has been reported to cause lymphocytopenia and monocytopenia and increased percentage of neutrophil counts [106]. In cattle, aflatoxins are reported to cause blood coagulation defects that may involve impairment of prothrombin, factors VII and X and possibly factor IX and similar effects are reported in dogs [5]. Generally aflatoxins have been reported to depress growth and alter many aspects of humoral and cellular immunity and thus affecting the hematological parameters [101, 107].

4.7. Effect of aflatoxins on the urinary system

The kidney is susceptible to many toxic agents due to the high amount of blood it receives and about 20-25% of blood that flows in at rest coupled with the large amounts of circulating toxicants that reach the kidneys [89]. The kidneys also have high oxygen and nutrient requirements because of their workload and therefore filters one-third of the blood reaching them and reabsorb 98-99% of the salt and water. Different parts of the nephrone are exposed to aflatoxins especially the AFB_1 and its metabolites leading to nephrotoxicity before it is excreted in the urine [24, 58]. The aflatoxin induced reduction in protein content has been reported to be due to increased necrosis of the kidney [58-60, 90]. AFB_1 has been reported to cause kidney tumors in experimental animals and a mixture of AFB and AFG was observed to cause renal and hepatic tumors in 80% of hamsters [24]. There were also renal lesions with features of megalocytosis in the proximal renal tubules. In Africa, birds exposed to AFB_1 were reported to develop fatty and hemorrhagic kidney syndrome, thickening of the glomerular basement membrane, abnormal development of glomerular epithelial cells and degenerative changes in renal tubular cells, congestion and parenchyma hemorrhage [24, 85]. In other animals, there was a reduction in the glomerular filtration rate, glucose reabsorption and tubular transport of electrolytes and organic anions, reduced activities of renal

glutamate-oxaloacetate and pyruvate transaminases and alkaline phosphatase in rats attributed to by the aflatoxins and their metabolites as well as the generated ROS. There was induced aggregation and loss of chromatin, mitochondrial degeneration and loss of microvilli induced by AFB1 in cultured kidney cell lines [24, 85].

4.8. Effect of aflatoxins on the endocrine system

Aflatoxin especially AFB has been reported to interfere with the functioning of the various endocrine gland by disrupting the enzymes and their substrates that are responsible for the synthesis of the various hormones. Aflatoxins and their metabolites as well as the generated ROS have been reported to cause various cancers in different endocrine glands like pituitary gland, granulosa cell tumors of the ovary and adenomas and adenocarcinomas of the adrenal gland, kidneys, thyroid gland, ovaries, testes, thyroid gland, parathyroid glands and endocrine pancreas [4, 90, 108]. The plasma testosterone and luteinizing hormone (LH) concentrations have been reported to reduce in aflatoxin-fed birds [90]. In laboratory animals, aflatoxin causes delayed maturation of both males and females [4, 22, 90, 109]. Aflatoxicosis in white leghorn males chicken decreased feed consumption, body weight, testes weight and semen volume (Sharlin et al., 1980) and decreased plasma testosterone values [22].

4.9. Effect of aflatoxins on the reproductive system

In humans exposed to chronic aflatoxin-contaminated foods, it has been reported that higher concentrations of aflatoxins occur in the semen of infertile men [3]. It is also associated with low birth weight, a risk factor for jaundice in infants as well as presence of AFM in maternal breast milk where it can cause deleterious effect in the newborns [102]. In Nigeria, about 37% of the infertile men had aflatoxin in their blood and semen hence contributing to the incidence of infertility in Nigerians [110]. Experimental results indicate that certain agents like aflatoxins can interfere with the reproductive capabilities of sexes, causing sterility, infertility, and abnormal sperm, low sperm count, and/or affect hormone activity in animals. Aflatoxins have been reported to disrupt the reproductive system in both male and female animals after ingestion of aflatoxin-contaminated foods. Aflatoxins also cause pathological alterations in the form of coagulative necrosis especially in the growing and mature follicles and decrease in number and size of graffian and growing follicles with increased number of atretic follicles and small areas of degenerative changes in experimental animals [111]. AFB_1 has been reported to have a deleterious effect on the reproductive capacity of laboratory and domestic female animals where they cause reductions in ovarian and uterine sizes, increases fetal resorption, implantation loss and intra-uterine death in the aflatoxin exposed female rats [111]. They also cause a reduction in the primary spermatocytes and spermatids [112] and affect the morphology of the sperm cells produced [113]. Stillbirths were reported in the 15th to the 18th days of pregnancy in rats [108]. The levels of plasma testosterone, plasma 5a-DHT and absolute and relative testes weights were reported in experimental animals of aflatoxin-treated males remained low in all age groups and a delay in the onset of sexual maturation during aflatoxicosis [114]. In cows, aflatoxins affected the repro-

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ductive system by causing abortion, the birth of weak, deformed calves, reduced fertility due to reduced vitamin A levels [109]. The teratogenic effects of AFB_1 were described as enlarged eye sockets and enlarged liver of embryos [60]. In poultry, AFB1 cause a reduction in semen volume, testes weight, spermatocrit and plasma testosterone as well as a reduction in egg output [24].

5. Effect of aflatoxins on the immune system

Chronic consumption of aflatoxin-contaminated foods has been reported to cause immunosuppression in both humans and animals worldwide [7, 89]. In human, aflatoxins affect both the cellular and humoral immune responses where they alter immunological parameters in participants with high AFB_1 levels resulting in impairments in cellular immunity hence decreasing the host resistance to infections [115-117]. Aflatoxin exposure has been shown to cause immune suppression, particularly in cell-mediated responses [115-117]. Chronic exposures of the individual to aflatoxins depress the phagocytic efficiency of the phagocytes and the delayed hypersensitivity reactions in birds [24]. Aflatoxins also deplete the cell populations of the thymus; reduce the bone marrow and the red and white blood cells count, macrophage numbers and the phagocytic activity of the cells [24]. It also depresses the T-cell-dependent functions of splenic lymphocytes in mice. The natural killer cell function of the peripheral blood lymphocytes are also affected by aflatoxins especially AFB1 [24]. A reduction in the leukocyte immunophenotypes in peripheral blood, $CD4^+$ T cell proliferative response, $CD4^+$ T and $CD8^+$ T cell cytokine profiles and monocyte phagocytic activity were reported. Children in developing countries appear to be naturally exposed to aflatoxin through their diet at levels that compromise the immune system. In general, the proportion of childhood growth stunting is directly correlated with the proportion of the population living below the national poverty line and is inversely correlated with gross domestic product per capita [7, 45]. As is the case with liver cancer, childhood stunting is prominent in regions such as Southeast Asia and Sub-Saharan Africa, where aflatoxin exposure through consuming contaminated food is common [7, 45]. It has been reported that the immunosuppression and nutritional effects of chronic aflatoxin exposure may be linked to the high prevalence of HIV in Southern Africa [7, 74, 118, 119]. The CD4 proteins that have been weakened by aflatoxin exposure have been reported to correlate positively with HIV infection [116]. Also high aflatoxin levels have been reported to increase risk of developing tuberculosis in HIV positive individuals. Persons who are exposed to aflatoxin and are HIV positive have decreased plasma vitamin A and vitamin E in the blood, although there was no interaction detected between aflatoxin and HIV infection [120]. HIV infection is likely to increase aflatoxin exposure by two possible routes: (1) HIV infection decreases the levels of antioxidant nutrients that promote the detoxification of aflatoxin, or (2) the high degree of co-infection of HIV-infected people with hepatitis B also increases the biological exposure to aflatoxin [7, 118, 119]. Aflatoxin induce immunosuppression and increases susceptibility of toxicated birds and animals to bacterial, viral and parasitic infections [58]. It also affects the lymphoid follicles of caecum thus depleting the lymphocytes that may contribute to the ob-

served immunosuppression [117]. Aflatoxin decreases the concentrations of immunoglobulins IgM, IgG and IgA in birds as well as decrease complement activity in chickens [22, 121]. The low dose of AFB_1 slightly decrease both mRNA and protein levels of lymphocytic IL-2, IFNγ and it preferentially affects macrophage functions as well as IL-1α, IL-6 and TNF production by these cells [121, 122]. Aflatoxin suppression of the immune system therefore subjects the individual to high risk of susceptible to infectious diseases like parasitic, bacterial and viral infections [123].

6. Conclusion

Chronic consumption of aflatoxin-contaminated foods is a common problem in both humans and animals worldwide especially in poor developing nations of south East Asia and sub-Saharan Africa where there is poor food harvesting, processing and storage of food and food products thus allowing the growth of mold on them. Aflatoxins, their metabolites, the aflatoxin-8,9-epoxide and the generated ROS causes deleterious effects on the various body organs and body systems including the development of cancers especially the liver cancer mainly due to AFB_1 exposure. Aflatoxins are also responsible for the suppression of both the humoral and cell-mediated immunity and thus making individuals susceptible to infectious diseases. Aflatoxins also responsible for the malabsorption of various nutrients thus leading to nutritional deficiencies, impaired immune function, malnutrition and stunted growth and hence the development of kwashiorkor and marasmus in infants. Aflatoxins also can affect almost all the different body systems and hence the health of the affected individuals especially in poor developing nations of south East Asia and sub-saharan Africa where there is poor food harvesting, processing and storage thus allowing the growth of mold on them.

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