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REVIEW ARTICLE

Mycotoxins' Toxicities - from Consumer Health Safety Concerns, to Mitigation/Treatment Strategies: A Perspective Review

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KEYWORDS

Consumer protection;
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Fungal invasion;
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ABSTRACT: Mycotoxins contaminating agricultural commodities like animal, and plant products result in human health complications, some are hidden, visible, chronic, and or acute, and others long-term. To understand the current status, published relevant reviews conducted between 2020-2021 about mycotoxins toxicities involving animals, food, and human showed the need for additional literature synthesis. This would help better the understanding of consumers of animal and plant food products about the importance of mycotoxins toxicities, and such knowledge should extend to other stakeholders within the food supply chain. In this perspective review, we discussed the mycotoxins' toxicities - from consumer health safety concerns, to mitigation/treatment strategies, drawing from: (a) Toxicology, consumer health safety concerns, and action mechanisms of mycotoxins; (b) Toxic effects of combined mycotoxins exposure; (c) Major mycotoxin effects on infants and children; (d) Mycotoxin exposures' complications/risks at various stages of human life; (e) Consumer health implications of mycotoxin exposure; as well as (f) Mycotoxin toxicities mitigation/removal strategies. Indeed, concerted efforts to solve the mycotoxins toxicities are warranted, which should help to deduce more lasting and sustainable ways of preventing fungal invasion and mycotoxins production in the food and feed value chain.

INTRODUCTION

As secondary metabolites produced by fungi, mycotoxins remain toxic to humans and animals. Such secondary metabolites like pigments, pharmaceutically useful compounds, plant growth regulators, etc, remain fundamental to the fungal survival [1]. Mycotoxins production may help fungi to successfully attune to a range of environmental conditions caused by many factors, inclusive of both environmental and climatic variations [2, 3]. Mycotoxin production may help fungi to favorably compete with other organisms or to resist against grazing by insects [4, 5]. On daily basis, animals and humans are exposed to mycotoxins through ingestion, skin, or inhalation. Industrial processing and agricultural practices are not sufficient for complete

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prevention of mycotoxins biosynthesis [6]. Most mycotoxins have many toxic effects that have been proven in in vivo and in vitro experiments, while others are yet to be proved whether they are toxic or not, largely due to inconclusive studies, insufficient or unreliable data, or inadequate attention [7]. The toxicities caused by some mycotoxins, including aflatoxins, fumonisins, ochratoxins, etc., in humans and animals can be acute when exposed in high levels, and can result in carcinomas, gene alteration, etc. [2]. Mycotoxins toxicity mainly depends on body weight, sex, and age, with children mostly affected compared to adults [8]. The world has to clearly deal with production and exposure to mycotoxins. Mycotoxins usually contaminate agricultural commodities, which can lead to visible, chronic or acute, long-term health complications that may be hidden [9, 10, 11, and 12].

Staple foods such as maize, wheat, peanut, and rice are among the most contaminated crops, and the mycotoxins presence in these foods and feeds pose a high risk of chronic mycotoxins exposure to the public [11, 13, 14]. These are constantly at the risks of mycotoxin poisoning, particularly in the regions affected with fungal proliferation and mycotoxin production. Although mycotoxicoses recently have been reported in developing countries, there is increasing evidence that developed nations also confront risks of exposure to mycotoxins [10, 15]. Molds occurrence, prevalence, and spread are influenced by many factors, such as environmental factors, economic conditions, and social factors [16]. Although developed nations mostly have moderate and temperate climate with rare cases of malnutrition, mycotoxigenic fungal species such as the species of Aspergillus are constantly drifting north because climate change and changes in weather patterns [17]. In recent years, mycotoxicoses and mycotoxin contaminations of foods and feeds are largely considered as a problem of the Third World countries [6]. Tropical and subtropical regions, such as sub-Saharan Africa and South America, are already grappling and combating the increasing mycotoxins prevalence and threat. For the reason that humans occupy the top position in food chain, mycotoxins exposure to humans also depends on animal consumption; consequently, feed contamination has to be thoroughly controlled and avoided [18]. The globalization nature of food production systems can contribute to unintentional consumers exposures to several mycotoxins, for various reasons, including (a) consuming foods contaminated with several mycotoxins, (b) additional mycotoxins production and contamination during storage and processing respectively, (c) several mycotoxigenic fungi can concomitantly infest the same crops, (d) some food processes (e.g. milling, stirring, etc.), up to redistribution of mycotoxins throughout the food chains.

The importance of mycotoxins toxicities as pertains to animal, food and human can never be over-emphasised. This is why research into this subject area is ever on the rise globally. A summary of recently (2020-2021) conducted literature reviews that involved mycotoxins toxicities relevant to animal, food and human, specific to aim/objective and key sections, are shown in Table 1. Recent literature reviews have involved the occurrence of toxigenic fungi and mycotoxins in workplaces [19], mycotoxins' impact on human and animal health and the biomarkers used to evidence exposure [20], and toxicological effects that mycotoxins can induce on human health [21]. Additionally, updates in the current knowledge on country-specific natural-occurrence data in global surveys, as well as in vitro and in vivo toxicology and metabolic investigations of masked mycotoxins [22], and negative effects of mycotoxins on animals and humans and identifies the impact of mycotoxins on environment [23] are among the selected recent literatures reviews. Ráduly et al. [6] reviewed the occurrence and toxicological features of major Aspergillus-derived mycotoxins are summarised and, furthermore, the possibilities of treatments in the medical practice to heal the deleterious consequences of acute and/or chronic exposures, whereas Adeyeye [24]

reviewed the presence of aflatoxigenic fungi and mycotoxins in foods, occurrence, control, socio-economic, and health implications. Additionally, Adegbeye et al. [25] reviewed the prevalence of mycotoxins in animal products, the need for farmers' awareness (of prevalence of mycotoxins), and elucidating different ways of reducing the (mycotoxins) residues from the food safety standpoint. Despite these very important reviews (and others not mentioned), it is clear that this very subject matter of mycotoxins' toxicities requires additional literature synthesis. Especially, to obtain a better understanding regarding the importance of mycotoxins' toxicities is very crucial in helping consumers as well as other stakeholders within the food supply chain. Additionally, the food supply chain stakeholders to be part of the debate/discussion about how mycotoxins contaminate the various animal/plant food products is equally very crucial. To supplement existing information, therefore, this perspective review discussed the mycotoxins' toxicities - from consumer health safety concerns, to mitigation/treatment strategies, drawing from: (a) Toxicology, consumer health safety concerns, and action mechanisms of mycotoxins; (b) Toxic effects of combined mycotoxins exposure; (c) Major mycotoxin effects on infants and children; (d) Mycotoxin exposures' complications/risks at various stages of human life; (e) Consumer health implications of mycotoxin exposure; as well as (f) Mycotoxin toxicities mitigation/removal strategies. We end this perspective review by providing our conclusions and future outlook.

Table 1. A summary of recently (2020-2021) conducted literature reviews that involved mycotoxins toxicities relevant to animal, food and human.

Aim/objective of literature review	Key sections of literature review	References
An overview of occurrence of toxigenic fungi and mycotoxins in workplaces, including recent data on biomarkers used for human biomonitoring of mycotoxins in exposed workers.	Occurrence of toxigenic fungi and mycotoxins in agricultural working environments; Human biomonitoring of mycotoxins; Health problems induced by the occupational exposure to fungi and mycotoxins,	[19]
To discuss the following mycotoxins: aflatoxins, fumonisins, zearalenone, deoxynivalenol and ochratoxins, with emphasis on their impact on human and animal health and the biomarkers used to evidence exposure to these substances	Mycotoxins, and looked at Aflatoxins, Fumonisins, Zearalenone, Deoxynivalenol, Ochratoxins,	[20]
Compilation of research developed up to date on the toxicological effects that mycotoxins can induce on human health, through the examination of selected number of studies in vivo.	Aflatoxins, Ochratoxin A, Patulin, Citrinin, Fumonisins, Deoxynivalenol, Zearalenone, as found in one or more of either alpacas, mice, rats, chicken, pigs and fish, pigs, together with Alternaria, and Fusarium emerging/other mycotoxins.	[21]
Review on updates in the current knowledge on country-specific natural-occurrence data in global surveys, as well as in vitro and in vivo toxicology and metabolic investigations of masked mycotoxins.	Natural occurrence and formation, toxicity, and metabolism of masked mycotoxins	[22]

Review on negative effects of mycotoxins on animals and humans and impact of mycotoxins on environment, with highlights on its global feed contamination, regulation in human food and animal feed, current analytical methods in food commodities, and control strategies.	Effects of Mycotoxins on AnimalsHealth, Effects of Mycotoxins on Human Health, Role of Mycotoxins Contaminated Environment in One-Health Aspect, Current Status of Mycotoxins Contamination in Feed from aGlobal Perspective, Regulation of Mycotoxins in Human Food and Animal Feed, Current Methods for Analysis of Mycotoxins in Food, Control Measures,	[23]
Review of occurrence and toxicological features of major Aspergillus-derived mycotoxins, including treatment possibilities in the medical practice to tackle deleterious consequences of acute and/or chronic exposures	Food Toxicology and Molecular Mechanism of Mycotoxins, Occurrence of Aspergillus-Derived Mycotoxins in the Feed and Food Chain, Prevention Strategies of Mycotoxicoses, Medical Aspects of Aspergillus-Derived Mycotoxins	[6]
Review of aflatoxigenic fungi and mycotoxins' presence in foods, occurrence, control, socio-economic, and health implications, with emphasis on safety and mycological quality of foods, effect on the people and economy of various countries.	Uses of fungi, Cultured foods, Types of aflatoxigenic fungi, Mycotoxins produced by aflatoxigenic fungi, Major groups of mycotoxins in foods, Health implications of eaten foods contaminated by mycotoxins	[24]
Review of mycotoxin prevalence in animal product, awareness to farmers, food safety organization as well as different approaches to reduce mycotoxin residue in animal products	Types and sources of mycotoxins; Mycotoxin consumption and consequences; Mycotoxin on animal health; Animal derived product contamination; Incidence of mycotoxin residue in monogastric/ruminant product; Animal product consumers; Mode of action; Mitigation strategies; Other antimycotoxingenic options	[25]

MATERIALS AND METHODS

To achieve the objective of this perspective review, the appropriate research questions that guided the search strategy were formulated. Essentially, it is the research questions that underpinned the pathway of searching relevant information. The conduct of literature searches was directed at published studies as found in indexed journals. The databases used for the search were varied, which included the likes of Pubmed, Science Direct, and Scopus, with Google Scholar, all of which helped to achieve access to the desired articles.

Importantly, there were a number of keywords employed in the search process. They included such terms like animal, humans, plants, crops, fungi, mycotoxins types, as well as mycotoxins toxicities. Other search terms used include mycotoxins prevention methods; mycotoxicoses treatment, mycotoxin removal, consumer safety, consumer protection, and health risks. Only articles published in the English Language were used.

The search process of this perspective review made efforts to utilize the full texts of the articles that were deemed relevant. But in the situation where the full texts were not obtainable, the abstracts supplemented with the hope to harness useful information from it. However, if the information in the abstract was deemed insufficient, that specific paper had to be excluded. In the search process also, it was also essential that the references of selected articles that were used for this perspective review had to be screened for related studies.

RESULTS AND DISCUSSION

Toxicology, consumer health safety concerns, and actions of mycotoxins.

Mycotoxins pose a serious health concern to humans and animals, with various potent action mechanisms. While the toxicological effects and action mechanisms of some mycotoxins have been established, others have not been sufficiently studied. It is believed that the nature, classification, and toxicology of mycotoxins are influenced by factors like the origin of biosynthesis as well as chemical structures [8, 11]. The relationship of between dose and response can specify the magnitude of an organism's response to exposure within a given time [26, 27]. Acute mycotoxicosis can be defined by general response and rapid onset [28]. Many species of fungi can produce many mycotoxins, although they usually have one predominant, characteristic mycotoxin in most cases [8]. How mycotoxins affect the major organs of the human body is shown in Figure 1. The liver is greatly affected by many mycotoxins, such as aflatoxins, zearalenone, citrinin, etc., and may result in liver damage, cancer, cirrhosis, among others; Some mycotoxins, such as ochratoxins, fumonisins, etc., are have strong nephrotoxic actions, and may induce kidney cancer, failure, damage, etc., which are serious concerns to both humans and animals; The brain and spinal cord can be significantly impaired by fumonisins, secalonic acids, and aflatoxins, where they can cause neurological impairment and also impair growth and development in children; mycotoxin also affect the cardiovascular system, increasing the risk of cardiovascular diseases such as heart diseases. Cyclopiazonic acid, aflatoxins, and fumonisins have been implicated; the esophagus,intestines, lungs, embryo, etc. are affected by mycotoxins, such as aflatoxins, zearalenone, citrinin, fumonisins, secalonic acids, deoxynivalenol, etc. [7, 8, 10, 29-31].

The common mycotoxins, their mycotoxigenic fungi, food and feeds found, and toxicities and adverse effects are shown in Table 2. It can be clearly seen from Table 2 that the mycotoxins, such as aflatoxins, aflatrem, ochratoxins, gliotoxin, citrinin, Alternaria toxins, fumonisins, sterigmatocystin, etc., exhibit several toxicities, including carcinogenic, nephrotoxic, genotoxic, immunotoxic, neurotoxic, teratogenic, embryotoxic, and hepatotoxic potencies [10, 29-57]. Take for instance, the carcinogenic, immunotoxic, hepatotoxic, mutagenic, as well as teratogenic effects of aflatoxins [10, 29], and the fact that ochratoxin A was shown to be nephrotoxic, genotoxic, immunotoxic, neurotoxic, teratogenic [30, 31], aflatrem causing staggers syndromes and visibly manifest as noxious food decay [32, 33] are very important concerns within the global public health picture. The fact that gliotoxin (GTX) has many toxic potentials, including cytotoxicity, apoptosis [34, 35], and that citrinin (CIT) is cytotoxic, embryocidal, fetotoxic, genotoxic, hepatotoxic, and nephrotoxic, found mostly in stored foods (grains, fruits, etc) [36, 37, 38], itself is very worrying. These toxic potencies make mycotoxins a serious health concern to the general public, including fetus, newborns, toddlers, children, and adults, especially those in regions where the staple foods include grains, beverages, vegetables, spices, milk, among others [39-57]. Subsequent sections will deliberate on these mycotoxins in greater depth.

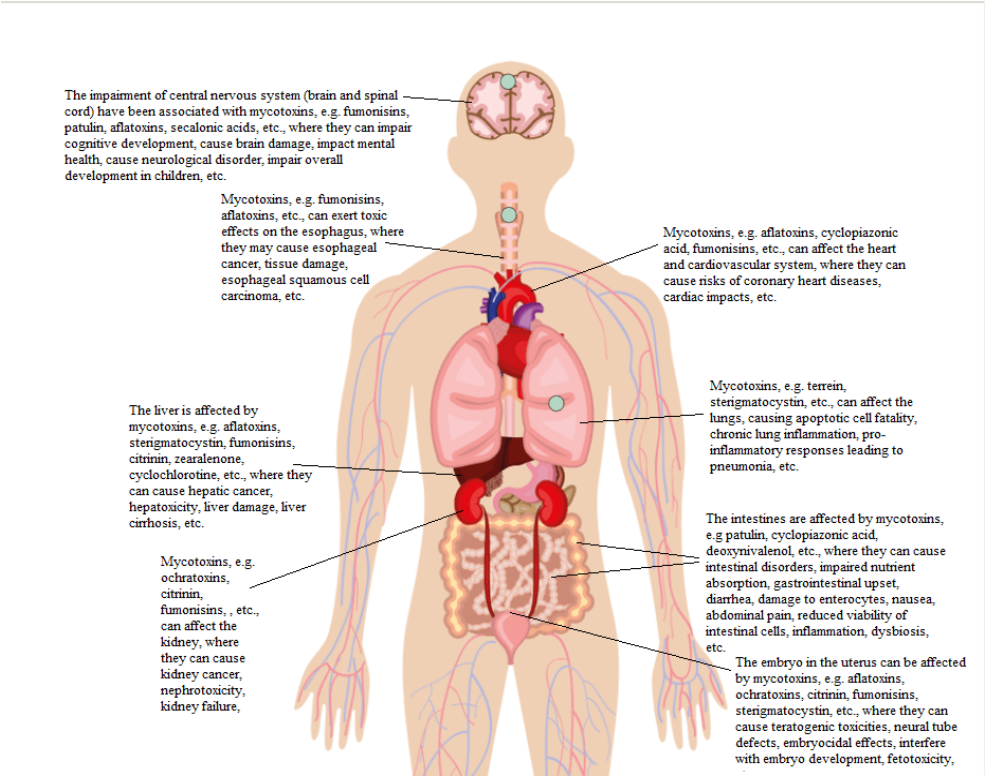

Figure 1. How mycotoxins affect the major organs of the human body.

Table 2. Common mycotoxins, their mycotoxigenic fungi, food and feeds found, and toxicities and adverse effects

Mycotoxins	Mycotoxigenic fungi	Foods and feeds found	Toxicities and adverse effects	References
Aflatoxins (AFB1, AFB2, AFG1, AFG2, AFM1, AFM2)	*Aspergillus flavus, A. pseudotamarii, A. nomius, A. Parasiticus*, etc.	Cereals (e.g. maize, rice, millet, acha, etc.), legumes (e.g. peanuts, beans, etc.), fruits, vegetables, seeds, nuts, etc.	The carcinogenic, hepatotoxic, mutagenic, teratogenic, and immunotoxic effects of aflatoxins are mostly linked to the difuran ring and the lactone ring presence. Aflatoxins and the metabolic compounds produced by hepatic CYP enzymes can interfere with nucleotide pairing, resulting in various changes in genes, breaks in DNA strand, and/or large-scale aberrations of chromosomes. Aflatoxins can impair hepatocytes directly or by changing the expression of genes (*Ahr*, *Scarb1*, *Lcat*, *Lipc*, and *Cpt1a*) connected with lipid metabolism. They have been shown to cause a lot of health complications to both humans and animals.	[10, 29]
Ochratoxins (A, B, C)	*Species of Aspergillus (Aspergillus ochraceus, A. carbonarius, A. niger*, etc.) and *some Penicillium species (P. Verrucosum,* etc.).	Cereals, dried fruit, red wine, coffee, spices, etc.	Ochratoxin A was shown to be nephrotoxic, genotoxic, immunotoxic, neurotoxic, teratogenic, embryotoxic, and hepatotoxic. OTA can cause kidney failure, kidney cancer, and kidney damage in humans.	[30, 31]

Aflatrem (AT)	*Aspergillus flavus, Aspergillus minisclerotigenes*, etc.	Cereals, legumes, nuts, etc.	Aflatrem causes staggers syndromes, including several disorders of neurodegeneration characterized by hyperexcitability and muscle tremors, and thus poses health risk to humans and animals. AT causes neurological disorders and can visibly manifest as noxious food decay which grows on several products	[32, 33]
Gliotoxin (GTX)	*Gliocladium fimbriatum, Aspergillus fumigatus, Penicillium, Trichoderma, Eurotium chevalieri*, etc.	Grain and grain products, e.g. Cereal (barley, wheat, rice, etc.), legumes, etc.	GTX has many toxic potentials, including cytotoxicity, apoptosis, immunosuppression, and genotoxicity. The mycotoxin has shown serious genotoxicity, DNA damage, and inhibition of human lymphocyte development. GTX has many toxicities, including cytotoxicity, apoptosis, immunosuppression, and genotoxicity	[34, 35]
Citrinin (CIT)	*penicillium Citrinum, Aspergillus flavipes, Aspergillus niveus, Aspergillus alabamensis, Aspergillus pseudoterreus, Aspergillus neoindicus*, etc.	Mostly stored foods (grains, fruits, etc.)	CIT is hepatotoxic, embryocidal, genotoxic, nephrotoxic, fetotoxic, and cytotoxic. It is a kidney toxin which affects humans, domestic animals, and poultry birds. Citrinin and ochratoxin A act synergistically to reduce RNA synthesis activities in renal tissues and cause renal disorders due to the DNA adduct development with increased C-C8dG-OTA adduct formation.	[36, 37, 38]
Alternaria toxins	*Alternaria triticina, Alternaria tenuissima, Alternaria solani, Alternaria japonica, Alternaria dauci, Alternaria brassicae, Alternaria alternata*	Fruit, vegetables, seeds, grains, wheat, plants, beer, fruit juices, vegetable juices, wine, peppers, fresh and dried tomatoes, flour, bran, dried fruit, sunflower seeds, cereal products (e.g. rice and oat flake), sunflower oil, etc.	Alternariol methyl ether and alternariol are mostly toxic because of their genotoxic, cytotoxic, carcinogenic, and mutagenic effects. Tenuazonic acid has phytotoxic and antibacterial activities and acute toxicities on dogs, chicken, and mice, as well as hematological disorders in humans.	[7, 39]
Fumonisins (B1, B2, B3, B4)	Many *Fusarium* species and their Liseola section, *Aspergillus welwitschiae, Aspergillus niger*	Maize and maize products, wine, sorghum, beer, rice, peanut, raisins, onions, grapes, asparagus, soybeans, beans, etc.	Toxicity induced by fumonisins usually leads to oxidative stress generation, altered cytokine expression, or apoptosis. Fumonisins may be implicated in esophageal cancer and can cause pulmonary edema in pigs and leukoencephalomalacia in horses. Fumonisins inhibit sphingolipids synthesis. Fumonisins have been shown to cause diseases such as renal carcinogenesis, nephrotoxicity, hepatotoxicity, pulmonary edema, leukoencephalomalacia, and neural tube defects.	[40, 41]
Sterigmatocystin (STC)	*Aspergillus nidulans, Aspergillus versicolor, Aspergillus flavus, Aspergillus parasiticus*, etc.	Peanuts, corn, barley, grain products, rice, wheat, etc.	After exposure through oral route, malignant and premalignant lesions, including angiosarcomas and hepatocellular carcinomas were reported in brown fat. STC is mutagenic, teratogenic, and carcinogenic effects. STC may induce double-strand breaks in DNA in epithelial cell line of human immortalized bronchia, possibly resulting in adenocarcinomas.	[42, 43]

Emerging mycotoxins of concerns from fusarium species (beauvericin, moniliformin, enniatins, NX-2 toxin, fusaproliferin, etc.)	Many *Fusarium Species*, including *Fusarium verticillioides, Fusarium acuminatum, F. avenaceum, F. arthrosporiodes, F. chlamydosporum, F. redolens, F. oxysporum, F. beomiforme, Fusarium subglutinans, Fusarium proliferatum, etc.; Beauveria bassiana*	Corn, rice, vegetable oil, coffee, tree nuts, corn products, seeds, nuts, dried fruits, beans, etc.	The interests in emerging mycotoxins are increasing as a result of their high prevalence in foods and feeds and their potential toxicity to human and animals. Beauvericin can have toxic effects including apoptosis induction, increased cytoplasmic calcium concentration, and fragmentation of DNA in mammalian cell lines.	[7, 44, 45]
Patulin (PAT)	Species of *Penicillium, Aspergillus (A. longivesica, A. clavatus, A. giganteus), Byssochlamys*, etc.	Apples and apple products, vegetables, cereals, seeds, nuts, fruits, legumes, etc.	Patulin is believed to wield its toxicity by its reaction with thiol groups (glutathione, cysteine, thiol protein moieties) in cytoplasm. Immunotoxicity, mutagenicity, teratogenicity, carcinogenesis, and neurotoxicity are chronic and acute effects patulin showed on cell cultures. Patulin shows acute toxicity, mutagenicity, and teratogenicity, and its emerging symptoms are usually not specific but mainly associated with enzyme inhibitions. Altered lipid metabolism, reduced weight, reduced food intake, and intestinal disorders may be observed in affected animals.	[46, 47]
Secalonic acids (A, B, C, D, E, F, G)	*Claviceps purpurea, Penicillium oxalicum, Aspergillus ochraceus*.	Some cereals (such as Corn), legumes, etc.	Some secalonic acids are very toxic, weakly mutagenic, neurotoxic, and teratogenic mycotoxin. Secalonic acids inhibit multidrug-resistant cells, induces leukemia, and obstructs responsive cell growth	[48]
Terrein (Ter A)	*Aspergillus terreus, Aspergillus stellates, Aspergillus fischeri, Aspergillus novofumigatus, Aspergillus lentulus*	Some cereals, legumes, etc.	Terrein has strong cytotoxic activities against cells that have colorectal carcinoma. Terrein acts as a proteasome inhibitor via lessening chymotrypsin activities, and promotes apoptotic cell fatality in the human lung tumoral cell lines (NCI-H292).	[49, 50]
Cyclopiazonic acid (CPA or α-CPA)	*Aspergillus* and *Penicillium species, e.g. Penicillium cyclopium*	Groundnuts, maize, poultry quail feed, cheese, rice, sunflower seed, Kodo millet, etc.	Cyclopiazonic acid is toxic because of its capability to inhibit calcium dependent ATPases seen in sarcoplasmic and endoplasmic reticulum. These inhibitory effects disrupt the calcium gradient and the muscle contraction-relaxation cycle maintained for proper cellular activities in cells. In addition to being toxic to rats, dogs, pigs, cattle, chickens, and guinea pigs, cyclopiazonic acid is also carcinogenic to human	[51, 52]
Deoxynivalenol (Vomitoxin)	*Fusarium graminearum, F. culmorum*, etc.	Grains, fruits, eggs, milk, liver, kidney, etc.	Intoxication with deoxynivalenol results in fever, dizziness, headache, diarrhea, vomiting, nausea, and abdominal pain	[53]

Zearalenone (previously called F-2 toxin)	*Fusarium Species, such as Fusarium graminearum, Fusarium culmorum, Fusarium crookwellense, Fusarium cerealis, Fusarium semitectum, Fusarium equiseti*, etc.	Maize, soybean, oats, barley, wheat, rice, rye, sorghum, etc.	Zearalenone and its metabolites can to bind transcription factors, such as pregnane X receptor involved in expressing enzymes in pathways of biosynthesis. Zearalenone can cause hepatocellular carcinoma, uterine fibroids, pituitary adenomas, and liver damage in mice, and chronic progressive hematotoxicity, cataracts, retinopathy, testicular atrophy, and nephropathy in rats. Pig is more prone to its toxicities	[54]
Ergot alkaloids	Clavicipitaceae (e.g. *Neotyphodium* and *Claviceps*), Trichocomaceae families (e.g., *Penicillium* and *Aspergillus* species). The dominant producer is *Claviceps purpurea*	Rye, triticale, wheat, oats, barley, etc.	Ergot alkaloids cause ergotism. They are both harmful and beneficial to humans, and can cause delirious seizures, fits, and St. Anthony's Fire, as well as convulsive and gangrenous forms of toxicities	[55]
Other mycotoxins (Fusarins A–F, Cyclochlorotine, 3-nitropropionic acid, Sporidesmin)	Cyclochlorotine is produced by *Penicillium islandicum; Pithomyces* chartarum produces Sporidesmin; 3-nitropropionic acid (3-NPA) is produced by *Arthrinium* species; *Fusarins* are produced by *Fusarium* species, such as *Fusarium verticillioides, Fusarium graminearum, Fusarium poae, Fusarium sporotrichioides, Fusarium oxysporum*, etc.	Several foods and feeds	Cyclochlorotine interrupts myofibrils and is hepatotoxic in animals; 3-nitropropionic acid interjects mitochondrial electron transport; Fusarins are mutagenic; sporidesmin can be easily integrated into cell membranes, and changes the organization of the bilayer.	[56, 57]

Aflatoxins (AFs)

Aflatoxins are toxic carcinogens and mutagens produced by some fungal species. In nature, there are at least 20 different types of aflatoxins and their derivatives. However, mostly four, including aflatoxins B1 (AFB1), B2 (AFB2), G1 (AFG1), and G2 (AFG2), have been shown to be toxic to humans and animals [10, 11, and 58]. Aflatoxins are furanocoumarins produced by many *Aspergillus* strains, such as Aspergillus flavus, A. *pseudotamarii*, *A. nomius*, and *A. parasiticus* as the major producers of aflatoxins. The carcinogenic, mutagenic, and immunotoxic effects of aflatoxins are mostly linked to the difuran ring and the lactone ring presence [29]. The most toxic, carcinogenic, and well-studied aflatoxin is the aflatoxin B1 (AFB1), which has a derivative known as aflatoxin M1 (AFM1) [59]. AFM1 is a 4-hydroxy derivative of aflatoxin B1, which is formed in liver and then excreted by mammary glands into milk by the humans and lactating animals that consumed diets contaminated with AFB1 [60, 61, 62]. AFM1 is also excreted through urine and is frequently used as biomarker for exposure to aflatoxins. In the liver, aflatoxin B1 is metabolized by the cytochrome P450 enzyme system (CYPs) and potent carcinogenic derivative is AFB1-8,9-epoxide (AFB0), which has endo

and exo isomer [7, 9]. The CYP1A2 and CYP3A4 are primarily responsible for biotransformation of aflatoxins, and the exo isomer is mostly formed as a result, and is highly electrophilic, suitable for spontaneous reactions with the nucleic acids' and proteins 'biological amines [63, 64]. For DNA, AFB1-8,9-epoxide covalently binds to the position of N7 on guanine, resulting in the formation of aflatoxin B1-N7-guanine adduct. The exo isomer has higher affinity than the endo, thus AFB1-exo-8,9-epoxide is believed to be the main carcinogenic metabolite. In addition, only aflatoxicol (AFL) could pass through the placenta and is also formed by placenta. AFL is usually detected in the liver preparations 'cytosolic fraction and is believed to be AFB1 reservoir, since it can be converted back to AFB1 by enzymes, using the system of cytosolic NADPH. The mechanism may be associated with the growth impairment caused by exposure to aflatoxins, which has been mostly observed in developing nations [9].

The International Agency for Research on Cancer (IARC) classified AFs, including aflatoxins B1, B2, G1, G2, and M1, as GROUP 1 carcinogens, i.e. carcinogenic to humans [65]. Aflatoxins and the metabolic compounds produced by hepatic CYP enzymes can interfere with nucleotide pairing, resulting in various changes in genes, breaks in DNA strand, and/or large-scale aberrations of chromosomes [66, 67]. One of the most commonly found mutations in AFB1-exposed human hepatocytes is the G→T transversion in the p53 gene's codon 249, leading to a mutation of Arg249Ser on p53 protein. The mutation of Arg249Ser improves clonal expansion and cell growth, and inhibits apoptosis and wild-type p53 activities [9, 68]. A major detoxification route is the AFBO's glutathione-S-transferase (GST) catalyzed glutathione conjugation, leading to the formation of an inert metabolic compound that is not capable of reacting with DNA [9]. The formed conjugate can then be converted in vivo to a mercapturic acid adduct and excreted through urine [9]. The expression of GST is more pronounced in mouse compared to other animals, which may explain why they show more resistance to aflatoxin B1 exposure.

Aflatoxins can impair hepatocytes directly or by changing the expression of genes (Ahr, Scarb1, Lcat, Lipc, and Cpt1a) connected with lipid metabolism. The elevated production of lipoprotein, triglyceride, and cholesterol can cause hepatocytes deterioration due to increased anaerobic cell metabolism and metabolic need [69]. In the blood, the changed ratio of HDL–LDL levels and the elevated lipid fraction can increase the coronary heart disease risks. The hepatocytes death will result in acute hepatitis, which may result in liver failure, reduce survival chance, or even cause death [70]. Hepatitis patients have impaired metabolic system, which may lead to malnutrition [71] and consequent prone to aflatoxicosis. Nutrients deficiencies also result in the decrease in reducing agents such as glutathione and consequently to decrease in antioxidative activities in hepatocytes. Without nutrients, the repair and regeneration of hepatic tissues will not function properly, making liver failure almost unavoidable [72].

Acute aflatoxicosis can lead to death, whereas chronic exposure can cause immunosuppression, cancer, gradually manifesting pathological impairments [73]. Chronic exposure to aflatoxin can cause impaired duplication of DNA in bone marrow, resulting in low levels of leukocyte, which in turn causes immunodeficiencies and several infections [74]. Aflatoxins have a unspecific, cell multiplication inhibitory effects on other types of cells [75]. This is the most common effect in the GI tract, where intact cell cycle is required for digestive system to function properly [76]. The values of aflatoxins lethal dose (LD50) range from 0.5 to 10 mg/kg, dependent on the derivative's chemical properties [4]. The liver is the mostly affected organ, and patients suffer from fatty acid infiltration, hepatic lesions, centrilobular necrosis, and bile duct proliferation, which usually results in liver cancer [77, 78].

Ochratoxins

Ochratoxins are a group of metabolites (mycotoxins) produced by some species of *Aspergillus* (such as *Aspergillus ochraceus*, *A. carbonarius*, *A. niger*, etc.) and some *Penicillium* species (such as *P. verrucosum*). Ochratoxin A (OTA) is the most common and concerning ochratoxin, while ochratoxin B (OTB) and C (OTC) are not too common [79]. OTA is among the most significant mycotoxins of concern, and is mainly produced by *A. ochraceus*, *P. verrucosum*, *A. carbonarius*, and *A. niger* [30, 80]. *Ochratoxin A*, a pentaketide compound, is a derivative of family of dihydrocoumarin coupled to β-phenylalanine [81]. The International Agency for Research on Cancer (IARC) classified OTA as possibly carcinogenic to humans (i.e. a Group 2B carcinogen). OTA was shown to be nephrotoxic, genotoxic, immunotoxic [82], neurotoxic, teratogenic, embryotoxic, and hepatotoxic [31]. OTA symptoms depend on dosage, and its carcinogenic activities have been reported in several animals. The toxicity of OTA to human have not been completely understood, however, it is known that OTA can cause kidney failure, kidney cancer, and kidney damage in humans [30].

Several human nephropathies associated with OTA have been described in Montenegro, Macedonia, Slovenia, Herzegovina, Bosnia, Croatia, Serbia, Romania, and Bulgaria [83]. Most countries in Africa, including Egypt, Morocco, Tunisia, South Africa, Congo, Uganda, and Nigeria, grapple with similar health challenge due to OTA exposure. OTA monitoring and diagnosis in humans depend on the OTA levels in urine and blood. Chronic exposures to low doses of OTA may be more damaging than high acute doses [82]. At least 20 derivatives of Ochratoxin A exist naturally and after biotransformation in human. Ochratoxin A forms covalent DNA adducts via benzoquinone and radical intermediates. Additionally, OTA hydroquinone (OTHQ) metabolite could undergo autoxidation to form OTA quinone (OTQ), which is quinone electrophile, and can also react with the DNA [30]. Also, OTQ formation or the formation of aryl and phenoxy radicals can lead to increased production of reactive oxygen species (ROS), which is linked to its cytotoxicities. Mechanisms leading to nephrotoxicity, immunotoxicity, and hepatotoxicity of OTA can be associated with the inhibition of lipid peroxidation, protein synthesis, and the MAP kinase cascade modulation, likened to the pentachlorophenol derivatives exposure [81, 84].

Aflatrem (AT)

Aflatrem is a tremorgenic mycotoxin and indole-diterpene produced by *Aspergillus flavus* and *Aspergillus minisclerotigenes*. These *Aspergillus* strains can produce paspalitrems, supinates, paxilline, janthitrems, lolitrems, penitrems, shearinines, terpen-doles, and paspaline [85]. AT causes neurological disorders and can visibly manifest as noxious food decay which grows on several products [32]. A precursor of all these metabolites is geranylgeranyl diphosphate (GGPP) and the metabolites also have a tryptophan-derived indole moiety [86]. Aflatrem causes staggers syndromes, including several disorders of neurodegeneration characterized by hyperexcitability and muscle tremors, and thus poses health risk to humans and animals [33]. Genes sequences with high similarity to paxillin synthesis were reported in the sequence data containing complete genomes of *Aspergillus oryzae* RIB40 and *Aspergillus flavus* NRRL3357. The genes atmM, atmC, and atmG, which are homologous to paxM, paxC, and paxG, respectively are essential for production of AT [87]. However, the locus of the ATM1 expresses the putative orthologs of just three out of seven genes required for the biosynthesis of paxilline. The other genes with similarity to the paxilline biosynthesis genes paxQ, paxP, paxB, and paxA, were detected at ATM2, the second locus, and

constituted a gene cluster of 25 kb. Aflatrem can show acute neurotoxicity.

Gliotoxin (GTX)

Gliotoxin (GTX) is a sulfur-containing mycotoxin belonging to 2,5 diketopiperazines produced by many fungi. GTX belongs to cyclic dipeptides class of metabolites of fungi epipolythiodioxopiperazin (ETP) first isolated from *Gliocladium fimbriatum* [88], after it was later identified to be produced in *Aspergillus fumigatus*, *Penicillium*, *Trichoderma*, and *Eurotium chevalieri*. The biosynthetic gene of gliotoxin is responsible for biosynthesis of ETP and at present, at least 12 biosynthetic pathway genes responsible for biosynthesis of GTX have been described in A. *fumigatus*. The biosynthesis genes code of ETP for the biosynthesis of sirodesmin and other toxins of ETP-type are sporidesmin A, sirodesmin A, epicoccin A, and gliovirin. The gene cluster of GTX encompasses 13 genes consisting of gliH, gliT, gliN, gliA, gliK, gliG, gliM, gliF, gliC, gliP, gliJ, gliI, and gliZ [89]. GTX has many toxic potentials, including cytotoxicity, apoptosis, immunosuppression, and genotoxicity. The mycotoxin has shown serious genotoxicity, DNA damage, and inhibition of human lymphocyte development [34]. The epipolythiodioxopiperazines (ETPs) molecular feature in gliotoxin may have a role to play in cross-linking with proteins' cysteine residues, which leads to ROS generation via redox cycling reactions, with necrosis and immunosuppression as the outcome. GTX changes the tight junction structure through a molecular mechanism has not been fully established and has also shown to be cytotoxic to astrocytes [35]. Like aflatoxins, gliotoxin is immunosuppressive, but with a different molecular mechanism. In low concentrations, gliotoxin inhibits activation of inflammatory cells. In leukocytes, gliotoxin in high concentrations of at least 250 ng ml^{-1} can induce apoptosis [90].

Citrinin (CIT)

Citrinin is a mycotoxin mainly produced by fungi in stored foods (especially grains, fruits, etc.) and has been shown to be hepatotoxic, embryocidal, genotoxic, nephrotoxic, fetotoxic, and cytotoxic. CIT is a polyketide P. Citrinum metabolite characterized as antibiotic with actions against bacteriophages, bacteria, animal cells, protozoa, and sarcomas. It is a kidney toxin which affects humans, domestic animals, and poultry birds [38]. Citrinin plays a role in the endemic nephropathy Etiology; although the molecular mechanisms of citrinin toxicity have not been completely established [36]. It is structurally similar to ochratoxin A. Many species of fungi can produce citrinin, including Aspergillus flavipes, *Aspergillus niveus*, *Aspergillus alabamensis*, *Aspergillus pseudoterreus*, *Aspergillus neoindicus*, *Aspergillus hortai*, *Aspergillus allahabadii*, *Aspergillus floccose*, and *Aspergillus carneus* [91]. Citrinin and ochratoxin A act synergistically to reduce RNA synthesis activities in renal tissues and cause renal disorders due to the DNA adduct development with increased C-C8dG-OTA adduct formation [37, 80]. Citrinin and ochratoxin A significantly increase carcinogenesis possibility in humans [92]. *M. ruber* cans biosynthesize citrinin together with natural red dye. In Aspergillus species, citrinin is formed by condensation of four malonyl CoA with a single molecule of acetyl-CoA along with three methyl units' addition.

Alternaria toxins

Alternaria species can be seen almost everywhere and, in several ecosystems, such as soil, atmosphere, agricultural commodities, seeds, and plants [93]. The species of Alternaria produce Alternaria toxins such as tenuazonic acid (TeA), tentoxin (TEN), alternariol methyl ether (AME), alternariol (AOH), altertoxins (ATXs), altenuene (ALT), altenuisol (AS), alteichin or alterperylenol (ALTCH), altersetin (ALS), stemphyltoxin (STE), etc., which usually contaminate foods during storage [94].

Over 70 secondary metabolites are produced by the *Alternaria* species that produce mycotoxins, including *Alternaria triticina*, *Alternaria tenuissima*, *Alternaria dauci*, *Alternaria brassicae*, *Alternaria alternata*, *Alternaria solani*, and *Alternaria japonica* [93, 95]. In addition, at least 30 mycotoxins have been isolated and belong to several classes based on their chemical structures [94]. The *Alternaria* genus includes pathogenic, endophytic, and saprophytic species; *Alternaria* is a cosmopolitan fungus that occurs in anthropogenic and natural environments [7]. *Alternaria alternata* is the most common among the *Alternaria* species in fruit and vegetables after harvesting, and also the most significant species that produce mycotoxins [95]. While ATXs is a member of perylene quinone derivatives, ALT, AME, and AOH are members of dibenzo-α-pyrone derivatives [96]. TeA is a member of tetramic acid derivatives that have phytotoxic and antibacterial properties and acute toxicities for dogs, chicken, and mice, in addition to hematological disorders in humans [39].

The most commonly studied Alternaria toxins include TeA, AME, and AOH [95]. More studies on Alternaria toxins are required. Although most Alternaria toxins show low acute toxicities, AME and AOH are mostly toxic because of their genotoxic, cytotoxic, carcinogenic, and mutagenic effects, with scientific-based findings from toxicological studies, in vitro, involving mammalian and bacterial cells. AOH has been shown to have more genotoxicity in carcinoma colon cells of humans than AME [39]. At present, monitoring guidelines or regulatory limits have not been fully established for Alternaria toxins in foods worldwide. After an EFSA study, the toxicological concern threshold (TTC approach) was put into use by the EFSA due to little or no data on Alternaria toxins toxicities with the aim of assessing the concern levels for humans. For genotoxic Alternaria toxins (AME and AOH), 2.5 ng kg^{-1}body weight per day TTC value was set, while for non-genotoxic Alternaria toxins (TEN and TeA), 1500 ng kg^{-1} body weight per day TTC value was set; these estimates of exposures are not likely to pose concern to humans [7]. Substrate composition, pH, aw and temperature are most significant abiotic and biotic parameters that affect mycotoxins biosynthesis and, consequently, the Alternaria toxins biosynthesis. pH and aw in particular affect most *A. alternata* biosynthesis [39]. Studies were done using red wine, juice samples, dried and fresh tomatoes, wheat and wheat products, and dried fruits. Alternaria toxins of interests in most studies include ALT, TeA, TEN, AME, and AOH [96]. Alternaria toxins occurrence has been reported in several countries including Italy, the Netherlands, China, Canada, Argentina, and Germany [39, 96 and 97]. Alternaria toxins are found in many food commodities, including beer, fruit juices, vegetable juices, wine, peppers, fresh and dried tomatoes, flour, bran, wheat, dried fruit, cereal products (e.g. rice and oat flake), sunflower oil, and sunflower seeds [96, 98, 99].

Fumonisins

Fumonisins are a group of polyketide-derived, non-fluorescent mycotoxins produced by many Fusarium species and their Liseola section. At least 53 various fumonisins have been described, and can be categorized into four major series (A, B, C, and P), although studies have focused more on the Bs, including fumonisins B1 (FB1), B2 (FB2), B3 (FB3), and B4 (FB4) which are mostly abundant naturally [40, 100, 101, 102]. Fumonisin Bs have a long chain of hydroxylated hydrocarbon, furnished with tricarballylic acid group, methyl group, and amino group. FB1, FB2, and FB3 have different patterns of hydroxylation [41]. Fumonisins have structural similarity to cellular sphingolipids and was reported to inhibit biosynthesis of sphingolipid at ceramide synthase [40, 100- 102].

The primary tricarballylic acid group and amino group of the mycotoxin are the reasons for the reactions with the ceramide synthase. Toxicity induced by fumonisins

usually leads to oxidative stress generation, altered cytokine expression, or apoptosis [41]. The IARC classified fumonisin B1 in Group 2B; probably carcinogenic to human. Black *Aspergilli* such as *Aspergillus welwitschiae* and *Aspergillus niger* may be responsible for the fumonisins B2 (FB2) and B4 (FB4) levels detected in some feeds and foods, including maize, wine, raisins, onions, grapes, etc. [101- 104]. However, *Fusarium* species such as *Fusarium proliferatum*, *Fusarium verticillioides*, etc., cause high levels of FB1 contaminations in foods and feeds [105]. Concurrence of fumonisin producing black Aspergilli and Fusaria in maize kernels may have influence on the observed ratios of FB1/FB2 [106, 107]. Studies show fumonisins may be implicated in esophageal cancer and can cause pulmonary edema in pigs and leukoencephalomalacia in horses [41]. Fumonisins have been shown to cause diseases such as renal carcinogenesis, nephrotoxicity, hepatotoxicity, pulmonary edema, leukoencephalomalacia, and neural tube defects [40]. A study reported increase in production of ROS after exposure to fumonisins, and may lead to DNA damage, enzyme defects, etc.; although more studies are required to firmly establish the mechanisms behind the reported effects [41].

Sterigmatocystin (STC)

Sterigmatocystin is a polyketide mycotoxin produced by some Aspergillus species and is naturally found some foods such as cheeses, grains, green coffee beans, etc. It is closely similar to aflatoxins and has a xanthone nucleus bound to a structure of bifuran. Sterigmatocystin (STC) is produced by over 50 fungi, especially *Aspergillus nidulans*, *Aspergillus versicolor*, *Aspergillus flavus*, and *Aspergillus parasiticus*. The pathways for the biosynthesis of STC and AFs several biosynthetic enzymes [43]. As *Aspergillus versicolor* and *Aspergillus nidulans* cannot transform Sterigmatocystin into O-methylsterigmatocystin, which is the direct precursor of aflatoxins B1 and G1, foods and feeds infested by these fungal species usually have high STC levels. Conversely, foods and feeds infested by *Aspergillus parasiticus* and *Aspergillus flavus* contain low STC levels, because most of the STC is transformed into aflatoxins [42]. This is quite interesting and very important to take note of. According to different animal models and cell culture experiments, STC can also induce tumors; therefore, IARC classified it in the Group 2B as possible human carcinogen [42].

Despite these phenomena, the maximum acceptable STC levels in foods have not been regulated in most countries. The sterigmatocystin acute oral toxicity is low, with values of LD50 ranging from 120 to 166 mg/kg bodyweight. After exposure through oral route, malignant and premalignant lesions, including angiosarcomas and hepatocellular carcinomas were reported in brown fat. Sterigmatocystin is carcinogenic, mutagenic, teratogenic, and genotoxic. STC metabolism by various CYP enzymes takes place in liver and lung, and is transformed into various hydroxy metabolites, with STC-metabolites excreted through the urine and bile [42, 43]. STC mutagenicity is as a result of the reactive epoxi-adducts that could bind covalently to DNA, generating STC-N7-guanine adducts. Another mechanism suggested that the aromatic ring hydroxylation generates a catechol that may react with DNA [108]. STC may induce double-strand breaks in DNA in epithelial cell line of human immortalized bronchia, possibly resulting in adenocarcinomas [43, 109].

Patulin (PAT)

Patulin is a polyketide lactone mycotoxin produced by several molds, especially by some species of *Penicillium*, *Aspergillus* (*A. longivesica*, *A. clavatus*, *A. giganteus*), and Byssochlamys [46, 47, 110 - 112]. Patulin is a colorless, water-soluble, polyketide lactone, believed to wield its toxicity by its reaction with thiol groups

(glutathione, cysteine, thiol protein moieties) in cytoplasm [46, 47]. Along with its antiviral, antiprotozoal, and antibacterial activities, patulin is also a mycotoxin. Patulin shows acute toxicity, mutagenicity, and teratogenicity, and its emerging symptoms are usually not specific but mainly associated with enzyme inhibitions [46, 111]. The enzymes mostly affected are those involved in digestion, energy production, and metabolism. Altered lipid metabolism, reduced weight, reduced food intake, and intestinal disorders may be observed in affected animals. Patulin can compromise human and animal immune system, modifying the host's response mechanisms, and can inhibit translation, transcription, and synthesis of DNA in leukocytes [113, 114]. Studies have shown that, in vitro, patulin inhibits functions of macrophage such as decreased protein synthesis of cytokines and lysosomal enzymes, causes phagocytosis, reduce ROS production significantly, altered functions of the membrane, and causes defect in phagosome–lysosome fusion [115].

Secalonic acids (SAs)

Secalonic acids are a group of mycotoxins that have chiral dimeric tetrahydroxanthones similar to ergochrysin A and ergoflavin, which are collectively known as ergochromes and grow on ryegrasses [116]. SAs were initially isolated from *Claviceps purpurea* (an ergot fungus). At least 22 secalonic acids have been structurally recognized as dimers of 6 monoxanthones, A–F [48, 117]. Secalonic acids A (SAA), B (SAB), C (SAC), and D (SAD) were isolated from *C. purpurea*, *Penicillium oxalicum*, and *Aspergillus ochraceus* [48]. Secalonic acids A attenuates the colchicine cytotoxicity in cortical neurons in rat [118]. Secalonic acids A, E, and G are yellow pigments obtained from *Penicillium terrestris*. Secalonic acids exhibit wide range of biological activity, including antitumor, anti-HIV, antimicrobial, and anticancer [119, 120 and 121]. SAs antitumor activities against mice tumors, sarcoma-180, and Ehrlich ascites carcinoma were reported. Secalonic acid D is very toxic, weakly mutagenic and teratogenic mycotoxin that commonly occurs in the US. Secalonic acid D is a teratogenic mycotoxin that affects pregnant mice along with its progeny and can result in neurotoxicity depending on dosage [122]. SAD may inhibit angiogenesis mediated by VEGF via the pathway of Akt/mTOR in breast cancers [123]. SAD inhibits multidrug-resistant cells, induces leukemia, and obstructs responsive cell growth [124].

Terrein (Ter A)

Terrein is a toxic secondary metabolite produced by many *Aspergillus species*, including *Aspergillus terreus*, Aspergillus stellates, Aspergillus fischeri, Aspergillus novofumigatus, *Aspergillus lentulus* [50, 125]. Ter A forms pale yellow crystal needles and has strong cytotoxic activities against cells that have colorectal carcinoma [50]. Although the entire pathway of terrein biosynthesis has not been fully established, however, the roles of 11 putative genes have been described in its biosynthesis [126]. Terrein has anti-oxidant, and skin-whitening, anti-inflammatory, and anti-proliferative properties. Ter A showed angiogenesis inhibitory properties in prostate cancer's androgen-dependent cell line (LNCaP-CR) [127]. At first, Terrein produces compounds 6 (2,3-dehydro-6-HM; 6-hydroxymellein), 4 (OA; orsellinic acid), and 5 (4-HMP; 4 hydroxy 6 methyl-pyranone) by condensing four, three, or two malonyl-CoA units with acetyl-CoA. 6-hydroxymellein (6-HM) functions as precursor for the production of terrein [126]. Terrein acts as a proteasome inhibitor via lessening chymotrypsin activities, and promotes apoptotic cell fatality in the human lung tumoral cell lines (NCI-H292) [49]. Also, Ter A inhibits cell proliferation of human breast cancer [128]. The cell lines study of Ter A toxicities on lung and Zaehleenocarcinoma epithelia of human demonstrated inhibition of cell viability, morphological changes, and

proliferation, which also results in vascular endothelial growth factor (VEGF) secretion and phosphorylation of JNK1/2, STAT3, and ERK1/2 in HGFs [129].

Cyclopiazonic acid (CPA)

Cyclopiazonic acid (CPA or α-CPA) is a mycotoxin produced by *Aspergillus* and *Penicillium* species, and was originally discovered in *Penicillium cyclopium* (*Penicillium griseofulvum*). It is a secondary metabolite and an indole-tetrameric acid which serves as a toxin because of its capability to inhibit calcium dependent ATPases seen in sarcoplasmic and endoplasmic reticulum. These inhibitory effects disrupt the calcium gradient and the muscle contraction-relaxation cycle maintained for proper cellular activities in cells. *Penicillium cyclopium* was reported in groundnuts that caused acute toxicosis in rats and ducklings [51, 52]. α-CPA occurs in plant foods and is commonly found in maize and peanuts. CPA prevalence has been reported in peanuts, corn, poultry quail feed, cheese, rice, sunflower seed, Kodo millet, etc., and has been associated with disease outbreaks [51, 130, 131]. In addition to being toxic to rats, dogs, pigs, chickens, and guinea pigs, cyclopiazonic acid is also carcinogenic to human. In addition to the production of cyclopiazonic acid, *Penicillium cyclopium* also produces indole derivatives that are not toxic, including α-cyclopiazonic acid-imine (α-CPA-imine).

Cyclopiazonic acid was found in the seed of Kodo millet (*Paspalum scrobiculatum*) that causes "Kodua poisoning" in human. CPA can cause tremors and sleepiness. Kodo millet is one of the staple foods in some regions such as North India, and when contaminated with *Aspergillus tamari* and *Aspergillus flavus*, its consumption was usually linked to poisoning and intoxication [132, 133]. Accidental household consumption of CPA was reported to cause nausea and giddiness [134]. Intra-peritoneal CPA injection can cause mobility defects and depression. CPA poisoning in cattle can be fatal, although they can recover within few days; CPA poisoning in cattle is characterized depressive disorders, overwhelming gait, reduced muscle strenGTXh, etc. [135]. Upon the consumption of CPA contaminated feed, animals suffered severe neurodegenerative disorders and gastrointestinal upsets. Cyclopiazonic acid has toxic effects on heart, liver, digestive tract, and kidney, along with inducing necrosis and degenerative changes in chickens and rats' skeletal muscles [131].

Humans are mostly exposed to cyclopiazonic acid by consuming eggs, meat, milk, and dairy products including cheese. Consuming contaminated milk can induce seizure, viscera, necrosis, weight loss, and even death [136, 137]. Synergistic activities of CPA and AFs can have adverse effect on broiler chicken performance, possibly resulting in increased mortality [138]. Cyclopiazonic acid was reported to be toxic when orally administered to dogs, guinea pigs, and swine, affecting the skeletal muscle, kidneys, liver, and alimentary tract. CPA is the main maize contaminant (51 %) in the US with 2.8 mg kg^{-1} average level; around 90 % of samples of peanut demonstrated clear damage [139]. *Penicillium camemberti* is commonly found in foods and feeds, especially in cheese products, and can produce CPA. *Aspergillus oryzae* and *Penicillium camemberti* are used to produce fermented foods worldwide [140]. Tetramide biosynthetic gene cluster carries out the biosynthesis of CPA. The cyclopiazonate scaffold related to CPA is derived from β-CPA and cyclo-acetoacetyl L-tryptophan (cAATrp).

Vomitoxin (Deoxynivalenol [DON])

Vomitoxin, also called Deoxynivalenol, is a trichothecene (type B), an epoxy-sesquiterpenoid that predominantly occur in grains, including wheat, corn, barley, oat, triticale, sorghum, etc. Many studies done in the field showed that *Fusarium* head blight intensity has linear relationship with DON accumulation [141].

Vomitoxin can be found in foods obtained from animals, including eggs, milk, liver, and kidney. Few studies, not all, showed that deoxynivalenol can transfer from dairy cow to its milk. Intoxication with vomitoxin results in fever, dizziness, headache, diarrhea, vomiting, nausea, and abdominal pain [53]. DON has high heat stability within 170 to 350°C; no decrease in concentration was reported at 170°C after 30 min [53]. Due to its solubility in water, levels of DON reduce during cooking of contaminated noodles/pasta, as it leaches into water used for cooking, but not when contaminated foods are fried in oil [53]. In grains contaminated with *Fusarium*, the DON levels increase as the number of damaged grains increase. A study mixed healthy kernels and *Fusarium*-damaged kernels in 5% additions from 0 to 100% within 2 consecutive years, and showed that after flours obtained from grains of each blend was evaluated; DON concentration increased as the number of *Fusarium*-infested kernels increased [141]. Among all the livestock species, Swine are most susceptible to the toxicity of DON; other species, including dogs and cats, are affected too, and sensitivity to DON can vary with gender and age [142].

Emerging mycotoxins of concerns from fusarium species

Some emerging mycotoxins are of a major concern due to their prevalent occurrence in foods such as grains, especially cereals and cereal products [45]. Emerging mycotoxins have been defined as "mycotoxins, which are neither routinely determined, nor legislatively regulated; however, the evidence of their incidence is rapidly increasing" [143]. An opinion on beauvericin (BEA) and enniatins (ENNs) presence in foods and feeds was presented by the European Food Safety Authority (EFSA) with no assessment of risk because relevant toxicity data was lacking [144]. Fusaproliferin (FU), a bicyclic sesterterpene mycotoxin, is produced by species of Fusarium, including *Fusarium verticillioides*, *Fusarium subglutinans*, and *Fusarium proliferatum* [145]. Fusaproliferin exhibited toxicity on brine shrimp larvae and chicken embryos [145]. In terms of structure, moniliformin (MON) is a 1-hydroxycyclobut-1-ene-3,4 dion, water soluble, a small molecule, and can be produced by *Fusarium* species [145, 146]. In terms of structure, beauvericin is cyclic hexadepsipeptide with alternating sequence of three N-methyl-l- and d-a-hydroxy-iso-valeryl-phenylalanyl residues [147].

Beauvericin was isolated from a fungus called *Beauveria bassiana* for the first time; *Beauveria* bassiana is known to cause disease in insects [147], and commonly occur in corn and corn products infected by species of *Fusarium*. BEA infects cereals and cereal products not just in countries in Europe including Czech Republic, Italy, Spain, and Romania, but also worldwide, including Morocco, Tanzania, Iran, Rwanda, and Japan [44, 148]. BEA has insecticidal, antifungal, and antibacterial properties, and can have toxic effects including apoptosis induction, increased cytoplasmic calcium concentration, and fragmentation of DNA in cell lines of mammals [147]. NX-2 toxin, a new trichothecene, was recently found in cultures of rice. In terms of toxicity and structure, NX-2 is similar to 3-ADON, although it has no keto group at C-8; and as a result, NX-2 is a type A trichothecene mycotoxin [149].

Fusarium species that produce ENNs include Fusarium Venenatum, F. merismoides, etc., and occur in various geographical regions, and seed contamination levels are rarely up to mg/kg [150]. Enniatins (ENNs) contaminate cereals, coffee, tree nuts, dried fruits, beans, vegetable oil, etc. The most commonly detected enniatins in food and feeds include enniatin A (ENA), enniatin B (ENB), enniatin A1 (ENA1), and enniatin B1 (ENB1) [151]. There is little or no indication that enniatins pose concern to human and animal; though, ENNs may have role to play in making other *Fusarium* toxins impact more pronounced (especially, DON) through cellular export inhibition [152]. As a result of their high prevalence in foods and feeds and their potential toxicity to humans

and animals, the huge interests in emerging mycotoxins are increasing [147]. More studies are needed for more understanding of these mycotoxins, including their possible toxicities to humans and animals, as well as how to effectively reduce their presence in foods and feeds to safe levels.

Ergot alkaloids

Ergot alkaloids are produced by Clavicipitaceae (e.g. *Claviceps* and *Neotyphodium*) and Trichocomaceae families (e.g. *Aspergillus* and *Penicillium*) [55]. Tetracyclic ergoline ring is their common structural characteristic. Ergot alkaloids are both harmful and beneficial to humans [55]. Ergot alkaloids, both natural and semisynthetic, are applied in several medicines [153]. There are many cases of widespread ergot alkaloids poisoning; ergot alkaloids were reported to be responsible for the Massachusetts' Salem Witch Trials [55]. In 1692, after many female teenagers were affected by delirious seizures and fits, traditional physicians blamed the cause on witchcraft. Innocent individuals were grossly accused of practicing witchcraft, tried, convicted, and then executed; however, records were later evaluated and showed that ergot alkaloids produced by *Claviceps purpurea* may have caused the intoxication [154]. Ergot alkaloids have also been implicated in several witchcraft accusations and trials [55, 154]. The name "St. Anthony's Fire" was derived from the St. Anthony's monastic Order, whose members administered treatment to the disease sufferers. Modern techniques used for grain cleaning have largely eliminated ergotism as disease in humans; however, it still poses threat to many animals, such as chickens, pigs, cattle, and sheep [155]. Livestock exposures to ergot alkaloids result in gangrenous extremities, agalactia, ataxia, abortion, and convulsions [155, 156].

Toxic effects of combined mycotoxins exposure

There is sufficient evidence available regards the co-contamination by various species of fungi (that colonise same commodities), as well as co-occurrent production of different mycotoxins. The main mixtures of mycotoxin that occur in foods appear to be DON–ZEA, aflatoxins–ochratoxin A, aflatoxins–fumonisins, patulin–aflatoxin, etc. [157]. A particular food can contain several mycotoxins; studies have found several mycotoxins occurring in same grains such as maize, acha, groundnut, rice, millet, sorghum, etc. [59, 79, and 114]. Consequently, several mycotoxin exposures to humans and animals for a long time can be harmful. There are insufficient studies focusing on the effects of co-occurrent mycotoxins, but such as extremely required for better understanding of their potential risks to humans and animals. It is well understood that the response to multi-mycotoxins exposure category is three-faceted, which include: (a) synergistic; if one mycotoxin effects are increased by the presence or occurrence of another mycotoxin; (b) antagonistic, if the responses are less than that expected from each mycotoxin when acting alone, and (c) additive, if total responses could be estimated by considering individual mycotoxin.

A combination of many mycotoxins often results in synergistic effects. One of the most known synergistic effects is the synergistic interactions between citrinin and OTA resulting in marked increase in nephrotoxicity compared to when acting alone. A combination of OTA and AFB1 is among the most frequent natural occurring combinations in foods [158]. Ingesting the two mycotoxins simultaneously cause higher OTA nephrotoxicity and also interferes in metabolism of OTA. The regulations of mycotoxins are not often focused on the interactions between commonly co-occurring mycotoxins. Figure 2 shows how cancer caused by factors such as mycotoxicosis increases its efficacy to bring about under two different conditions. Currently, the concerns about the effects of mycotoxins co-exposure on

humans and animals are gaining more attention. Notably, in both nutrient-replete and nutrient-deprived conditions, mycotoxins such aflatoxins, ochratoxins, citrinin, etc., can cause cancer as shown; the severity is stronger in nutrient-deprived conditions, wherein the cancer progression can be propelled by lack of nutrients, with little or insignificant effect from micropinocytosis and autophagy within the cells of the affected cells/tissues; in nutrient-replete condition, the cancer progression can be slower, as the little available nutrients can help to boost the body natural detoxification mechanisms [59].

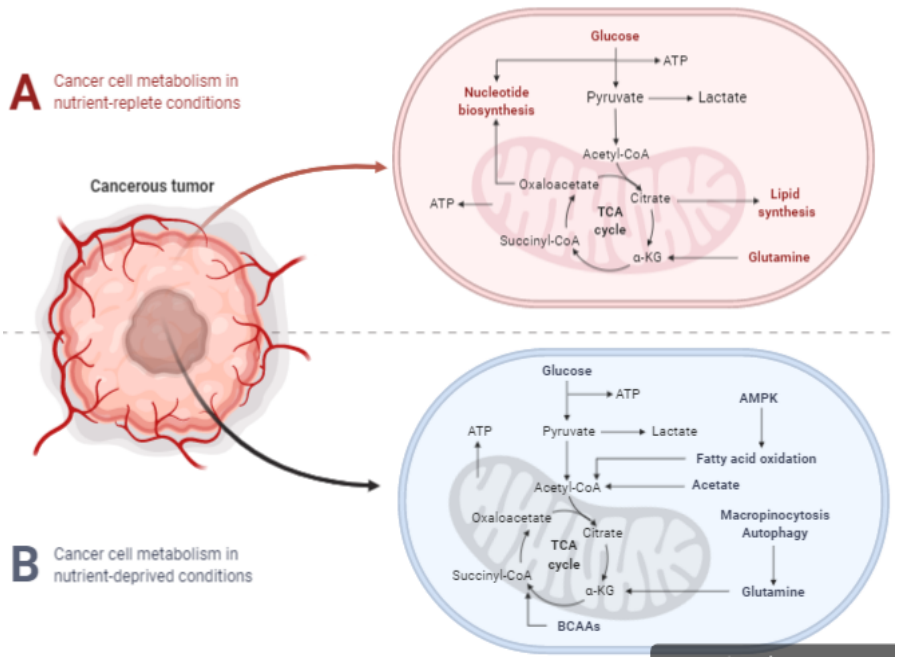

Figure 2. Metabolism of cancers initiated by mycotoxicosis via (A) conditions replete of nutrient, and (B) conditions deprive of nutrient (Adapted from [59]).

A number of mycotoxicoses can occur by consuming foods and feeds with multiple mycotoxins contamination. There have been reports of simultaneous food contamination by two or more mycotoxigenic fungi. In addition, some fungi can produce two or more mycotoxins, and the combined biological effects of mycotoxins can be as significant as the toxic effects of one mycotoxin [159, 160]. The harmful effects of simultaneous exposures to mycotoxins cannot be predicted solely relying on their individual toxicities [157]. Synergistic, additive, or below additive toxic effects of mycotoxins have been reported in several mycotoxins. A dose-dependent interaction involving AFs, OTA, and their metabolic compounds has been described, and their effect was additive in levels [157, 161]. The description is mainly because the two mycotoxins affect duplication and pairing of DNAs, possibly inducing carcinogenicity. These combined effects were below additive at higher levels, but it is definitely not antagonistic [161, 162]. The various physiological impacts can be due to OTA and aflatoxins go through same routes of bioactivation by the liver CYP enzymes.

Major mycotoxin effects on infants and children

The constant exposure to mycotoxins has caused a lot of health complications to humans, with infants and children being among the vulnerable groups. Children and infants are exposed to several mycotoxins through

the foods and supplements (e.g., milk, dairy products, cereals, legumes, cereal products, etc.) they consume. Consuming such contaminated foods can lead to various toxicities starting from infancy, such as stunting, growth impairment, poor development, underweight, etc., and may further result in immune deficiencies, nephro- and hepatic diseases, high susceptibility to infections, etc [7]. Mycotoxins co-occurrence in infant formula and foods, including wheat, apples, barley, banana, sweet potatoes, corn, apple products, etc., can result in various health complications [163]. Aflatoxins control in the production process and preparation of infant foods is critical for the safety of infant [164]. Exposure to aflatoxin has severe effects on development and growth [165].

For children in regions grossly affected by aflatoxin contamination of food products, such as children in West and East Africa, growth impairment could occur during the solid foods' introduction. Patulin has also been shown to have toxicity in mice born to mothers given patulin; deaths were reported in both females and males. Aflatoxins and citrinin can be detected in processed and unprocessed foods, and also in homemade infant formula in high levels sufficient to induce health complications to infants and young children. A study examined AFT-albumin adducts occurrence of about 720 pg aflatoxin-lysine equivalent/mg albumin in serum samples from Gambian children [8]. In the children with Plasmodium falciparum and hepatitis B surface antigen (HBsAg), the AFT-albumin adducts level was higher than control. Aflatoxin M1 levels were 0.16 to 0.33 µg/kg in lactating mothers breast milk in Ogun State, Nigeria; 82 % of the samples of breast milk had AFM1 [166].

Mycotoxin exposures' complications/risks at various stages of human life

Mycotoxin exposure can occur at any stages of life, and can affect different individuals in different ways. The toxic effects mycotoxins have on cell division may result in dire consequences, which can be more serious during intrauterine life. Data on mycotoxicoses is available in infants, children, and embryonic stage. A study used human embryonic stem cells (hESCs) and reported the OTA toxicity's dose dependency [167]. Mycotoxins may influence gametes production and thus impregnation success, because the mycotoxins' cytotoxic effects may impair the gametes division and differentiation, thus may result in infertility through interfering with, for example, spermatogenesis [168]. AFL (an AFB1 derivative) can penetrate the placenta to affect embryo, and has already been reported in humans, although its adverse effects has not been sufficiently studied [169]. Studies on animal models have shown that mycotoxins may increase the chance of stillbirth [170]. AFM1 can be secreted from breast milk during lactation, indicating additional risks of mycotoxin exposure to infants from lactating mothers [9, 171]. Mycotoxins pose significant risks to human development, especially infants and children, who are mostly affected.

Mycotoxicosis can potentiate several conditions mostly associated with the cytotoxic, genotoxic, carcinogenic, mutagenic, teratogenic, hepatotoxic, and nephrotoxic properties of mycotoxins. In young children and newborn babies, the symptoms of mycotoxicosis can be more severe because most mycotoxins, such as aflatoxins, ochratoxin A, and STC, affect cell multiplication and growth. In development and growth phases, inadequate cell division may result in growth retardation/delayed, severe immunosuppression, mental retardation, and poorly developed body system [172, 173]. Studies indicate that gliotoxin, in vitro, may alter neurons and astrocytes connections, which may impair cognitive development and have effect on brain formation [35]. Fumonisins may cause neuronal tube defects because of their inhibitory effects on sphingolipid biosynthesis [174]. Mycotoxin exposure in children can cause the immature gastrointestinal tract to malfunction or damage, and consequently affect nutrient absorption in the affected children [175]. Thus, malnutrition is among the common factors in mycotoxicosis, as with no sufficient nutrient absorption, the normal functions and

detoxification mechanisms of the body will be impaired. Additionally, the impaired digestive functions complicate treatment, making it less effective and more difficult [165]. In developed nations with apple juice popularly consumed by children, the levels of PAT in such beverages have to be strictly controlled [46, 176]. Urine, maternal milk, and blood samples were studied for aflatoxins, fumonisin B1, and OTA [177]. The study concluded that children are usually at high risks of exposure and toxic effects of mycotoxins.

Although healthy adults are at risk of mycotoxin exposure and the resulting mycotoxicosis, but their mature detoxification mechanisms usually handle acute and chronic exposure to mycotoxins. However, some factors, such as malnutrition, alcoholism, drug abuse, and occurrence of other diseases, e.g. obesity and cancer, may increase their risk of mycotoxicoses [59, 178, and 179]. For chronic exposures to mycotoxins, developmental disorders in adults are not significant compared with children, although tissues that require high rate of cell division for proper functioning may be affected. Hematopoiesis, enterocytes function, or immune system requires adequate cell multiplication; and xenobiotics, such as mycotoxins, may have severe effects on cell cycle [16, 180]. Interestingly, clay is among components able to reduce toxicity of mycotoxins, e.g., aflatoxins. Similarly, Novasil® has been studied via clinical trials, suggesting its safety, given its capsule-based delivery [62].

Consumer health implications of mycotoxin exposure

Despite all the stringent regulations and prevention methods, mycotoxins continue to persist in foods and feeds, consequently causing mycotoxicoses (that is, diseases caused by exposures to mycotoxins), and to exposed individuals [16]. Mycotoxin exposure leading to disease outbreak was reported in Kenya in 2004 with over 125 deaths, in Tanzania in 2016 with at least 68 cases, and also occurred in the former Yugoslavia nations [1, 162, and 181]. The symptoms of mycotoxicosis depend on the age, dose, genetic background, mycotoxin type, sex, patients' health status, poisoning duration, etc. [1, 28], some of which also would influence the absorption of the different forms of the mycotoxins [26, 182]. In the human body, the mycotoxins undergo detoxification and might form deposits in some bother tissues and organs, such as the liver, kidney, GI tract, etc (Refer to Figure 1). The formed derivatives of mycotoxins particularly in humans and animals may exert a number of pathological as well as physiological effects. As stated in previous sections, many mycotoxins exert hepatotoxic, nephrotoxic, carcinogenic, cytotoxic, teratogenic, genotoxic, immunotoxic actions, and can also affect the development of tumor because of their antineoplastic potentials [183]. The levels of mycotoxins in blood and urine can be measured, but with no information on intake ratio, it will be difficult to accurately interpret [184]. Although data have been reported about large outbreaks of mycotoxins in different parts of the world, especially in tropical and subtropical regions, the connection between the severity of symptoms and the levels of mycotoxins is difficult to ascertain [10, 11, and 184]. Some affected individuals without detectable levels of mycotoxins presented symptoms. Affected individuals that had same urine concentrations of mycotoxins presented different symptoms and clinical signs [11, 184 and 185].

Mycotoxicosis can be chronic or acute, just like most other poisonings. Chronic poisoning of mycotoxins is a problem worldwide, with higher incidence compared to acute mycotoxin poisoning, although chronic mycotoxicoses have been poorly documented. Chronic mycotoxin poisoning is often due to prolonged exposure in low doses for long period of time, which may lead to irreversible effects, e.g. neoplastic diseases, liver damage, kidney impairment, teratogenicity, etc. [72, 77]. A number of factors can also influence on the mycotoxin's chronic toxicity or the manifestation of first

perceptible symptoms. Examples of such factors include the exposure route, dosage, type of mycotoxin, and health status of affected individuals. In chronic poisoning, the symptoms appear rather slowly, and would not necessarily point to a particular disease. In acute poisoning of mycotoxins, the symptoms would be more rapid, and expressed with more specific toxic-related symptoms, like damaged enterocytes, diarrhea, gastrointestinal discomfort, general fatigue and malaise, immunosuppression, etc. Acute mycotoxin poisoning occurs when excessive levels of mycotoxins are consumed within a short time, and may lead to death in severe cases. The most common symptoms of acute mycotoxin poisoning include acute hepatitis, liver impairment, kidney disfunction, etc. The types of symptoms mostly depend on the type of mycotoxins involved. The occurrence of hepatitis due to mycotoxins can be increased by several factors, such as Kwashiorkor, viral hepatitis infections, etc. [78, 186]. Additionally, other hepatotoxic factors, including alcohol use, heavy metals, drug use, etc., may increase the risk of hepatitis [78].

Mycotoxin toxicities mitigation/removal strategies

Options for treating mycotoxin poisoning appear somewhat limited. Given this, various workers [171, 187, and 188] have considered preventing fungal entrance and mycotoxin production in the food and feed chain as the best approach. Despite prevention approach being theoretically probable, it is practically improbable to totally prevent the fungal presence and mycotoxin production in foods and feeds. The aim should, therefore, be to prevent the presence of fungi and mycotoxins, which will significantly reduce their occurrence and outbreaks [189].

We note that fungal presence may not necessarily imply mycotoxin production. This is because the conditions required for fungal growth differ from those of mycotoxin production. Preventing the fungal presence and mycotoxin production in agrofood products remains advantageous given the public health and economic benefits [190]. A number of novel nanotechnological approaches have been developed to help detect and control mycotoxins. To elaborate on this, novel DNA aptamer-based bio-sensing for mycotoxins in foods and feeds using nanotechnology approaches can be seen in Figure 3. Whilst such novel nanotechnological approaches might not be easily affordable especially by small-scale agrofood enterprises, their acquisition need to be encouraged given the accuracy of detection as well as specificities. These nanotechnologies can be widely applied in controlling mycotoxins [8]. The essence of detecting as well as controlling mycotoxins is underpinned from that fact that mycotoxigenic fungi can enter foods/feeds at several stages [182], especially before harvest and during storage. The complexation of some factors such as production, mycotoxins stability, poor farming practices, climate change, co-occurrence of mycotoxins, etc., make it more challenging to establish comprehensive secure protocols for holistic prevention, international pipeline, and sampling methods [7, 191and 192]. The wide range of mitigation as well as prevention methods able to influence fungal presence and mycotoxins production largely involve pre- and post-harvest measures, even though some measures occur during the harvest process itself. For emphasis, a schematic flow of the mycotoxins mitigation/removal strategies, involving both pre- and post-harvest measures is depicted in Figure 4, which would be deliberated upon subsequently.

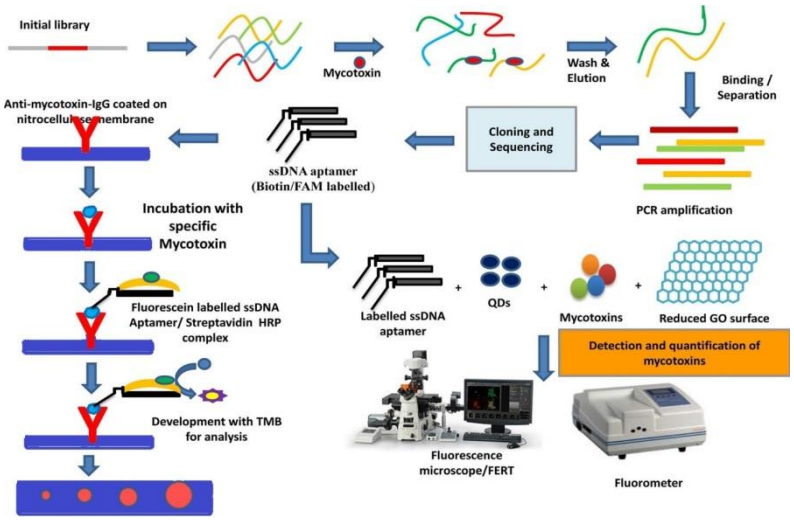

Figure 3. Novel DNA aptamer-based bio-sensing for mycotoxins in foods and feeds using nanotechnology approaches (Adapted from [8]).

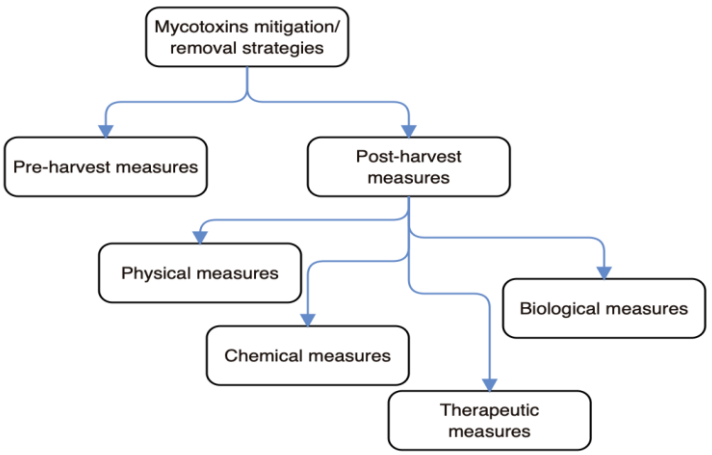

Figure 4. Schematic flow of the mycotoxins mitigation/removal strategies, involving pre- and post-harvest measures.

Pre-harvest measures

Pre-harvesting measures involve crop production, growing conditions, and preventing fungal entrance/growth in crops [193, 194, and 195]. Preventing fungal infestation, limiting/preventing fungi spread across plants, and removing mycotoxins already present before harvest remain promising preharvest control measures. Atoxigenic and competitive fungal species would supersede mycotoxigenic fungal species, making it useful biocontrol candidates for mycotoxins [196]. Monoculture farming at large scale is highly susceptible to fungal colonization. Cultivating a wide range of crops with different dates of harvest on reduced areas may help reduce the risks of fungal colonization; There are could be potentials to reduce the production of mycotoxin even when there is presence of fungi [197]. Crops co-cultivation with genetically engineered organisms, including microorganisms and plants, may alter mycotoxins chemical structure by changing the metabolic pathways as one of the defense mechanisms [194]. Vitamin C (ascorbic acid) regulates genes for mycotoxin

production, and consequently inhibits the expression of the involved enzymes [198]. With modern farming methods such as optimizing environmental conditions to prevent fungal contamination of crops and with polyculture farming, the toxic and economic effects of the fungal occurrence in crops and consequent mycotoxins production can be reduced [199]. Extensive crop examination prior to harvest should precede any other measures [15]. Infected fields should be disinfected using measures such as instant harvesting and disposal of affected crops to stop further spreads.

Post-harvest measures

Fungal proliferation and mycotoxin production remains of high risk in foods and feeds after harvest, and influential post-harvest conditions could include transporting circumstances, methods and criteria of harvest, environmental conditions, sampling methods, climate change, storage conditions pre- and post-processing, inspection protocol, international and national regulations/pipelines, nature of storage facilities, etc. [200]. The post-harvest measures can involve physical, chemical, biological and/or therapeutic approaches.

Physical measures

Sorting and grading before crop storage is critical, as in large scale storage, fungi can spread more rapidly within the different commodities [201, 202]. Further, the storage building cleanliness is also essential in control mycotoxin production [203, 204]. If storage conditions like temperature, humidity, water activity, etc., are not selected properly, the fungal growth and mycotoxin production can rise. Therefore, to prevent fungal growth or at least reduce the growth rate, crops have to be well-dried prior to storage. If fungal infection and mycotoxin production have already taken place before or after harvest, there levels can still be reduced to zero or at least lessen the effects of the toxins [16, 205]. Although mycotoxins are heat stable even in temperature range of 150 to 200°C, their levels can be significantly reduced using heat treatment [7, 189, and 206]. However, the duration of heating, as well as heat temperature should be conducted carefully, so as to avoid destroying the bioactive constituents/nutrients of the food/feed. Due to the heat stability of mycotoxins and thermal sensitivity of most nutrients and bioactive compounds, use of heating for decontamination of mycotoxins should be done carefully. In normal conditions, the effectiveness of mycotoxin decontamination may be low due to most mycotoxins are resistant to heat, especially within the temperature range of 60 to 121oC usually used in food processing [207]. Ionized radiation can be applied in decontamination of mycotoxins [208, 209]. While irradiation is among the good methods used to reduce the level of mycotoxins, its wide application is limited, especially in rural and underdeveloped regions where there is little or no access to the facilities required for this purpose. However, portable machines for irradiation of foods are available and accessible, although their usage is limited by the problems of funding and required operational expertise [210]. Irradiation might present a safe and reliable alternative for mycotoxins decontamination. Irradiation may lead to generation of radiolytic mycotoxins from foods with high levels of mycotoxins [210, 211, 212]. Although the radiolytes have significant fewer effects on humans, however, more studies are required [210, 211 and 212]. Other physical measures include removal of affected parts, microwave heating, grading, baking, peeling, extrusion, cleaning, washing, roasting, boiling, segregation, use of mycotoxin binders (e.g. bentonite clay, montmorillonite, etc.), drying, cold plasma, etc.

Chemical measures

Some chemicals can change mycotoxins properties and reduce their physiological activities and potencies. The chemicals are commonly used because most of them,

such as formic, acetic, succinic, hydrochloric, tartaric, lactic, citric, and propionic acids, are usually used food industries [213, 214]. Chemical treatment can result in mycotoxins conversion into less toxic substances. Ozonation can also be considered as a chemical treatment. Ozone treatment can also be used to effectively and reliably detoxify contaminants such as mycotoxins. In ozonation, there is generation of oxygen radicals via splitting of the molecules of reactive ozone, which would then pose detoxifying effects on several contaminants [7, 8]. Ozone can be applied in liquid or gas form. One of the downsides of ozonation is that the ranges within which the radicals are effective are short, and, as a result, do not deeply penetrate into the substances under treatment. Chemical treatments can include ammonization, acidification, etc. [215]. Other chemicals such as chitosan, ammonia, hydrated oxide, calcium hydroxide, glycerol, sodium hydroxide, potassium hydroxide, etc. can be applied for decontamination of mycotoxins [7]. Some chemical measures may result in the formation of unwanted chemical substances. Consequently, care should be taken in using any chemicals for mycotoxins decontamination.

Biological measures

Biological methods can be employed to control mycotoxins in foods and feeds [216, 217, and 218]. Biological measures have been considered among the most effective preventive strategies with some methods presenting promising results. The biological protocols make use of various biocontrol agents (BCAs) that have the ability to modulate mycotoxin decontaminations in several ways. The BCAs can be microorganisms such as atoxigenic and highly competitive fungi that can outcompete mycotoxigenic fungi, thereby preventing the production of mycotoxins. One way of doing this is to inoculate different microorganisms such as the species of Saccharomyces and *Lactobacillus* into the food contaminated with mycotoxigenic fungi [219]. Additionally, yeasts application in several food handling processes can direct inhibitory effects on production mycotoxins from some molds [197]. Genetically modified biocontrol agents can produce various compounds, such as ascorbic acid, that can silence gene clusters that regulate the production of mycotoxins. Enzymes isolated from several species of *Bacillus* showed promising high effectiveness. Plant extracts and their many enzymes may be effective as BCAs. Lactic acid bacteria (LAB), *Micrococcus luteus*, *Bacillus subtilis*, *Bifidobacterium* species, *Saccharomyces cerevisiae*, *Aspergillus parasiticus*, *Flavobacterium aurantiacum*, *Nocardia corynebacterioides*, *Saccharomyces cerevisiae*, *Enterococcus faecium*, *Mycobacterium fluoranthenivorans*, *Lactobacillus rhamnosus*, etc. are among the microorganisms reported for use in mycotoxin control. Fermentation, some fungi (e.g. species of *Penicillium*, *Clonostachys*, *Trichoderma*, *Rhizopus*, *Aspergillus*, etc.), and some bacteria (e.g., *Mycobacterium fluoranthenivorans*, *Nocardia asteroides*, *Rhodococcus erythropolis*, *Flavobacterium aurantiacum*, *Devosia* species, *Lactobacillus reuteri*, *Lactobacillus casei*, *Lactobacillus rhamnosus*, *Lactobacillus amylovorus*, *Lactobacillus fermentum*), have efficient capabilities for mycotoxins detoxification. In general, combining different methods can reliably reduce the levels of mycotoxins in contaminated foods and feeds [189].

Therapeutic measures

Mycotoxicoses are serious threat to public health, and while setting suitable differential diagnosis is fairly challenging, their symptoms can be treated. In the acute poisoning of mycotoxins, the exposure source can be recognized easily as the contaminated foods are analyzed to identify the specific mycotoxin. Besides effective and specific treatments for the all mycotoxicoses not yet fully established [220], the treatment of acute mycotoxin poisonings somewhat dependent on the symptoms, which

appears not always sufficient. To aid the natural body detoxification mechanism, the discontinuation of the mycotoxin exposure and the consumption of suitable nutritious diet may better reduce these symptoms more than any medical or surgical procedure. The glutathione system boosting can aid in mycotoxin detoxification in the body. Since the liver detoxification capacity varies according to the factors such as sex, age, etc., to boost this detoxification mechanism alone would not be sufficient in the mycotoxins neutralization. Additional substances, such as Vitamins C, D, and E, as well as Q10 with zinc, butylated hydroxytoluene (BHT), butylated hydroxy anisole (BHA), etc., can aid in preventing the toxic effects ROS generated by some mycotoxins. However, the effects of these compounds are non-specific, and their action mechanisms are mainly based on free radicals' reduction [220, 221]. Supplementary therapeutic procedures, such as dialysis, can aid to protect affected organs, including the liver, kidney, bone marrow, etc. Sequestering agents, which are non-absorbable substances, can bind to mycotoxins in the gastrointestinal tract and neutralize them [14]. The sequestering agents possess large surface–volume ratio, and with large absorption capacity. The activated carbon has been used for this purpose in food and water treatment. For adults, intake of 3 g/day of activated carbon is safe; for children, a study reported that 0.75 g per day is safe [172, 220]. An anion exchange resin called cholestyramine (CSM) acts as sequestering agent for bile and can decrease the fat-soluble mycotoxins' enterohepatic recirculation. Studies indicated that cholestyramine has very higher affinity to ochratoxin A compared with bile salts, and several studies on CSM used animal models and reported reduction in urine and plasma levels of ochratoxin A, with increased secretion of ochratoxin A via feces [220].

Conclusion and future outlooks

Since humans occupy the top position in the food chain, their exposure to mycotoxins and its corresponding toxicities that largely depends on animal consumption as well as feed contamination, the dynamic nature of the global food production and safety systems, added to the unintentional consumers' exposures to mycotoxins, makes vital the continuous synthesis of relevant literatures of this subject matter. In our opinion, this perspective review has improved our understanding regarding the importance of mycotoxin toxicities from the consumer environmental health standpoint, and we are convinced it is very relevant for the various stakeholders of the food supply chain. Specifically, our conviction is drawn from the useful information about mycotoxins' toxicology, consumer safety concerns, as well as its associated action mechanisms, which we have synthesised in this work. Noteworthy to mention is the toxic effects of combined mycotoxins exposure, as well as major mycotoxin effects on infants and children. Also, very crucial to consider as relevant by the stakeholders within the food supply chain include the understanding the complications/risks associated with mycotoxin exposures at various stages of human life, together with the consumer environmental health implications of mycotoxin exposure. Importantly, the information about mycotoxin toxicities prevention strategies, from pre- to post-harvest measures also contribute to the discourse of this global public health issue.

Clearly, tackling the mycotoxins toxicities within the agrofood supply chain requires preventing fungal infestation, as well as limiting/preventing its spread across livestock and plant products. More effort is warranted especially on the implementation of more robust analytical methods to help better the determinations of mycotoxins toxicities across/along the food supply chain, and at various parts of the globe. For stakeholders of the food supply chain to better understand the pattern of mycotoxins toxicities'

occurrence and spread, there is the urgent need to have them vigorously engaged. On one hand, the food supply chain stakeholders need to understand the analytical detection/outcomes of mycotoxins toxicities and its challenges/implications, and how it (mycotoxins toxicities) impacts on the consumers' environment and health, particularly in the context of food and feed products. For emphasis, the use of analytical detection instruments largely operate at microscopic/spectroscopic levels are usually combined with robust specialist facilities [222]. Given that such robust analytical detection instruments/techniques are usually expensive, there is need for increased government involvement in leading the tackling of the challenges of mycotoxins toxicities. On the other hand, there is need for increased food quality safety standards, and proper implementation of good practices as well as compulsory aspects of quality management that are relevant to the agro-food industry [223], which would contribute to reduce mycotoxins infestation together with the associated health issues. Besides, more robust review synthesis especially at the level of meta-analysis are required , which could include, among others, elaboration of consumer environmental health safety issues associated with mycotoxins toxicities across regions within a country, as well as countries within a continent, in the view to provide a more robust global perspective. Concerted efforts to solve the mycotoxins toxicities are warranted, which should help to deduce more lasting and sustainable ways of preventing fungal invasion and mycotoxins production in the food and feed value chain.

Author contribution

Author C.G. Awuchi conceptualised, developed the initial draft of the manuscript, with the help of authors S. Nwozo, M. Salihu, and G.A. Odongo. The validation, visualisation and revision of the manuscript was performed by authors M. Sarvarian, and C.O.R. Okpala. All authors contributed to the intellectual content and agreed to the final submitted version.

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Conflict of interest

The authors hereby declare that there is no conflict of interest associated with this work.

REFERENCES

1. Keller N. P., 2019. Fungal secondary metabolism: regulation, function and drug discovery. Nat Rev Microbiol. 17, 167–180.

2. Medina A., Gilbert M.K., Mack B.M., OBrian G.R., Rodríguez A., Bhatnagar D., 2017. Interactions between water activity and temperature on the *Aspergillus flavus* transcriptome and aflatoxin B1 production. Int J Food Microbiol. 256, 36–44.

3. Van der Fels-Klerx H.J., Camenzuli L., 2016. Effects of milk yield, feed composition, and feed contamination with aflatoxin B1 on the aflatoxin M1 concentration in dairy cows' milk investigated using Monte Carlo simulation modelling. Toxins. 8, 290.

4. Hymery N., Vasseur V., Coton M., Mounier J., Jany J.L., Barbier G., 2014. Filamentous fungi and mycotoxins in cheese: a review. Compr Rev Food Sci Food Saf. 13, 437–456.

5. Rohlfs M., 2015. Fungal secondary metabolite dynamics in fungus-grazer interactions: novel insights and unanswered questions. Front Microbiol. 6,788.

6. Ráduly Z., Szabó L., Madar A., Pócsi I., Csernoch L., 2020. Toxicological and Medical Aspects of *Aspergillus*-Derived Mycotoxins Entering the Feed and Food Chain. Front Microbiol. 10, 2908.

7. Awuchi C.G., Ondari E.N., Ogbonna C.U., Upadhyay A.K., Baran K., Okpala C.O.R., 2021. Mycotoxins

Affecting Animals, Foods, Humans, and Plants: Types, Occurrence, Toxicities, Action Mechanisms, Prevention, and Detoxification Strategies—A Revisit. Foods. 2021, 10, 1279.

8. Navale V., Vamkudoth K.R., Ajmera S., Dhuri V., 2021. *Aspergillus* derived mycotoxins in food and the environment: Prevalence, detection, and toxicity. Toxicol Rep. 8, 1008–1030.

9. Rushing B.R., Selim M.I., 2019. Aflatoxin B1: a review on metabolism, toxicity, occurrence in food, occupational exposure, and detoxification methods. Food Chem Toxicol. 124, 81–100.

10. Udovicki B., Audenaer K., De Saeger S., Rajkovic A., 2018. Overview on the Mycotoxins incidence in Serbia in the period 2004-2016. Toxins. 10, 279.

11. Smith M.C., Madec S., Coton E., Hymery N., 2016. Natural Co-Occurrence of mycotoxins in foods and feeds and their in vitro combined toxicological effects. Toxins. 8, 94.

12. Souers A.J., Leverson J.D., Boghaert E.R., Ackler S.L., Catron N.D., Chen J., 2013. ABT-199, a potent and selective BCL-2 inhibitor, achieves antitumor activity while sparing platelets. Nat Med. 19, 202–208.

13. Rodrigues I., Handl J., Binder E.M., 2011. Mycotoxin occurrence in commodities, feeds and feed ingredients sourced in the middle east and Africa. Food Addit Contam Part B Surveill. 4, 168–179.

14. Jard G., Liboz T., Mathieu F., Guyonvarc'h A., Lebrihi A., 2011. Review of mycotoxin reduction in food and feed: from prevention in the field to detoxification by adsorption or transformation. Food Addit Contam Part A Chem Anal Control Expo Risk Assess. 28, 1590–1609.

15. Cleveland T., Dowd P.F., Desjardins A.E., Bhatnagar D., Cotty P., 2003. United States Department of Agriculture-Agricultural Research Service research on pre-harvest prevention of mycotoxins and mycotoxigenic fungi in U.S. crops. Pest Manag Sci. 59, 629–642.

16. Omotayo O.P., Omotayo A.O., Mwanza M., Babalola O.O., 2019. Prevalence of mycotoxins and their consequences on human health. Toxicol Res. 35, 1–7.

17. Battilani P., Toscano P., Van der Fels-Klerx H.J., Moretti A., Camardo Leggieri M., Brera C., 2016. Aflatoxin B1 contamination in maize in Europe increases due to climate change. Sci Rep. 6, 24328.

18. Gruber-Dorninger C., Jenkins T., Schatzmayr G., 2019. Global mycotoxin occurrence in feed: A ten-year survey. Toxins. 11, E375.

19. Franco L.T., Ismail A., Amjad A., de Oliveira C.A.F., 2021. Occurrence of toxigenic fungi and mycotoxins in workplaces and human biomonitoring of mycotoxins in exposed workers: a systematic review. Toxins Rev. 40(4), 576-591.

20. da Silva J.V.B., de Oliveira C.A.F., Ramalho L.N.Z., 2021. An overview of mycotoxins, their pathogenic effects, foods where they are found and their diagnostic biomarkers. Food Sci Technol. (In-press), https://doi.org/10.1590/fst.48520.

21. Cimbalo A., Alonso-Garrido M., Font G., Manyes L., 2020. Toxicity of mycotoxins in vivo on vertebrate organisms: A review. Food Chem Toxicol. 137, 111161.

22. Zhang Z., Nie D., Fan K., Yang J., Guo W., Meng J., Zhao Z., Han Z., 2020. A systematic review of plant-conjugated masked mycotoxins: Occurrence, toxicology, and metabolism. Crit Rev Food Sci Nutr. 60(9), 1523-1537.

23. Imran M., Cao S., Wan S., Chen Z., Saleemi M.K., Wang N., Naseem M.N., Munawar J., 2020. Mycotoxins - A Global One Health Concern: A Review, Agrobiological Record. 2, 1-16.

24. Adeyeye S.A.O., 2020. Aflatoxigenic fungi and mycotoxins in food: a review, Crit. Rev. Food Sci Nutr. 60(5), 709-721

25. Adegbeye M.J., Reddy P.R.K., Chilaka C.A., Balogun O.B., Elghandour M.M.M.Y., Rivas-Caceres R.R., Salem A.Z.M., 2020. Mycotoxin toxicity and residue in animal products: Prevalence, consumer exposure and reduction strategies – A review, Toxicon. 177, 96-108.

26. Dellafiora L., Dall'Asta C., Galaverna G., Dellafiora L., Dall'Asta C., Galaverna G., 2018. Toxicodynamics of

mycotoxins in the framework of food risk assessment-an in silico perspective. Toxins. 10, 52.

27. Shaw C.I., 2014. Chemical residues, food additives and natural toxicants in food – the cocktail effect. Int J Food Sci Technol. 49, 2149–2157.

28. Marroquín-Cardona A.G., Johnson N.M., Phillips T.D., Hayes A.W., 2014. Mycotoxins in a changing global environment – A review. Food Chem Toxicol. 69, 220–230.

29. Vanhoutte I., Audenaert K., De Gelder L., 2016. Biodegradation of mycotoxins: tales from known and unexplored worlds. Front Microbiol. 7, 561.

30. Heussner A., Bingle L., Heussner A.H., Bingle L.E.H., 2015. Comparative ochratoxin toxicity: a review of the available data. Toxins. 7, 4253–4282.

31. Bui-Klimke T.R., Wu F., 2015. Ochratoxin a and human health risk: a review of the evidence. Crit Rev Food Sci Nutr. 55, 1860–1869.

32. Saeger S.D., Logrieco A., 2017. In: Belgium, Toxins Report from the 1st Mycokey International Conference Global Mycotoxin Reduction in the Food and Feed Chain Held in Ghent. 9, pp.276.

33. Reddy P., Guthridge K., Vassiliadis S., Hemsworth J., Hettiarachchige I., Spangenberg G., Rochfort S., 2019. Tremorgenic mycotoxins: structure diversity and biological activity. Toxins. 11, 302.

34. Nouri M.A., Al-Halbosiy M.M., Dheeb B.I., Hashim A.J., 2015. Cytotoxicity and genotoxicity of Gliotoxin on human lymphocytes in vitro, J King Saud Univ Sci. 27, 193–197.

35. Patel R., Hossain A., German N., Alahmad A., 2018. Gliotoxin penetrates and impairs the integrity of the human blood-brain barrier in vitro. Mycotoxin Res. 34, 257–268.

36. Doughari J.H., 2015. The occurrence, properties and significance of citrinin mycotoxin, J Plant Pathol Microbiol. 6, 1–6.

37. Gayathri L., Dhivya R., Dhanasekaran D., Periasamy V.S., Alshatw A.A., Akbarsha M.A., 2015. Hepatotoxic effect of ochratoxin a and Citrinin, alone and in combination, and protective effect of vitamin e: in vitro study in HepG2 cell, Food Chem Toxicol. 83, 151–163.

38. Barnett L.M.A., Cummings B.S., 2018. Nephrotoxicity and renal pathophysiology: a contemporary perspective, Toxicol Sci. 164, 379–390.

39. Romero Bernal Á.R., Reynoso C.M., García Londoño V.A., Broggi L.E., Resnik S.L., 2019. Alternaria toxins in Argentinean wheat, bran, and flour. Food Addit Contam Part B Surveill. 12, 24–30.

40. Nair M.G., 2017. Fumonisins and human health. Ann Trop Paediatr. 18, S47–S52.

41. Kouzi S.A., Wright N.J.D., Dirks-Naylor A., Uddin M.N., 2018. Fumonisins: effects on human and animal health and mechanisms of toxicity. EC Pharmacol Toxicol. 6, 187–208.

42. EFSA (2013). Scientific opinion on the risk for public and animal health related to the presence of sterigmatocystin in food and feed. EFSA J. 11, 3254.

43. Díaz C.H., Granero A.M., Zon M A., Fernández H., 2018. Sterigmatocystin: a mycotoxin to be seriously considered. Food Chem Toxicol. 118, 460–470.

44. Yoshinari T., Suzuki Y., Sugita-Konishi Y., Ohnishi T., Terajima J., 2016. Occurrence of beauvericin and enniatins in wheat flour and corn grits on the Japanese market, and their co-contamination with type B trichothecene mycotoxins. Food Addit Contam Part A Chem Anal Cont Expo Risk Assess. 33, 1620–1626.

45. Sadiq F.A., Yan B., Tian F., Zhao J., Zhang H., Chen W., 2019. Lactic Acid Bacteria as Antifungal and Anti-Mycotoxigenic Agents: A Comprehensive Review. Compr Rev Food Sci Food Saf. 18, 1403–1436.

46. Pal S., Singh N., Ansari K. M., 2017. Toxicological effects of patulin mycotoxin on the mammalian system: an overview. Toxicol Res. 6, 764–771.

47. Vidal A., Ouhibi S., Ghali R., Hedhili A., De Saeger S., De Boevre M., 2019. The mycotoxin patulin: An updated short review on occurrence, toxicity and analytical challenges. Food Chem Toxicol. 129, 249–256.

48. Wezeman T., Bräse S., Masters K.S., 2015. Xanthone Dimers: A Compound Family which is both common and privileged. Nat Prod Rep. 32, 1–104.

49. Demasi M., Felicio A.L., Pacheco A.O., Leite H., Lima C., Andrade L.H., 2010. Studies on terrein as a new class of proteasome inhibitors. J Braz Chem Soc. 21, 299–305.

50. Asfour H.Z., Awan Z.A., Bagalagel A.A., Elfaky M.A., Abdelhameed R.F.A., Elhady S.S., 2019. Large-Scale Production of Bioactive Terrein by Aspergillus terreus Strain S020 Isolated from the Saudi Coast of the Red Sea. Biomolecules. 9(9), 480.

51. Ostry V., Toman, J., Grosse Y., Malir F., 2018. Cyclopiazonic acid: 50th anniversary of its discovery, World Mycotoxin J. 11, 135–148.

52. Okoth S., Boevre M.D., Vidal A., Mavungu J.D.D., Landschoot S., Kyallo M., Njuguna J., Harvey J., De Saeger S., 2018. Genetic and toxigenic variability within Aspergillus flavus population isolated from maize in two diverse environments in Kenya. Front Microbiol. 9, 57.

53. Sobrova P., Adam V., Vasatkova A., Beklova M., Zeman L., Kizek R., 2010. Deoxynivalenol and its toxicity. Interdisciplinary Toxicol. 3, 94–99.

54. Danicke S., Winkler J., 2015. Invited review: diagnosis of zearalenone (ZEN) exposure of farm animals and transfer of its residues into edible tissues (carry over). Food Chem Toxicol. 84, 225–249.

55. Robinson S.L., Panaccione D.G., 2015. Diversification of ergot alkaloids in natural and modified fungi. Toxins. 7, 201–218.

56. Eriksen G.S., Jaderlund K.H., Moldes-Anaya A., Schonheit J., Bernhoft A., Jaeger G., Rundberget T., Skaar I., 2010. Poisoning of dogs with tremorgenic Penicillium toxins. Med Mycol. 48, 188–196.

57. Vettorazzi A., López de Cerain A., 2016. Chapter 17-Mycotoxins as Food Carcinogens. Environmental Mycology in Public Health. pp. 261–298.

58. Wu F., Stacy S.L., Kensler T.W., 2013. Global risk assessment of aflatoxins in maize and peanuts: are regulatory standards adequately protective? Toxicol Sci. 135, 251–259.

59. Awuchi C.G., Amagwula I.O., Priya P., Kumar R., Yezdani U., Khan M.G., 2020. Aflatoxins in foods and feeds: A review on health implications, detection, and control. Bull Environ Pharmacol Life Sci. 9(9), 149-155.

60. Cherkani-Hassani A., Mojemmi B., Mouane N., 2016. Occurrence and levels of mycotoxins and their metabolites in human breast milk associated to dietary habits and other factors: a systematic literature review, 1984–2015. Trends Food Sci Technol. 50, 56–69.

61. Benkerroum N., 2016. Mycotoxins in dairy products: a review. Int. Dairy J. 62, 63–75.

62. Alshannaq A., Yu J.H., Alshannaq A., Yu J.H., 2017. Occurrence, toxicity, and analysis of major mycotoxins in food. Int J Environ Res Public Health. 14, E632.

63. Dellafiora L., Dall'Asta C., 2017. Forthcoming challenges in mycotoxins toxicology research for safer Food-A need for multi-omics approach. Toxins. 9, E18.

64. Flores M., González-Peñas E., 2016. An LC-MS/MS method for multi- mycotoxin quantification in cow milk. Food Chem. 218, 378–385.

65. International Agency for Research on Cancer, 2012. Aflatoxins IARC Monographs. Int Agency Res Cancer 100, 225–248.

66. Wild C.P., Gong Y.Y., 2009. Mycotoxins and human disease: a largely ignored global health issue. Carcinogenesis. 31, 71–82.

67. Ostry V., Malir F., Toman J., Grosse, Y., 2017. Mycotoxins as human carcinogens-the IARC Monographs classification. Mycotoxin Res. 33, 65–73.

68. Dumenco L., Oguey D., Wu J., Messier N., Fausto N., 1995. Introduction of a murine p53 mutation corresponding to human codon 249 into a murine hepatocyte cell line results in growth advantage, but not in transformation. Hepatology. 22, 1279–1288.

69. Rotimi O., Rotimi S., Uchechukwu Duru C., Ebebeinwe O., Obhio Abiodun A., Oluwamayowa Oyeniyi B., 2017. Acute aflatoxin B1 – Induced hepatotoxicity alters gene expression and disrupts lipid

and lipoprotein metabolism in rats. Toxicol Rep. 4, 408–414.

70. Hamid A.S., Tesfamariam S.G., Zhang Y., Zhang Z.G., 2013. Aflatoxin B1-induced hepatocellular carcinoma in developing countries: Geographical distribution, mechanism of action and prevention (Review). Oncol Lett. 5, 1087–1092.

71. Nurul Adilah Z., Liew W.P.P., Mohd Redzwan S., Amin I., 2018. Effect of high protein diet and probiotic lactobacillus casei shirota supplementation in aflatoxin B(1)-Induced rats. BioMed Res Int. 2018, 9568351.

72. Magnussen A., Parsi M.A., 2013. Aflatoxins, hepatocellular carcinoma and public health. World J Gastroenterol. 19, 1508–1512.

73. Dharumadurai D., Shanmugapriya S., Thajuddin N., Annamalai P., 2011. "Aflatoxins and Aflatoxicosis in Human and Animals," in Aflatoxins - Biochemistry and Molecular Biology, ed. R. G. Guevara-Gonzalez, (Rijeka: Intech Open Access publishers), pp 285–304.

74. Benedict K., Chiller T.M., Mody R.K., 2016. Invasive fungal infections acquired from contaminated food or nutritional supplements: a review of the literature. Foodborne Pathog Dis. 13, 343–349.

75. Khlangwiset P., Shephard G., Wu F., 2011. Aflatoxins and growth impairment: a review. Crit Rev Toxicol. 41, 740–755.

76. Liew W.P.P., Mohd-Redzwan S., 2018. Mycotoxin: its impact on gut health and microbiota. Front Cell Infect Microbiol. 8, 60.

77.Wu H.C., Santella R., 2012. The role of aflatoxins in hepatocellular carcinoma. Hepatitis Monthly. 12, e7238–e7238.

78. Saha N., Wu F., 2019. Risk assessment of aflatoxin-related liver cancer in Bangladesh. Food Addit Contam Part A Chem Anal Cont Expo Risk Assess. 36, 320–326.

79. Awuchi C.G., Owuamanam I.C., Ogueke C.C., Hannington T., 2020. The Impacts of Mycotoxins on the Proximate Composition and Functional Properties of Grains. Eur Acad Res. 8(2), 1024-1071.

80. Ostry V., Malir F., Ruprich J., 2013. Producers and important dietary sources of ochratoxin a and citrinin, Toxins 5(9), 1574–1586.

81. Zhu L., Zhang B., Dai Y., Li H., Xu W., Zhu L., 2017. A review: epigenetic mechanism in ochratoxin a toxicity studies. Toxins. 9, 113.

82. Pfohl-Leszkowicz A., Manderville R.A., 2007. Ochratoxin a: an overview on toxicity and carcinogenicity in animals and humans. Mol Nutr Food Res. 51, 61–99.

83. Reddy L., Bhoola K., Reddy L., Bhoola K., 2010. Ochratoxins-food contaminants: impact on human health. Toxins. 2(4), 771–779.

84. Malir F., Ostry V., Pfohl-Leszkowicz A., Malir J., Toman J., 2016. Ochratoxin A: 50 years of research. Toxins. 8, E191.

85. Barikbin B., Allahresani A., Khosravi R., Khodadadi M., 2015. Detection of aflatoxin M1 in dairy products marketed in Iran, Health Scope: International Quarterly J. 4(1), e18925.

86. Calvo A.M., Cary J.W., 2015. Association of fungal secondary metabolism and sclerotial biology. Front Microbiol. 6, 62.

87. Kozák L., Szilágyi Z., Tóth L., Pócsi I., Molnár I., 2019. Tremorgenic and neurotoxic paspaline-derived indole-diterpenes: biosynthetic diversity, threats and applications. Appl Microbiol Biotechnol. 103, 1599–1616.

88. Gardiner D.M., Cozijnsen A.J., Wilson L.M., Pedras M.S.C., Howlett B.J., 2004. The sirodesmin biosynthetic gene cluster of the plant pathogenic fungus leptosphaeriamaculans, Mol Microbiol. 53, 1307–1318.

89. Gardiner D.M., Howlett B.J., 2005. Bioinformatics and expression analysis of the putative gliotoxin biosynthetic gene cluster of Aspergillus fumigatus, FEMS Microbiol Lett. 248, 241–248.

90. Lewis R.E., Wiederhold N.P., Chi J., Han X.Y., Komanduri K.V., Kontoyiannis D.P., 2005. Detection of gliotoxin in experimental and human aspergillosis. Infect Immun. 73, 635–637.

91. Samson R., Peterson S., Frisvad J., Varga J., 2011. New species in *Aspergillus* section terrei, Stud Mycol. 69, 39–55.

92. Culig B., Berardi M., Bosnir J., Serdar S., Lasic D., Racs A., Galic A., 2017. Presence of Citrinin in grains and its possible health effects. Afr J Tradit Complement Altern Med. 14, 22–30.

93. Logrieco A., Moretti A., Solfrizzo M., 2009. *Alternaria* toxins and plant diseases: An overview of origin, occurrence and risks. World Mycotoxin J. 2, 129–140.

94. Sivagnanam K., Komatsu E., Rampitsch C., Perreault H., Gräfenhan T., 2017. Rapid screening of *Alternaria* mycotoxins using MALDI-TOF mass spectrometry. J Sci Food Agric. 97, 357–361.

95. European Food Safety Authority, 2011. Scientific Opinion on the risks for animal and public health related to the presence of *Alternaria* toxins in feed and food. EFSA J. 10, 2407.

96. Zwickel T., Klaffke H., Richards K., Rychlik M., 2016. Development of a high performance liquid chromatography tandem mass spectrometry based analysis for the simultaneous quantification of various *Alternaria* toxins in wine, vegetable juices and fruit juices. J Chromatogr A. 2016, 1455, 74–85.

97. Agriopoulou S., Stamatelopoulou E., Varzakas T., 2020. Advances in Occurrence, Importance, and Mycotoxin Control Strategies: Prevention and Detoxification in Foods. Foods. 9, 137.

98. Sanzani S.M., Gallone T., Garganese F., Caruso A.G., Amenduni M., Ippolito A., 2019. Contamination of fresh and dried tomato by Alternaria toxins in southern Italy. Food Addit Contam Part A Chem Anal Cont Expo Risk Assess. 36, 789–799.

99. Walravens J., Mikula H., Rychlik M., Asamd S., Ediagea E.N., Di Mavungua J.D., Landschoote A.V., 2014. Development and validation of an ultra-high-performance liquid chromatography tandem mass spectrometric method for the simultaneous determination of free and conjugated Alternaria toxins in cereal-based foodstuffs. J Chromatogr A. 1372, 91–101.

100. Mogensen J.M., Nielsen K., Samson R., Frisvad J., Thrane U., 2009. Effect of temperature and water activity on the production of fumonisins by *Aspergillus niger* and different Fusarium species. BMC Microbiol. 9, 281.

101. Månsson M., Klejnstrup M.L., Phipps R.K., Nielsen K.F., Frisvad J.C., Gotfredsen C.H., 2010. Isolation and NMR characterization of fumonisin B2 and a new fumonisin b6 from *Aspergillus niger*. J Agric Food Chem. 58, 949–953.

102. Gherbawy Y., Elhariry H., Kocsubé S., Bahobial A., Deeb B., El Altalhi A., 2015. Molecular characterization of black *Aspergillus* Species from Onion and their potential for ochratoxin A and Fumonisin B2 Production. Foodborne Pathog Dis. 12, 414–423.

103. Varga J., Kocsubé S., Szigeti G., Man V., Tóth B., Vágvölgyi C., 2012. Black *Aspergilli* and fumonisin contamination in onions purchased in Hungary. Acta Aliment. 41, 414–423.

104. Logrieco A.F., Haidukowski M., Susca A., Mulè G., Munkvold G.P., Moretti A., 2014. Aspergillus section Nigri as contributor of fumonisin B2 contamination in maize. Food Addit Contam Part A Chem Anal Cont Expo Risk Assess. 31, 149–155.

105. Kamle M., Mahato D.K., Devi S., Lee K.E., Kang S.G., Kumar P., 2019. Fumonisins: impact on agriculture, food, and human health and their management strategies. Toxins. 11, E328.

106. Susca A., Proctor R.H., Butchko R.A.E., Haidukowski M., Stea G., Logrieco A., 2014. Variation in the fumonisin biosynthetic gene cluster in fumonisin-producing and nonproducing black aspergilli. Fungal Genet Biol. 73, 39–52.

107. Logrieco A.F., Ferracane R., Cozzi G., Haidukowsky M., Susca A., Mulè G., 2011. Fumonisin B2 by *Aspergillus niger* in the grape-wine chain: an additional potential mycotoxicological risk. Ann Microbiol. 61, 1–3.

108. Pfeiffer E., Fleck S.C., Metzler M., 2014. Catechol Formation: a novel pathway in the metabolism of sterigmatocystin and 11- Methoxysterigmatocystin. Chem Res Toxicol. 27, 2093–2099.

109. Tong P.Z., Zhang G.J., Zhang X.H., Yan X., Wang J.L., 2013. Effects of sterigmatocystin on esophageal epithelium and experimental reflux esophagitis in rats. Mol Med Rep. 8, 1043–1048.

110. Sant'Ana A.S., Simas R.C., Almeida C.A.A., Cabral E.C., Rauber R.H., Mallmann C.A., 2010. Influence of package, type of apple juice and temperature on the production of patulin by *Byssochlamys nivea* and *Byssochlamys fulva*. Int J Food Microbiol. 142, 156–163.

111. Puel O., Galtier P., Oswald I. P., 2010. Biosynthesis and toxicological effects of patulin. Toxins. 2, 613–631.

112. Frisvad J.C., 2018. A critical review of producers of small lactone mycotoxins: Patulin, penicillic acid and moniliformin. World Mycotoxin J. 11, 73–100.

113. Mahfoud R., Maresca M., Garmy N., Fantini J., 2002. The mycotoxin patulin alters the barrier function of the intestinal epithelium: mechanism of action of the toxin and protective effects of glutathione. Toxicol Appl Pharmacol. 181, 209–218.

114. Awuchi C.G., Owuamanam C.I., Ogueke C.C., Igwe V.S., 2019. Evaluation of Patulin Levels and impacts on the Physical Characteristics of Grains. Int J Adv Acad Res. 5 (4), 10 – 25.

115. Wichmann G., Herbarth O., Lehmann I. 2002. The mycotoxins citrinin, gliotoxin, and patulin affect interferon-γ rather than interleukin-4 production in human blood cells. Environ Toxicol. 17, 211–218.

116. Masters K.S., Bräse S., 2012. Xanthones from Fungi, lichens, and Bacteria: the natural products and their synthesis. Chem Rev. 112, 3717–3776.

117. Zhang W., KrohnK., Ullah Z., Flörke U., Pescitelli G., Di Bari L., Sandor A., 2008. New mono- and dimeric members of the secalonic acid family: blennolides a–g isolated from the fungus *blennoria sp*. Chem Eur J. 14, 4913–4923.

118. Zhai A., Zhu X., Wang X., Chen R., Wang H., 2013. Secalonic acid a protects dopaminergic neurons from 1-methyl-4-phenylpyridinium MPP + -Induced cell death via the mitochondrial apoptotic pathway. Eur J Pharmacol. 71, 58–67.

119. Qin T., Porco J.A., 2014. Total syntheses of secalonic acids a and d. Angewandte Chemie. 126, 3171–3174.

120. Barbero M., Artuso E., Prandi C., 2018. Fungal anticancer metabolites: synthesis towards drug discovery. Curr Med Chem. 25(2), 141-185.

121. Ganapathy D., Reiner J.R., Loeffler L.E., Ma L., Gnanaprakasam B., Niepoetter B., Koehne I., 2015. ChemInform abstract: enantioselective total synthesis of secalonic acid E. Cheminform 47, 15.

122. Flieger M., Stodůlkov´a, E., Wyka, S.A., ˇCerný, J., Grob´arov´a, V., Píchov´a, K., Novak, P., et al., 2019. Ergochromes: heretofore neglected side of ergot toxicity. Toxins. 11(8), 439.

123. Guru S.K., Pathania A.S., Kumar S., Ramesh D., Kumar M., Rana S., Kumar A., 2015. Secalonic Acid-D represses HIF1/VEGF-Mediated angiogenesis by regulating the Akt/mTOR/p70S6K signaling cascade. Cancer Res. 75(14), 2886–2896.

124. Cho H.J., Jung M.J., Woo S., Kim J., Lee E.S., Kwon Y., Younghwa N., 2010. New benzoxanthone derivatives as topoisomerase inhibitors and DNA cross-linkers. Bioorg Med Chem. 18(3),1010–1017.

125. Boruta T., Bizukojc M., 2014. Culture-based and sequence-based insights into biosynthesis of secondary metabolites by *Aspergillus terreus* ATCC 20542. J Biotechnol. 175, 53–62.

126. Zaehle C., Gressler M., Shelest E., Geib E., Hertweck C., Brock M., 2014. Terrein biosynthesis in Aspergillus terreus and its impact on phytotoxicity. Chem Biol. 21, 719–731.

127. Arakawa M., Someno T., Kawada M., Lkeda D., 2008. A new terrein glucoside, a novel inhibitor of angiogenin secretion in tumor angiogenesis. J Antibiot. 61, 442–448.

128. Liao W.Y., Shen C.N., Lin L.H., Yang Y.L., Hsin-Ying H., Jing-Wei C., Kuo S.C., 2012. Asperjinone, a nor-neolignan, and terrein, a suppressor of ABCG2-expressing breast cancer cells, from thermophilic Aspergillus terreus. J Nat Prod. 75, 630–635.

129. Hiroki M., Kazuhiro O., Daisuke Y., Toki T., Kyouta M., Satoshi Y., Koichi M., 2014. Synthetic + -terrein suppresses Interleukin-6/Soluble Interleukin-6 receptor induced-secretion of vascular endothelial growth factor in human gingival fibroblasts. Bioorg Med Chem. 22, 5338–5344.

130. Maragos C.M., Sieve K.K., Bobell J., 2017. Detection of cyclopiazonic acid CPA in maize by immunoassay. Mycotoxin Res. 33,157–165.

131. Heperkan D., Somuncuoglu S., Karbancioglu-Güler F., Mecik N., 2012. Natural contamination of cyclopiazonic acid in dried figs and co-occurrence of aflatoxin. Food Cont. 23, 82–86.

132. Hariprasanna K., 2015. Genetic improvement in kodo millet, in: V.A. Tonapi, J.V. Patil (Eds.), Book Millets: Ensuring Climate Resilience and Nutritional Security, Daya Publishing House, New Delhi.

133. Rasheed U., Wu H., Wei J., Ou X., Qin P., Yao X., Chen H., 2019. A polyphasic study of Aspergillus section Flavi isolated from corn in Guangxi, China- a hot spot of aflatoxin contamination. Int J Food Microbiol. 310, 108307.

134. Goron T.L., Raizada M.N., 2015. Genetic diversity and genomic resources available for the small millet crops to accelerate a new green revolution. Front Plant Sci. 6, 157.

135. Dwivedi S., Upadhyaya H., Senthilvel S., Hash C.T., Fukunaga K., Diao X., Prasad M., 2012. Millets: genetic and genomic resources. Plant Breed Rev. 35, 247–375.

136. Deabes M.M.Y., Amara H.A., Damaty E.L.M., Rowayshed G.H., 2018. Natural Co-occurrence of aflatoxins, cyclopiazonic acid, and their production by Aspergillus flavus isolates from corn grown in Egypt. Adv Clin Toxicol. 3(3), 136.

137. Maragos C., 2018. Complexation of the mycotoxin cyclopiazonic acid with lanthanides yields luminescent products. Toxins. 10, 285.

138. Sugiharto S., 2019. A review of filamentous fungi in broiler production. Ann Agric Sci. 64, 1–8.

139. King E.D., Bassi A.B., Ross D.C., Druebbisch B., 2011. An industry perspective on the use of "Atoxigenic" strains of Aspergillus flavus as biological control agents and the significance of cyclopiazonic acid. Toxin Rev. 30, 33–41.

140. Dupont J., Dequin S., Giraud T., Tacon F., Marsit S., Ropars J., Richard F., 2017. Fungi as a source of food. Microbiol Spectrum. 5(2), 30.

141. Wegulo S.N., 2012. Factors influencing deoxynivalenol accumulation in small grain cereals. Toxins. 4, 1157–1180.

142. Audenaert K., Vanheule A., Hofte M., Haesaert G., 2014. Deoxynivalenol: a major player in the multifaceted response of Fusarium to its environment. Toxins. 6, 1–19.

143. Vaclavikova M., Malachova A., Veprikova Z., Dzuman Z., Zachariasova M., Hajslova J., 2013. "Emerging" mycotoxins in cereals processing chains: Changes of enniatins during beer and bread making. Food Chem. 136, 750–757.

144. European Food Safety Authority, 2014. Scientific Opinion on the risks to human and animal health related to the presence of beauvericin and enniatins in food and feed. EFSA J. 12, 3802.

145. Gruber-Dorninger C., Novak B., Nagl V., Berthiller F., 2017. Emerging Mycotoxins: Beyond Traditionally Determined Food Contaminants. J Agric Food Chem. 65, 7052–7070.

146. Fraeyman S., Croubels S., Devreese M., Antonissen G., 2017. Emerging fusarium and alternaria mycotoxins: Occurrence, toxicity and toxicokinetics. Toxins. 9, 228.

147. Luz C., Saladino F., Luciano F.B., Mañes J., Meca G., 2017. Occurrence, toxicity, bioaccessibility and mitigation strategies of beauvericin, a minor Fusarium mycotoxin. Food Chem Toxicol. 107, 430–439.

148. Stanciu O., Juan C., Miere D., Loghin F., Mañes J., 2017. Presence of enniatins and beauvericin in Romanian wheat samples: From raw material to products for direct human consumption. Toxins. 9, 9060189.

149. Varga E., Wiesenberger G., Hametner C., Ward T.J., Dong Y., Schöfbeck D., McCormick S., 2015. New tricks of an old enemy: Isolates of Fusarium graminearum produce a type A trichothecene mycotoxin. Environ Microbiol. 17, 2588–2600.

150. Venkatesh N., Keller N.P., 2019. Mycotoxins in conversation with bacteria and fungi. Front Microbiol. 2019, 10, 201900403.

151. Agriopoulou S. 2016. Enniatins: An Emerging Food Safety Issue. EC Nutr. 3, 1142–1146.

152. Gunter A.B., Hermans A., Bosnich W., Johnson D.A., Harris L.J., Gleddie S., 2016. Protein engineering of Saccharomyces cerevisiae transporter Pdr5p identifies key residues that impact Fusarium mycotoxin export and resistance to inhibition. Microbiology Open. 5, 979–991.

153. Wallwey C., Li S.M., 2011. Ergot alkaloids: structure diversity, biosynthetic gene clusters and functional proof of biosynthetic genes. Natural Product Rep. 28, 496–510.

154. Rimar Y., Rimar D., 2003. Witches saints and other diseases. Harefuah. 142, 383–386396.

155. Craig A.M., Klotz J.L., Duringer J.M., 2015. Cases of ergotism in livestock and associated ergot alkaloid concentrations in feed. Frontiers Chem. 3, 8.

156. Klotz J.L., 2015. Activities and effects of ergot alkaloids on livestock physiology and production. Toxins. 7, 2801–2821.

157. Gil-Serna J., Vázquez C., Patiño B., 2019. Mycotoxins: Toxicology. Reference Module in Food Sciences, https://doi.org/10.1016/B978-0-08-100596-5.22630-9.

158. Marín S., Ramos A.J., Cano-Sancho G., Sanchis V., 2013. Mycotoxins: occurrence, toxicology and exposure assessment. Food Chem Toxicol. 60, 218–237.

159. Wang H., Zhai N., Chen Y., Fu C., Huang K., 2018. OTA induces intestinal epithelial barrier dysfunction and tight junction disruption in IPEC-J2 cells through ROS/Ca2+-mediated MLCK activation. Environ Pollut. 242, 106–112.

160. Assunção R., Pinhão M., Loureiro S., Alvito P., Silva M.J., 2019. A multi- endpoint approach to the combined toxic effects of patulin and ochratoxin a in human intestinal cells. Toxicol Lett. 313, 120–129.

161. Alassane-Kpembi I., Schatzmayr G., Taranu I., Marin D., Puel O., Oswald I.P., 2017. Mycotoxins co-contamination: methodological aspects and biological relevance of combined toxicity studies. Crit Rev Food Sci Nutr. 57, 3489–3507.

162. Klarić M.S., Rašić D., Peraica M., 2013. Deleterious effects of mycotoxin combinations involving ochratoxin A. Toxins. 5, 1965–1987.

163. Erdoğan A., Ghimire D., Gürses M., Çetin B., Baran A., 2018. Patulin contamination in fruit juices and its control measures, Eur J Sci Technol. 14, 39–48.

164. Hernández-Martínez R., Navarro-Blasco I., 2010. Aflatoxin levels and exposure assessment of Spanish Infant Cereals. Food Addit Contam: Part B Surveill. 3(4), 275–288.

165. Lombard M.J., 2014. Mycotoxin exposure and infant and young child growth in Africa: what do we know? Ann Nutr Metab. 64, 42–52.

166. Adejumo O., Atanda O., Raiola A., Somorin Y., Bandyopadhyay R., Ritieni A., 2013. Correlation between aflatoxin M1 content of breast milk, dietary exposure to aflatoxin B1 and socioeconomic status of lactating mothers in Ogun State, Nigeria. Food Chem Toxicol. 56, 171–177.

167. Erceg, S., Mateo E., Zipancic I., Rodríguez Jiménez F., Pérez Aragó M., Jiménez M., 2019. Assessment of toxic effects of ochratoxin a in human embryonic stem cells. Toxins. 11, E217.

168. El-Khoury D., Fayjaloun S., Nassar M., Sahakian J., Aad P.Y., 2019. Updates on the effect of mycotoxins on male reproductive efficiency in mammals. Toxins. 11, E515.

169. International Agency for Research on Cancer, 2015. "Mycotoxin Control in Low- and middle Income Countries, Chapter 5," in Fetal and Neonatal Toxicities of *Aflatoxins* and *Fumonisins*, eds C. P. Wild, J. D. Miller, and J. D. Groopman, (Lyon: International Agency for Research on Cancer).

170. Kanora A., Maes D., 2009. The role of mycotoxins in pig reproduction: a review. Vet Med. 54, 565–576.

171. Ortiz J., Jacxsens L., Astudillo G., Ballesteros A., Donoso S., Huybregts L., De Meulenaer B., 2018. Multiple mycotoxin exposure of infants and young children via breastfeeding and complementary/weaning foods consumption in Ecuadorian highlands. Food Chem Toxicol. 118, 541–548.

172. Watson S., Moore S.E., Darboe M.K., Chen G., Tu Y.K., Huang Y.T., 2018. Impaired growth in rural Gambian infants exposed to aflatoxin: a prospective cohort study. BMC Public Health. 18, 1247.

173. Khlangwiset P., Shephard G., Wu F., 2011. Aflatoxins and growth impairment: a review. Crit Rev Toxicol. 41, 740–755.

174. Lumsangkul C., Chiang H.I., Lo N.W., Fan, Y.K., Ju J.C., 2019. Developmental toxicity of mycotoxin fumonisin b1 in animal embryogenesis: an overview. Toxins. 11, 114.

175. Herrera M., Bervis N., Carramiñana J.J., Juan T., Herrera A., Ariño A., 2019. Occurrence and exposure assessment of aflatoxins and deoxynivalenol in cereal-based baby foods for infants. Toxins. 11, 150.

176. Al-Jaal B.A., Jaganjac M., Barcaru A., Horvatovich P., Latiff A., 2019. Aflatoxin, fumonisin, ochratoxin, zearalenone and deoxynivalenol biomarkers in human biological fluids: a systematic literature review, 2001–2018. Food Chem Toxicol. 129, 211–228.

177. Chen C., Mitchell N.J., Gratz J., Houpt E.R., Gong Y., Egner P.A., 2018. Exposure to aflatoxin and fumonisin in children at risk for growth impairment in rural Tanzania. Environ Int. 115, 29–37.

178. Tufail T., Ijaz A., Noreen S., Arshad M.U., Gilani S.A., Bashir S., Din A., Shahid M.Z., 2021. Pathophysiology of Obesity and Diabetes. In C Egbuna, S Hassan (Ed.). Dietary Phytochemicals: A Source of Novel Bioactive Compounds for the Treatment of Obesity, Cancer, and Diabetes. Switzerland. Springer International Publishing. https://doi.org/10.1007/978-3-030-72999-8_2

179. Yasmin I., Khan W.A., Naz S., Iqbal M.W., Awuchi C.G., Egbuna C., Hassan S., 2021. Etiology of Obesity, Cancer, and Diabetes. In C Egbuna, S Hassan (Ed.). Dietary Phytochemicals: A Source of Novel Bioactive Compounds for the Treatment of Obesity, Cancer, and Diabetes. Switzerland. Springer International Publishing. https://doi.org/10.1007/978-3-030-72999-8_1

180. Sobral M.M.C., Faria M.A., Cunha S.C., Miladinovic B., Ferreira I.M., 2019. Transport of mycotoxins across human gastric NCI–N87 and intestinal Caco-2 cell models. Food Chem Toxicol. 131, 110595.

181. Probst C., Njapau H., Cotty P.J., 2007. Outbreak of an acute aflatoxicosis in kenya in 2004: identification of the causal agent. Appl Environ Microbiol. 73, 2762–2764.

182. Gallo A., Giuberti G., Frisvad J., Bertuzzi T., Nielsen K., 2015. Review on mycotoxin issues in ruminants: occurrence in forages, effects of mycotoxin ingestion on health status and animal performance and practical strategies to counteract their negative effects. Toxins. 7, 3057–3111.

183. Pócsi I., Kiraly G., Banfalvi G., 2018. Antineoplastic potential of mycotoxins. Acta Microbiol Immunol Hung. 65, 267–307.

184. Escrivá L., Font G., Manyes L., Berrada H., 2017. Studies on the presence of mycotoxins in biological samples: an overview. Toxins. 9, E251.

185. Peraica M., Radic´ B., Lucić A., Pavlovic´ M., 1999. Toxic effects of mycotoxins in humans. Bull World Health Organ. 77, 754–766.

186. Shephard G., 2008. Impact of mycotoxins on human health in developing countries. Food Addit Contam Part A Chem Anal Cont Expo Risk Assess. 25, 146–151.

187. Kumar P., Mahato D.K., Kamle M., Mohanta T.K., Kang S.G., 2017. Aflatoxins: a global concern for food safety, human health and their management. Front Microbiol. 7, 2170.

188. Arroyo-Manzanares N., Rodríguez-Estévez V., Arenas-Fernández P., García-Campaña A.M., Gámiz-Gracia L., 2019. Occurrence of mycotoxins in swine feeding from spain. Toxins. 11, 1–13.

189. Udomkun P., Wiredu A.N., Nagle M., Müller J., Vanlauwe B., Bandyopadhyay R., 2017. Innovative technologies to manage aflatoxins in foods and feeds and the profitability of application – A review. Food Cont. 76, 127–138.

190. Ehrlich K., 2014. Non-aflatoxigenic Aspergillus flavus to prevent aflatoxin contamination in crops: advantages and limitations. Front Microbiol. 5, 50.

191. Tasheva-Petkova Y.R., Christova-Bagdassarian V.L., Tachev A.K., Atanassova M.S., 2014. Harmonize approaches to analysis and risk assessment of mycotoxins in foodstuffs. Int J Adv Res J. 2, 1097–1106.

192. Paterson R., Venâncio A., Lima N., Guilloux-Bénatier M., Rousseaux S., 2017. Predominant mycotoxins, mycotoxigenic fungi and climate change related to wine. Food Res Int. 103, 478–491.

193. Kabak B., Dobson A., Var I., 2006. Strategies to prevent mycotoxin contamination of food and animal feed: a review. Crit Rev Food Sci Nutr. 46, 593–619.

194. Berthiller F., Crews C., Dall'Asta C., Saeger S., De Haesaert G., 2013. Masked mycotoxins: a review. Mol Nutr Food Res. 57, 165–186.

195. Mahuku G., Nzioki H.S., Mutegi C., Kanampiu F., Narrod C., Makumbi D., 2019. Pre-harvest management is a critical practice for minimizing aflatoxin contamination of maize. Food Cont. 96, 219–226.

196. Kagot V., Okoth S., De Boevre M., De Saeger S., 2019. Biocontrol of Aspergillus and Fusarium mycotoxins in Africa: benefits and limitations. Toxins. 11, 1–9.

197. Pfliegler W., Tünde P., Pócsi I., 2015. Mycotoxins - prevention and decontamination by yeasts. J Basic Microbiol. 55, 805–818.

198. Dana M.A., Kordbacheh P., Ghazvini R.D., Moazeni M., Nazemi L., Rezaie S., 2018. Inhibitory effect of vitamin C on *Aspergillus parasiticus* growth and aflatoxin gene expression. Curr Med Mycol. 4, 10–14.

199. Atehnkeng J., Ojiambo P., Cotty P., Bandyopadhyay R., 2014. Field efficacy of a mixture of atoxigenic Aspergillus flavus Link: FR vegetative compatibility groups in preventing aflatoxin contamination in maize (*Zea mays* L.). Biol Cont. 72, 62–70.

200. Zain M.E., 2011. Impact of mycotoxins on humans and animals. J Saudi Chem Soc. 15, 129–144.

201. Fandohan P., Zoumenou D., Hounhouigan D.J., Marasas W.F.O., Wingfield M.J., Hell K., 2005. Fate of aflatoxins and fumonisins during the processing of maize into food products in Benin. Int J Food Microbiol. 98, 249–259.

202. Williams S.B., Baributsa D., Woloshuk C., 2014. Assessing purdue improved crop storage (PICS) bags to mitigate fungal growth and aflatoxin contamination. J Stored Prod Res. 59, 190–196.

203. Khlangwiset P., Wu F., 2010. Costs and efficacy of public health interventions to reduce aflatoxin-induced human disease. Food Addit Contam Part A Chem Anal Cont Expo Risk Assess. 27, 998–1014.

204. Adda C., Atachi P., Hell K., Tamo M., 2011. Potential use of the bushmint, hyptis suaveolens, for the control of infestation by the pink stalk borer, Sesamia calamistis on Maize in Southern Benin, West Africa. J Insect Sci. 11, 33.

205. Yang J., Li J., Jiang Y., Duan X., Qu H., Yang B., 2014. Natural occurrence, analysis, and prevention of mycotoxins in fruits and their processed products. Crit Rev Food Sci Nutr. 54, 64–83.

206. Herzallah S., Alshawabkeh K., Al Fataftah A.R., 2008. Aflatoxin decontamination of artificially contaminated feeds by sunlight, -radiation, and microwave heating. J Appl Poult Res. 17, 515–521.

207. Karlovsky P., Suman M., Berthiller F., De Meester J., Eisenbrand G., Perrin I., 2016. Impact of food processing and detoxification treatments on mycotoxin contamination. Mycotoxin Res. 32, 179–205.

208. Jalili M., Jinap S., Noranizan A., 2010. Effect of gamma radiation on reduction of mycotoxins in black pepper. Food Cont. 21, 1388–1393.

209. Di Stefano V., Pitonzo R., 2014. Effect of gamma irradiation on aflatoxins and ochratoxin a reduction in almond samples. J Food Res. 3, 113.

210. Roberts P.B., 2016. Food irradiation: standards, regulations and world-wide trade. Radiat Phys Chem. 129, 30–34.

211. Wang F., Xie F., Xue X., Wang Z., Fan B., Ha Y., 2011. Structure elucidation and toxicity analyses of the radiolytic products of aflatoxin B1 in methanol–water solution. J Hazard Mater. 192, 1192–1202.

212. Yang Q., 2019. "Decontamination of Aflatoxin B1," in Aflatoxin B1 Occurrence, Detection and Toxicological Effects. London: IntechOpen. Available at: https://cdn.intechopen.com/pdfs/68690.pdf

213. Wu F., Khlangwiset P., 2010. Health economic impacts and cost- effectiveness of aflatoxin-reduction strategies in Africa: case studies in biocontrol and post-harvest interventions. Food Addit Contam Part A Chem Anal Cont Expo Risk Assess. 7, 496–509.

214. Bryła M., Waśkiewicz A., Szymczyk K., Jędrzejczak R., 2017. Effects of pH and temperature on the stability of fumonisins in Maize Products. Toxins. 9, 88.

215. Karaca H., Velioglu Y.S., 2014. Effects of ozone treatments on microbial quality and some chemical properties of lettuce, spinach, and parsley. Postharvest Biol Technol. 88, 46–53.

216. Komala V.V., Ratnavathi C.V., Vijay Kumar B.S., Das I.K., 2012. Inhibition of aflatoxin B1 production by an antifungal component, eugenol in stored sorghum grains. Food Cont. 26, 139–146.

217. Sultana B., Naseer R., Nigam P., 2015. Utilization of agro-wastes to inhibit aflatoxins synthesis by Aspergillus parasiticus: a biotreatment of three cereals for safe long-term storage. Bioresour Technol. 197, 443–450.

218. Quiles J.M., Manyes L., Luciano F., Mañes J., Meca G., 2015. Influence of the antimicrobial compound allyl isothiocyanate against the Aspergillus parasiticus growth and its aflatoxins production in pizza crust. Food Chem Toxicol. 83, 222–228.

219. Tsitsigiannis D.I., Dimakopoulou M., Antoniou P.P., Tjamos E.C., 2012. Biological control strategies of mycotoxigenic fungi and associated mycotoxins in Mediterranean basin crops. Phytopathol Mediterr. 51, 158–174.

220. Hope J., 2013. A Review of the mechanism of injury and treatment approaches for illness resulting from exposure to water-damaged buildings, mold, and mycotoxins. Sci World J. 2013, 1–20.

221. Rea W.J., Pan Y., Griffiths B., 2009. The treatment of patients with mycotoxin-induced disease. Toxicol Ind Health. 25, 711–714.

222. Okpala C.O.R., 2019. Towards enhancing the detection of adulteration in bioactive food products. J Food Bioact. 6, 6-9.

223. Okpala C.O.R., Korzeniowska M., 2021. Understanding the Relevance of Quality Management in Agro-food Product Industry: From Ethical Considerations to Assuring Food Hygiene Quality Safety Standards and Its Associated Processes. Food Rev Int. 1-74. https://doi.org/10.1080/87559129.2021.1938600