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Occurrence, health implications, and management of aflatoxin in cereal: A current review

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REVIEW ARTICLE

Cereals are consumed globally because of their nutritional values and potential to reduce malnutrition. Despite their usefulness, cereals are prone to aflatoxin contamination. Aflatoxins are highly toxic and carcinogenic secondary metabolic products that contaminate agricultural products consumed by humans. Studies have shown that aflatoxin is found in cereals at a high level. Human exposure to aflatoxin through food and feed results in a wide range of health issues, including a weakened immune system and cancer. Worst, it can cause death depending on the level and extent of exposure. Several climate-induced factors, such as drought, can trigger aflatoxin production worldwide, especially in Africa, where the environment is conducive. Several precautions have been taken to mitigate human exposure to aflatoxin, including strict regulations, pre- and post-harvest contamination prevention, detoxification, and decontamination. In addition, good farm management and practices, and awareness creation and education can help to reduce aflatoxin contamination and exposure, if not eradicate it. The current review detailed the up-to-date information on aflatoxin occurrence, health implications, and control measures for aflatoxin in cereals to ensure food safety and human well-being. This review also illuminated the potential hazards of human exposure to aflatoxin beyond the permissible level, particularly in children.

Keywords: *Aspergillus* spp., carcinogenic, food contamination, health complications, aflatoxins

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INTRODUCTION

Cereals, such as, maize, and have gained popularity worldwide due to their nutritional value and potential to reduce malnutrition (Temba et al., 2017). Currently, the annual cereal production globally is pegged at 1513.0 million tons, which is below expectations by 3 million tons based on the projected output (Anon, 2021). The 20th century has seen a massive rise in the global population due to an increased birth rate from 1.65 billion to 6 billion (Kobayashi et al., 2020). The increase in cereal demand and consumption has doubled due to the rapidly escalating population. As the production capacity increases, proper and adequate resource management at various processing and production stages is required (Nazir et al., 2019). However, this process is undermined due to the susceptibility of cereal to aflatoxin contamination, thus threatening food safety.

Aflatoxin groups are highly toxic secondary metabolites produced by *Aspergillus* spp., principally *Aspergillus flavus*, *Aspergillus parasiticus,* and *Aspergillus nomius.* They are derived chemically from difuranocoumarin with a lactone ring or a pentanone ring, and a coumarin nucleus-based bifuran group (Nazhand et al., 2020). Aflatoxins are compounds that have mutagenic, estrogenic, and immunosuppressive effects on the well-being of humankind and animals (Peles et al., 2021). The most common types of aflatoxin include B1 (AFB1), B2 (AFB2), G1 (AFG1), and G2 (AFG2), among others. These types of aflatoxin can intoxicate the human body system via several pathways, such as the cutaneous layers, mucous layers, and respiratory tract, subsequently promoting the activation of an inflammatory response. Aflatoxin M1 (AFM1) and M2 (AFM2) are found in milk and are the hydroxylated metabolites of AFB1 and AFB2. *A. flavus* produces AFB whereas *A. parasiticus* produces both AFB and AFG. The toxic nature of the common types of aflatoxin decreases in the order of B1, G1, B2, and G2 (Kumar et al., 2017). AFB1 is considered the most poisonous of all mycotoxins, with a lethal dose (LD50) of 0.36 mg/kg, placing it among the highly hazardous group of toxins (Ndagijimana et al., 2020). Based on experimental results, AFB1 toxicity was ten times higher than potassium cyanide, sixty-eight times higher than arsenic, and seventy times more carcinogenic than dimethylnitrosamine (Yan et al., 2020). The International Agency for Research on Cancer (IARC) has categorized AFB1 as a group 1 carcinogen ("carcinogenic to humans") owing to its genotoxic and carcinogenic effects (Jallow et al., 2021).

Aflatoxin exists everywhere in nature. Factors, such as high humidity, poor harvesting, climatic change, and storage methods trigger aflatoxin growth and development in different regions. Compounded by these factors is the policymakers' inappropriate enforcement of aflatoxin safe limit, contributing to several outbreaks, especially in developing nations (Yard et al., 2013). Aflatoxin contamination is common in cereals, dry fruits, spices, tree nuts, cottonseed, and cowpea, among other crops (Awuchi et al., 2021). Contamination of crops can occur before and after harvest. The occurrence of aflatoxin at the pre-harvest stage is not common compared to the storage stage because the associated fungi are frequently regarded as storage molds. Grain deterioration at the post-harvest stage is attributed to *A. flavus* and *A. parasiticus* contamination, while *A. flavus* is the primary fungus that contaminates crops in the field (Liu et al., 2006). Due to the heat resistance of these fungi, the current food processing methods are insufficient to eliminate aflatoxin from contaminated agricultural commodities. The consumption of human aflatoxin-contaminated products has resulted in severe health problems and complications (Mahato et al., 2019), such as malaise, fever, anorexia, vomiting, acute hepatitis and liver problems, and in severe cases, death (Udomkun et al., 2017).

To control the amount of aflatoxin intake in food, the Codex Alimentarius Commission (an intergovernmental agency) created by the World Health Organization (WHO) in cooperation with the Food and Agriculture Organization (FAO) aims to safeguard consumer health and enhance trade by developing an international standard for food and feed (Sirma et al., 2018). Moreover, in 2007, the European Union (EU) set a safe limit for total aflatoxin and AFB1 at 4 g/kg and 2 g/kg, respectively, for human intake. In 2010, the limit was revised and set at 5 g/kg and 10 g/kg for AFB1 and total aflatoxin, respectively. The United States and Canada set their limits at 20 g/kg and 15 g/kg, respectively. Bosnia and Herzegovina and Switzerland have the lowest limit for AFB1, which is 1 g/kg (Ali, 2019). In Japan, any concentration of aflatoxin in crops is prohibited (Dadzie et al., 2019). In Malaysia, based on the 1985 Malaysia Food Regulation, the maximum limit of all mycotoxins was set at 35 μg/kg initially. Later, it was reviewed and set at 5 g/kg for all mycotoxins, including aflatoxin (Sabran et al., 2013). Egypt set its limit at 4–15 g/kg and 2–12 g/kg for total aflatoxin and AFB1, respectively, while 0.01 g/kg was set as the limit for AFB1 in processed cereal-based foods and baby foods for infants and young children (Marrez and Ayesh, 2022). Furthermore, the Food and Agriculture Organization (FAO) has also set the safe limit for AFB1 to be 1–20 g/kg in food (Ndagijimana et al., 2020).

Aflatoxin Occurrence in Cereals

Cereals, such as corn, rice, and wheat are vulnerable to aflatoxin contamination by aflatoxigenic fungi. The natural appearance of aflatoxin in cereals, notably in rice and corn, is a problem that has become worrisome due to the continuous changes in agricultural practices. According to the FAO survey, mycotoxins contaminate approximately one-quarter of the world's cereal crops (Jallow et al., 2021). A previous study revealed that out of 18,097 cereal samples tested for aflatoxin contamination, 36.7% of the samples were contaminated with a form of aflatoxin (Andrade and Caldas, 2015). The occurrence of aflatoxin in grains is not restricted to a particular geographical or climatic zone. It is prevalent in tropical, subtropical, and a few temperate regions with conducive environmental factors that favor its production. Besides these regions prone to aflatoxin contamination, the Mediterranean zones are now vulnerable to aflatoxin contamination due to a shift in local occurrence areas of AFs driven by the main changes in climate variables, consequently bringing about a rapid increase in aflatoxin contamination of cereals globally (Mahato et al., 2019). Furthermore, most developing countries' suitable social and environmental conditions have triggered and aided the prevalence of mycotoxins in agricultural commodities. Table 1 shows the occurrence of aflatoxin in cereals in different countries worldwide.

Rice

Globally, rice is one of the most important sources of calories for more than 50% of the world’s population. Asian countries constitute the major rice producers and consumers; approximately 600 million tons are produced yearly on more than 150 million hectares of land (Mohd Ikmal et al., 2019). Rice cultivation is typically done in humid and warm climatic conditions (Lai et al., 2015). When stored under poor conditions, rice is easily contaminated by mycotoxin-producing fungi. Harvested rice in waterlogged areas and with high moisture levels is vulnerable to mold infection and mycotoxin contamination (Majeed et al., 2018). In certain parts of India, frequent and heavy waterfalls

Table 1. Worldwide Occurrence of Aflatoxins in Cereal.

Country	Food Matrix	Type of Aflatoxin	Range (μg/kg)	References
Ghana	Cereals based product	AFB1	0.18–23.27	Blankson et al., 2019
Costa Rica	Maize	Total Aflatoxin	24	Mahato et al., 2019
Zambia	Maize	AFB1	16	Thakur et al., 2022
Zimbabwe	Maize	AFB1	0.5 -26.6	Murashiki et al., 2017
Vietnam	Maize	AFB1	1-34.8	Lee et al., 2017
India	Maize	AFB1	62	Thakur et al., 2022
Togo	Maize	AFB1	Max 256	Hanvi et al., 2019
China	Maize	AFB1	4.4	Zhao et al., 2021
Vietnam	Maize	AFB1	>5	Nguyen et al., 2018
Pakistan	Rice Noodles	AFB1	3.60	Iqbal et al., 2016
Indonesia	Rice products	AFB1	2.0 to 7	Ali, 2019
Korea	Rice	AFB1	1.8-7.3	Ali, 2019
China	Rice bran	AFB1	7.5	Zhao et al., 2021
China	Rice	AFB1	Max 20	Lai et al., 2015
China	Rice	AFB1	0.1–136.80	Mahato et al., 2019
Iran	Rice Flour	AFB1	0.46-10.16	Mottaghianpour et al., 2021
Saudi Arabia	Rice	Total Aflatoxin	0.07-7.09	Elzupir et al., 2018
Togo	Sorghum	AFB1	6–16	Hanvi et al., 2019
Uganda	Sorghum	Total Aflatoxin	11.8 ± 1.8	Echodu et al., 2019
Tunisia	Sorghum	Total Aflatoxin	0.4-25.8	Filazi and Tansel Sireli, 2013
Turkey	Wheat	AFB1	0.21–0.35	Turksoy and Kabak, 2020
Malaysia	Wheat	AFB1	0.55–5.07	Mahato et al., 2019
Iran	Wheat	AFB1	Max 7.08	Mohadeseh et al., 2016
Algeria	Wheat	AFB1	0.22–13.96	Riba et al., 2010
Lebanon	Wheat	AFB1	1.05 - 7.36	Joubrane et al., 2020
Iran	Wheat Flour	AFB1	0.1-0.26	Mottaghianpour et al., 2021

are witnessed during harvest, causing the crop to become damp and vulnerable to fungi attacks. Furthermore, farmers cannot sun-dry the grains during this period, which is the norm. As a result, the grain moisture content remains unchanged. Thus, transporting grains with a moisture content higher than the average level (>14%) into the storage system makes them susceptible to fungal attack. The detrimental consequences of such contamination include reduced seed quality, grain discoloration or husk, and losses in viability (Reddy et al., 2009). Several nations worldwide, including Pakistan, Brazil, Indonesia, China, India, Korea, and Austria, have reported the presence of aflatoxin in rice samples. A study in Pakistan showed that 72 out of 208 samples were contaminated with AFB1 at a concentration of 3.60 g/kg (Iqbal et al., 2016). In Canada, AFB1 was reported in imported rice from USA and Asia, with the mean concentration ranging between 0.34 and 0.39 g/kg (Ndagijimana et al., 2020). A recent study conducted in Iran showed that all 24 samples of rice flour analyzed tested positive for AFB1, with the concentration ranging between 0.46 and 10.16 g/kg (Mottaghianpour et al., 2021). Despite the average aflatoxin contamination level being within the safe limit, a previous study indicated a positive correlation between daily consumption of aflatoxin-contaminated rice and hepatocellular carcinoma (HCC) incidences in some rice-consuming countries in Asia. Chronic exposure to aflatoxin explains this relationship (Elzupir et al., 2018).

Maize

Maize is considered a staple food by the world population. The United States is regarded as the world's largest producer of maize, with 370 million metric tons in 2017 while countries, such as Ethiopia, Brazil, China, and the EU combined produce 436 million metric tons, making a total of more than 807 million metric tons of maize by the world's major maize producers (Block et al., 2018). Despite maize's global impact, the natural enemy's existence and invasion of maize have considerably impacted its production. Insects and other herbivores' invasion results in nearly 6–19% grain damage, with pathogen attacks, such as fungus, causing an additional 10% damage (Di Domenico et al., 2016). One of the significant challenges encountered by corn at the storage stage is fungal attack and contamination. This can be attributed to corn's high starch content, which serves as a good substrate, thus making it vulnerable to contamination by fungi, especially *Aspergillus* sp. and *Fusarium* sp. (Di Domenico et al., 2016). Maize can be contaminated with airborne fungi and mycotoxins at pre- and post-harvest stages. In maize, aflatoxin occurs during pre-harvest activities, such as cultivation (i.e., in the field); the harvesting period; and post-harvest stages, such as transportation, storage, and processing. Poor farm management during cultivation allows aflatoxin to enter the post-harvest stage. Inadequate and poor storage conditions result in fungal attacks and aflatoxin contamination (Singh et al., 2019). Other variables, including humidity and temperature, trigger fungal growth in grains (Mtega et al., 2020).

According to a previous study, maize was considered as one of the crops mainly contaminated by aflatoxin in sub-Saharan Africa. Moreover, other studies found that the level of aflatoxin in contaminated crops, such as maize was unacceptable, with samples having up to 1000 ppb of aflatoxin (Nakavuma et al., 2020). Due to their socio-economic significance, investigations have been conducted worldwide to determine the occurrence and extent of aflatoxin in maize samples. A study in Vietnam revealed that 204 and 141 maize samples tested positive for AFB1 out of 378 samples at concentrations of >5 g/kg and >20 g/kg, respectively (Nguyen et al., 2018). In South Africa, AFB1 was reported in six maize samples out of 29, with the concentration ranging from 1-149 g/kg (Mngqawaa et al., 2015). The prevalence of aflatoxin has caused a considerable reduction in net yield and economic profits. For example, the total money spent on reducing aflatoxin in the US is around $500 million yearly through aflatoxin on maize and other grown crops, in addition to that spent on animal health maintenance (which is a small fraction of the cost) (Wu, 2015). Similarly, it was estimated that $163 million was lost annually on average to US maize growers through the prevention of aflatoxin infection (Wu, 2015). Yearly, approximately $1.2 billion is lost due to contaminated agricultural products, of which African countries account for 38% of the losses ($450 million) (Gbashi et al., 2018).

Sorghum

Sorghum is one of the essential grains consumed by the world's populace. In Sub-Saharan Africa, it is considered the second most cultivated and important grain after maize. Globally, it is fifth based on consumption and is significantly behind wheat, maize, rice, and barley. Based on 2013 data, 61.5 million metric tons were produced and cultivated on approximately 42.3 million hectares (Garba, 2019). Despite these huge global production capacities, mycotoxin production threatens sorghum production. The presence of mycotoxins in sorghum has been proven, thus making it one of the major sources of mycotoxin exposure for animals and humans (Garba, 2019). Contaminants of sorghum grains include fungal genera, occurring during the panicle and grain developmental stages. The most common grain mold pathogens that contaminate sorghum include *Aspergillus* sp*., Alternaria, Fusarium, Cladosporium, Curvularia,* and *Penicillium* (Lahouar et al., 2016). In the first comprehensive study of aflatoxin contamination in sorghum, 70% of the samples exhibited aflatoxin levels greater than 10 ppb. The great amount of aflatoxin level in the sorghum samples can be attributed to improper agricultural management, such as poor storage and processing techniques because the production of sorghum is mostly carried out at the subsistence level, at which there is no standard mechanism to inspect and regulate the quality of the produce (Lukwago et al., 2019). Other studies have also reported the presence of aflatoxin in sorghum. For instance, in Togo, AFB1 was reported in three sorghum samples out of 12, with a concentration between 6 and 16 g/kg (Hanvi et al., 2019).

Climate-Induced Factors Affecting Aflatoxin Production

The frequent changes in climatic conditions are considered the main factor significantly contributing to food insecurity worldwide. Therefore, there is considerable concern about the possible implication of environmental changes on the existence of mycotoxins in agricultural commodities (Battilani et al., 2016). Fungal proliferation and mycotoxin secretion can occur at any developmental stage during the plant life cycle depending on environmental factors, such as rainfall, temperature, humidity, and agricultural management methods. Plant immunocompromising factors, which include injury, water stress, poor fertilization, and pest infestation, are recognized as enablers of aflatoxin growth in agricultural commodities (Jallow et al., 2021). These variables impact mycotoxigenic fungi's development, survival, frequency, distribution, and subsequent toxin accumulation (Daou et al., 2021).

Temperature, Humidity, and Water Activity

Temperature and humidity have tremendous impacts on which fungi that attack crops, with warm climates favoring aflatoxin production. The infection of crops by fungi has brought about a drastic decrease in the yield of agricultural commodities, especially cereals and their derivatives. Variation in the temperature of the immediate environment significantly impacts aflatoxin production and the levels of expression of regulatory genes (*aflR* and *aflS*). Previous research reported a strong relationship between an early structural gene (*aflD*) expression and AFB1. Temperature reacts with water activity (a_w) and affects the ratio of regulatory genes (*aflR*/*aflS*), which is directly proportional to the production of AFB1. *Aspergillus spp.* and the production of aflatoxin are greatly influenced by the interaction between temperature and water activity (AW) (Kumar et al., 2017). Documentation from previous studies has shown that environmental stresses, including low a_w temperature, play a crucial role in the regulation of *A. flavus* growth and trigger aflatoxin production. Aflatoxins' production in several grains differs in terms of sensitivity to AW and temperature (Tai et al., 2020). Based on a previous study Mousa et al., (2013), the rapid growth of *A. flavus* and aflatoxin production were observed in brown rice between 25 and 35 °C at 0.82 AW, but not in polished rice in a similar condition. However, brown and polished rice showed increased aflatoxin production at maximum AW values (0.90 to 0.92 at a temperature of 20 °C after 21 days of incubation). Even though it was recorded that progressive toxin production happened at 25 to 30 °C within a wider range of 0.82 AW values, it could be concluded that polished rice did not seem to allow *A. flavus* growth and aflatoxin production as compared to brown rice. Another study done on the effects of environmental factors on aflatoxin production indicated that the growth of *A. parasiticus*, *A. flavus,* and *A. oryzae* was observed at 25 °C in 0.82 AW and 0.81 AW at 30 °C and 37 °C. The study did not assess the relationship between aflatoxin production and *A. flavus and A. parasiticus* (Milani, 2013). A study by Lv et al., (2019) revealed that optimal growth of fungi was observed between 28 °C and 37 °C with an AW value of 0.92 to 0.96. A study by Battilani et al., (2016) predicted the occurrence of AFB1 in cereals was due to the changes in climatic conditions in European countries; for every 2 °C rise in temperature, there is an increase in aflatoxin risk in countries such as Italy, Greece, Turkey, Cyprus, Spain, Bulgaria, and Albania. Naturally, the control of ambient temperature is impossible, but its implications on the later stages of plant development can be avoided by early planting. For instance, in North Carolina, maize planted in April was reported to experience low aflatoxin contamination compared to maize grown in May (Abbas et al., 2009).

Drought

Drought incidence during crop production makes them vulnerable to diseases and fungal attacks, increasing aflatoxin contamination and reducing grain yield, fertility, and livestock production. The 2016 El-Nino drought events experienced in South Africa caused losses of several million dollars, and it was identified as the hottest year in nearly a century (Gbashi et al., 2018). Yearly, climate change causes a significant economic loss of about US$ 1.68 billion to the U.S. maize sector (Thakur, et al., 2022). In 2018 and 2019, a severe drought hit central Europe, with the continent experiencing all-time high summer temperatures. This trend is expected to continue and occur more often if greenhouse gas emissions increase, significantly impacting agricultural productivity (Valencia-Quintana et al., 2020). Water deficits induced by climate change weaken plant systems. It makes them more vulnerable to fungal attacks and aflatoxin production, which could be triggered if the crop is cultivated in the rainy season (Benkerroum, 2020). Water stress triggers aflatoxin biosynthesis, as witnessed in tropical nations, where acute aflatoxicosis cases are frequently reported upon ingesting contaminated crops (Valencia-Quintana et al., 2020). A study conducted in South Africa as early as 1965 established the relationship between drought and high aflatoxin contamination. This association was also reported in studies conducted on agricultural products in the USA and Nigeria (Sanders et al., 1993). Moreover, research has been performed extensively to determine the linkage between pre-harvest aflatoxin contamination and drought. For instance, studies conducted by Wilson and Stansell reported the presence of aflatoxin in agricultural products under drought-stress conditions Under similar conditions, an increase in aflatoxin contamination of crops is observed due to a reduction in water activity, allowing easy *A. flavus* penetration into the crop due to the cracking of the pod (Girdthai et al.,2010) Furthermore, research conducted in Niger demonstrated that a drought lasting less than ten days caused a significant increase in aflatoxin contamination in the field. However, the extent of aflatoxin contamination depends on the severity of the water stress, the stage at which the stress is induced, and the soil and/or ambient temperature. The effect of terminal drought on aflatoxin contamination has been well established (Hamidou et al., 2014). In another study by Jones and his peers, a higher level of aflatoxin concentration was observed in corn under drought stress compared to non-stress conditions (Abbas et al., 2009). Although a significant amount of aflatoxin contamination was reported under drought conditions, using tolerant varieties under drought stress could help reduce aflatoxin contamination in the field. Drought-tolerant corn varieties were also found to produce significantly less aflatoxin under drought conditions than aflatoxin-resistant controls (Guo et al., 2008).

Flooding/Excessive Rainfall

Flooding is considered one of the most severe environmental stresses affecting plant productivity. Yearly, several floods are experienced on many farmlands, causing the loss of millions of dollars' worth of agricultural products. It was reported that flooding events caused damage to approximately 40 million hectares of rice fields worldwide (Mohd Ikmal et al., 2021). This situation is expected to get worse due to climate change. Simultaneous flooding and aflatoxin production may incur more economic losses and worsen food safety issues. Based on the author's knowledge, although no studies have specifically reported the effect of flooding on aflatoxin production, a study by Das et al., (2012) reported that under ambient conditions (submerged fermentation), rice straw could favor aflatoxin production. Since the increase in moisture is positively correlated with aflatoxin production, it can be safely concluded that aflatoxin growth is favored when plants are submerged, affecting plant metabolism and functionality. Moreover, a recent survey conducted in West Africa on food contamination reported that crop samples collected during the rainy season recorded higher aflatoxin content than dry-season crop samples (Benkerroum, 2020). This report also indicated that flooding might promote aflatoxin production. The increased aflatoxin level is also linked to delayed harvest, late rainfall, irrigation, and dew during warm weather conditions. Aflatoxin levels were observed to be higher in crops that received more than 50 mm of rain during boll opening Furthermore, when high rainfall is experienced at the pre-flowering stage, the crop has a high amount of aflatoxin concentration (Benkerroum, 2020). Concerning this, research needs to be conducted on the impact of submergence on aflatoxin production, focusing on the extent to which aflatoxin contaminates plants at different stages of plant production, whether crop resilience to submergence can help reduce aflatoxin contamination, and to what extent. This research is significant to ensure food security due to increased flooding on farmland, especially paddy fields. Since the production of aflatoxin is dependent on climate, it has been suggested and established that climatic change can result in a drastic change in the fungal population. This would trigger the emergence of new mycotoxigenic fungal strains, favoring the already existing mycotoxin productions in food (Gbashi et al., 2018)

Other Factors

Apart from climate change factors, other factors such as pH, fungal strain, substrate, nature of the soil, and availability of nutrients like carbohydrates, phosphates, zinc, and nitrogen play an important role in aflatoxin production (Benkerroum, 2020; Daou et al., 2021). The immediate fungi environment and its pH value play significant roles in the fungal growth and development, and production of mycotoxin. Studies have shown that the presence of "hydrogen ion concentration" (pH) in the fungus' immediate surroundings directly impacts fungal development, either through its action on cell surfaces or through an indirect effect on nutrient availability (Daou et al., 2021; Abubakar et al., 2013). For instance, at pH 4.0 and 7.0, the growth of *A. carbonarius*, a fungus isolated from wine and table grapes, was enhanced compared to that at pH 2.6, irrespective of water activity (Abubakar et al., 2013).

Another important factor influencing fungal contamination is the type of soil. Aflatoxin occurrences differ considerably among crops depending on the soil type. Based on the report, light sandy soils promote fungi growth, especially when subjected to water stress, while lower fungal infectionexperienced in heavier soils possibly due to their water retention ability, which helps to maintain irrigation frequency and to decrease the water stress effect (Marrez, 2022). Finally, to avoid aflatoxin contamination at the pre-harvest stage, sufficient nutrient availability to plants is required, especially nitrogen. Crops may be susceptible to aflatoxin contamination if the root zone lacks mineralized nitrogen. Inadequate levels of mineralized nitrogen may be caused by leaching due to high amounts of water droplets and water stress (Abbas et al., 2009). Based on experimental results, a low quantity of aflatoxin was observed in corn produced with higher nitrogen (120 kg/ha). In contrast, corn produced with a lower amount of nitrogen (80 kg/ha) recorded high aflatoxin contamination (Abbas et al., 2009). This signifies that a proper mixture of macronutrients is essential in crop management.

Impact of Aflatoxin Consumption on Human Health Food insecurity issues are predominant in undeveloped and developing nations and emerging and transitional economies as a significant portion of the population lacks access to safe, nutritious, and cheap agricultural products (Udomkun et al., 2017). Estimates suggest that approximately 1500 diarrheal cases are reported annually across the globe, and more than 70% are associated with biological contamination of food, causing about 3 million deaths (Yáñez, et al.,2002). This may be attributed to several factors, including consuming contaminated agricultural commodities. In the future, many health-related problems may be encountered due to the emergence and prevalence of aflatoxin in agricultural commodities ingested by humans.

In the 1960s, hundreds of deaths were reported in Turkey because the peanut was severely infested by mold, leading to the discovery of aflatoxin (Khlangwiset et al., 2011). Since then, Turkey has recorded a series of outbreaks that have resulted in morbidity and mortality (Atherstone et al., 2016). Diseases caused by the ingestion of aflatoxin are referred to as aflatoxicosis. AFB1 is absorbed in the small intestine and transported to the bloodstream, where red blood cells and plasma proteins are transferred to the liver. The toxin transported to the liver is broken down by an enzyme known as microsomal-mixed function oxidase (MFO), a member of the Cytochrome P450 (CYP450) superfamily (Janik et al., 2020). AFB1 is converted to reactive 8, 9-epoxide formed by Cytochrome P450 enzymes which can bind to DNA and proteins. Mechanistically, it is understood that the reactive AFB1 epoxide binds to the guanines at the N7 position. Furthermore, TA to GC transversions may result from AFB1-DNA adducts. A reactive glutathione S-transferase system located in the cytosol and microsomes catalyzes the conjugation of activated AFB1 with decreased glutathione, resulting in aflatoxin being excreted (Bennett and Klich, 2003). Aflatoxin can be excreted through bile, feces, urine, semen, milk, and eggs. In humans, aflatoxin M1 (AFM1), aflatoxin P1 (AFP1), and free guanine residues (AFB1-N7-guanine) are excreted in urine while they are excreted via the bile in rats. In ruminant animals, AFB1 is excreted via feces and AFM1 predominantly through urine and milk (Thakur et al., 2022).

The previous study showed that disruption of the human immune system was caused by aflatoxin infection, making it vulnerable to other infectious diseases. Aflatoxin has also been associated with congenital disabilities and stunted growth in children exposed for a long time (Jallow et al., 2021). AFB1 intoxication is hazardous, especially in regions where the hepatitis B virus (HBV) is prevalent. A survey indicated that HBV-positive people are at greater risk of developing liver cancer than HBV-negative people. AFB1 was regarded as the primary causative agent of hepatocellular carcinoma (HCC), a common type of liver cancer (Janik et al., 2020). The metabolic implication of aflatoxin intoxication includes disruption of the synthesis of protein, RNA, and DNA; depletion of the activities of the miscellaneous enzymes; disruption of the synthesis of lipids as well as esters, phospholipids, and triglycerides; and depletion of glucose metabolism (Giray et al., 2007). The occurrence of hepatocellular carcinoma is triggered by dominant-negative oncogenes and changes in the P53 tumor-suppressing gene (Giray et al., 2007).

Aflatoxin's unpleasant impacts on human health are highly dynamic based on the type of exposure to contaminated feed. The effects can either be acute, witnessed within a few days after consumption of a significant amount of aflatoxin-contaminated food, or chronic, showing after many months or years of ingestion. Acute effects experienced can be vomiting, jaundice, liver problems, and even death for the affected person while chronic consequences can be associated with weakened immunity, poor growth, cancer development, mutagenicity (Barajas-Ramirez et al., 2021; Yard et al., 2013), liver damage, and even death because of the accumulation of toxins within the body (Yan et al., 2020). Several studies on aflatoxin toxicity, especially AFB1, have been conducted with sufficient animal and human epidemiological findings that prove the teratogenicity, mutagenicity, and carcinogenicity of aflatoxin. Even more, studies have shown that aflatoxin can cause cancer, attacking different organs such as the stomach, lung, and liver (Ndagijimana et al., 2020).

The severity of an aflatoxin outbreak is influenced by several variables, including the contamination level of the mycotoxin, the individual's age and prior health condition, and the toxicity and possible impacts of other chemicals the person is exposed to (Majeed et al., 2018). In 2004, over 317 individuals were admitted to the hospital due to the ingestion of aflatoxin-contaminated food in Kenya, resulting in 125 fatalities. Recurrent incidences of this nature were reported in 1981 and 2005 in Kenya, with 12 and 16 deaths recorded, respectively (Agriopoulou *et al.,* 2020). In 1975, an aflatoxin outbreak was witnessed in India among the Bhils Tribe, which had earlier fed on aflatoxin-contaminated maize. This led to ascites and portal hypertension, affecting about 400 individuals (Filazi and Tansel Sireli, 2013). Similarly, 100 people were reported dead in India due to a hepatitis outbreak that may have been attributed to the ingestion of contaminated maize (Bennett and Klich, 2003). In addition, 14.1 million new cancer cases and 8.2 million fatalities were recorded globally in 2012. Liver cancer is the second-leading cause of human death after lung cancer, accounting for approximately 745,000 deaths per year. In the same year, various parts of Africa recorded 847,000 cancer cases and 591,000 fatalities. Over 80% of the cases of hepatocellular carcinoma (HCC) occur in poor countries due to the risks of dietary aflatoxin exposure and chronic hepatitis B and C (Lukwago *et al.,* 2019). In Nigeria, ingestion of aflatoxin-contaminated agricultural products was linked to 7,761 liver cancer cases. Elsewhere, in Tanzania, approximately 3,334 cases of hepatocellular carcinoma were estimated, with 95% of the cases resulting in death (Gbashi *et al.,* 2018). In the same country, another aflatoxicosis outbreak was reported recently. This outbreak caused the deaths of 20 out of the 68 individuals affected (Benkerroum, 2020). Mycotoxin contamination of agricultural products is considered a big threat to public health in sub-Saharan Africa, with approximately 250,000 hepatocellular carcinoma-related fatalities yearly caused by aflatoxin alone (Echodu *et al.,* 2019).

The Implication of Aflatoxin Exposure on Infants and Children

Globally, most children are exposed to a significant amount of aflatoxin at an early stage of their development and throughout their entire life because most communities rely heavily on the subsistence agriculture system for their daily diet, and they are unaware of the existence of aflatoxin (Mupunga *et al.,* 2017). Children and infants are exposed to aflatoxin at different growth and developmental stages through maternal food ingestion during pregnancy, breastfeeding, and post-weaning diets, particularly in areas where maize is the primary food source. After children are weaned from breastfeeding, their exposure to aflatoxin skyrockets; on the other hand, exposure during pregnancy also tremendously affects the infants (Khlangwiset *et al.,* 2011). A study was reported on the effect of aflatoxin exposure on Gambian infants (6, 12, and 18 months). The result revealed that aflatoxin was the infants' leading cause of growth retardation (Watson *et al.,* 2018)**.** It was also found that aflatoxin exposure was associated with lifelong cognitive and physical deficits (Passarelli *et al.,* 2020). In 1988, Malaysia experienced an aflatoxicosis outbreak in Perak state due to consumption of contaminated noodles with up to 3 mg of aflatoxin, resulting in the deaths of 13 children (Sowley, 2016). Research carried out by Gong and his colleagues reported that out of 479 children and infants studied, aflatoxin and aflatoxin-albumin (AF-alb) were found in 99%, and the amount increased as they got older due to the consumption of complementary foods (Achaglinkame *et al.,* 2017)**.** At the early stage, exposure to aflatoxin and AF-alb was attributed to stunted growth in infants and children (Gong *et al.,* 2003). Aflatoxin was also found in the umbilical cords, signifying the presence of toxins around the placenta and beyond. Furthermore, maternal exposure was found to correlate positively with breast milk aflatoxin levels (Achaglinkame *et al.,* 2017).

Stunted growth in children has become predominant in certain parts of the world, including in South and East Asia and Sub-Saharan Africa, despite significant feeding and the adoption of other nutrition intervention schemes in affected regions (Mitchell *et al.,* 2017). In Bangladesh, childhood stunting is prevalent. Approximately 36% of children below the age of 5 years are shorter than the normally expected height of their age or are stunted, with 15% being severely stunted (Mahfuz *et al.,* 2019). Based on the low height-for-age z-score (HAZ) recorded, stunting can be defined as height below two standard deviations (SD) of the standard average. The HAZ score is a metric that indicates how far a child is from the average height-for-age, with a HAZ of 2 indicating stunting growth in a child (more than two standard deviations below average height) and a HAZ of 3 indicating severe stunting in a child (Ahlberg *et al.,* 2018). According to a review of nutritional interventions on child growth, the highest growth improvement provided by feeding and dietary programs is a 0.7 increase in HAZ (Mitchell *et al.,* 2017). Stunting is a well-documented risk indicator of poor development in a child and chronic malnutrition, and it has been linked to aflatoxin exposure (Ahlberg *et al.,* 2018). Impaired growth and stunting are considered significant problems because stunting has long-term consequences beyond infancy and childhood. The long-term impact may include reduced productivity, increased health complications, and lower academic achievements (Ahlberg *et al.,* 2018). Chronic aflatoxin exposure has been associated with kwashiorkor. Research conducted in the last 30 years has shown that children with kwashiorkor have significant amounts of aflatoxin in their urine and blood samples compared to healthy children. Similarly, a study in Cameroon revealed the presence of AFB1 in the blood and urine of kwashiorkor patients (Mupunga *et al.,* 2017). A survey conducted on Egyptian infants showed that aflatoxin is prevalent in the urine of children suffering from kwashiorkor, followed by marasmus patients. At the same time, no aflatoxin was detected in the urine samples of the control group (Hatem *et al.,* 2005). In Nigeria, a post-humous autopsy study conducted on children with kwashiorkor and other miscellaneous diseases showed significant amounts of aflatoxin in their lungs due to the ingestion of infected maize (Oyelami *et al.,* 1997; Gbashi *et al.,* 2018). Out of the 20 children who suffered from kwashiorkor, 18 cases ended in death, while 13 out of the 20 children with miscellaneous diseases were reported dead. This study has shown that infants are exposed to a significant level of aflatoxin, which may be accumulated in the lungs (Oyelami *et al.,* 1997).

Based on available and established data, aflatoxin prevalence is experienced in Africa and certain Asian countries. This can be attributed to the lack of strict safety regulations to curb the level of aflatoxin present in food commodities consumed by the population. This has resulted in major health consequences for people in this part of the world. In addition, the presence of suitable environmental conditions for aflatoxin development, technological hurdles, a high rate of illiteracy among farmers and consumers, lack of awareness, poor storage conditions and facilities, and an overall high rate of poverty may also be considered as possible reasons for a high level of aflatoxin in Africa and a certain part of Asia (Ismail *et al.,* 2018). Thus, adequate detection techniques and control methods are essential to combat the problems of aflatoxin in food.

Possible Strategies for Mitigating Aflatoxin Exposure

Development of a Tolerant Cultivar

The development of resistant varieties has been established as one of the most effective methods for preventing aflatoxin contamination in crops. This can be done through molecular plant breeding or genetic engineering approaches. The molecular breeding technique, which includes the pyramiding of quantitative trait loci (QTLs) via marker-assisted selection, has extensively been used to develop tolerant varieties to abiotic stresses, such as submergence and drought. Since it has been established that using drought-tolerant cultivars helps reduce aflatoxin contamination, many newly developed genotypes using molecular markers can be screened in the field for their tolerance against aflatoxin production. This can help discover more genotypes and germplasm, which can be used for further breeding programs. The development of resistant varieties of crops such as maize has been realized through the screening of new tools during field and laboratory screening. The techniques (RFLP analysis for corn populations) have shown that different resistant traits can be successfully developed into agronomically useful germplasm while proteomics has helped identify proteins associated with resistance (RAPs). The pin-bar technique has been used to discover two resistant inbreeds (Mp420 and Mp313E), which have passed field trials in various locations and been distributed as sources of resistant germplasm (Brown *et al.,* 2004). Furthermore, 36 inbred maize lines collected from West and Central Africa were screened and evaluated for aflatoxin resistance. The result showed that aflatoxin levels in over half of the inbred lines were lower than in resistant US lines. The same research team registered six tropical maize germplasm lines resistant to aflatoxin (Xu, et al., 2022).

To better understand the resistance mechanisms and identify genes, proteins, and pathways involved during host-pathogen interactions for aflatoxin contamination in the crop, a wide range of biotechnology techniques, including RNA interference, microarray, whole genome sequencing, RNA-sequencing, proteomics, and metabolomics, have been widely adopted (Xu, et al., 2022). The genetic engineering approach has been used to achieve over 80% decrease in groundnut content via the *RNAi* technique to silence aflatoxin-producing genes (*aflC, aflep, aflR,* and *aflS*). Furthermore, by silencing the genes (*aflM* and *aflP*) via host-induced gene silencing (HIGS) and overproducing genes responsible for plant defense (*MsDef1* and *MtDef4.2*), groundnuts with reduced aflatoxin content was developed (Pandey *et al.,* 2019). Another study by Thakare et al. (2017) showed that host-induced gene silencing could efficiently eliminate aflatoxin content in transgenic maize. This research established that small interfering RNA molecules could be used to silence aflatoxin biosynthesis in maize. Regulation of enzymatic antioxidants has been proven to inhibit aflatoxin production. For instance, superoxide's intracellular accumulation helps inhibit aflatoxin production by downregulating *aflR* expression, and the addition of Cu/ZnSOD externally decreased aflatoxin production (Furukawa and Sakuda, 2019). The use of genetic engineering as well as plant breeding techniques for the development of resistant crops is considered a sustainable and eco-friendly long-term strategy for pre-harvest interventions.

Biological Methods

The biological detoxification of mycotoxins works in two major processes: enzymatic degradation and sorption, both of which can be accomplished through biological systems (Aliabadi *et al.,* 2013). Biological methods have been proven effective and promising in mitigating aflatoxin contamination. Several organisms have been tested for their ability to control aflatoxin contamination: yeasts, bacteria, and some non-toxigenic fungal strains of *A. flavus* and *A. parasiticus*. Application of non-toxigenic strains of *A. flavus* and *A. parasiticus* in the maize field has significantly reduced aflatoxin contamination. The non-toxigenic strains compete with aflatoxin strains in the field, occurring in the same niches. Hence, they displace the toxigenic strains (Thakur et al., 2022). The use of lactic bacteria (LABs) such as *Lactococcus lactis* subsp*. lactis, Pediococcus acidilactici, Lactobacillus acidophilus, and Enterococcus avium* has been proven effective in preventing and eradicating aflatoxin in agricultural commodities (Peles *et al.,* 2021). This has been established in several studies. For instance, an experiment by Asurmendi *et al.* (2014) showed that the LABs inhibited the activities of two strains of *A. flavus* assayed as well as the production of AFB1 in brewer's grains. Similarly, another study by Saladino *et al.* (2016) reported an 84.1–99% reduction in the aflatoxin content of bread and an increase in the shelf-life due to the inhibitory activities of LABs on aflatoxin. Apart from LABs, non-lactic acid bacteria, including *Pseudomonas* spp*., Myxococcus* spp*., Brachybacterium* spp*., Cellulosimicrobium* spp*., Nocardia* spp*., Escherichia* spp*., Stenotrophomonas* spp., and *Klebsiella* spp*.,* also cause inhibitory activities on the aflatoxin growth and production of molds. For instance, the *Bacillus subtilis* strain was shown to decrease the concentration of AFB1 by 60–95% in contaminated agricultural commodities (Peles *et al.,* 2021). Using yeast species such as *Debaryomyces, Aureobasidium pullulans, Zygosaccharomyces, Saccharomyces,* and *Schizosaccharomyces* has been proven effective in reducing the aflatoxin production of molds in food. However, partially or wholly eradicating aflatoxin using yeast depends on the strain. The aflatoxin reduction varies from 15–100% for AFB1 and 60–90.3% for AFM1 (Pickova *et al.,* 2021). Aflatoxin contamination can also be controlled by using mycotoxin absorbents and binders, which aim to prevent mycotoxins from entering the intestinal tract of animals by absorbing toxins from the surface (Kamle *et al.,* 2019).

Pre-harvest Practices

Pre-harvest strategies for preventing aflatoxin include good manufacturing practices (GMPs), appropriate environmental factors, good agricultural practices (GAPs), and favorable storage practices. Good farming practices include the implementation of a crop rotation program; the use of registered fungicides, insecticides, and herbicides for control of insect damage, fungal infection, and weed eradication; proper treatment of the seed bed; soil analysis to determine the need to add fertilizers, and improvements in genetic synthesis to reduce mycotoxin production (Agriopoulou *et al.,* 2020; Marrez and Ayesh, 2022). For instance, legume crop rotation with maize can help improve soil fertility and disrupt pest and disease cycles. Additionally, rotating maize with non-host crops can help minimize plant residues that could allow the buildup of inoculum. Adopting and maintaining GAPs in the proper manner helps to enhance the safety and quality of food and other agricultural commodities. GAPs also offer smallholder farmers the additional advantages of enhanced yield and decrease overall post-harvest losses (Xu, et al., 2022).

Chemical Methods

Hydrochloric acid (HCL) has been proven effective in reducing AFB1 concentration by 19% in 24 hours. Alkalinity also makes aflatoxin unstable. Ammonization has been shown to decrease aflatoxin content by more than 99%. The use of ammonia to destroy aflatoxin has been extensively investigated and proven to be a success both on the field and in the laboratory (Pickova *et al.,* 2021). Moreover, a study by Abubakar *et al.,* (2013) revealed that certain alkaline media could help to prevent *A. parasiticus* growth and sporulation. Ozone treatment was reported to help reduce contamination by the degradation of mycotoxin. It can also be used in gaseous form to avoid an increase in moisture. However, treatment using this method can take a long time to work and can result in the oxidation of fat components, thus reducing the quality of the food (Daou *et al.,* 2021). Using fungicide is also considered one of the most effective methods of preventing fungal invasion before harvest and, consequently, mycotoxin contamination. However, research on fungicide usage is debatable; while other literature found them effective, some believe that, in some cases, it can enhance aflatoxin production and pose a threat to human and animal health (Daou *et al.,* 2021).

Physical Methods

The use of physical methods, including adequate drying and physical treatment, can assist in mitigating aflatoxin contamination at the post-harvest stage and reduce the effects of contamination and the subsequent accumulation of mycotoxins in crops. One of the prerequisites for completely eradicating aflatoxin content is the restriction of colonization by aflatoxin-producing fungi on the surface layers of grains. Dehulling techniques are used to remove the grain's outer layers, removing around 93% of aflatoxin (Pickova *et al.,* 2021). Up to 50% of the aflatoxin content in corn is eliminated by milling. Extrusion can help to reduce aflatoxin content by 50-80% depending on the temperature and grain moisture (Karlovsky *et al.,* 2016). Furthermore, 40% of aflatoxin content was reduced in maize by roasting, while temperatures beyond 160 °C destroyed AFB1 (Karlovsky *et al.,* 2016).

Irradiation is a valuable method for inhibiting some mycotoxin's action. Previous study had shown that exposure of feed and food to γ-radiation, microwave heating, and solar radiation were effective ways to decontaminate any left residues of aflatoxin present in food. However, the efficiency of these methods is dependent on factors, such as the type of fungus, dosage applied, food composition, moisture content, and storage conditions (Adejumo and Adejoro, 2014). New technologies such as electron beam and gamma irradiation, microwave heating, electrolyzed water and cold plasma, UV, and pulsed light have been proven effective in mitigating the contamination of aflatoxin (Pankaj *et al.,* 2017). A previous study reported 59–88% aflatoxin reduction when 10 kGy irradiation was induced while in another study, 11-21% aflatoxin reduction was observed when 15 kGy irradiation was employed (Pickova *et al.,* 2021). UV-A irradiation has also been reported to reduce AFB1 and AFM1 concentrations in pure water by 70% and 84%, respectively, at a dose of 1200 mJ/cm (Stanley *et al.,* 2020). Because of high temperatures on food, non-thermal approaches such as pulsed electric fields (PEF) have been adopted and proven effective in reducing aflatoxin concentration in agricultural commodities without losing their quality and nutritional value (Vijayalakshmi *et al.,* 2018). Apart from PEF, cold plasma has also been effective in controlling mycotoxin contamination by destroying the cell wall of fungi and their DNA, allowing the leakage of intercellular components. Other studies on the effect of cold plasma on mycotoxins have shown that they are either partially or destroyed (Daou *et al.,* 2021). The use of silver nanoparticle AgNPs at a lower concentration than the minimum inhibitory concentration was reported to inhibit AFB1 production. This suggests that AgNPs can be considered an important weapon to mitigate aflatoxin contamination in vulnerable crops in the field (Mousavi and Pourtalebi, 2015).

CONCLUSIONS

Cereals are considered staple foods and raw materials for the food industry. The contamination of cereals by aflatoxin is a global concern, posing a significant threat to food security and the well-being of humankind and thus, disrupting the world economy. In this review, the types of aflatoxins, their occurrence and the environmental factors responsible for their production were discussed. The impact of aflatoxin on crop safety, human health, and control measures, such as breeding of resistant varieties via genetic engineering, biological, chemical, physical and proper post-harvest handling of cereal crops all aimed at mitigating its production were extensively explained. The paper recommended that due to limited available knowledge on the antioxidant role in preventing aflatoxin contamination, more studies should be conducted to determine the role of over-expression or down-regulation of specific genes in controlling aflatoxin contamination. Moreover, complete detoxification of any aflatoxin residues in agricultural commodities through advanced technology should be encouraged. Lastly, raising awareness regarding the detrimental consequences of aflatoxin should be prioritized, especially in developing nations where outbreaks frequently occur due to suitable climate, high levels of illiteracy, and poverty, resulting in consuming contaminated foods.

CONFLICT OF INTEREST

There is no conflict of interest

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