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MYCOTOXINS IMPACT IN FOOD, HUMAN AND ANIMAL HEALTH WITH SPECIAL REFERENCE TO AFLATOXINS, FUMONISINS, OCHRATOXINS, ZEARALENONE, AND DEOXYNIVALENOL: A 13-YEAR REVIEW (2010-2023)

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ABSTRACT

This study aimed to review fungal mycotoxins in foods, their impacts, and their significance in human and animal health from 2010 to 2023. The study was conducted using electronic databases including Elsevier (Science Direct), Web of Science, Google Scholar, and PubMed to ensure sufficient and satisfactory coverage were searched from inception to December 31, 2023. The results from this review showed that mycotoxins, including Aflatoxin (AFs), Ochratoxins (OTA), Fumonisins (FMNs), Zearalenone (ZEN), and Deoxynivalenol (DON), can exhibit a wide range of toxic effects on both humans and animals. AFs, particularly AFB1, pose hepatotoxic, immunotoxic, and carcinogenic risks, leading to both acute and chronic health complications. OTA specifically targets the kidneys and induces nephrotoxic, mutagenic, carcinogenic, and teratogenic effects, while its genotoxicity remains a subject of debate. FMNs are linked to liver cancer and developmental issues in humans. DON inhibits protein synthesis, resulting in immunosuppression effects, as well as gastrointestinal, and dermatological complications. Furthermore, this review explored mycotoxin control strategies. It is therefore recommended that policies be designed to build awareness programs about the health risks associated with mycotoxins in food and animal feed.

Keywords: Mycotoxins; Review, Food; Human and animal health, Aflatoxins, Fumonisins, Ochratoxins, Zearalenone, Deoxynivalenol.

Introduction

Mycotoxins are secondary metabolites produced by different filamentous fungi such as Aspergillus, Fusarium, and Penicillium, and can cause serious diseases in humans and animals (Umereweneza, et al. 2018; Kebede, 2016). They are heterogeneous compounds of low molecular weight. Their notorious reputation is due to their ability to cause serious diseases in humans and animals. Mycotoxins enter the food chain through infected crops that can be consumed by either humans or animals. This leads to the accumulation of mycotoxins in different organs and tissues in the human and animal bodies, which makes them conducive to deadly diseases. Mycotoxins first came into notice in 1962 in England when 100,000 turkey poultry y died due to peanut feed- stock poisoning with the fungi Aspergillus flavus. According to the Food and Agricultural Organization (FAO), 25% of the cereals produced globally are contaminated with mycotoxins. Mycotoxins can contaminate stored feedstock and food products. Mycotoxin contamination is a global risk to food crops, including cereals (corn, rice, wheat, barley), lentils, fruits, peanuts, almonds, walnuts, pistachios, coffee, cotton seeds, spices (pepper, paprika, ginger), and meat (Pleadin et al., 2019; Darwish et al., 2014). Different spices, fruits, and nuts are also susceptible to the mycotoxins infection (Marin et al., 2013). Mycotoxins can affect human health by consumption of fungal infected animal product like meat, eggs and milk. Most mycotoxins are chemically and thermally stable during food processing, including cooking, cooking, baking, frying, baking, and pasteurizing. Mycotoxins can also cause cancer, allergies, and organ toxicity (Alshannaq and Yu, 2017). The severity of their effects relies on the degree of exposure and their mutagenic and teratogenic effects. For instance, consuming certain fungal-contaminated foods can lead to various long-term health effects, including liver cancer, immune suppression (AFB1, OTA), abdominal pain (DON), endocrine disruption (ZEN), stunted growth (T-2 toxin), and genotoxicity (Amuzie and Pestika, 2010; Rasic et al 2019). Long-term exposure to multiple mycotoxins may also result in synergistic health impacts (Zhou et al., 2017; Sun et al., 2015).

Mycotoxin-producing fungi contaminate food and feed, leading to socio-economic and health implications (Abdi-Elgany and Sallam, 2015; Montana et al., 2016). According to Mesterh´azy et al. (2020), contamination with mycotoxins is responsible for the wastage of approximately 1.3 billion metric tons of food annually, equivalent to one-third of global food production. Currently, 400 types of mycotoxins have been reported so far. Out of these, five categories of mycotoxins have enormous economic and health worth. They are aflatoxins (AFs), ochratoxin A (OTA), zearalenone (ZEN), fumonisins (F), and deoxynivalenol (DON), (Alshannaq and Yu, 2017). Among mycotoxins, AFs are particularly concerning as they are highly toxic and considered as Group 1 human carcinogens by the International Agency for Research on Cancer (IARC) (Anfossi et al., 2016). The majority of mycotoxins currently known are grouped, according to their toxic activity, under chronic conditions as mutagenic, carcinogenic, or teratogenic. The purpose of this review is to discuss the following mycotoxins: aflatoxins, fumonisins, zearalenone, deoxynivalenol, and ochratoxins and raise the main topics about their impact on human and animal health. The review also identified new research efforts to control mycotoxin contamination of food.

Mycotoxins' Toxicity

Mycotoxins, produced by pathogenic fungi, pose a health risk when they contaminate cereal crops, fruits, and vegetables. A recent review suggests that about 60 to 80% of the global food crops are contaminated with mycotoxins (Eskola et al., 2020). This estimation pushed back the widely cited 25% estimation attributed to the Food and Agricultural Organization (FAO) of the United Nations.

The chemical structures of major mycotoxins are depicted in Figures 1, 2, 3 4, and 5 while their extent of toxicity is given in Table 1.

Aflatoxins

Aflatoxins were first isolated in the early 1960s when 100,000 turkey poultry died after consuming aflatoxin-contaminated peanut meal in the UK (the so-called Turkey X disease); this event was followed by the proliferation in research on fungal toxins contaminating food and feeds. Aflatoxins (AFs) are a group of greatly toxic mycotoxins produced by certain fungi of the genus *Aspergillus,* such as *Aspergillus flavus* and *Aspergillus parasiticus* (Markaki, 2010; Okoth et al., 2012). AFs are potent carcinogenic, teratogens, hepatocarcinogenic, nephrotoxic, and mutagens mycotoxins (Markaki, 2010). Structurally, AFs are difurocoumarin derivatives that fluoresce under ultraviolet light. Depending upon the color of the fluorescence. AFs are divided into aflatoxin B1 and B2 (AFB1, AFB2) for blue, and G1 and G2 (AFG1, AFG2) for green (Galaverna and Dall'Asta, 2012) (Figure 1). Aflatoxin M1 and M2 (AFM1, AFM2), known as milk-AFs, are the metabolites of AFB1 and AFB2, respectively.

Aflatoxin B1 (AFB1) has classified in Group 1 as human carcinogen (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans 2012; FAO/WHO 2015) which usually is the most concerning and poisonous among these toxins. Darwish et al. (2014) reported that aflatoxins are the most common mycotoxins (43.75%) in Africa followed by fumonisin (21.87%), ochratoxins (12.5%), zearalenone (9.38%), deoxynevalenol (6.25%) and beauvericin (6.25%). They reported high levels of aflatoxin in samples collected from several African countries including South Africa, Lesotho, Egypt, Tunisia, Morocco, Sudan, Tanzania, Zambia, Uganda, Kenya, Ethiopia, Nigeria, Ghana, Benin, Mali, Togo and Bourkina Faso. Aflatoxin B1 (AFB1) has been linked to human primary liver cancer, in which it acts synergistically with HBV infection and it has been classified as a carcinogen in humans (Group 1 carcinogen). While primarily affecting the liver, AFB1 can also impact another physiological process. However; its hepatotoxicity and the interaction of its epoxide derivative with liver cell DNA remain the primary concerns. This interaction is linked to liver tumor development following chronic exposure to low AFB1 levels. In addition, aflatoxin B1 is the most prevalent and biologically active AF with a "pro-carcinogen" that is usually activated to the carcinogenic and reactive AFB1-8, 9-epoxide (AFBO) intermediate by hepatic cytochrome P450 (CYP450) enzymes (Kemboi, 2023). This compound can bind to DNA in the liver cells, forming the unstable AFB-N7-guanine adduct that when present in urine forms a potential biomarker of AFB1 exposure (Lauwers et al., 2019). AFB1 and its major metabolites AFM1 and aflatoxin (AFL) have been found in chicken liver, blood, muscle, and eggs (Magnoli et al., 2011). Biotransformation of AFB1 to AFL is hypothesized as a coping mechanism to prevent conversion of AFB1 to AFBO and subsequently to AFB1-dihydrodiol, which is the metabolite responsible for the toxicity of AFB1 (Murcia & Diaz, 2020).

One of its effects would be the impairment in the development of children, in addition to the association with nutritional disorders such as Kwashiorkor (McMillan et al., 2018). Consequently, the detection of AFB1 has become important regarding the safety, import, and export of food products. Aflatoxin contamination of food and feed is a serious problem worldwide. Studies focusing on AF contamination in foodstuffs have been reported in many countries, especially those in tropical and subtropical regions, such as Asia and Africa (Bankole et al., 2010). Poor agricultural practices coupled with a lack of awareness and laxity in enforcing regulatory laws have resulted in widespread contamination and toxicity of AFs in Sub-Sahara Africa (SSA) (Nakavuma et al., 2020; Nishimwe et al., 2019). Aflatoxins were reported to be present in over 60% of poultry feeds from SSA, with levels above the East Africa Community (EAC) guidance value of 20 µg/kg (ppb) for AFB1 in poultry feeds mainly found in tropical regions and levels above 1,000 µg/kg reported in one study. Aflatoxins (AFs) are the best-known and most widely studied mycotoxins.

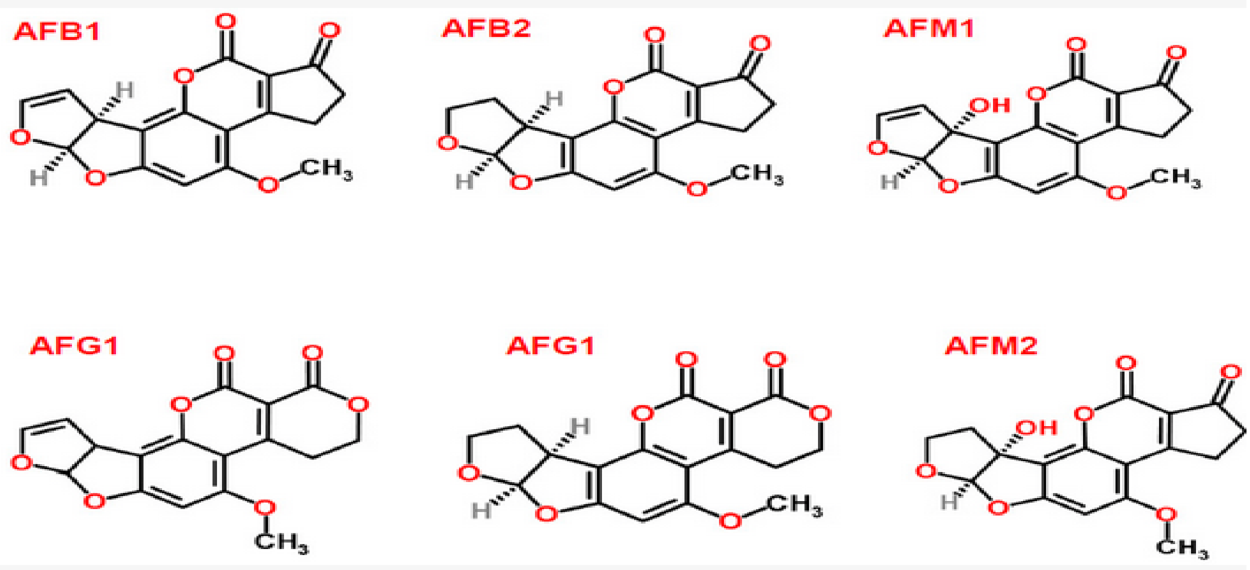


Figure 1: **Chemical structure of aflatoxins B1, B2, G1, G2, M1, and M2 (adapted from Zhang et al., 2014).**

Fumonisins

Fumonisins (Figure 2) are a group of mycotoxins produced mainly by fungi of the genus *Fusarium verticillioides* and *Fusarium proliferatum*. Fusarium proliferatum occurs predominately in maize and maize-based feeds(Marin et al 2014). Currently, more than 28 fumonisins have been isolated and are classified into four groups (A, B, C, and P) (Alshannaq and Yu, 2017). Among the fumonisins B (FB), FB1, FB2, and FB3 are the most abundant. FB1 is the most toxic form and can coexist with other forms of fumonisin, namely FB2 and FB3. These three forms of fumonisin are the primary food contaminants (Chen et al., 2021).FB1, the most widespread in human food and also the most toxic, is the cause in humans of developmental abnormalities of the embryo (malformations of the brain and spinal cord), kidney damage, cardiac damage (idiopathic congestive heart disease), and immune system damage (Kamle et al., 2019; Chen et al., 2021). It is also classified in group 2B (probably carcinogenic) by the IARC (Alshannaq and Yu, 2017), with a role in the initiation of esophageal and liver cancer. This mechanism would be reinforced by the interaction of fumonisin with AF (Kamle et al., 2019; Chen et al., 2021).In food, fumonisin is mainly found in corn and corn products (FB1 is the most commonly found) but also in many other cereals such as rice, wheat, barley, corn, rye, sorghum, soybeans, oats, and millet (Alshannaq and Yu, 2017). It is also found in other foods, such as asparagus, garlic, figs, and black tea. However, it should be noted that, unlike other mycotoxins, fumonisin is hydrophilic. There is, therefore, very little contamination from animal milk and very little accumulation in meat (especially FB1) (Alshannaq and Yu, 2017).

Fumonisin B1 is generally the most abundant member of this mycotoxin family; it comprises about 70 % of the total fumonisin content of *Fusarium* cultures (Reddy et al., 2010). Fumonisins are polyketide metabolites, derived from the repetitive condensation of acetate units or other short carboxylic acids, via a similar enzymatic mechanism to that responsible for fatty acid synthesis (Huffman et al., 2010). The fumonisin biosynthetic pathway in *Fusarium* species begins with the formation of a linear dimethylated polyketide and condensation of the polyketide with alanine, followed by a carbonyl reduction, oxygenations, and esterification with two propane-1,2,3-tricarboxylic acids. Major contamination occurs in maize, maize-based products, sorghum, rice, etc (Bulder *et al*., 2012). Fumonisin contamination is carcinogenic. The mechanism of action of FB1 consists of the interruption of sphingolipid synthesis by inhibiting sphingosine-N-acetyltransferase, inducing oxidative stress, altering DNA methylation, and modulating autophagy and stress of the endoplasmic reticulum (Voss & Riley, 2013; Liu et al., 2019). The toxic action of fumonisins occurs mainly by inhibiting the function of the enzyme ceramide synthase, leading to a decrease in the production of sphingolipids and, therefore, accumulation of sphinganine (Sa) and sphingosine (So). Sphingosine and sphinganine in serum, tissues, urine, and feces can be used as biomarkers of exposure to fumonisins (Marin et al., 2013). In underdeveloped countries where maize and derivative feeding rates are high, the fumonisins present in these foods seem to be related to impaired child development (Chen et al., 2018).

In addition, FB1 has been shown to cause hepatotoxicity and nephrotoxicity in rats (Voss & Riley, 2013). In humans, fumonisins are constantly found in places with a high incidence of esophageal cancer, which is therefore a sign that these toxins may play a role in the development of this neoplasm (Come et al., 2019). In rats, liver damage caused by FB1 can lead to an imbalance in the mineral composition of bones, leading to decreased bone strength (Rudyk et al., 2019). Among the diseases caused by fumonisins in animals are leukoencephalomalacia in horses and pulmonary edema in swine (Source). In addition, FB1 has been shown to cause hepatotoxicity and nephrotoxicity in rats (Voss & Riley, 2013). The chemical structure of FB1 is 1,2, 3-Propanetricarboxylic acid, 1,1N-[1- (12 amino-4,9,11-trihydroxy-2-methyltridecyl)- 2-(1-methylpentyl)-1,2-ethanediyl] Ester (Figure 3). FB2 is the C-10-deoxy analogue of FB1 and FB3 is the C-5-deoxy analogue of FB1.

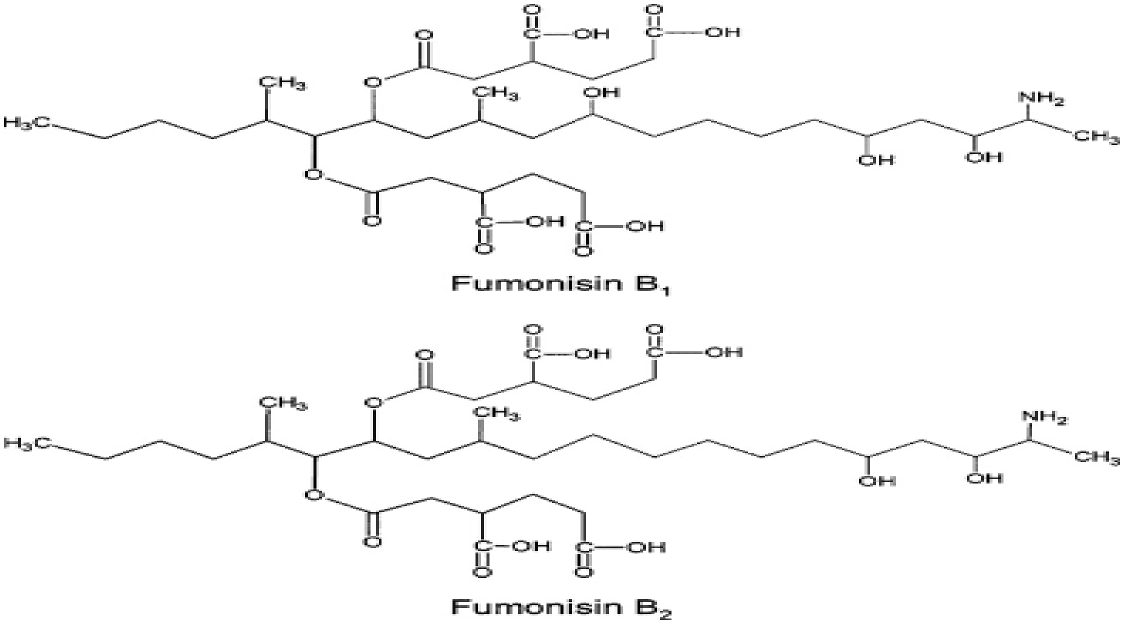


Figure 2: Chemical structure of fumonisins B1 and B2

Ochratoxins

Ochratoxins (Figure 3) are secondary metabolic products of fungi of the genus *Aspergillus spp. and Penicillium spp.* found mainly in nuts, dried fruits, grapes, and grapes-derived drinks (Rocha et al., 2014). It has a structure similar to that of phenylalanine, which makes this mycotoxin act to inhibit protein synthesis. Its effects include nephrotoxicity, hepatotoxicity, immunosuppression, and teratogenesis (Al-Jaal et al., 2019). Within the group of Ochratoxins, the most important is Ochratoxin A (OTA), due to its ability to cause damage to human and animal health, is categorized by the International Agency for Research on Cancer as a potential carcinogen for humans, remaining in the group 2B. Considering the mechanism of adduct formation with DNA, hypotheses are raised that a series of epigenetic mechanisms are related to the carcinogenic potential of OTA (Pfohl-Leszkowicz & Mandeville, 2012). Its effects include nephrotoxicity, hepatotoxicity, immunosuppression, and teratogenesis (Al-Jaal et al., 2019). Ochratoxin is a mycotoxin that comes in three secondary metabolite forms, A, B, and C. The three forms of Ochratoxins differ in that Ochratoxin B (OTB) is a non-chlorinated form of Ochratoxin A (OTA) and that Ochratoxin C (OTC) is an ethyl ester form of Ochratoxin A (Ashiq, 2015; Jeswal & Kumar, 2015). *Aspergillus ochraceus* is found as a contaminant of a wide range of commodities including beverages such as beer and wine. *Aspergillus carbonarius* is the main species found on vine fruit, which releases its toxin during the juice-making process. OTA has been labeled as a carcinogen and a nephrotoxin and has been linked to tumors in the human urinary tract, although research in humans is limited by confounding factors (Ashiq, 2015; Jeswal & Kumar, 2015). Toxicity due to OTA is through the generation of DNA adducts that cause impairment of protein synthesis increased oxidative stress, and inhibition of mitochondrial function (Bhatti et al., 2019). In poultry, OTA is reported to be nephrotoxic, immunosuppressive, teratogenic, and neurotoxic

As shown in experimental studies, OTA, which is metabolized in the liver via cytochrome P450, acts on hepatic metabolism, inducing changes in its metabolic pathways, thus leading to the development of liver diseases over time (Qi et al., 2014). The mechanisms by which OTA operates in the liver are mostly increased production of reactive oxygen species in hepatocytes, followed by lesions in DNA and stimulation of intrinsic apoptosis pathway activation (Gayathri et al., 2015). OTA contamination of many other raw agricultural products has been well documented; such contamination occurs in a variety of food and feeds, such as coffee beans, pulses, spices, meat, and cheese products (Abrunhosa et al., 2010).

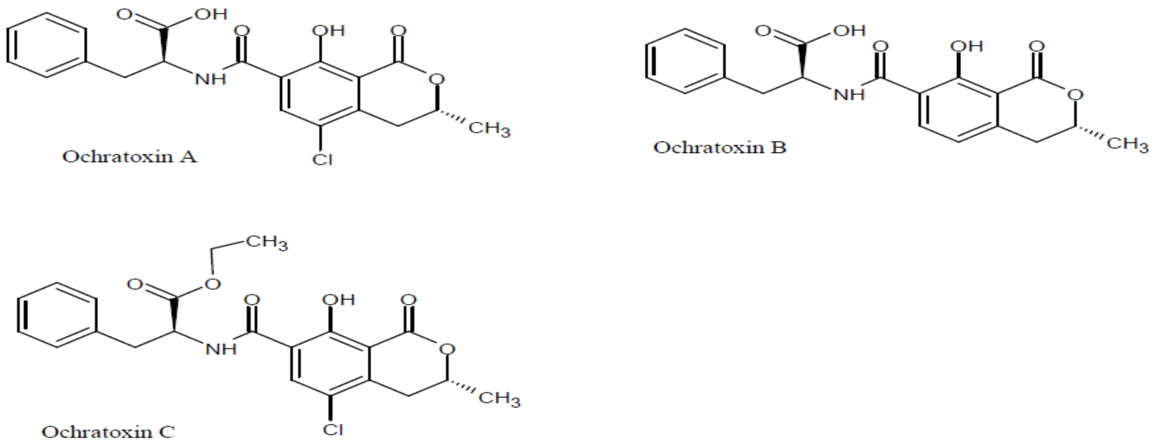


Figure 3: Chemical structure of Major Ochratoxins

Zearalenone

Zearalenone (ZEN) (Figure 4) is a nonsteroidal estrogenic mycotoxin produced mainly by fungi of the genus *Fusarium spp*. ZEN can be produced in colder climates and can be found in various foods, mainly in corn. This mycotoxin acts in the body as an estrogenic substance, and its mechanism consists of binding to receptors for 17β estradiol, leading to hyperestrogenism and reproductive disorders. The ingestion of food contaminated with ZEN leads to endocrine disorders due to its similarity to naturally produced estrogenic hormones, and constant hormonal stimulation can lead to the development of hormone-dependent neoplasms (Kowalska et al., 2016). In Tunisia, significant amounts of ZEN and metabolites in the urine of patients with breast cancer have been identified, indicating a possible role of this mycotoxin in the development of this neoplasm (Belhassen et al., 2015). The association between ZEN and carcinogenesis is the subject of discussion, considering that experimental studies demonstrate the ability of this substance to decrease the possibility of the development of malignant neoplasms in rats in the prepuberty period. Other experimental studies also evaluated whether ZEN is related to the progression of breast cancer through inhibition of apoptosis mechanisms and promotion of cell proliferation mechanisms.

Experimental studies also demonstrate that exposure to ZEN can lead to the death of Sertoli cells in mice by inducing reactive oxygen species and the ATP/AMPK pathway (Zheng et al., 2018). Other mechanisms that induce apoptosis by ZEN are due to the stress of the endoplasmic reticulum and the activation of autophagy, as demonstrated with immortalized Leydig cells from goats (Yang et al., 2017). In humans, consumption of food contaminated with ZEN during pregnancy can expose the fetus to this mycotoxin and its metabolites (Warth et al., 2019). Experimental studies in rats indicate that gestational exposure to ZEN blocks the fetal development of Leydig cells, which is an important indicator that this exposure leads to anomalies in the development of the male reproductive tract (Pan et al., 2020).

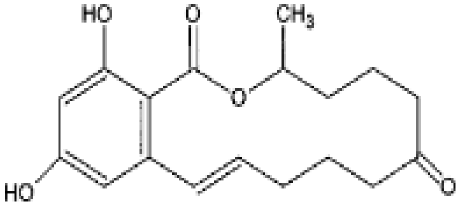


Figure 4: Chemical structure of Zearalenone

Deoxynivalenol

Deoxynivalenol (DON) is a mycotoxin produced by fungi of the genus *Fusarium spp.* that can be found in several grains and products of animal origin. The main damage to human and animal health occurs mainly in an acute form leading to nausea, emesis, diarrhea, abdominal and head pain, dizziness, and fever, which can evolve to death depending on the amount ingested. The chronic effects are mainly on the immune, reproductive, and gastrointestinal systems. This toxin acts mainly on the neuroendocrine system, inhibiting the growth hormone cascade and stimulating inflammatory responses. In addition, it acts on the gastrointestinal tract, inhibiting gastric emptying and causing an imbalance in the intestinal mucosa, consequently affecting the absorption of nutrients (Pestka, 2010; Sobrova et al., 2010). Ingestion of DON, in addition to its acute effects, can lead to genotoxicity on human lymphocytes, probably resulting from the decrease in antioxidant substances, leading to DNA damage by oxidative stress (Yang et al., 2014). Furthermore, DON seems to have a genotoxic effect on *E. coli* strains present in the human intestine, which is a possible indicator of its participation in intestinal carcinogenesis, although previous studies have ruled out that DON may play some role in the development of neoplasms (Pestka, 2010; Payros et al., 2017). DON seems to cause emetic effects in humans, and when its effects are evaluated in animals, it is possible to observe effects on the immune system, anorexia, and loss of nutritional efficiency as well as adversely affect reproductive capacity. Reviews carried out in cell lines of human intestinal mucosa suggest that DON acts by modulating the activity of intestinal transporters, thus acting on nutrient absorption, and the main mechanism of injury occurs by the inhibition of protein synthesis and the decrease in intercellular junction constituents (claudina-4) (Van de Walle et al., 2010). Figure 5 shows the chemical structure of deoxynivalenol (DON).

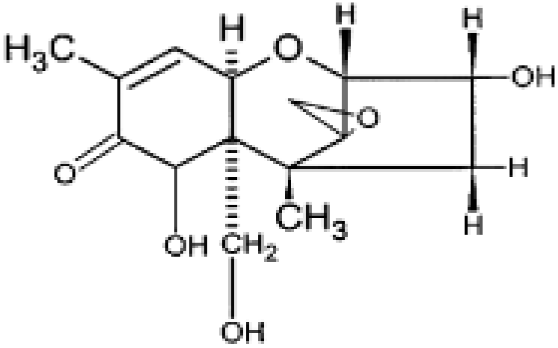


Figure 5: Chemical structure of Deoxynivalenol (DON)

Experimental studies demonstrated that DON may have teratogenic potential related to disorders of bone and cartilage development; however, such findings are open to discussion, considering that other studies do not show changes in embryonic development, which is a point to be clarified in the future. The main route of DON metabolism includes conjugation with glucuronic acid to free DON and conjugation with glucuronic acid, for example, DON-Glucuronide (DON-GlcA), the most commonly used way to measure exposure. In addition to free DON and DON-GlcA, de-epoxy deoxynivalenol (DOM-1) is another metabolite present in body fluids associated with microbiota (Al-Jaal et al., 2019). Table 1 summarizes the common mycotoxins (AFs, Fums, OTA, DON & ZEN), commodity affected, toxic effects, and diseases.

Table: Common mycotoxins, commodity affected, toxic effects and diseases

Mycotoxins	Commodities affected	Fungal source(s)/Causative fungi	Toxic effects and diseases/Health Implications	References
Aflatoxins B1, B2, G1, G2, M1, and M2	Cereal grains, Legumes, Fruits, Coconut, Cotton seeds, Vegetables, Spices, and Peanuts,	*Aspergillus flavus,* and *Aspergillus parasiticus*	Hepatocellular carcinoma, mutagenic and teratogenic effects AFM1 cause abnormalities in fetal development, carcinogenic, mutagenic, immunosuppressive agents	Prisvade et 2019, El-sayed et al., 2020, Ogodo et al. 2016, Blanchard and Manderville, 2016

Deoxynivalenol (DON)	Corn, wheat, Barley, and Animal-based foods like Eggs, Kidney, and Milk	*Fusarium. graminearum, Fusarium culmorum Fusarium cookwellense Fusarium poae and Fusarium sporotrichoid*	Human toxicosis, Toxic to animals, especially pigs. It also hinders the production of DNA, RNA, and proteins, causing apoptosis, lipid peroxidation, and cytokinesis and disrupt brain neurochemistry	Patocka & Bolsatine(2018); Bhat et al., 2010; Foroud et al., 2019; Klaban, 2021, Adeso et al. 2017, Pinton, and Oswald, 2014; Ali, 2013.
Zearalenone	Corn, Cereals, Silage, Fodder, Wheat	*Fusarium graminearum, Fusarium culmorum, Fusarium crookwellense Fusarium cerealis Fusarium equiseti,* and *Fusarium vertillioides*	ZEN induces liver cancer, tumors in the uterus, and thyroid adenoma in rats. Infertility, arbotion or other breeding poblems, ZEN causes testicular atrophy, retinopathy, nephropathy, and cataracts in rats. ZEN regulates enzyme expression Within biosynthetic pathways.	Ostry et al., 2017, Mazaheri et al., 2021, Tola and Kabede, 2016, Blanchard and Manderville, 2016.
Ochratoxins (OTA, OTB, and OTC	Cereals, Legumes, Fruits, Vegetables, Nuts	*Aspergillus ochraceus, Aspergillus. niger, Aspergillus carbonarius, Penicil nordicum, Penicil viridicatum, and Penicil verrucosum*	Kidney and liver damage, loss of appetite, nausea, vomiting, suppression of immune system carcinogenic. OTA exhibits hepatotoxic, neurotoxic, teratogenic, and nephrotoxic properties, causing nephropathy in pigs. OTA is associated with renal failures, interstitial nephropathy, urothelial tumors, sex-specific toxicological differences	Ismaiel &Papenbrock,2015 , Gupta et al. 2018, Blanchard and Manderville 2016, Faucet-Marquis, et al.,2014.
Fumonisins B1, B2, B3	Corn, Cereals, Rice and Sorghum, Wheat noodles, Beer and Corn-based brewing adjuncts beans, Soybeans, Oats	*Fusarium moniliforme, Fusarium oxysporum, Fusarium proliferatum*	Encephalomalacia (ELEM), a fatal disease of horses, pulmonary edema, carcinogenic, Neurotoxicity, liver damage, heart failure, Esophageal cancer in humans. Inhibiting sphingolipid synthesis Linked to esophageal and liver cancers in people. In monkeys, associated with ELEM. In horses, causing respiratory inflammation, Leukoencephalomalacia, liver diseases and tumors	Tao et al. 2018, Martin et al., 2013, Kamle et al., 2019, Adeyeye(2016), Geldeerblom & Marasas, 2012, Landoni et al., 2020, Chang, et al. 2014; Tian et al., 2016.

Source: Literature survey, 2024

Methods for Avoiding or Mitigating the Presence of Mycotoxins in Foods

The most effective approach to reducing mycotoxins in the food chain is by preventing the growth of fungi in food and inhibiting toxin production. Different physical, chemical, and biological methods have been used at both industrial and laboratory levels to achieve this goal (Liu et al., 2020). Numerous steps can be implemented to reduce the risk of mycotoxin exposure and related health and socio-economic challenges. These measures may involve preventing contamination by limiting fungal growth or intervening after growth to eliminate or reduce toxin availability. Pre-harvest treatments are primarily focused on controlling fungal infection spread in the field, while post-harvest methods aim at decontaminating substrates after toxin production or reducing toxin absorption by exposed organisms (Auchi et al., 2021). Cereal grains and feed are inevitably prone to contamination, with a lack of cost-effective detoxification methods. Hence, it is crucial to regularly monitor the quality of animal-derived foods, raw materials, and feed for the well-being of food animals, economic sustainability, and consumer food safety (Peles et al. 2019).

Good Agricultural Practice

The first critical point in limiting the occurrence of Aspergillus or Penicillium isolates and their mycotoxin contamination is the adoption of agricultural practices that can create an unfavorable environment for the proliferation of fungal spores present in the soil. These practices include plowing the soil before sowing, weeding, respecting the specific sowing time for each type of crop and the optimal harvest time, manuring, soil amendment and fertilization, irrigation management, and crop rotation with crops less susceptible to the growth of Aspergillus spp (Tore s et al., 2014). Mycotoxin contamination can be minimized by certain cultural practices, curing, drying, and storage methods. However, these techniques may be incompatible with small-scale agriculture in emerging countries, particularly in tropical regions. Thus, the development of mycotoxin-resistant varieties is a multi-step process that may involve direct selection for resistance to FG and aflatoxin formation, indirect selection for resistance or tolerance to biotic factors or environmental stresses, or selection for morphological characteristics that inhibit or delay fungal invasion or growth (Tore s et al., 2014). Due to the scarcity of resistance genes, the development of cultivars resistant to preharvest mycotoxin contamination has been limited. Numerous efforts have been made to produce mycotoxin-resistant cultivars, resulting in the creation of selected resistant types that have gradually been released as improved germplasm in several regions of the world. However, complete resistance to mycotoxin contamination has not been achieved and genetic efforts continue.

Similarly, mechanical damage should be avoided as it increases the grain's susceptibility to fungal and insect attacks. For example, it is preferable to harvest maize cobs with their leaves intact and avoid damaging the leaves, as they are critical in protecting the cobs from insects, particularly weevils such as *Sitophilus zeamais*, which are the most common pests of maize crops. Not only can these insects increase the surface area of the ear susceptible to fungal infection, but their metabolic activity can also wet the grain and promote fungal growth (Manu et al 2019). Mechanical damage caused by milling should also be minimized as it facilitates insect penetration. Even if climatic conditions are not optimal, grain lesions caused by insect infestation can lead to mycotoxin contamination of the grain (Omotayo et al., 2019). The fungi may then grow inside the grain, where they are isolated from environmental conditions and in direct contact with nutrients, creating a micro-atmosphere (Ndemera et al 2020).

Harvesting at the optimal time is also critical to avoid fungal growth. Harvesting should occur shortly after physiological maturity to minimize mycotoxin contamination. Crops harvested at immature stages, on the other hand, must be dried promptly and effectively to achieve moisture levels that are no longer conducive to mold growth (10–13%) for cereals), thus preventing mold development throughout the storage period (Neme and Mohammed, 2017). Climatic conditions in many developing countries, which often combine inadequate early drying with excessive humidity, play a significant role in crop contamination and the often-high mycotoxin levels observed in agricultural commodities. In addition, although prolonged drying in the field may reduce grain moisture, this technique increases the time exposed to insect attack, resulting in increased losses during storage (Kumar and Kalita, 2017). Therefore, unfortunately, the implementation of these storage and drying practices is often difficult for farmers with small plots of land, especially when the general climatic conditions are unfavorable (tropical and subtropical regions). To make matters worse, the effect of crop rotation and most agricultural practices on toxicity is generally more limited than the effect of environmental factors (temperature and humidity).

Surveillance and awareness creation

Creating awareness among stakeholders (farmers, consumers, policymakers, etc.) does not often receive much attention compared to other aflatoxins mitigation and control measures despite many reports documenting the generally low awareness as to the risks posed by aflatoxins in many developing countries (Udomkun et al., 2018). For instance, a study by Ayo et al. (2018) found that aflatoxin awareness was deficient among uneducated and socially unexposed farmers in Tanzania. Similar low awareness levels are reported in Ethiopia and Uganda (Guchi, 2015; Nakavuma et al., 2020). Studies in Vietnam and Nigeria also reported similar low aflatoxin-related awareness among consumers (Adekoya et al., 2017; Lee et al., 2017). Interestingly, this low awareness among stakeholders regarding mycotoxins' occurrence in agricultural products, is not confined to developing countries. A study by Sanders et al. (2015) revealed that Belgians are more aware of bacterial-related food contamination than mold contamination. In the same study, it was observed that 39.3% of 140 people working in the agricultural sector did not know whether toxic plants, bacteria, molds, or viruses are producers of mycotoxins. An increase in the understanding of the issues surrounding aflatoxins-contamination of food, its health, and economic effects, preventive and control measures will go a long way in alleviating the menace. A more recent study by Anitha et al. (2019) observed that despite adverse weather conditions mean aflatoxin levels in grains were reduced from 83.6 to 55.8 ppb as a result of training farmers on aflatoxin-related issues.

Raising aflatoxin-related awareness among consumers indeed can be a useful tool in preventing human exposure to aflatoxins, however, as an extremely "scientific" topic; care must be taken to avoid misunderstanding and unnecessary panic among consumers. For example, in Ghana and Ethiopia, misleading aflatoxin-related news headlines resulted in panic among consumers, warranting governments' and the scientific community's interventions (Stepman, 2018). Therefore, aflatoxin-related risk communicators must ensure that the right information is adequately delivered to stakeholders. It is imperative for African countries to strengthen nationwide surveillance, increase food and feed inspections to ensure food safety, and local education and assistance to ensure that food grains and animal feeds are harvested correctly, dried completely, and stored properly. Awareness of what mycotoxins are and the dangers that they pose to human and animal health could be done through government bodies, private organizations, non-governmental organizations, national media networks such as radios and television programs as well as features in newspapers and magazines.

Seminars and workshops could be used as avenues and bridges of information exchange and dissemination between researchers and the populace respectively. Such events also serve as forums to assess past and present work and define and streamline areas of future studies.

Chemical Approaches

Synthetic antifungal agents represent chemical compounds engineered to inhibit fungal growth and proliferation. They find widespread application in the preservation of food items, aimed at averting spoilage and enhancing their shelf life (Leyva et al 2017). Despite their evident utility, synthetic antifungal agents are accompanied by certain drawbacks warranting critical consideration (Leyva et al 2017). One primary advantage associated with fungicides lies in their efficacy. Engineered to exhibit potent activity, they afford prolonged protection against a diverse spectrum of fungal species. Notably, synthetic fungicides offer effective mitigation against food contamination while also being relatively economical and user-friendly, rendering them a preferred choice among food manufacturers. Consequently, their adoption has become pervasive (Ons et al., 2020).

Moreover, fungicides offer greater convenience compared to their natural counterparts. They can be produced in large quantities and transported and stored with ease, without the threat of spoilage. This is attributed to their suitability for food producers, requiring swift and efficient treatment of sizable food volumes, unlike biopesticides, which hinge on the availability of plant sources (Lahlali, et al., 2022). Despite their myriad benefits, synthetic antifungal substances are not devoid of drawbacks. This approach appears to be nearing its thresholds due to several factors: environmental contamination and adverse effects on animal and plant biodiversity, diminishing efficacy owing to the development of resistance among microbial populations, and the inevitable toxicity of these substances upon chronic exposure in animals. A primary concern revolves around their potential repercussions on human health and the environment. Certain synthetic antifungal substances have exhibited toxic effects, raising concerns about residue persistence on treated food items (Hossain et al., 2022).

When fungicides are applied to plants or products, they can disrupt the cell membrane of fungal pathogens or impede crucial cellular processes. In some instances, fungicides serve as preventive measures by establishing a protective barrier that immobilizes toxigenic fungi, curbing or preventing their colonization of the plant (Zubrod, et al., 2019]. However, exercising caution in fungicide usage is paramount due to its potential impact on human health and the environment, coupled with the risk of fostering resistant fungal strains (Matumba, et al 2021). Striking a balance between the benefits and risks associated with synthetic antifungal substances in food production is paramount. Regarding mycotoxin detoxification, various chemical agents, including acids, bases, reducing agents, and oxidizing agents, have been employed to transform mycotoxins into less toxic derivatives through structural alteration. Among these, ozone and ammonia stand out as extensively studied chemical detoxification treatments (Conte et al., 2020).

Ozone finds application in disinfecting vegetables, fruits, cereals, and mycotoxin detoxification processes (Botondi, et al 2021). The antifungal mechanism of ozone gas involves damaging the fungal membrane, enhancing mitochondrial degradation, inducing cytoplasmic disintegration, and promoting plasmolysis (Ong and Ali, 2015). Furthermore, ozone has demonstrated efficacy in degrading AFs and OTA (Torlak, 2019; Agriopoulou et al., 2016). Oxidizing agents interact with functional groups within mycotoxin molecules, inducing changes in their molecular structures, resulting in the formation of products with reduced double bonds, molecular weight, and toxicity (Wang et al 2016). In addition to ozone, other bases like ammonia have been utilized to reduce several mycotoxins, including FUM, AFs, and OTs, to non-detectable levels (Luo et al., 2018). However, the use of certain bases such as potassium hydroxide and sodium hydroxide may lead to undesirable and toxic reactions. Notably, seed treatment employing ammonia has been found effective in suppressing the growth of mycotoxigenic fungi (Jalili, et al., 2011).

Detoxifying by Physical Method

Traditional decontamination methods for mycotoxins in food and feed involve various physical techniques utilized when preventive measures fail. These methods encompass several procedures such as dehulling, heating, plasma treatment, sorting and separation, radiation, immersion and washing, and adsorption. However, the efficacy of these techniques hinges on the extent of contamination and the distribution of mycotoxins within the product. Nevertheless, these methods may yield uncertain outcomes and can result in significant product losses (Luo et al., 2018). Sorting, dehulling, or washing are typically employed as pre-processing methods. They serve as common approaches to eliminating low-quality particles from food and maintaining food quality. For instance, cereal grains can be sorted based on various physical attributes such as density, color, shape, and size, while also identifying broken grains afflicted with fungal growth. Given the uneven distribution of mycotoxin contamination among grains, sorting, washing, or separating damaged food can markedly reduce the contamination levels (Matumba et al 2015). Immersing and washing contaminated grains in water and discarding the floating fractions can generally eliminate some amounts of AFs and FUM. Furthermore, cleaning and scouring procedures, as highlighted by Milani and Heidari Heidari, (2017), can substantially diminish ochratoxin contamination in grains.

Research indicates that ionizing radiation, including gamma radiation, electron beams, or X-rays, presents a safe and effective alternative to chemical treatments for eradicating microorganisms from food and feed or reducing mycotoxin levels (Sebaei et 2022). This technology, known as food irradiation, constitutes a physical-cold process widely adopted in the food industry across many nations. In particular, Khalil et al. (2021) have demonstrated that gamma radiation effectively curtails the growth of A. flavus and A. ochraceus, thereby significantly reducing AFs and OTA levels by 33.3–61.1%, contingent upon the mycotoxin involved. The efficacy of UV radiation varies depending on different conditions such as exposure time and wavelength. While UV radiation can stimulate sporulation and fungal growth in some cases, the incidence of shorter wavelengths has the opposite effect on biological organisms. García-Cela et al. (2015) demonstrated the effectiveness of UV-B and UV-A against A. carbonarius and A. parasiticus, resulting in reduced production of OTA and AFs in a time-dependent manner. Chemical methods employed for mycotoxin reduction may yield negative consequences, including alterations in nutritional value and palatability or the presence of toxic residues. Conversely, biological methods may be constrained by factors such as prolonged degradation time or incomplete degradation. Consequently, adsorption has emerged as a promising option for mycotoxin treatment (Li et al., 2018).

Adsorption entails both chemical and physical forces, making it the most commonly utilized method to safeguard animals against mycotoxins. By employing a range of adsorbents such as clay, activated charcoal, and other modified polymers, mycotoxins can be effectively bound and immobilized, thereby reducing their toxic impact by preventing their absorption from the gastrointestinal tract (Colovi´c et al., 2019). However, selecting efficient adsorbents can be challenging since various mycotoxins may co-occur in foods, potentially amplifying their toxic effects through synergistic interactions (Li et al., 2018). Despite its efficacy, concerns persist regarding the safety of adsorbent materials, the removal from feed, and the disposal of adsorption chemicals and adsorbent-mycotoxin complexes. Consequently, some chemical adsorbents have been prohibited as detoxification materials in the food industry by the European Union (EU) (Azam et al. 2021).

Bio-control of Toxigenic Fungi and Biodegradation of Mycotoxins

In the literature, several conventional physical, chemical, and adsorption-related technologies have been reported for the elimination or inactivation of mycotoxins (Stoev et al., 2013).Unfortunately, these approaches suffer from drawbacks such as safety concerns, loss of nutritional value and palatability, limited effectiveness, and cost implications. Recent research indicates promising prospects for using mycotoxin-adsorbing compounds to bind mycotoxins in the gastrointestinal tract of animals, thereby reducing their bioavailability and toxicities, particularly in the feed industry. However, the effectiveness of various adsorption agents differs, with some being more beneficial in preventing aflatoxicosis than others (Zain 2011; Stoev et al., 2013). Consequently, there is a pressing need for decontamination technologies that are efficient, practical, and environmentally friendly. To address these challenges, biological control techniques have been developed to manage foodborne pathogens more effectively and rapidly. Biocontrol involves controlling pathogenic microorganisms or their derivatives using natural sources such as microorganisms, plant-derived fungicides, and detoxifying enzymes. This approach has gained traction due to its ease of application and cost-effectiveness, positioning biological management as an eco-friendly alternative to synthetic compounds (Tian et al., 2016).

Currently, bio-protective crops, ferments, and purified molecules with antifungal activity are being developed. Microbial strains with potential antifungal properties have been isolated from various sources, leading to increased food shelf life and decreased fungal contamination, particularly from Aspergillus and Penicillium as described by Leyva et al. (2017). LAB are commonly employed for food biopreservation, while Trichoderma spp. plays a significant role in plant biocontrol, promoting growth and inducing defenses against biotic and abiotic stresses (Adnan et al., 2019). Additionally, microorganisms such as Debaryomyces hansenii yeast and Penicillium spp. fungi combat meat product decay caused by fungi (Delgado et al, 2019, Núñez et al 2015). Moreover, fungal strains of Trichoderma have been reported to control pathogenic molds by mechanisms such as competition for nutrients and space, rhizosphere modification, mycoparasitism, biofertilization and the stimulation of plant-defense mechanisms (Bhat et al., 2010)

Biodetoxification techniques offer another viable solution for managing mycotoxins, involving the use of microorganisms or enzymes to break down mycotoxins into non- or less harmful compounds. This method may entail using live or dead microorganisms to bind toxins to their cell wall components or decompose them into less harmful substances (Kim et al. 2017). However, if mycotoxins are only adsorbed and not completely degraded, there is a risk of their delayed release in the gastrointestinal tract (Schaarschmidt and Fauhl-Hassek, 2021). Numerous studies have identified fungal and bacterial strains capable of effectively breaking down mycotoxins, although concerns about food quality and consumer acceptance of meals enhanced with microorganisms persist. Consequently, microorganisms employed in food and feed additives must meet specific criteria, including safety, nonpathogenicity, production of stable and non-toxic metabolites, proficiency in mycotoxin degradation, formation of irreversible complexes, activity during storage, absence of unpleasant odors or tastes, retention of nutritional value, and minimal cultivation and production efforts. While various microorganisms have been proposed as potential detoxifiers for food and feed, only a few have undergone thorough testing to determine their efficacy. The use of mycotoxin-degrading enzymes produced by bacteria and fungi may overcome some of these constraints (Loi et al., 2011).

LAB as a Potential Biocontrol Agent

Lactic Acid Bacteria (LAB) comprise a group of oxygen-tolerant, Gram-positive bacteria pivotal in the fermentation of diverse food and beverage products. These bacteria are characterized by their ability to metabolize carbohydrates during fermentation, yielding lactic acid as a primary product, which contributes significantly to the sensory attributes such as flavor, texture, and aroma unique to each fermented product (Papadimitriou et al., 2016). The inhibitory efficacy of LAB in food preservation is primarily attributed to the synthesis of metabolites during the fermentation process, with nutrient and space competition also recognized as contributing mechanisms (Siedler et al., 2019). Throughout fermentation, LAB produces a diverse array of antifungal metabolites, including organic acids, phenolic acids, volatile acids, CO_2, hydrogen peroxide, antimicrobial peptides (AMPs), fatty acids, ethanol, and diacetyl, among others (**Figure 6**). These metabolites can exhibit synergistic or additive effects, complicating the precise elucidation of LAB's antifungal mechanisms (Nasrollahzadeh et al., 2020).

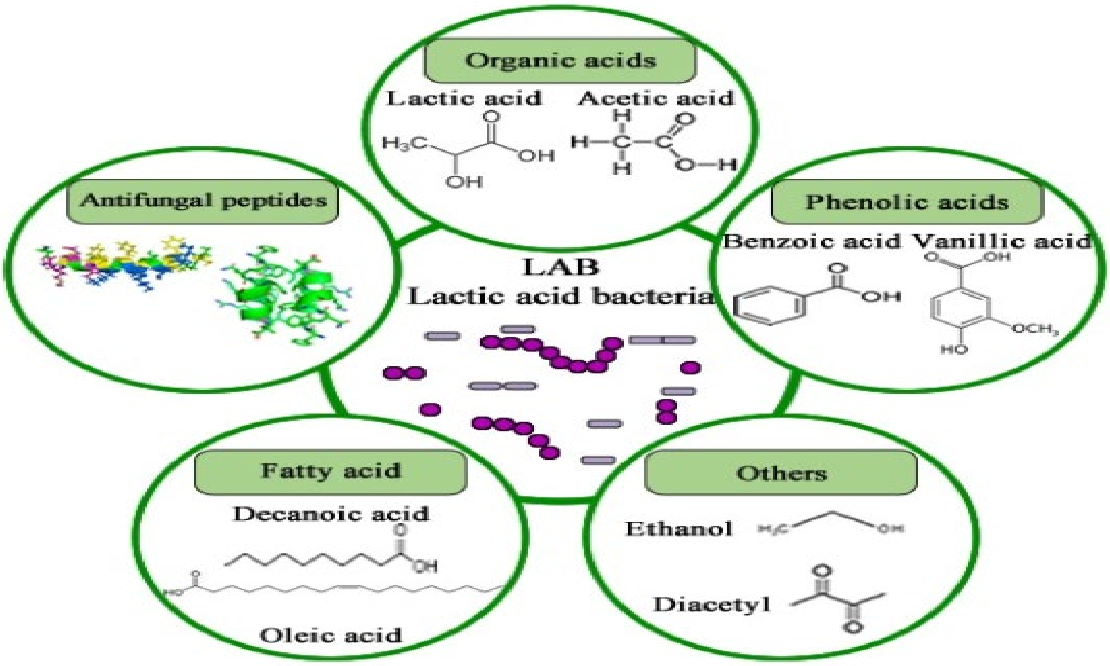


Figure 6: Chemical structure of antifungal compounds produced by LAB.

Organic acids such as lactic, acetic, and propionic acids exert antifungal effects primarily by disrupting the proton gradient essential for fungal cellular processes. Lactic acid, for instance, permeates the fungal cell membrane in a hydrophobic state, subsequently hydrolyzing within the cell to release H+ ions, inducing cytoplasmic acidification. Acetic and propionic acids similarly inhibit fungal amino acid absorption, albeit their efficacy is contingent upon the low pH environment created by lactic acid (Chen et al., 2021).

Antifungal peptides (AFPs), a subset of AMPs, are small, cationic peptides synthesized by LAB, capable of perturbing fungal membranes or interfering with proton gradients across the cell membrane. Notably, lactoferricin B demonstrates an affinity for the fungal surface, disrupting membrane integrity and exhibiting potent antifungal activity (Struyfs et al., 2021). AFPs represent a focus of contemporary research into natural biological control agents, sourced from plant, animal, and microbial origins, and composed of amino acids linked via peptide bonds (Bahar and Ren, 2013). Numerous phenolic compounds have been identified in foods or media fermented with LAB, boasting varied properties encompassing antioxidant, antifungal, and antitoxigenic activities (Guimarães et al., 2018; Antognoni, et al., 2019). Key among the phenolic acids produced by LAB is phenyl-lactic acid and its derivative, 4-hydroxyphenyl acetic acid, recognized for their contribution to the antifungal activity of LAB-fermented media, thereby enhancing food shelf (Guimarães et al., 2018, Mishra et al., 2021). Other phenolic acids generated during LAB fermentation include succinic acid, 4-hydroxybenzoic acid, vanillic acid, caffeic acid, p-coumaric acid, salicylic acid, ferulic acid, and benzoic acid (Salman et al., 2022).

Preventive and Control Strategies for Mycotoxins

Mycotoxin contamination prevention strategies can be pre-harvest or post-harvest measures (Awuchi et al 2021). Preventive measures during the harvesting process include ensuring timely harvesting, avoiding harvesting with excess moisture, and, if necessary, drying crops before storage (Zhang et al. 2019; Kumar et al., 2017). Today, the agri-food industry strives for a high standard of quality and safety, using modern technology such as filtration, air sterilization, overpressure sectors, and disinfection of atmospheres and surfaces to produce food under aseptic conditions. Currently, in agriculture, preventing fungal contamination is a challenging task. However, it is essential to avoid superinfection of seeds and fruits through contact with soil and contaminated equipment.

Additionally, these contacts cause injuries, which facilitate the penetration of hyphae into the plant. When handling fungal contamination, it is imperative to prevent conidial germination and hyphal development. When mycotoxins are already present in food, it is necessary to implement control strategies to minimize their adverse effects (Awuchi et al 2021, Zhang et al. 2019). Various decontamination methods can be employed to process food, including physical, chemical, or biological approaches. Most of them can partially destroy or inactivate mycotoxins, but they rarely eliminate them (Ostry et al., 2013).

Decontamination of Food

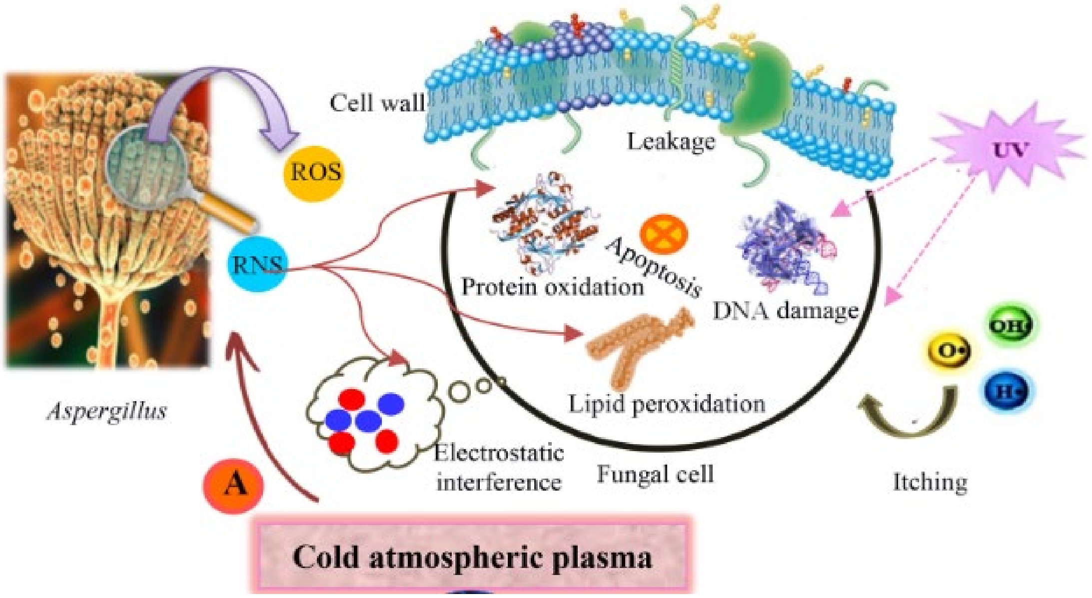
Decontamination procedures are necessary to reduce mycotoxin contamination in food products (Villarreal-Barajas et al., 2022). In this context, physical, chemical, and microbiological approaches are applicable. Combining multiple strategies with an integrated approach is often more effective The Food and Agriculture Organization (FAO) established guidelines for decontamination procedures, such as reducing mycotoxins, preventing toxic residue production, preserving product nutritional and technological attributes, and eliminating spores or mycelial filaments that can produce mycotoxins. Following the given guidelines can effectively reduce the incidence of mycotoxins in foods and feeds, ensuring the safety of both humans and animals.

Conventional Approaches

Physical methods, like cooking, baking, and roasting, are often used for food preparation. Some methods, like ozonization or radiation, can help reduce mycotoxin levels in food. However, these methods may not eliminate mycotoxins (Afsah-Hejri et al., 2020; ˇColovi´c, et al. 2019, Mir et al., 2021). Chemical compounds, such as hydrogen peroxide, sodium hypochlorite, ascorbic acid, calcium hydroxide, ammonium hydroxide, sulfur dioxide, and ammonium carbonate, can convert mycotoxins into non-toxic substances. However, these chemicals are unsuitable for food or feed meant for direct consumption (Mir et al., 2021). Various additives like vitamin C, bisulfides, curcumin, bentonite, activated carbon, silicate, and glucan-based adsorbents could mitigate the impacts of mycotoxins in infected foods. Similarly, esterified glucomannan has been shown to bind AFs, FMNs, and ZEN simultaneously when added to feed; caution must be exercised as these binders could intensify the harmful effects of certain mycotoxins (Afsah-Hejri et al., 2020). Mycotoxins are harmful substances that may contaminate food products. Missiological methods aim to mitigate their toxicity through microbial biodegradation and transformation. For example, the Flavobacterium aurantiacum bacterium degrades AFB1 in milk and meat (Afsah-Hejri et al., 2020). Bacteria like Lactobacillus, Bifidobacterium, Streptococcus thermophilus, and Lactococcus lactis can bind AFs to their cell walls, rendering them harmless. Additionally, Kluyveromyces yeast inhibits Aspergillus growth and AF production, suggesting they could help reduce AF contamination (Khan et al., 2021). Microbial binders and inhibitors are being investigated for their efficacy in fighting mycotoxin contamination. Naturally occurring macroorganisms show promise in mitigating mycotoxin toxicity in food products, ensuring safety for humans and animals.

Innovative Mitigation Strategies

Researchers are exploring new strategies to combat mycotoxin toxicity, addressing customer concerns about food hygiene, and improving control measures. These strategies include cold atmospheric plasma (CAP), polyphenols, magnetic materials and nano-particles, and natural essential oils (NEOs), which aim to mitigate mycotoxin-related health risks without leaving harmful residues on food products (Figure 7).



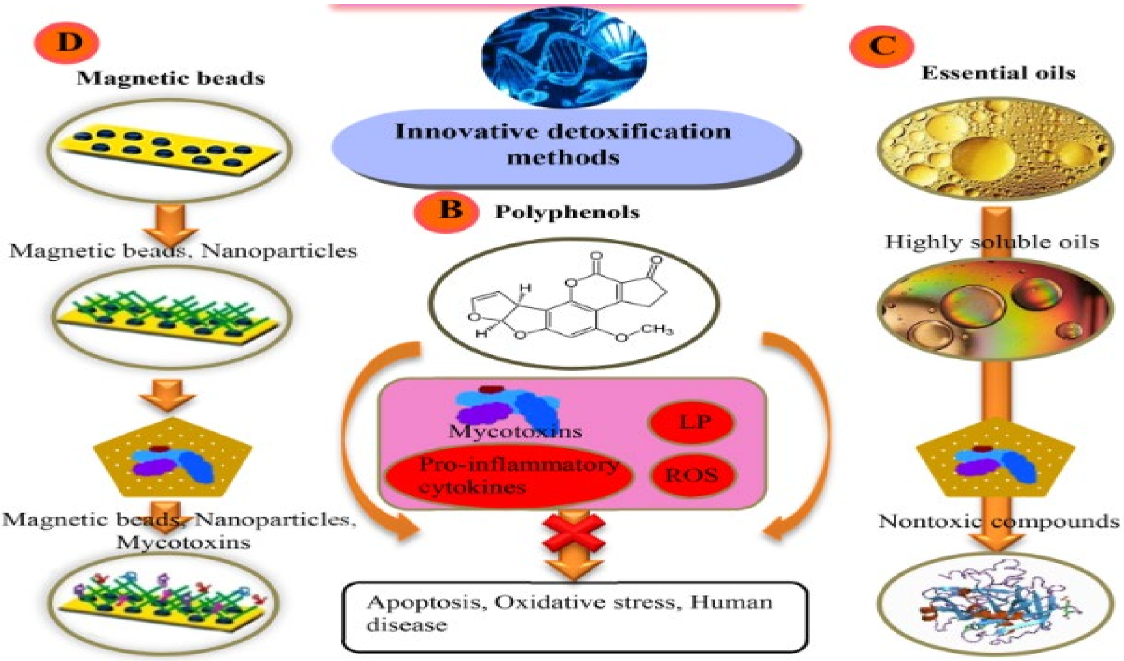


Figure 7: Methods for controlling mycotoxin contamination: (A) cold atmospheric plasma method, (B) polyphenols, (C) natural essential oils, and (D) magnetic materials and nanoparticles

Cold Atmospheric Plasma (CAP)

CAP is a state of matter achieved by subjecting a neutral gas to an electric field, which ionizes certain atoms or molecules within the gas, producing plasma. Reactive oxygen and nitrogen species are produced when the voltage exceeds the breakdown threshold, leading to the formation of CAP at ambient temperature and atmospheric pressure. CAP utilization involves exposing water, buffer solutions, and acids to plasma discharge, which generates sanitizers for washing and disinfection (Ali et al., 2022, Esu et al 2021). The system's antimicrobial activity and aptitude to reduce complex biochemical compounds are attributed to a combination of reactive chemistries, including O_2 (superoxide), O3 (ozone), H_2O_2 (hydrogen peroxide), OH (hydroxyl radicals), ONOO— (peroxynitrite), NO2 (nitrite), NO3 (nitrate), ultraviolet (UV) radiation, and a voltage. These elements collectively maintain a temperature comparable to the ambient levels, giving the nonthermal characteristics of CAP. The efficacy of CAP is influenced by mycotoxin's molecular structure and the conditions under which they are processed. For instance, the effectiveness of degrading DON in wheat-based food is influenced by various factors, including gas type, processing duration, matrix attributes, water, and plasma voltage. Similarly, nitrogen-based CAP produces reactive nitrogen species (RNS) like nitric oxide (NO) and nitrogen dioxide (NO2), which have antimicrobial properties and are used in food safety, sterilization, and surface disinfection. On the other hand, oxygen-based CAP produces reactive oxygen species (ROS) like ozone (O3), singlet oxygen ($1O_2$), and atomic oxygen (O), which are also used in surface decontamination of mycotoxins. Inert gases like argon or helium serve as carriers for reactive species produced by electrical discharge. Despite its lower reactivity, inert gas-based CAP is still effective in applications such as material surface modification. Therefore, researchers must select an appropriate gas for CAP that aligns with the desired reactive species and specific application requirements, such as antimicrobial treatment.

Chen et al. (2017) found that exposing samples to 50 kV atmospheric air plasma for 8 min reduced DON by 25.82 % while increasing water content from 8 % to 20 % enhanced its effectiveness by

36.10 %. Similarly, reducing T-2/HT-2 toxins in oatmeal is affected by factors like relative humidity, time of exposure, and types of gases employed in CAP production. Ki˘s et al. (2020) found that CAP efficiently oxidized samples through nitrogen (N2), reducing T-2 and HT-2 toxins to 42.24 % and 37.53 %, respectively. Wang et al. (2022) discovered that adjusting voltage from 10 to 30 kV reduced alternariol and monomethyl ether by 1.3 %–56.5 % in jujube juice.

Polyphenolic Compounds

Polyphenols are garnering attention for their diverse properties including antimicrobial, antiviral, and anti-inflammatory effects (Mehany et al., 2021). They have different modes of action towards mycotoxins, such as antioxidant properties, lipophilicity, suppression of mycotoxin production-related genes, and inhibition of enzymatic activity linked to mycotoxin synthesis (Fig. 4B). Hamad et al. (2021) found that plant-based extracts and polyphenolic compounds possess inhibitory properties against fungal development and can effectively decrease mycotoxins. Likewise, chlorogenic and gallic acids inhibit AFB1 in beans (Telles and Kupski, 2017). Moreover, Salas et al. (2012) found that citrus-derived flavanones such as hesperidin and naringin can reduce PAT production by 95 %. Similarly, a β-cyclodextrin-based nanosponge with bioactive phenols can prevent fungal attacks and detoxify mycotoxins (Makhuvele et al., 2020). These natural food products have antioxidant and medicinal properties, potentially mitigating mycotoxin-related harm (Sharma, 2021). Recent studies on polyphenols suggest their potential to mitigate the detrimental effects of fungi and mycotoxins, indicating their promising prospects for future applications.

Natural essential oils (NEOs)

NEOs are eco-friendly additives that can limit fungi growth and reduce mycotoxin levels in various foods. These additives disrupt essential enzymes in carbohydrate degradation, mycotoxin production (Fig. 4C), and fungal cell structure integrity (Tian et al., 2011). They modulate fungal gene expression and interfere with cell membranes through polyphenols, causing damage to cell membranes (Cai et al., 2022). Research has shown that NEOs can inhibit mycotoxins. Origanum majorana L. essential oil has demonstrated antifungal properties in vitro studies, inhibiting the growth of A. flavus and AF production. This indicates its ability as an emerging food-preserving agent to enhance food safety (Chaudhari et al., 2020). Further research revealed that capsaicin can inhibit OTA production by A. niger. Additionally, garlic, rosemary, sage, and mint EOs effectively inhibit OTA production (Kollia et al., 2019). Similarly, turmeric oil exhibits a strong antifungal effect against A. flavus, reducing AF infestation in corn. According to Kedia et al. (2016), Mentha spicata essential oils effectively inhibited mycotoxins produced by A. flavus in chickpeas by targeting the plasma membrane. On the other hand, EOs from lemon, grapefruit, and eucalyptus effectively inhibit ZEN production. Similarly, recent studies showed that EOs from Curcuma longa effectively inhibited Fusarium graminearum growth and ZEN production (Kumar et al 2016). While NEOs show promise in mitigating mycotoxins in food, it is important to be aware of their limitations. For example, the effectiveness of NEOs may be reduced in comparison to synthetic or chemical alternatives and can vary based on the type of mycotoxin and environmental factors. Additionally, the flavors and enticing aromas of these ingredients can affect the overall sensory characteristics of processed foods. The lack of regulations and limitations pose challenges to achieving widespread acceptance, while safety concerns arise due to instability and risk of allergies. The practicality of these products is limited due to concerns regarding their cost, residue, and negative environmental impacts during their production.

Magnetic Materials and Nanoparticles

Recent research has found that magnetic materials and nanoparticles can effectively manage mycotoxin contamination. These techniques are eco-friendly, cost-effective, and efficient in mitigating mycotoxins. Chitosan-coated magnetic particles (Fe3O4) have been shown to adsorb PAT from fruit juice efficiently. However, chitosan-coated magnetic particles could interact with other components in the juice, leading to changes in taste, aroma, color, or texture. This could affect the sensory attributes and overall quality of the juice. Moreover, nano-cellulose and retinoic acid effectively adsorbed AFB1 from different food sources. These approaches are non-toxic and effective in optimal pH levels (Kumar et al., 2016). Various magnetic nanoparticles, including surface-active maghemite (SAMNs), silver nanoparticles (SLN), copper nanoparticles (CN), selenium nanoparticles (SEN), and zinc oxide nanoparticles (ZON), are effective in removing mycotoxins from food products(Jebali et al., 2015). SEN derived from Trichoderma harzianum JF309 has been shown to reduce FB1 by 63 % and DON by 76 % (Abd-Elsalam, et al., 2017). SLN inhibits the proliferation of mycotoxin-producing molds, suppressing the synthesis of AF and OTA in corn-based media. Besides, ZON efficiently suppresses the development of Aspergillus, Penicillium, and Fusarium species (Hu et al., 2019). Magnetic carbon nanocomposites derived from corn byproducts efficiently remove AFB1 in poultry, achieving a 90 % removal at pH 7 within 3 h. A mixture of chitosan and glutaraldehyde demonstrated excellent adhesion capacities for various mycotoxins (Zahoor and Khan, 2016).

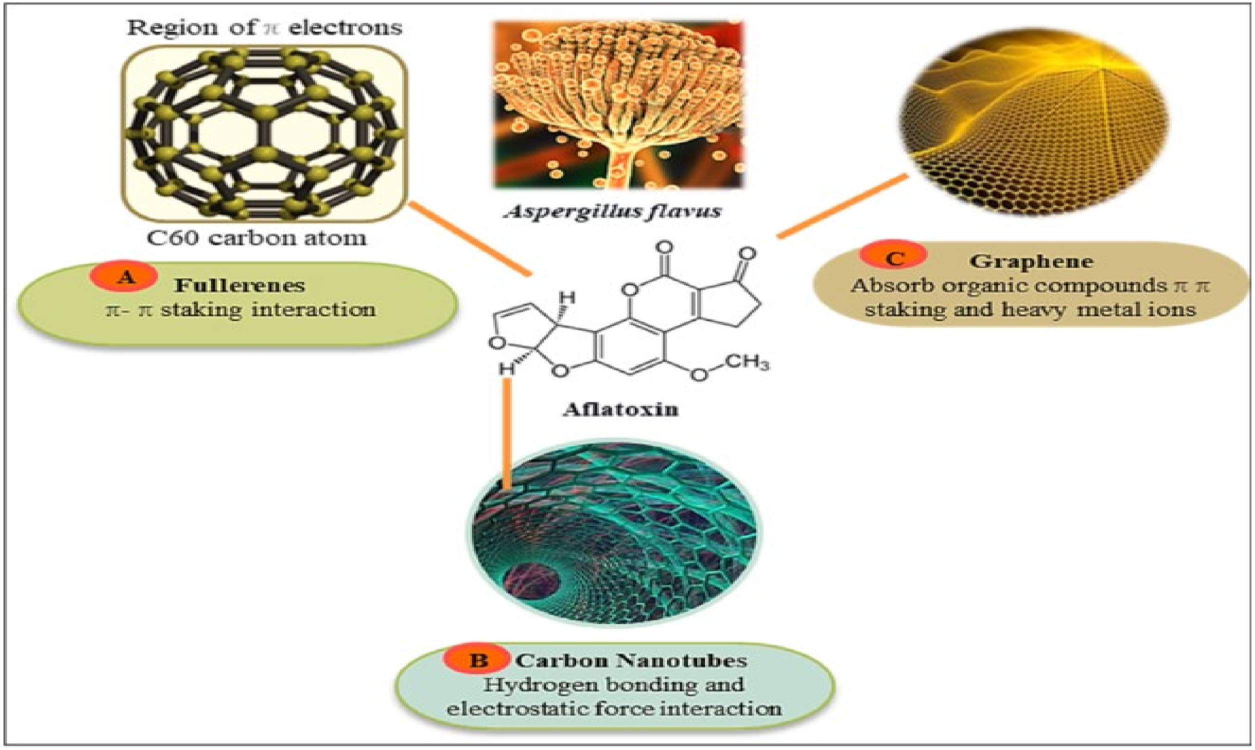


Figure 8: Mechanism of binding interaction between mycotoxins and nano-scaled adsorbents and, A = fullerenes; B = carbon nanotubes; and C = graphene

Reduction of aflatoxin uptake during digestion through consumption of adsorbent compounds

Adsorption, a very common treatment for mycotoxin reduction, involves binding the toxin to an adsorbent compound during the digestive process in the gastrointestinal tract. The adsorption of aflatoxins requires polarity and suitable positions of functional groups. Some more common aflatoxin adsorbents include active carbon, diatomaceous earth, aluminum compounds (clay, bentonite, montmorillonite, sodium and calcium aluminum silicates mainly zeolite, phyllosilicates and hydrated sodium calcium aluminosilicate (HSCAS)), complex carbohydrates (cellulose and polysaccharides) present in cell walls of yeasts and bacteria (such as glucomannans, peptidoglycans), and synthetic polymers (such as cholestyramine, polyvinyl pyrrolidone, and its derivatives). Most often, these compounds have been used for binding aflatoxins in animals through their addition to feeds. However human trials in immune-compromised populations have also shown their efficacy if taken daily (Jolly et al. 2015). However, most adsorbents are not selective and thus also adsorb nutrients which are then washed out and can have adverse effects on nutrition

Mycotoxin Regulations in Food Commodities

The FAO/WHO estimates that roughly 25% of global grain production exceeds permissible mycotoxin levels, leading to an annual loss of about 1 billion tons of grains and flour. Studies in Europe and the US highlight widespread mycotoxin presence, with significant economic impacts (Owusu-Apenten and Vieira, 2023; Eskola, et al., 2020). To prevent their detrimental effects on humans, mycotoxins are regulated by maximum permissible levels (MLs) in food (Claeys et al., 2020). The contents of mycotoxins in food commodities have been restricted in several countries (Puel et al., 2010). Additionally, a number of national and international agencies, including the FAO, WHO, EU Commission, and Codex Alimentarius Commission (CAC), have established regulations regarding different types of mycotoxins present in different foods aimed at protecting consumers (Adeyeye, 2016). Most countries have no specific limits on specific foods or food products, but all food products are subject to general regulations. There are, however, some countries in Europe and the USA that have legislated dietary limits for specific foods.

The permitted level of aflatoxins in food and feed by the World Health Organization is 0 ppb for children, 20 ppb or 20μg kg-1) for adults, and 55 ppb or 5μg kg-1) for animals. In the EU, the intervention total aflatoxin level for cereals and oilseeds for direct consumption is set at 4 ppb or 4 μg kg-1), with a maximum of aflatoxin B1 at 2 ppb or 2 μg kg-1. In tree nuts (e.g. almonds, pistachios, hazelnuts, Brazil nuts), aflatoxin levels are limited to 10 ppb for total aflatoxins and 8 ppb for aflatoxin B1 as they are consumed in smaller quantities. Aflatoxin regulatory limits are formulated using risk assessment models. They are often developed by specialized national and multilateral agencies, like the FAO/WHO Joint Expert Committee on Food Additives of the United Nations (JECFA), EFSA, The Ministry of Health of the People's Republic of China, and the FDA in the United States (Zhang et al., 2018). Differences in countries' risk perception, data, approaches, and risk assessment models create disparities between countries in terms of aflatoxin regulatory limits. Developed countries with better scientific and technical know-how often tend to adopt lower regulatory limits (more stringent) than those set by the global food safety regulatory body/FAO joint Codex Alimentarius Commission.

In some instances, these disparities have brought up trade disputes between importing and exporting countries, with importing countries often accused of using food safety regulations to disguise trade barriers. Fortunately, The World Trade Organization's Sanitary and Phyto-sanitary (SPS) Agreements recognized the limits set by the Codex Alimentarius Commission as the standards upon which international trade dispute settlements will be based. According to the SPS Agreements, Countries could impose more stringent limits, provided that these are based on logical scientific reasoning reached through a risk assessment.

Notwithstanding, setting up and enforcing regulations requires a considerable amount of resources and effort. Some countries have been more successful than others in doing so. For instance, The EU possesses arguably the best food safety (including aflatoxins) surveillance and information-sharing system in the Rapid Alert System for Food and Feed (RASFF). The system enables the simple, rapid collection, sharing, and storage of food safety-related data (Parisi et al., 2016). This allows fast decision-making among relevant institutions to prevent the entry of aflatoxin-contaminated food products into the EU. European standards are more stringent than those of the United States which has an action level of 20 µg kg-1 for human food except milk (Schmalle and Munkvold, 2015). In Europe, the maximum levels of aflatoxin M1 in milk meant for adult consumption and milk meant for infants or baby food production are 0.050 and 0.025 µg kg-1, respectively (Iqbad et al., 2014) while that for the United States is 0.05 µg kg-1 (Augusto, 2004).

Globally about 120 countries have enacted regulatory limits on allowable aflatoxin levels in human food and animal feed (Bui-Klimke et al., 2014). Some countries set limits for the four most prominent types of aflatoxins in food: B1, B2, G1, and G2. For example, the US and Kenyan regulations stipulate a maximum limit of 20 and 10 ppb for the sum of the four types of aflatoxins (total aflatoxins), respectively. In contrast, the EU has different limits for different aflatoxin–food combinations has a maximum level of 2 and 4 ppb for aflatoxin B1 and total aflatoxins in maize and peanuts, respectively (European Commission, 2006). Additionally, many countries have adopted maximum limits for milk and dairy products (aflatoxins M1 and M2; Lalah et al., 2019). In Latin America, several countries, including non-members of the Mercosur group, have enacted regulations to prevent aflatoxins in food and feed (Miranda et al., 2013).In Asia, almost all the states have written regulations for aflatoxin, mostly for cereals, nuts, and their products (Anukul et al., 2013). Members of the Gulf Cooperation Council (the United Arab Emirates, Saudi Arabia, Qatar, Oman, Kuwait, and Bahrain) have also jointly adopted aflatoxin-related regulations (Al-Jaal, Salama, et al., 2019).

Notably, despite the high occurrence and exposure levels often reported from Africa, only a few African countries have aflatoxin regulations (Matumba et al., 2017); among them are Nigeria, Kenya, Ivory Coast, Zimbabwe, Senegal, Mauritius, Algeria, South Africa, Malawi, Egypt, Morocco, and Tunisia (Chauhan, 2016; Lahouar et al., 2018). Socio-economic issues, such as food scarcity, lack of proper infrastructure, expertise, and technical know-how are among the many reasons few African countries have aflatoxins regulations, and those with regulations barely enforce them (Shephard & Gelderblom, 2014). Regulation development and enforcement is an essential piece in the overall institutional setup against human- exposure to aflatoxin. When effectively implemented and enforced they serve as the last line of defense against human-aflatoxins exposure. Therefore, they should be developed through robust risk assessments, sound, and representative data obtained from unbiased sources or means.

Food production systems in developing countries do not favor the implementation of international regulations such as those set by the Codex Alimentarius Commission to regulate the amounts of aflatoxin in food (William et al., 2004). As a result, there is a higher risk of exposure in developing countries because where there is trade, the least contaminated foods and feeds are exported, and the more highly contaminated products are retained at home for consumption. It is therefore not surprising that African countries are greatly concerned about the standards imposed on their exports.

Therefore, in most food commodities, government agencies have established maximum levels of aflatoxins, including AFB1 (Bhat and Reddy, 2017). Countries in Africa that have set MLs for aflatoxins in food prescribe 5 ppb for aflatoxin B1 and 10 ppb for total aflatoxins. In the East Africa region limits are set for aflatoxins and fumonisins (; IITA, 2015). Codex Alimentarius Commission (CAC) is responsible for setting maximum limits for mycotoxins in Food and feed ML of 100 ppb for Zearalenone in cereals and cereal-based products (CAC, 2015).

Materials and methods

Search strategy

The search strategy was performed to obtain all primary research regarding the fungal mycotoxins (AFs, FUMs, OTA, DON, and ZEN), their roles, and significance in human nutrition and health 13 years study (1 January 2010–31 December 2023) was selected as a period of the investigation. The English language was used in the search process. The study was conducted using electronic databases including Elsevier (Science Direct), Web of Science, and PubMed to ensure sufficient and satisfactory coverage (Bramer et al. 2017) and Google Scholar was also used. Google Scholar and references list of included researches were reviewed to obtain more relevant studies (Figure. 9). Keywords included or search strings were: (("mycotoxins*" OR "fungal toxin*") AND ("food safety" OR "food contamination" OR "human health" OR "animal health" OR "livestock) AND ("aflatoxin*" OR "fumonisins*" OR "ochratoxin*" OR "deoxynivalenol" OR zearalenone") AND ("mitigation strategies")). The search covered articles published between 2010 and 2023, with a focus on peer-reviewed studies, reviews, and relevant reports. After the title and abstract screening, the selection process was carried out based on the full text of the selected publications. The following criteria were used to include research: (a) studies that provided insights into the sources, distribution, and impacts of mycotoxins on human and animal health, (b) studies that focused specifically on mycotoxins (aflatoxins, fumonisins, DON ZEA, and OTA or have relevance to the main themes of the review. However, all articles not discussing Aflatoxins, Fumonisins, Deoxynivalenol, Zearalenone, and Ochratoxins in the year 2010-2023 were excluded from the study.

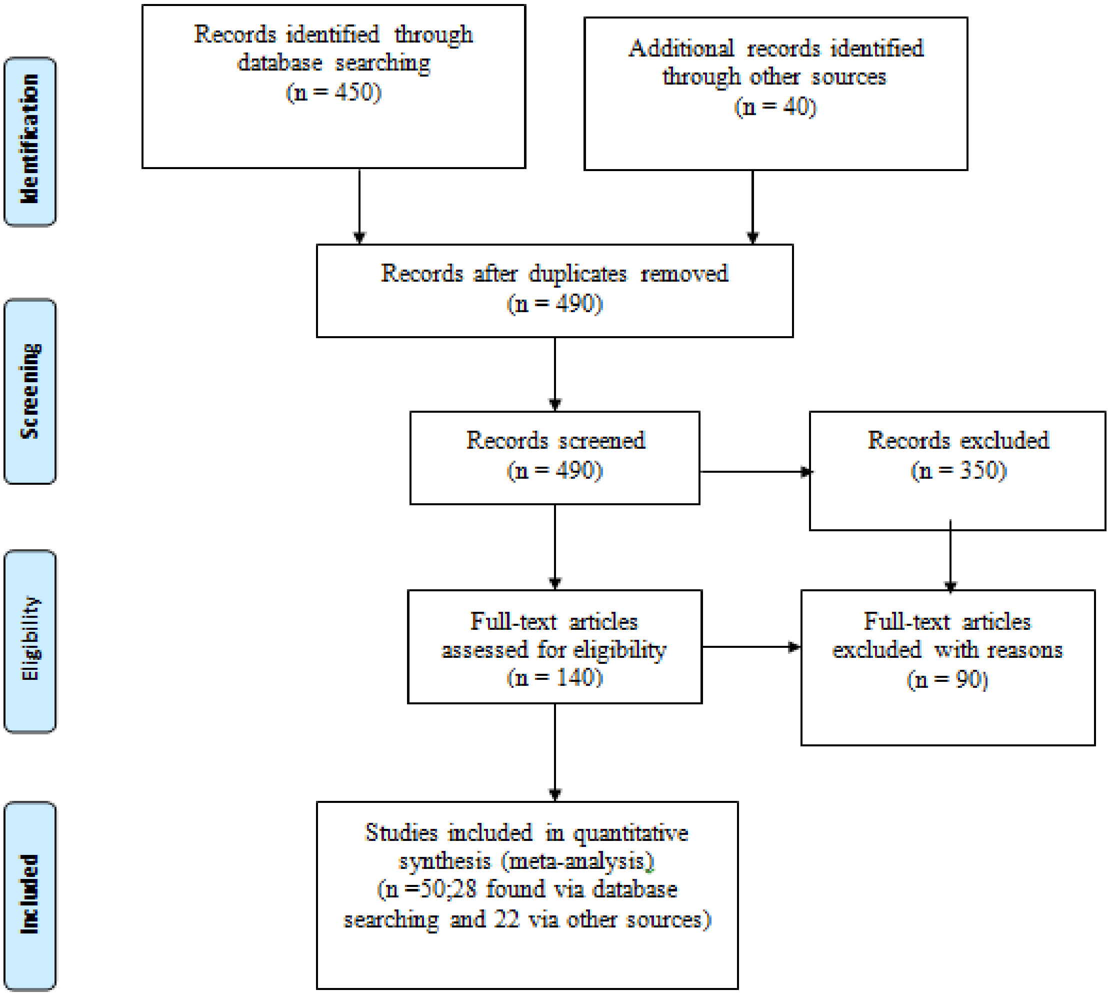


Figure 9: PRISMA flow diagram

Key Findings of the Review

This study reviewed all primary research regarding the fungal mycotoxins (Aflatoxins, Fumonisins, Ochratoxins, Zearalenone, and Deoxynivalenoin), their roles and significance in human nutrition and health 13 years study (1 January 2010–31 December 2023). Issues related to quality control, inappropriate production technologies, hot climate, and improper storage conditions support the growth of mold and the development of mycotoxins, resulting in the more frequent incidence of mycotoxin contamination of food in developing countries (Agriopoulou et al. 2020). It is well known worldwide that aflatoxins, especially aflatoxin B1, is the most toxic mycotoxin with severe debilitating effects on humans and animals alike.

It is well known that aflatoxins are potent hepatotoxic, teratotoxic, mutagenic, and carcinogenic mycotoxins produced by members of the Aspergillus section Flavi namely A. flavus, A. parasiticus, A. nomius, A. pseudonomius, A. arachidicola, A. minisclerotigenes, A. ochraceoroseus, A. korhogoencis, A. pseudocaelatus, A. pseudotamarii, and A. bombycis (Norlia, et al., 2019). Aflatoxins B 1, B 2, G 1, and G 2 can occur in foods such as groundnuts, tree nuts, maize, rice, figs, dried spices, crude vegetable oils, cocoa beans, cocoa powder, chocolate, cotton seeds, copra, etc. VAflatoxins M 1 and M 2 are found in milk and milk products. Human hepatic cancer and acute fatal diseases eg. Hepatitis have occurred in association with the consumption of heavily contaminated foods in Asia, Africa, Africa, and elsewhere (Ostry et al.2017).

Ochratoxins are the main mycotoxin with nephrotoxic effects and have been associated with Balkan Endemic Nephropathy and tumor development in the urinary tract (Reddy & Bhoola, 2010). Ochratoxin A (OTA) is a toxic secondary metabolite produced by several species of Aspergillus and Penicillium genera. For example, OTA is produced by Aspergillus carbonarius, A. sclerotiorum, A. sulphureus, A. alliaceous, A. affinis, A. alertness, A. welwitschia, A. pretenses, A. gluteus (= A ochraceus) and A. niger and species belonging to the A. niger aggregation(Wang et al., 2016; Ayoub et al. 2010) in tropical zones(Wang et al.2016). The European Food Safety Authority affirmed that OTA is nephrotoxic in all animal species tested and exerts immunotoxic, neurotoxic, and teratogenic effects at high dose levels. OTA has been detected in high contamination levels in maize, rye, coffee, cocoa powder, chocolate, and other related foods in Africa (Brera et al. 2011; Copetti, et al. 2014). Penicillium verrucosum and P. nordicum also grew well and produced OTA (Wang et al., 2016).

Fumonisin is a group of fifteen (15) closely related mycotoxins produced by species of Fusarium i.e. F. proliferatum, F. globosum, F. nygum, F. subglutinans, F. verticillioides = (F. moniliforme) all included in the Gibberella fujikuroi species complex (Altomare et al. 2021). F. verticillioides is important in veterinary medicine as a cause of porcine pulmonary edema and equine leucoencephalomalacia and oesophageal cancer in humans. Several cogenes of fumonisins A1, A 2, B 2, B 3, and B 4 as well as P are known (Altomare et al. 2021). Studies have also shown that some strains of Aspergillus niger, A. welwitschiae as well as Alternaria alternata, and Fusarium oxysporum also produce fumonisins. Fumonisins have been shown to occur in barley, wheat, sorghum, rice, millet, and corn products (Altomare et al. 2021). The most common syndromes associated with fumonisins are leucoencephalomalacia in horses, pulmonary edema and hydrothorax in pigs, and hepatotoxicity, carcinogenicity, and oesophageal cancer in humans (Smith, 2018).
Zearalenone, ZEA, previously known as F2-toxin in a isocyclic acid lactone produced by Fusarium graminearum, F. colmorum, F. crookwellense, and F. equiseti (Ferrigo et al. 2016); Frizzel et al 2011).

Another mycotoxin of health importance is Vomitoxin which is also known as deoxynivalenol (DON) and is a type B trichothecene, an epoxy sesqueterpenoid. It occurs predominantly in grains, e.g. wheat, maize, barley, rye, and oat, and less so in rice, sorghum, and triticale (Sobrova, et al 2010). It is a secondary metabolite of Fusarium culmorum and F. graminearum.

Conclusion and recommendations

This review provided a detailed explanation of the toxicological effects of the most important mycotoxin contamination in food, human, and animal health and their management/ prevention strategies. Mycotoxins, including AFs, OTA, FMNs, ZEN, and DON, can exhibit a wide range of toxic effects on both humans and animals. AFs, particularly AFB1, pose hepatotoxic, immunotoxic, and carcinogenic risks, leading to both acute and chronic health complications. OTA specifically targets the kidneys and induces nephrotoxic, mutagenic, carcinogenic, and teratogenic effects, while its genotoxicity remains a subject of debate. FMNs are linked to liver cancer and developmental issues in humans. DON toxins inhibit protein synthesis, resulting in immunosuppression effects, as well as gastrointestinal, and dermatological complications. ZEN, a non-carcinogenic estrogenic toxin, affects the reproductive systems and various other organs. Therefore, it is imperative to regularly monitor foods and feeds and implement preventive measures to effectively mitigate the health risks associated with mycotoxins.

As we can see above, there are various methods aimed at minimizing the aflatoxins in foods, but there still exists an Aflatoxin problem in food. Since it is difficult to achieve zero tolerance for AF contamination in commodities, AFs should be minimized in foods as much as possible to prevent the risk of cancer and other health problems. Thus, legal tolerance limits based on scientific evidence obtained from risk assessments in different countries have been set for AFB1 and total aflatoxin (AF) in foods and feeds. The limits vary between 4 and 20 parts per billion (ppb) through different countries. The Codex Alimentarius Commission (CAC) has adopted the maximum permissible limits for AFs in unprocessed peanuts and tree nuts, which is 15 ppb as well as 10 ppb in ready-to-eat tree nuts. However, the European Union (EU) has adopted the level of 4ppb, which is the strictest limit in the world for AFs.

The review has demonstrated that AFB1, OTA, DON, ZEN, and FUM are harmful to both human and animal health. Mycotoxins not only pose a risk to both human and animal health but also impact food security and nutrition by reducing people's access to healthy food.

Impoverished and less privileged people of developing countries stand an even greater risk of further impoverishment and starvation if stringent measures are not applied for the management of aflatoxin contamination. Implementation of recommended prevention and control strategies could make food more expensive and less affordable since farmers will have to invest in drying and storage equipment among others. Their plight is worsened by the absence of laboratories for testing foods which are economically and financially inaccessible. However, it will be better to ensure that contamination levels are minimal to safeguard the health of people in developing countries whose lifespan is relatively short. The plight of people in developing countries is worsened by the fact that international bodies like the World Health Organisation (WHO) do not consider aflatoxin as a high-priority risk; hence, little attention is paid to the health issues resulting from the consumption of contaminated food.

Recommendations

i. To prevent the proliferation of mycotoxins, measures such as timely grain harvesting, proper drying, and good storage conditions are essential. In this context, the inclusion of LAB can be beneficial, as their potential to inhibit the growth of mycotoxigenic fungi and reduce mycotoxin levels in food and feed has been studied.
ii. Integrating alternative food crops less prone to mycotoxin contamination, such as root and tuber crops: e.g. sweet potato-based recipes may lead to a reduction in the dietary intake of aflatoxins by infants and young children.
iii. Integrating more legumes such as cowpeas, beans, Bambara beans, and soya beans, which are less prone to aflatoxin contamination than peanuts into the diet (Achaglinkame et al., 2017)
iv. Increasing consumption of fresh products like vegetables and fruits. Certain vegetables may have a protective effect; e.g. consumption of green, leafy vegetables seems to have some protective effect by impeding aflatoxin absorption. Cruciferous vegetables, onions, and garlic

contain protective phytochemicals that impede the processes through which aflatoxins lead to liver cancer (Wu et al. 2014).

v. Also purchasing products from countries that have a well-established food safety system such as Europe, America and some countries in Asia reduces the risk.

vi. Consumers also need to become more aware of the health risks posed by exposure to aflatoxin-contaminated food and in return demand safe, high-quality food. Such campaigns should also inform on the nutritional qualities of a more diverse and traditional African diet. Risk communication includes information about simple risk reduction measures. Food safety risks need to be addressed using a dietary rather than a commodity perspective.

vii. It is therefore recommended that policies be designed to build awareness programs about the health risks associated with spoilage molds in food. Integrating the topic into agricultural and health sciences subjects from as early as primary school could be much more effective. Unless the general public is equipped with adequate information on the health problems associated with mycotoxins and their prevention and management options, they will continue to carry the moldy foodstuffs from fields onto their tables.

viii. Developed countries and international agencies such as the FAO and WHO should provide the necessary financial and technical assistance to enable developing countries to carry out research and education. This would ultimately inure to the benefit of developing countries in terms of increased foreign exchange earnings, from the sale of products that meet required standards and better health through the consumption of safer food, devoid of or containing minimal levels of aflatoxins.

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Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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