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Highlights

- Systematically synthesizes classic and recent studies on the health impacts of various mycotoxins.
- Highlights diverse/synergistic effects, severe health risks, and underlying mechanisms.
- Discusses prevention and control strategies, emphasizing the promise of biological approaches.
- Proposes integrated management frameworks to mitigate mycotoxin-related health risks.

Effects of mycotoxins in foods on human health and strategies for prevention and control: A review

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ABSTRACT

Toxigenic fungi and mycotoxins have been widely spreading in foods all over the world. During the growth, processing, and storage, crops are prone to be contaminated by mycotoxins, which are heat-stable and can persist in grains and cereal-derived-foodstuffs in the food chain, causing serious health issues and huge economic loss. Herein, we summarize and discuss the toxicity, mechanism, and occurrence of some mycotoxins in contaminated food matrix. Animal data and epidemiological statistics indicate that mycotoxins can be mutagenic, carcinogenic, teratogenic, immunosuppressive, neurotoxic, and even fatal. Oxidative stress, cytotoxicity, DNA damage, metabolic disorders, and other mechanisms are closely related to the play of their adverse effects. Some studies have observed mycotoxin synergies, suggesting that mixtures of mycotoxins pose a significant threat to humans. Additionally, this review briefly summarizes some possible prevention and control strategies for these toxic effects to ensure food safety referring to physical, chemical, and biological strategies.

***Keywords*:** Mycotoxin; Food; Human health; Toxicity; Prevention and control

1. Introduction

In recent years, global concerns have been expressed regarding food safety, which is closely related to people's lives and health. As one of the most significant factors affecting food safety, exogenous contaminants would do great harm to human health. These contaminants are not produced by the food itself. They are "exotic species", mainly from overuse, improper storage, environmental pollution, unofficial addition, etc. Numerous studies have reported contamination of foods with exogenous contaminants, including pesticide residues, mycotoxins, antibiotics, etc[1]. Among them, mycotoxin has attracted much attention due to its intense toxicity, such as pathogenicity and lethality at a trace level, and wide distribution.

Mycotoxins, the secondary metabolites of some toxigenic fungi, are produced by the specific species of *Aspergillus*, *Penicillium*, *Fusarium*, etc. They are named and classified according to the species of fungi from which they are produced. For example, aflatoxin is produced by the fungus *Aspergillus flavus*. The presence of mycotoxins usually indicates the presence of the associated molds. Fungi generally exist in the form of communities in various food samples[2]. Most fungi are beneficial to humans. Only a few strains of fungi cause disease or produce toxic secondary metabolites. For example, douchi and cheese are produced through fungus fermentation; many antibiotics are fungus metabolites. Thus, we should not be afraid of fungi. Not all fungi are harmful. We need to pay more attention to the rational and safe application of fungi in foods. Mycotoxins in food can be categorized as common mycotoxins, emerging mycotoxins, and modified mycotoxins. Hundreds of mycotoxins have been isolated and chemically characterized but only about 50 of them have been studied in detail so far. The widely studied and well-characterized mycotoxins are aflatoxin B1, ochratoxin A, zearalenone, deoxynivalenol, fumonisin B1, HT-2, and T-2 toxins[3]. Contamination of foods or agricultural products by mycotoxins is usually at trace amount and widespread. Considering the economic burden and potential health risk, many countries and regions have set limits on the maximal allowable amount of certain mycotoxins in agricultural products or foods[4].

Mycotoxins exist all over the world. Multiple studies have reported the prevalence

of mycotoxins in foods. According to estimates from the Food and Agriculture Organization (FAO), about 25 percent of cereals produced worldwide are contaminated with mycotoxins. However, due to differences in standards of limit and detection methods, the actual numbers are believed to be much higher[5]. Many countries and regions are affected by mycotoxin contamination. On one hand, mycotoxin contamination decreases product quality and may cause significant economic losses to the producing countries. On the other hand, it directly reduces the availability of food and may aggravate famine and malnutrition, especially in developing countries with food shortages[6]. The aflatoxin contamination of food crops alone would cause severe economic burdens in the world. In addition, health risks from mycotoxins are generally irreversible. When foods are contaminated by mycotoxin, there are usually no obvious sensory warning signs on the surface of the product. Thus, the developments of sensitive and accurate detection methods and green and low-cost mycotoxin-reducing strategies have become research hotspots[7-8].

The wide distribution of toxigenic fungi and the stable nature of mycotoxin have created favorable conditions for mycotoxin contamination. Various toxigenic fungi and mycotoxins have been found to exist in soil, water, grains, herbs, spices, meat, and other matrices[9]. Mycotoxin-producing molds tend to grow in food substrates of plant and animal origin and prefer to inhabit areas characterized by persistently high relative air humidity and moderate to high temperatures[3]. Due to its stable physical and chemical properties, mycotoxin is difficult to degrade once it is produced. It can enter the food chain through contaminated grains and may appear at any given stage of food production. From the planting and harvesting of grains in the field to the storage and consumption of the final products of plants and animals, toxigenic fungi and mycotoxins can be introduced in these stages. Once the foods contaminated with these mycotoxins (exceeding the limits) were ingested, they would pose serious threats to human health through long-term exposure or short-term exceeding intake.

When food is contaminated with mycotoxin, humans can be exposed to the risk of mycotoxin through oral ingestion, inhalation, and dermal routes, resulting in irreversible health damage. The effects of mycotoxin on human health can be classified

as acute (high-dose mycotoxins, short-term exposure) effects and chronic (low-dose mycotoxins, long-term exposure) effects. According to literature, mycotoxins mainly act on target organs like the liver, lung, kidney, central nervous system, and immune system after entering the human body. Some toxic effects of mycotoxins like mutagenic, carcinogenic, teratogenic, dermal, immunosuppressive, or neurotoxic are summarized in Table 1. Only a few mycotoxins have been thoroughly studied, however, and most of them have yet to be characterized for their effects on human health. Considering that these mycotoxins can cause serious and irreversible damage to human health covering organism level, organ level, cellular level, and molecular level once they enter the human body with food, multiple corresponding strategies are adopted to control their production or reduce their content to detoxify these pollutants [8]. Of note, the threats posed by fungi to food safety are different, including the microorganisms themselves (biological) and their metabolites (chemical). Risk control strategies should be addressed simultaneously and, where possible, collaboratively. Preventing the growth of molds and avoiding mycotoxin production are often considered the early steps in the production and post-harvest storage of grain-based foods. If the growth of fungi cannot be avoided or mycotoxins have been produced, it is necessary to take various processing measures to remove these mycotoxins and mitigate their effects, including physical, chemical, and biological methods. Although the occurrence, production, toxicity, and detoxification strategies of mycotoxins have been summarized in some reviews during the past decades, such reviews are not enough and systematic, especially in the past three years. More reviews are still needed with some new discussion and insights from different perspectives. Therefore, we not only systematically summarize some classic landmark discoveries about mycotoxins, but also discuss them in the light of new research in the past five years and put forward our proposal. This review will provide a powerful reference for future toxicological research, risk assessment, and the development of new prevention and control technologies for mycotoxins. Hence, this review mainly emphasizes: (a) the effects and probable mechanisms of mycotoxin on humans; (b) the approaches to prevent and control mycotoxins.

Table 1

2. Effects of common mycotoxins

Mycotoxins contaminated in food come from a wide variety of sources. The impacts of mycotoxins on human health differ depending on their unique physical and chemical properties whose roots come from structural differences (Figure 1). Next, we will take a close look at the effects of several common mycotoxins (highly toxic and concerned) on human health and their mechanisms of action, including aflatoxins, ochratoxins, zearalenone, fumonisins, as well as deoxynivalenol.

Figure 1

2.1. *Aflatoxins*

Aflatoxins (AFs) are secondary metabolites produced by *Aspergillus* fungi, which is frightening because of its strong toxicity. Aflatoxins are difuran ring compounds, which are heat stable, fluorescent, and insoluble in water. Aflatoxins can be divided into B-group aflatoxins (blue fluorescence) and G-group aflatoxins (green fluorescence) according to their fluorescence. AFB1, AFB2, AFG1, and AFG2 are representative aflatoxins. Aflatoxin M1 and M2 are hydroxylation metabolites of aflatoxin B1 and B2, respectively, and their toxicity is lower than that of group B aflatoxins[10].

Aflatoxins are known to be associated with toxicity and carcinogenicity in both human and animal populations. Acute aflatoxicosis can lead to severe disease and even death, while chronic aflatoxicosis can result in more long-term pathological changes, including cancer and immunosuppression[11]. In recent years, high concentrations of AFs (over 1000 μg/kg) have been reported in food[12], which may trigger acute aflatoxicosis and death. Notably, chronic aflatoxicosis is more likely to happen than acute aflatoxicosis. Owing to the daily intake of various AFs-contaminated products, the public is often exposed to low levels of AFs, which gradually accumulates in human bodies and causes chronic disease. An estimated 4.5 billion people worldwide are chronically exposed to AFs through contaminated foods. Most of them live in developing countries with poor economies and food shortages[13].

Repeated exposure to low doses of aflatoxin in humans can lead to chronic diseases due to the accumulation of its toxicity, among which hepatocellular carcinoma (HCC) is the most infamous. AFs (AFB1, B2, G1, and G2) are classified as Group 1

"carcinogenic to humans" by the International Agency for Research on Cancer (IARC)[14]. In addition, other scholars have reported their genotoxic, mutagenic, teratogenic, immunosuppressive, nephrotoxic, and cytotoxic effects[15]. However, most of these studies are based on animal experiments, and the data on humans are still lacking. The liver is the target organ of AFs' action. After ingestion of aflatoxin B1, it will go through a series of metabolic reactions *in vivo* (Figure 2)[16]. The initial symptoms of a normal adult are loss of appetite and weight, followed by liver injury [3]. Acute aflatoxin toxicity is often manifested as acute hepatitis in the clinic. It can further develop into liver fibrosis or liver cancer. Hepatitis B virus-infected persons are prone to be induced by aflatoxin B1 to develop hepatocellular carcinoma[17]. People exposed to chronic hepatitis B virus infection and aflatoxin have a 30-fold higher risk of liver cancer than those exposed to aflatoxin alone. Interestingly, aflatoxin and hepatitis B virus are the two most important risk factors for HCC. In addition, aflatoxins also appear to have a synergistic effect on hepatitis C virus-induced liver cancer, although the quantitative relationship in HCC induction is not as clear as that of aflatoxins and hepatitis B virus[18]. Aflatoxins have also been associated with nutritional disorders such as malnutrition and growth retardation, possibly through interference with the absorption of micronutrients (zinc, iron, and vitamins), protein synthesis, and metabolic enzyme activity[19].

Figure 2

Aflatoxins have different toxic effects and mechanisms of toxicological action, most of which have not been fully elucidated. Since the discovery of aflatoxin, the mutagenesis of AFB1 has been the focus of most studies, mainly attributed to the intermediate metabolite AFB1-exo-8,9-epoxide (AFBO)[20]. AFBO is a highly unstable molecule that can react with macromolecules in cells (including nucleic acids, proteins, and phospholipids) to induce a variety of genetic, metabolic, signaling, and cellular structural disruptions[21]. However, increasing evidence suggests that AFB1 has equally significant or higher effects on cell function and integrity by inducing oxidative stress (OS)[15]. Figure 3 summarizes the different toxic mechanisms involved in AFB1. AFBO and OS cause genotoxicity, immunotoxicity, and acute toxicity by acting on genomic

DNA, other functional macromolecules, and immune functional cells.

Long-term exposure to low-dose aflatoxin can produce similar effects to those observed for acute toxicity. The mechanism of acute aflatoxicosis is not well understood. As above mentioned, aflatoxins can bind to macromolecules (proteins, phosphor lipids, and nucleic acids) in cells to form adducts that interfere with the physiological functions and structure of these macromolecules. In particular, aflatoxins interact with proteins and block protein synthesis, including enzymes involved in critical functions. The acute toxicity of aflatoxins is a result of their effects on normal metabolic pathways, DNA replication and repair, protein synthesis, and immune response[15]. In addition, studies have proved that aflatoxin-phospholipid adducts and ROS (Reactive Oxygen Species)-induced lipid peroxidation (LPO) are the main issues of damage to the integrity and function of cell membranes, mitochondria, and endoplasmic reticulum[15]. DNA fragmentation is another major effect of acute aflatoxicosis. AFB2a has also been found to be related to acute toxicity as a dietary contaminant or AFB1-phase I metabolite. In addition to participating in aflatoxin-albumin adduction, AFB2a also covalently binds to cellular proteins and phospholipids to produce lipid adduction and protein adduction, resulting in acute adverse effects[21]. These adverse effects can be mitigated by cellular antioxidant defense mechanisms or DNA repair to prevent mutations. However, if the organism is continuously exposed to low-dose AF, these adverse effects will gradually accumulate and eventually lead to HCC. Interestingly, excessive aflatoxin can overcome the detoxification ability of cells and promote the metabolism of toxins to produce toxic metabolites, resulting in severe DNA damage, interruption of the cell cycles, DNA fragmentation, metabolic disorders, cytotoxicity, tissue necrosis, and ultimately organ failure in a short period[11] (Figure 3). Therefore, acute aflatoxicosis can be understood as a sudden exacerbation of the damages mentioned above in a short period due to an excessive dose.

Figure 3

2.2. *Ochratoxins*

Ochratoxin is a group of secondary metabolites produced by fungal species of *Penicillium* and *Aspergillus*[3]. The ochratoxin group consists of ochratoxin A, B, C,

and TA. An ochratoxin molecule is usually composed of dihydroisocoumarin and L-β-phenylalanine. Ochratoxin A (OTA) is the most toxic and representative member of ochratoxin with the properties of heat stability, poor water solubility, and fluorescence. As one of the most common pollutants in agricultural and food products, OTA has been found to contaminate cereals, coffee, wine, dried fruits, nuts, and meat products[22]. OTA is widespread in the environment and of high thermal stability. Once they contaminate food, they are difficult to eradicate from the food chain. Several animal studies have confirmed their nephrotoxicity, hepatotoxicity, teratogenicity, and immunotoxicity[23]. OTA has also been shown to be carcinogenic to the kidney and liver and is classified as a Group 2B human carcinogen by the International Agency for Research on Cancer (IARC) and the World Health Organization (WHO).

OTA can cause a variety of toxicological effects in humans, poultry, and laboratory animals. Species, gender, and the route of exposure can affect the toxicity of OTA. Metabolic pathways of OTA in humans have been obtained through various *in vitro* methods (Figure 4a). OTA mainly acts on the kidney, liver, and cardiovascular systems. Its nephrotoxicity is thought to be the primary cause of Balkan endemic nephropathy (BEN), which is common in some parts of southeastern Europe. This is a serious chronic bilateral kidney disease that can further develop into urinary tract tumors[24]. The renal toxicity of OTA has been confirmed in birds and mammals, but the data from human studies are still lacking. In addition, the toxin is a potent teratogenic agent in various animal experiments. It can also penetrate the placental barrier, and the accumulation in fetal tissue may lead to central nervous system malformations[25]. Equally important, this toxin can also cause significant immune system damage, further leading to a series of toxic effects[23]. Multiple mechanisms have been proposed that are closely related to OTA toxicity and OTA kidney tumor formation: inhibition of mitochondrial respiration and DNA damage, interference with the metabolic system, inhibition of protein synthesis, promotion of membrane lipid peroxidation, and disruption of calcium homeostasis[26]. Various *in vitro* and *in vivo* studies have identified OTA-induced oxidative stress as one of the important mechanisms responsible for its toxicity and carcinogenicity. Oxidative stress and ROS production may be closely

related to various types of toxicity of OTA, including induced cytotoxicity, genotoxicity, and inflammation[27]. Oxidative stress and nitrosative stress are closely associated with OTA-induced DNA damage and provide evidence supporting the role of this mechanism in OTA carcinogenicity[28]. Other studies on the mechanisms of OTA toxicity have focused on interfering with cell signaling, regulating cell viability and proliferation, and regulating physiological signals. Currently, most studies have focused on the following aspects: (i) toxicity mediated by oxidative stress metabolism, (ii) the function of intracellular OTA accumulation as an organic anion transporter, and (iii) intracellular and intercellular signal transduction at nanomolar concentrations[29]. However, the relationship between oxidative stress and OTA metabolism remains to be illustrated. More research is needed to clarify the relationship between oxidative stress and toxicity in different animal species.

Figure 4

2.3. *Zearalenone*

Zearalenone (ZEN) is a non-steroidal estrogen mycotoxin with the chemical structure of resorcylic acid lactone, which is mainly produced by fungi of the *Fusarium* genus[30]. Like other mycotoxins, zearalenone is heat-stable and insoluble in water. At present, more than 150 zearalenone derivatives have been identified. Alpha-zearalenone has attracted much attention due to its higher toxicity than zearalenone. In addition, its β-isomer, with essentially identical toxicity to α-zearalenone, is also noteworthy[3]. ZEN has been detected in crops feed and foods, as well as agricultural sideline products in many regions of the world, including moldy corn, wheat, oats, and other crops. It has also been found in medicinal plants. When these plants are consumed as dietary supplements, ZEN can cause serious harm to human health. *Fusarium* is widely distributed and is found in most countries and regions of the world. It is most common in the north temperate zone, so the detection rate of ZEN is very high in cereals grown there[31]. ZEN can be enriched through the food chain. Humans are exposed to health risks from ZEN through ingestion of ZEN-contaminated livestock and poultry, and more often, through ingestion of ZEN-contaminated grains and processed products. Due to its thermal stability, ZEN residues may be present in foods made from

contaminated raw materials. In addition, after getting into the body through contaminated foods, ZEN will accumulate in the body leading to adverse effects on human health and huge economic losses[30].

Ingestion of ZEN-contaminated foods can cause a variety of toxic effects (Figure 5), including reproductive toxicity, liver toxicity, immunotoxicity, genotoxicity, and carcinogenicity[32]. The toxic effects depend on the concentration of zearalenone ingested, the duration of exposure, and the overall physiological state of the host organism. Firstly, ZEN is known for its reproductive toxicity, which affects the development of human and animal reproductive systems due to its estrogen activity. Since ZEN and its derivatives are chemically similar to natural estrogens, they also have estrogenic activity and can bind to the estrogen receptor (ER). Subsequently, it can produce endocrine-disrupting effects in humans and animals, resulting in reproductive changes[33]. Numerous studies have shown that chronic ingestion of ZEN can cause: (i) infertility or decreased fertility, (ii) fetal malformation and reproductive dysfunction in offspring, and (iii) histological changes in the reproductive organs[33,34]. Hepatotoxicity is also one of the most important toxic effects of ZEN. The liver is an important metabolic and detoxification organ of the human body. When the exogenous toxic substance (ZEN) enters the human body, it can be accumulated and metabolized in the liver[35]. ZEN intake not only causes histological changes and increased liver weight but also changes in biochemical and antioxidant parameters[36]. In addition, ZEN has been reported to affect the liver through interactions with metabolites and gut microbiota[37]. Next, ZEN can change the level of immunoglobulin, destroy the structure of immune cells, affect the secretion of inflammatory factors, and produce immunotoxicity[38]. Apart from the above, ZEN can induce genotoxicity and teratogenic effects. Long-term exposure to ZEN causes DNA lysis, chromosomal aberrations, and micronuclei[39]. Owing to the effect of DNA damage, cell proliferation rate, and cell cycle arrest are further reduced, and cell apoptosis is promoted[40]. Unlike other mycotoxins, ZEN is classified as a Class III carcinogen, or "not classifiable as to its carcinogenicity to humans" by the International Agency for Research on Cancer[41], although studies have shown that exposure to ZEN can increase the risk of cancer. High

concentrations of ZEN reduce cell viability, inhibit DNA and protein synthesis, and inhibit cell proliferation. Low doses of ZEN can promote cell proliferation, and exert effects of estrogen and carcinogenicity[42]. More studies need to be done to elucidate the potential carcinogenic effects of ZEN.

Figure 5

2.4. *Fumonisins*

Fumonisin is a mycotoxin produced by *Fusarium verticillioides*, *Fusarium proliferatum*, and *Fusarium moniliforme*. So far fumonisins are made up of four groups: FA, FB, FC, and FP. Among them, FB1, FB2, and FB3 are commonly found in food[43]. Notably, fumonisin B1 is the most toxic, abundant, and representative. Their structure is characterized by an eicosane skeleton esterified with two tricarboxylic acid groups. Fumonisin is highly polar and soluble in water, acetonitrile, and methanol. They are also thermally stable. The high temperatures used in food processing do not affect their stability. FB1 mainly pollutes grains and grain products. Among them, corn is the most common contaminated material. FBs also contaminate rice, oats, rye, barley, and wheat. Different from aflatoxin and ochratoxin, FB1 is mainly produced by toxigenic fungi before harvest. Therefore, it is difficult to prevent and control fumonisin contamination in food. The contamination of fumonisin in food, feed, and spices has been reported all over the world[44]. Given its widespread contamination and risk to human health, the European Union has set a limit of maximal allowable amounts of fumonisin in foods and feed[45].

The toxic effects of FB1 on humans include immune toxicity, organ toxicity (liver, kidney, intestinal, heart, lung, brain), and reproductive toxicity[44]. Although epidemiological studies on humans are insufficient, the IARC classifies fumonisin B1 as a group 2B human carcinogen due to sufficient evidence of carcinogenicity in animals[46]. The toxic mechanism of FB1 is complex. Since the structure of FB1 is similar to sphingolipid, its main biochemical effect is to inhibit ceramide synthetase, thus affecting sphingolipid metabolism. Meanwhile, oxidative stress (OS) induced by FB1 is considered to be the basis of these toxic effects. It can not only induce cytotoxicity and reduce cell activity but also induce DNA damage, leading to cell

canceration[47]. Oxidative stress of FB1 can also induce apoptosis and autophagy[48]. In addition, FB1 can also cause endoplasmic reticulum stress. Many studies have confirmed that FB1 can induce endoplasmic reticulum stress in mouse hepatocytes and HepG2 cells[49]. Recently, it has been reported that the toxicity of FB1 is related to the TNF signaling pathway. It was found that FB1 induced a dose-dependent increase in the expression of tumor necrosis factor (TNF-α) and IL-1β in gastric epithelial and human colon adenocarcinoma cell lines, suggesting that FB1 can promote the production of cytokines in gastrointestinal cells. This may be the basis for subsequent inflammation[50]. It has also been reported that FB1 can up-regulate the expression of mRNA related to the TNF signaling pathway in porcine kidney cells (PK-15), and tumor necrosis factor α (TNFα) is a key toxic substance[51]. In addition to FB1, other fumonisins also have toxic effects, but the relevant studies are few and human data are lacking. Studies in rat livers have shown that FB2 and FB3 mimic the toxicological and cancer-initiating activity of FB1[52]. Therefore, more studies *in vitro* and *in vivo* are needed to evaluate the toxic effects of other FBs, such as FB2 and FB3, and to uncover other potential toxic effects.

2.5. *Deoxynivalenol*

Deoxynivalenol (DON), also known as vomitoxin, is a tetracyclic epoxide sesquiterpene compound produced by the molds *Fusarium graminerarum* and *Fusarium culmorum*. DON is soluble in polar solvents, such as water, methanol, and ethanol. It is widely found in cereals such as maize, wheat, barley, rice, and sorghum[53]. Grains can be contaminated by DON both in the field and during storage. It is stable in nature and will remain stable even during the process of grain storage, grinding, and processing. It can also resist the hot processing of food and feed to a certain extent. Therefore, DON can also be found in grain-based foods and ready-to-eat feeds. Additionally, DON may also be present in products of animal origin, such as meat and milk[54]. DON is less toxic than ochratoxin and aflatoxin. Due to the lack of sufficient animal experimental evidence, IARC classifies DON as a group 3 carcinogen[55]. Although being regarded as less toxic, it is the most prevailing food-related mycotoxin. It is becoming increasingly essential due to its high prevalence in foods worldwide. The

allowable quantity of DON in foods and feed has been regulated in more than 40 countries, mainly in North America and Europe[56].

The impacts of DON on human health have been mainly reported in terms of its intestinal toxicity, hematotoxicity, myelotoxicity, neurotoxicity, carcinogenesis, mutagenicity, and reproductive toxicity. Among them, the most well-known is its enterotoxin effects. After digesting the food contaminated by DON, people will suffer from acute nausea, vomiting, diarrhea, abdominal pain, headache, fever, and other symptoms. Long-term exposure to DON will lead to the accumulation of its toxic effects, causing some chronic diseases and increasing susceptibility to other chronic diseases, resulting in pathological changes in organs and tissues[23]. At the molecular level, the binding of DON to ribosomes inhibits the extension of the peptide chain during protein synthesis. At the same time, nuclear stress caused by the toxin leads to the activation of some key cellular kinases involved in signal transduction[57]. At the cellular level, DON mainly mediates oxidative stress response, cell cycle disruption, and cell apoptosis[58]. In the gut, DON damages the barrier function of the intestine mucosa membrane and interferes with nutrient absorption[59]. It is important to note that the mechanism of action of DON on intestinal flora is not clear. Subchronic ingestion of DON by animals results in a "transient ecological imbalance" of gut microbes and affects the diversity of gut flora in the colon. It reduces the number of Clostridium perfringens without changing the number of bacteria in the gut[60]. Further studies are needed to determine the effects of DON on the flora, including its composition, function, and possible pathways involved. In addition, DON induced immunotoxicity mainly through the activation of MAPKs, endoplasmic reticulum stress, mitochondrial signaling pathway, and inhibition of protein synthesis. There may also be some interaction between these mechanisms[61]. Some animal studies have also pointed out the potential chronic effects of DON on growth and reproduction[62].

3. Effects of emerging and modified mycotoxins

In recent years, the continuous development of liquid chromatography combined with mass spectrometry (LC-MS) has made it possible to analyze non-exhaustive lists of mycotoxins in various food matrices. LC-MS has been of great help in the discovery

of new mycotoxins as well as disguised or otherwise modified mycotoxins[63]. These emerging mycotoxins may occur with high frequency and sometimes in high concentrations in grains and foods made from grains. Emerging mycotoxins are generally used to describe fusaproliferin (FP), beauvericin (BEA), enniatins (ENNs), and moniliformin (MON). Nowadays, the term has been extended to describe "mycotoxins that are neither routinely measured nor regulated by legislation, but whose incidence evidence is rapidly increasing"[64].

In fact, there are multiple emerging mycotoxins. Next, we will mainly introduce the adverse effects of three representative mycotoxins on human health, beauvericin (BEA), enniatins (ENNs), and moniliformin (MON). ENNs are cyclic hexapeptides, produced by several *Fusarium* fungi. Most *in vivo* animal studies have shown low toxicity of ENNs[65]. ENNs are toxic *in vitro*, but most *in vivo* data show no or low toxicity. This may be due to its high metabolic rate[66]. The European Food Safety Authority (EFSA) concluded that acute exposure to ENN did not affect human health. However, conclusions cannot be drawn regarding chronic exposure due to the lack of relevant *in vivo* toxicity data[67]. BEA is also a cyclic hexapeptide compound and an ionic carrier, showing cytotoxic effects[68]. In addition, the toxin was further demonstrated to be an enzyme inhibitor in liver microsomes[69]. As for whether oxidative stress is related to BEA toxicity, there are conflicting reports[70] and further verification is needed. Like ENN, EFSA believes that acute exposure to BEA does not affect human health, while the toxic effects of chronic exposure cannot be concluded at present[67]. MON is a small, water-soluble molecule called semisquaric acid. The current literature mainly reports its cytotoxicity and genotoxicity. However, its genotoxic effects are considered ambiguous[71] and will not be elaborated on here. The toxicity of MON to animal cells has been extensively tested *in vitro*, and its effects depend on the cell line used. For example, MON has no inhibitory effect on the proliferation of human leukocyte progenitors and platelet progenitors but is cytotoxic to human erythrocyte progenitors[72].

As for modified mycotoxins, they are usually metabolites that are not normally detected during maternal mycotoxin detection. These modified mycotoxins can be

produced by fungi or as part of an infected plant's defense mechanism. In some cases, they are formed during food processing[73]. Although lacking sufficient toxicological data on the modified mycotoxins themselves, some modified mycotoxins can be converted into parent mycotoxins when digested by humans, resulting in adverse health effects. Some of these compounds are even more toxic if they are more bioaccessible and bioavailable than the parent mycotoxins[74]. In-depth toxicokinetic and toxicodynamic studies of modified mycotoxins are still lacking. In addition, understanding of the mechanism of mycotoxin transformation is limited. These hinder the determination of maximum tolerance levels of these metabolites in foods, which is a major challenge in the future[75].

4. Effects of combined mycotoxins

Although the mechanism of action, toxic dose and tolerance limits of a single mycotoxin have been extensively reported, the high frequency of mycotoxin occurrence raises issues about the interaction between various mycotoxins[76]. The coexistence of multiple mycotoxins in food is relatively common. Moreover, due to the variety of food intake, people are likely to ingest multiple mycotoxins at the same time. Harmful effects are possible even when they are present in concentrations at or below the limits (regulated mycotoxins), or persistently at low or high levels (unregulated/emerging mycotoxins)[77].

However, there are not many studies on the combined toxicity of mycotoxin. Therefore, the understanding of toxic interaction between mycotoxins should be deepened. The co-toxicity of mycotoxins is very complex and is affected by toxin type and dose, host, and action time. The combined toxic effects of mycotoxins mainly include synergistic, additive, and antagonistic effects[76]. Some reviews have clearly clarified and summarized the adverse effects of combined mycotoxins *in vitro* or *in vivo* experiments[76]. Hence, we will not discuss it in this review. Obviously, current studies on the combined toxicity of mycotoxin mostly focus on two toxins, while there are few reports on the combined toxicity of three or more mycotoxins, and the mechanism of the combined toxicity of mycotoxin is still unclear and needs to be further studied.

5. Preventive methods and controllable strategies

Owing to their strong toxicity and widespread pollution, mycotoxins pose a significant threat to food safety, resulting in food waste, economic losses, and health losses. Under the stimulus of these factors, effective preventive and detoxification approaches are urgently needed. It should be noted that these strategies first need to ensure the quality of the food itself and further play a role. They are divided into two parts: one is to prevent the production of mycotoxins and inhibit fungal growth and the other is to reduce their content in contaminated food.

5.1. *Inhibition of the growth of fungi and the production of mycotoxins*

Since mycotoxins are secondary metabolites of toxigenic fungi, the most fundamental and effective method to prevent and control mycotoxins is to inhibit the growth of fungi. However, it is difficult to absolutely avoid the fungal contamination in food manufacturing and processing. Of note, the production of mycotoxins is not systematic, that is to say, the presence of toxigenic fungi in food does not mean that mycotoxins are definitely produced. Actually, the production of mycotoxins could be inhibited by simply blocking their biosynthesis process. At present, a series of physical, chemical, and biological prevention methods have been developed and improved for application to various food production activities.

The most common and widely adopted physical strategies include the control of relative humidity (RH) and temperature. Fungi depend on water and suitable temperature to survive and reproduce. Especially in the storage process of food, if the RH and storage temperature of food are controlled outside the suitable conditions of microorganisms, the metabolic activity of microorganisms can be reduced and their growth can be further inhibited. So far, lots of studies have been implemented in terms of exploring the temperature and humidity conditions to inhibit the growth of toxigenic fungi growth in food. Choi et al.[78] found that when rice was stored at 21 ℃ and 85% RH, the population of aflatoxin remained unchanged and no more aflatoxin was produced. Conversely, when the humidity further increased to 97% RH or the temperature to 30 ℃, aflatoxins would still be produced. Under the condition of 21 ℃/97% RH, the content of fungi *A. flavus* and the relevant produced aflatoxin B1 were both the highest. The study also found that when rice was stored at 85% RH, the

number of *F. graminearum* populations continued to decrease, and no deoxynivalenol (DON) was produced regardless of storage temperature. Under the condition of 21 ℃/97% RH, the number of *F. graminearum* increased significantly, accompanied by the production of DON. The study revealed that the control of RH and the storage temperature could significantly affect the growth and production of virulent fungi (*A. flavus, F. gramineum*). Interestingly, the influence of RH was greater than that of temperature. Similarly, many reports have confirmed the effects of RH and temperature on the biosynthesis of mycotoxins in other types of food as well[79]. Thus, strict supervising and controlling of the temperature and humidity conditions in food production, storage, and other procedures play a critical role in restraining fungal growth and toxin production, especially in countries and regions with high temperatures and humidity.

The method of modified atmosphere, mainly including application in the large-scale storage period and in packaging (MAP), is currently widely used in food preservation. It inhibits the growth of foodborne microorganisms by controlling the gas components around the food. It has been reported that the composition of high CO_2 and low O_2 can inhibit the growth of toxigenic fungi and the production of mycotoxins[80]. Compared with the large-scale modified atmosphere, MAP is more efficient, convenient, safe and cheap, consequently being a widely used food preservation method at present[81].

Irradiation is another way of physical control of growth and mycotoxin production, in which ionizing energy is used to modify the cell structure or physiological function of microorganisms and hereby to inactivate them. The mechanism includes DNA strand breakage, cell membrane rupture/leakage, or mechanical damage to the cell wall[82]. The methods of radiation treatment in food mainly include gamma radiation, ultraviolet radiation, microwave, and electron beam radiation. Several studies have found that higher dose gamma irradiation can inhibit the growth and change the content of Fusarium spp.[83]. However, radiation treatment can lead to loss of nutrition in foods, deterioration of sensory quality, and the dubious safety of secondary products[82]. Therefore, electron beam technology has been favored in recent years due to its weak

effects on the nutritional composition of products, facilitating its further use in the food industry[84].

The chemical strategies are based on chemical antifungal agents, such as organic acids and their salts[85], emerging nanomaterials[86], and antimicrobial peptides[87], etc. Chemical antifungal agents are easy to use, low cost, convenient in the production, processing, sales, and other processes of food, exhibiting dose-dependent characteristics[88]. Antifungal agents can be added to the coating of fruits and vegetables to control the internal gas composition and water vapor for inhibiting their respiration, delaying the color change and softening, controlling the fungi growth, and hindering the toxin synthesis[89]. However, the residues of the chemicals presenting in products treated with antifungicides would be a safety concern. It highlights the need to use antifungal compounds that are safe for humans and animals, and urges us to look for antimicrobials that are edible or easy to clean up. In addition, resistance to antimicrobials is also a noteworthy issue, which calls into question their use in large-scale crops and food storage. Therefore, the exploration of more types of antimicrobial agents remains a great challenge.

Comparing with the physical and chemical methods, biological method includes the use of plant extracts, microorganisms and their metabolites, which are derived from the nature, and are more environment-friendly and safer. The inhibitory effect of polyphenol-rich extracts on fungal growth has been reported. For example, butanol extract and oxime derivatives of fresh mint were found to inhibit the growth of *F. moniliforme*[90]. Low fumonisins and aflatoxins production by *Fusarium* sp. or *Aspergillus* sp. were found in maize with high carotenoid content[91]. Plant essential oils play a critical role in inhibiting the growth of mycotoxigenic fungi and eliminating mycotoxin. Studies conducted over the past decade, oregano, cinnamon, thyme, rosemary, fennel, clove, palm grass, and eucalyptus oils were the most frequently applied to reducing these fungi and their mycotoxins[92]. The authorities in European countries have approved some essential oil ingredients as spice additives in food, such as carvsol, carvone, cinnamaldehyde, menthol, linalsol, vanillin, and thymol[93]. So the application of essential oils rich in these plant ingredients is a safe and effective strategy

to avoid or mitigate fungi and mycotoxins.

Bio-control using microbial antagonists, bacteria, fungi, and yeasts, or their metabolites, may be a viable substitution of antifungal chemicals. Lactic acid bacteria (LAB) are important microbial antagonists, showing the advantages of being edible and small environmental pollution. A recent study examined the inhibitory capacity of 11 LAB strains against various toxigenic fungi and AFs and OTA production under different temperature conditions[94]. In the same time and space, different fungi will snatch resources and compete with each other. Hence, biological control can be achieved by inhibiting the growth of virus-producing strains with non-virus-producing strains[95]. As a group of organisms widely found in nature, yeast can also be used as anti-fungal agents to inhibit the growth of virus-producing fungi, and plant epiphytic yeast can used as the source for this purpose[96]. Fungal growth and toxin production may also be influenced by metabolites produced by other microorganisms. It has been found that some proteins and peptides derived from microorganisms can inhibit the growth and development of virus-producing fungi, so they are named antifungal proteins (AFPs) and antifungal peptides (AMPs), respectively[97]. They have the advantages of diverse structures and functions, wide antimicrobial spectrum, good stability, and can be produced by biotechnological methods.

5.2. *Degradation of mycotoxins in contaminated food*

In general, foods go through several steps from crop growing to ingestion, making it a challenge to control the contamination of fungi. Considering that the prevention of fungi growth or mycotoxin production is not always effective and mycotoxin contamination may be introduced at other stages, exploring methods to remove mycotoxins from the edible part of foods must be taken into account. These methods can be classified into physical, chemical, and biological categories as well.

First, sorting and cleaning are the most common and cost-effective mycotoxin removal processes for crop foods. A report[98] using white corn found that manual sorting had the greatest reduction in mycotoxins (over 90%), followed by peeling (over 70%, except for DON and AcDON). The combination of the two methods can minimize the contamination of mycotoxins. In addition, high temperature is also considered an

important way to degrade and reduce mycotoxin levels, depending on the temperature and duration of exposure[99]. For example, the reduction of DON and ZEN in cereals is different with different heat treatments. A report compared the content variation of DON and ZEN after roasting at 96 ℃ and 220 ℃ for 30 min, respectively. At 96 ℃, the DON and ZEN is only 11% reduction, while at 220 ℃, the decrease is 40% and 46%, respectively. It was found that the degradation rates of DON and ZEN were the highest in extrusion cooking (135 ~ 190 ℃), 75% and 80%, respectively[100]. However, with high temperature treatment, the composition and quality of the food will also be affected. On the other hand, the degradation temperature varies with the different types of mycotoxins, and it is difficult to find a uniform temperature condition to control. Therefore, the method of heat treatment is usually suitable for baked foods, while other strategies are suitable for other foods. It is worth noting that irradiation is a treatment that can not only inhibit fungi but also degrade mycotoxins, and has been successfully applied in food production activities. There are two types of radiation: ionizing radiation, including gamma rays, X-rays, and electron beams; non-ionizing radiation, including ultraviolet, microwave, radio waves, infrared, and visible light[101-102]. Recently, Luo et al.[103] determined the effects of the physical and chemical properties of corn contaminated with ZEN and OTA after electron beam irradiation (EBI) and assessed the toxicity through a mouse experiment. Although EBI treatment could make the toxicity of ZEN and OTA lower by reducing their contents, it can also influence the quality of corn to some extent. In fact, in practical applications, these methods are often combined to remove mycotoxin contamination. At the same time, special attention should be paid to the effect of these methods on the quality and flavor of the food itself.

Mycotoxins can also be eliminated by many chemical treatments, such as chemical adsorbents, alkalis, and plasmas. Chemical adsorbents can form weak interactions with mycotoxins, including calcium sodium aluminate hydrate, clay, activated carbon, esterification glucomannan, emerging nanomaterials, etc.[104-105]. A recent study has prepared magnetic graphene oxides (MGO), a kind of nano-adsorbent material with two-dimensional layered nanostructures. Fe_3O_4 nanoparticles can be coated in composite materials. MGO adsorbent has the advantages of easy magnetic separation

and high removal efficiency, which can significantly decrease AFB1 by 86.33% from contaminated oil, but it is also found that the removal process will lead to the loss of some nutrients, including triglycerides, pigments, and beneficial micronutrients[105]. However, the addition of adsorbents also introduces new issues, including the safety of adsorbent materials, how to remove excess adsorbent chemicals from foods, and adsorbent-mycotoxin complexes. Some major mycotoxins have been proven unstable in alkaline environments. In recent reports, baking soda has been shown to reduce the amount of OTA in grain-based foods. When 0.5% and 1% soda were added, OTA decreased by 36.1% and 43.4%, respectively[106]. In addition, many studies have shown that plasmas have mycotoxin detoxification effects, of which ozone is the most concerned plasma and can be used as a safe and green food preservation as well as the contaminant control technology. Although the mechanism of detoxification is not well understood, it is thought that ozone reacts with functional groups of mycotoxin molecules to change their structure and form products with smaller molecular weight, fewer double bonds, and less toxicity[107]. The degradation rates of DON- and ZEN-contaminated wheat bran treated with ozone for 15 minutes were about 29% and 52%, respectively[108]. Physical and chemical changes have taken place in the ozone-treated food, however. Whether these changes will affect the safety of food needs to be further studied.

Most biological control pathways are based on microbial degradation technology. In the process of microbial degradation, the toxic groups of mycotoxins are broken down and destroyed by secreted enzymes of microorganisms, resulting in non-toxic or low-toxic degradation products. In contrast to physical or chemical treatment, microbial degradation can theoretically degrade mycotoxins completely, leaving any remaining toxic ingredients behind. Therefore, it can avoid some adverse consequences on food, with high efficiency and strong specificity. Some fungal and bacterial bio-enzymes have been found to degrade mycotoxins[109]. For example, Stander et al.[110] found that a crude lipase from *Aspergillus Niger* was able to hydrolyze OTA to non-toxic OT and phenylalanine at pH 7.5 and 37 °C by screening 23 commercial hydrolases. In addition, protease A, prolyve PAC, carboxypeptidase A, and pancreatin (Figure 4b) showed

similar activity at suitable temperature and pH conditions[111]. Several enzymes with detoxification capabilities have been found in mushrooms as well, with a detoxification rate of up to 90% for AFB1 under optimal conditions[112]. A biological enzyme, AKR18A1, is a new aldo/keto reductase superfamily member from *Sphingomonas* sp. S3-4, was reported the ability to oxidize DON to 3-keto-DON (less toxic), thereby reducing toxicity[113]. The environmental and health friendliness is their advantages. However, biological control, usually limited to liquid media, is less effective but more expensive than physical and chemical methods. At present, there is little evidence to show the toxicity of enzymatic hydrolysis products, therefore its application is worth exploring.

Each degrading strategy has its advantages and disadvantages (Table 2), so these methods are applied in different situations. Actually, it is difficult for one single strategy to achieve the ideal detoxification due to the diversity of foods and the complexity of the food industry. In practical application, the combination of multiple methods should be considered, and specific strategies should be formulated according to a certain food substrate.

Figure 4

Table 2

6. Conclusions and future perspectives

As one of the most common exogenous contaminants in food, mycotoxins have attracted much attention since their discovery in the 1970s. Because of the widespread distribution of fungi and the stability of mycotoxins, cereals contaminated with mycotoxins are easy to enter the food chain and eventually be ingested by humans, causing a variety of adverse effects on human health. Reports of the mycotoxin contamination are common all over the world, especially in some economically backward developing countries and regions. Although many countries and regions have set limits on mycotoxins in foods, the contamination rate of mycotoxins is still very high. For one thing, consumers and manufacturers do not do quantitative testing for mycotoxins in all foods. For another thing, even if mycotoxins are produced in foods, they will still be ingested into the human body when there is no obvious mold visible

to the naked eye. In most cases, humans are exposed to low doses of mycotoxins over time. When mycotoxins are ingested in excess of the limits, they can cause toxic effects ranging from acute (caused by high dose and short-term exposure of mycotoxins) to chronic (caused by low dose and long-term exposure of mycotoxins).

In this review, we mainly summarized various adverse effects and mechanisms of mycotoxins in foods, covering common mycotoxins (AFs, OTA, ZEN, DON, FUMs), some emerging mycotoxins, and modified mycotoxins. These effects may be carcinogenic, mutagenic, teratogenic, organotoxic, immunotoxic, neurotoxic ect., and may even be fatal. These mycotoxins lead to toxic effects by exerting cytotoxicity, inducing oxidative stress, blocking the cell cycle, and causing DNA damage. However, the data are based on *in vivo* animal experiments and *in vitro* cellular and molecular experiments restrained by ethics. Epidemiological data based on humans are still lacking, especially for emerging mycotoxins and modified mycotoxins. In addition, stimulated by diversification and enrichment of human food sources, humans and animals may frequently be exposed to combined mycotoxins that can produce synergistic, additive, and inhibitory toxic effects, but studies on the effects of combined mycotoxins are inadequate. This is a great challenge in the future.

We have already mentioned the prevalence, stability, and toxicity of mycotoxins. To eliminate adverse effects and avoid food waste, multiple degradation and control measures of mycotoxins have been developed, including the inhibition of fungi growth and mycotoxin production, as well as the mitigation of mycotoxin contamination. Of note, multiple strategies should be combined to reduce the contamination of mycotoxins, which should be carried out at the front end (fungi growth and metabolites production) and the back end of mycotoxin production (reducing mycotoxin). Actually, these physical, chemical, and biological technologies are suitable for different situations and procedures in the manufacturing and consumption of foods. No single method is universally applicable to all substrates or can 100% completely eliminate the risk of contamination with a particular mycotoxin. So far, people have paid more and more attention to food safety, and strategies for mycotoxin reduction have become multi-dimensional. In the physical treatment methods, nutritional loss and deterioration of

sensory properties of foods caused by these strategies such as irradiation and heating treatment must be addressed. It is important to note that data on toxicity studies of chemical agents and degrading products derived from them are still lacking. As for biological control methods, attention should be paid to the difference in effectiveness between laboratory applications and actual food production activities. The combination of multiple control methods as an integrated management strategy is more suitable for mycotoxin control in the food industry. It should be pointed out that food contaminated with mycotoxins is passed by farmers, food manufacturers, and consumers, three crucial roles in integrated management, but now, we often blame the prevention and control of mycotoxins on the manufacturer. Therefore, people involved in each link, especially farmers and consumers, should be educated about mycotoxin toxicity and targeted training on relevant prevention and control strategies to reduce the harmful effects of mycotoxins on human health (Figure 6). As more and more data are available on the contamination and toxicity of mycotoxins, the regulation of mycotoxins will be improved. In short, studies on mycotoxin detection, toxicity, prevalence, control and degradation, risk assessment, standard-setting, etc., are interlinked. A milestone in any study can promote the progress of other researchers to make contributions to human health.

Figure 6

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CRediT authorship contribution statement

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Declaration of Competing Interest

All of authors declare no conflict of interest.

Data availability

No data was used for the research described in the article.

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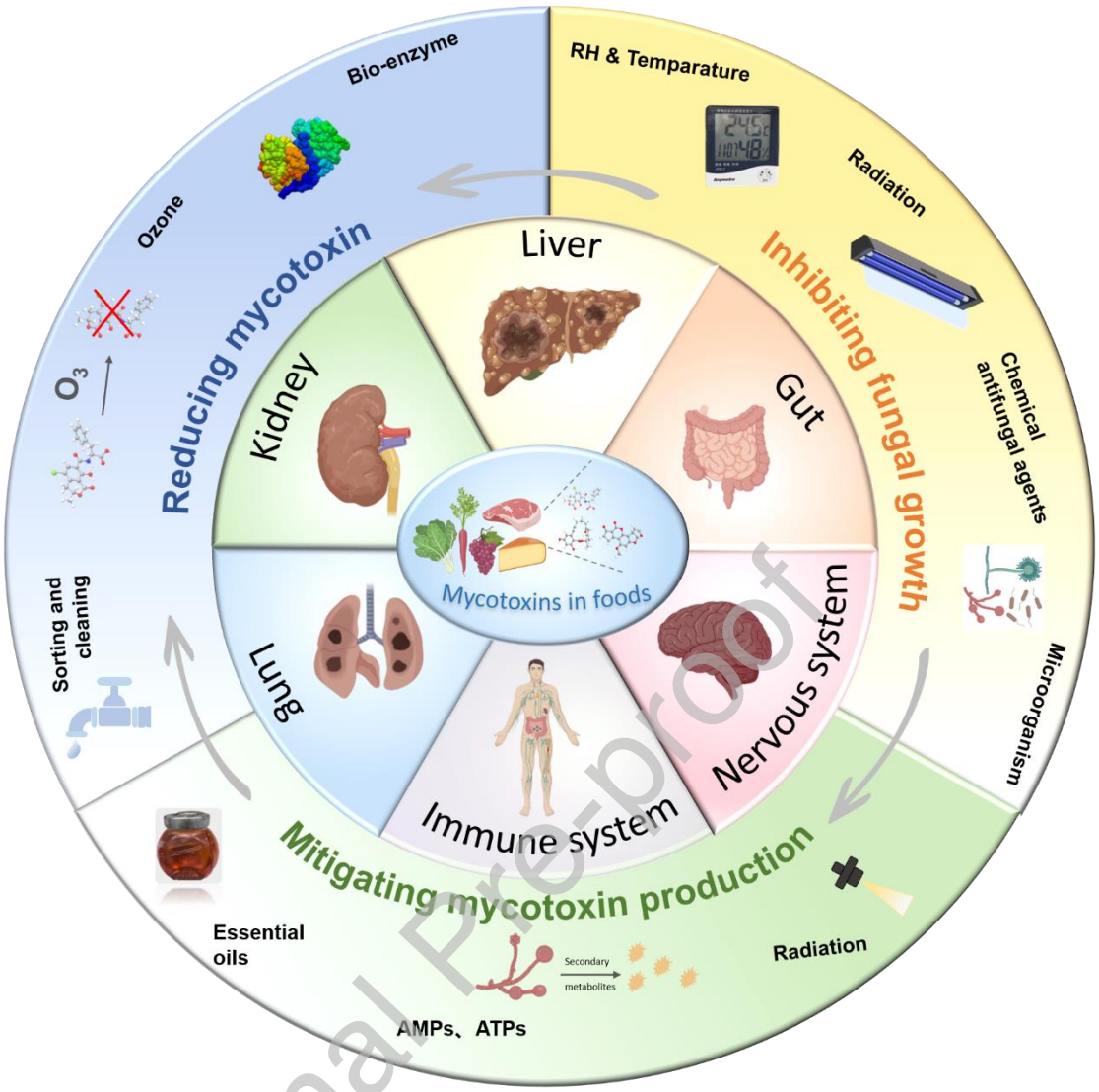
Table 1 Toxic effects of mycotoxins in foods

Mycotoxin	Representative toxigenic fungi	Main categories	Toxicity	Ref.
AFs	*Aspergillus flavus* *A. parasiticus*	AFB_1, AFB_2, AFG_1, AFG_2	Carcinogenicity, hepatotoxicity, genotoxicity, mutagenicity, teratogenicity, immunosuppression, nephrotoxicity, and cytotoxic effects	[4],[10],[11]
OTs	*A. carbonarius* *A. niger* *A. ochraceus*	OTA, OTB, OTC	Nephrotoxicity, hepatotoxicity, carcinogenicity, teratogenicity, and immunosuppression	[22],[26]
ZEN	*Fusarium graminearum* *F. tricinctum* *F. culmorum*	-	Reproductive toxicity, hepatotoxicity, nephrotoxicity, immunotoxicity, genotoxic and teratogenic effects, and estrogenic effects	[30]
DON	*F. graminearum* *F.culmorum*	-	Cytotoxicity, immunosuppression, intestinal toxicity, increasing inflammatory responses	[23]
FBs	*F. verticillioides* *F. proliferatum*	FB_1, FB_2, FB_3, FB_4	Immunotoxicity, organ toxicity (liver, lung, kidney, heart, brain, and intestine), reproductive toxicity, carcinogenicity	[52]
ENNs	*F. acuminatum* *F. poae*	ENNs A, ENNs A_1, ENNs B, ENNs B_1	Cytotoxicity, reproductive toxicity, immunomodulating effects	[72]

MON	*F. moniliforme* *F. begoniae*	-	Cytotoxic effects, muscular weakness, respiratory stress, myocardial degeneration, histopathological changes in organs (kidney, lung, and pancreas)	[71]
BEA	*Beauveria bassiana* *F. acuminatum* *F. poae*	-	Cytotoxicity, immunotoxicity, estrogenic activity, genotoxicity, neurotoxic and myotoxic effects	[69]

Table 2 Comparison of different strategies for mycotoxins degradation

Categories	Strategies	Advantages	Disadvantages
Physical methods	Sorting and cleaning Thermal treatment Radiation	Low-cost, convenient, do not affect food quality Complete degradation, produce non-toxic or low toxic products Suitable for solid and liquid matrices, easy operation	Eliminate incompletely, causing environmental pollution Change the appearance and flavor of food Deteriorate the sensory quality, loss of nutrition, doubt safety of secondary products
Chemical methods	Chemical absorbents Alkalis Plasma (O_3)	Low-cost, easy operation, user-friendly Safe and green	Narrow scope of application Minor physicochemical changes in foods, unknown toxicity of by-products
Biological methods	Enzyme	Green, strong specificity, promising	Expensive, immature, laboratory development stage



GRAPHICAL ABSTRACT

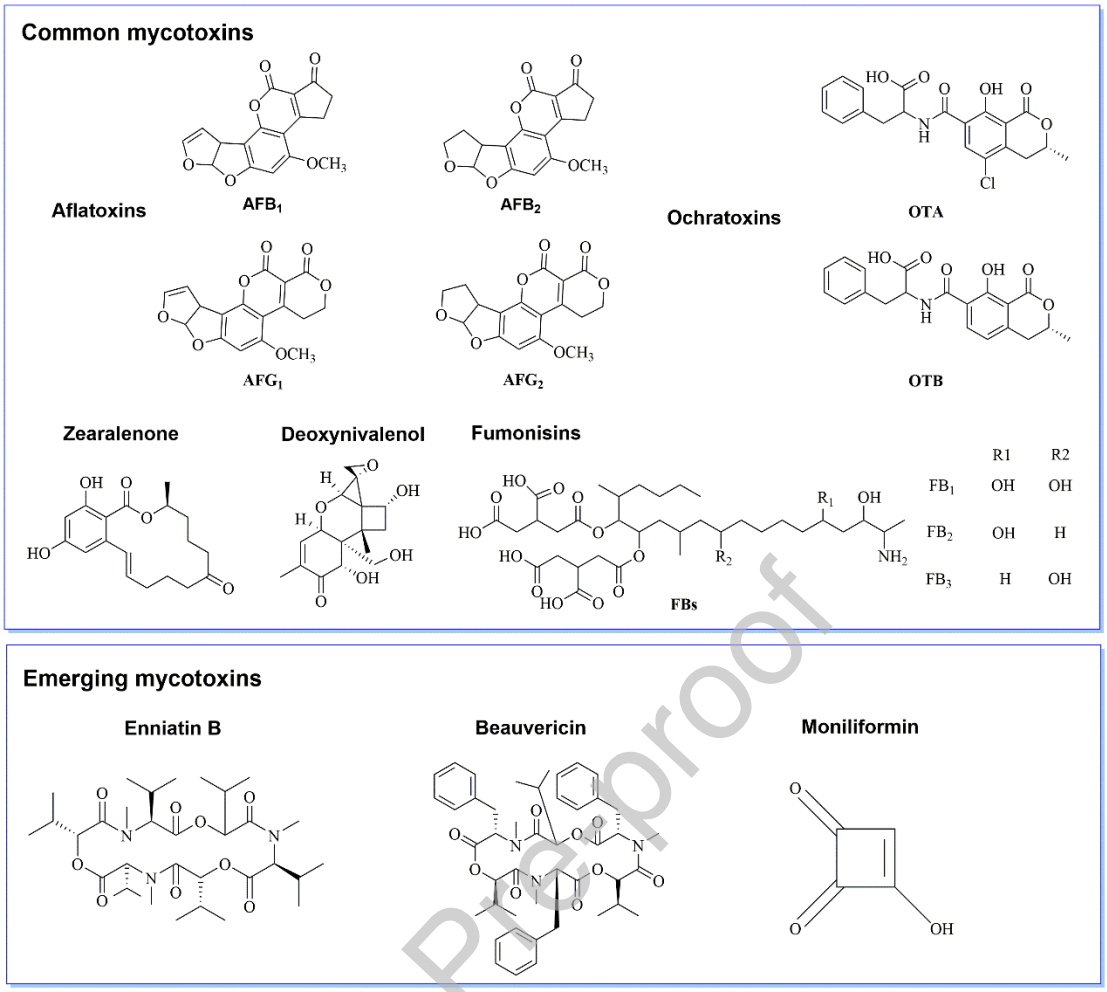


Figure 1. Structures of common mycotoxins and emerging mycotoxins

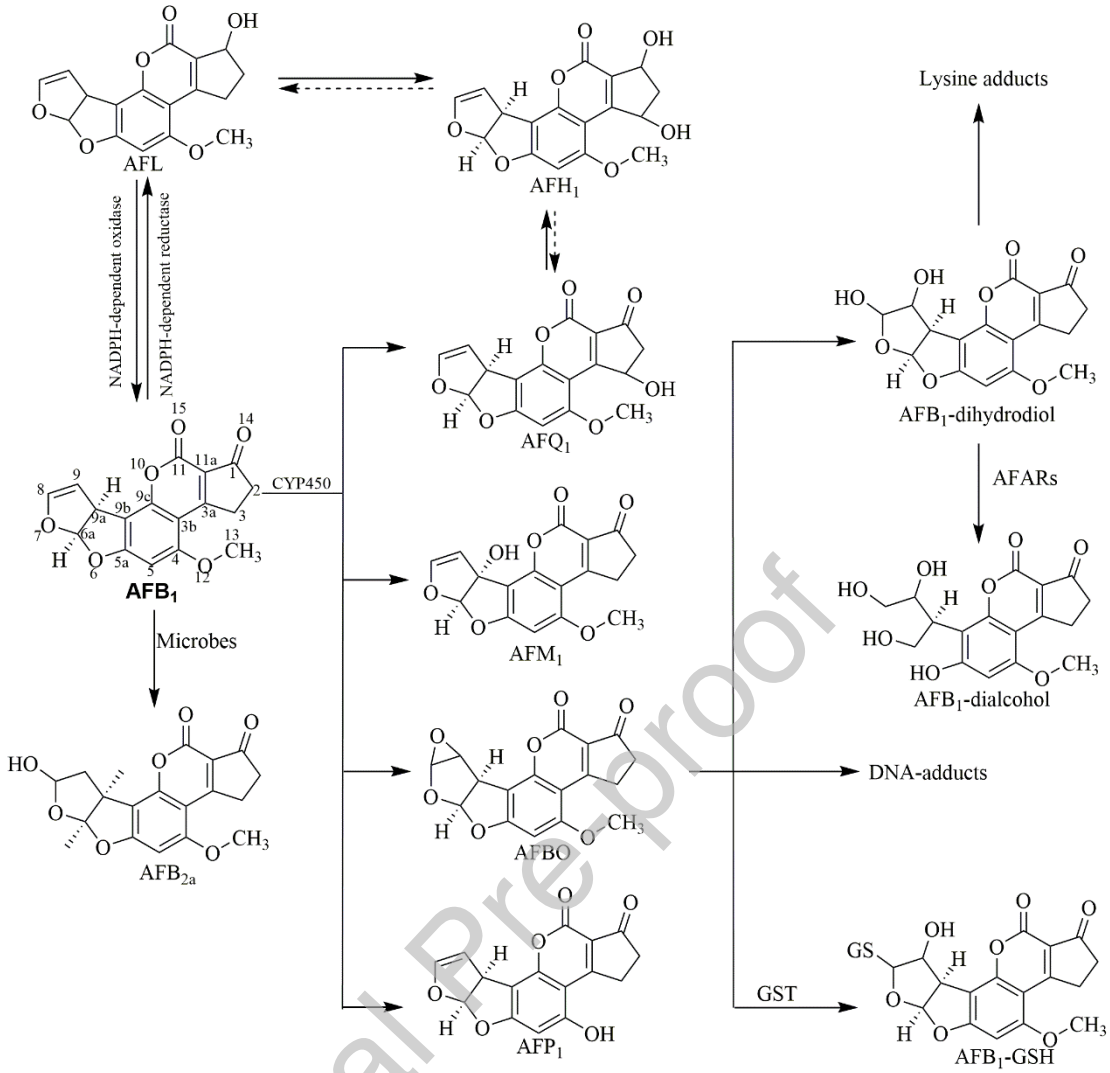


Figure 2. The Illustration of metabolic pathways of aflatoxin B1 in humans and animals[16]

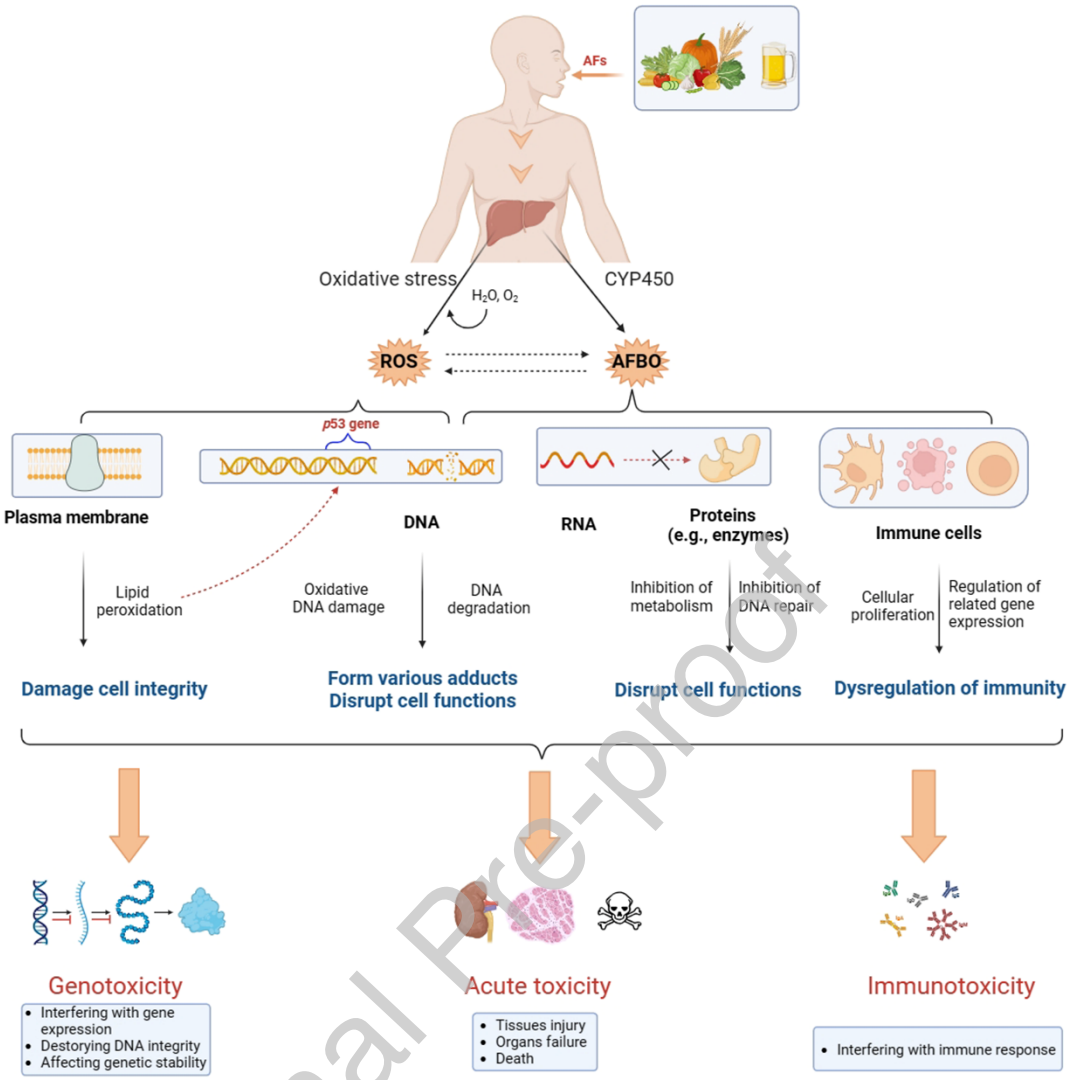


Figure 3. Toxic mechanisms of AFB1 characterized by oxidative stress and AFB1-exo-8,9-epoxide. Created using BioRender.com. AFBO: AFB1-exo-8,9-epoxide. ROS: Reactive oxygen species. AFB1: Aflatoxin B1

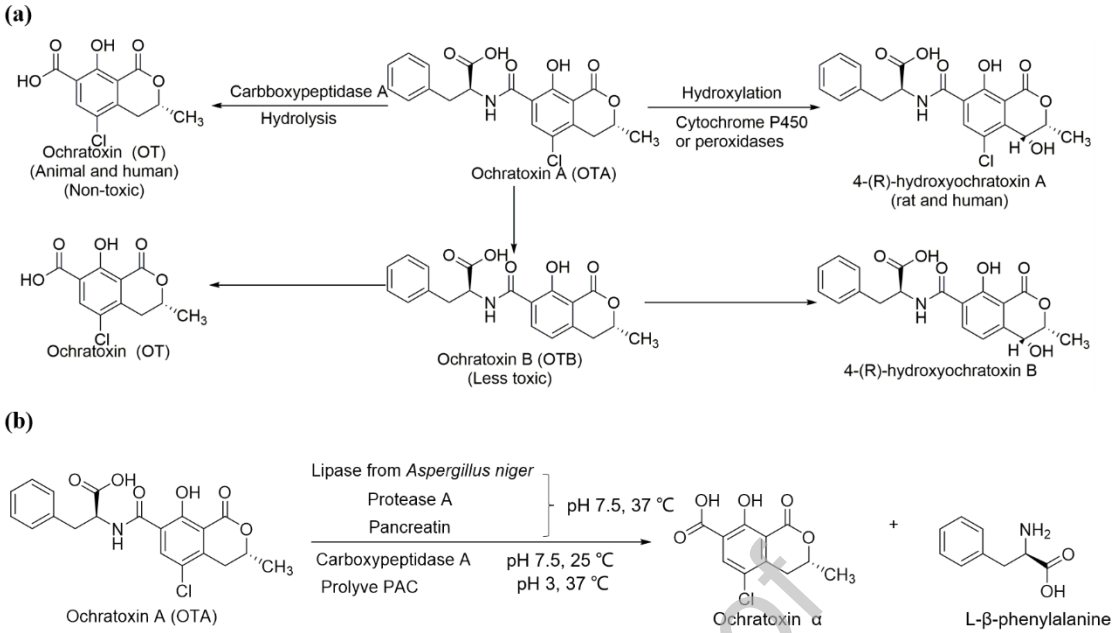


Figure 4. Metabolic pathways in humans (a) and biological enzymes-based degradation (b) of ochratoxin A[111]

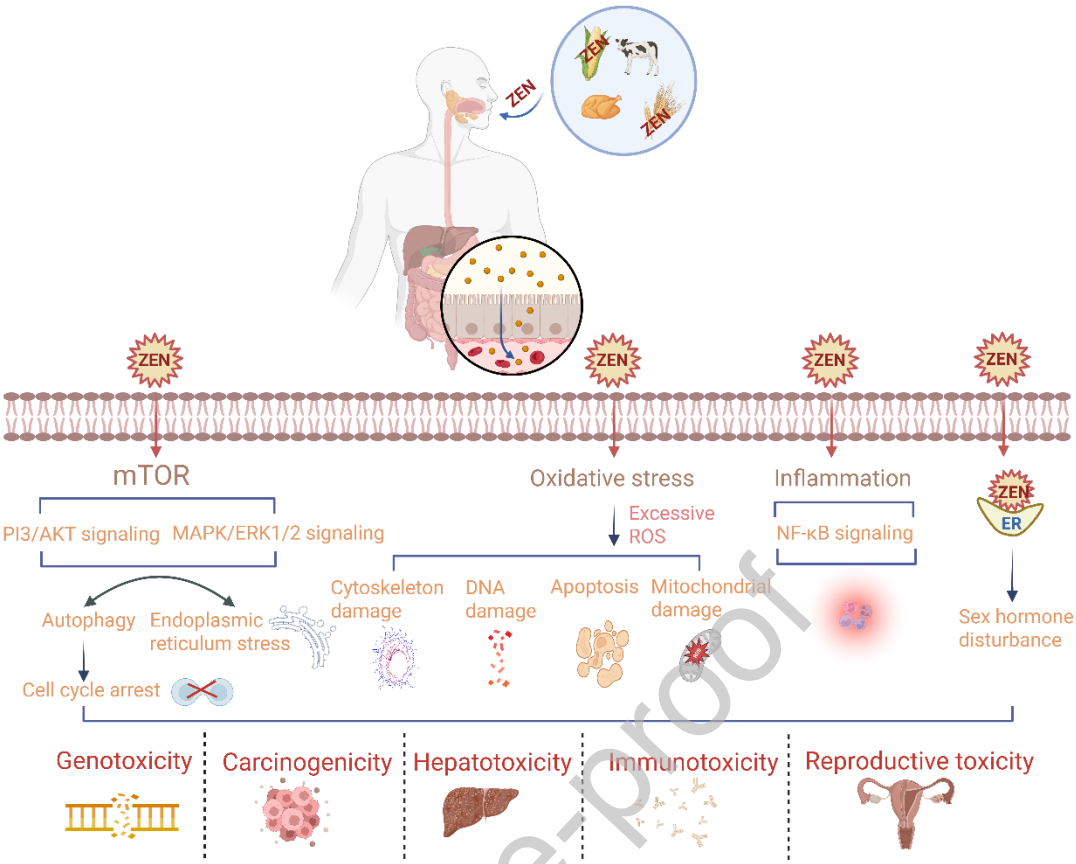


Figure 5. Mechanisms of ZEN toxicity. Created using BioRender.com. ZEN: Zearalenone. ROS: Reactive oxygen species. ER: estrogen receptor

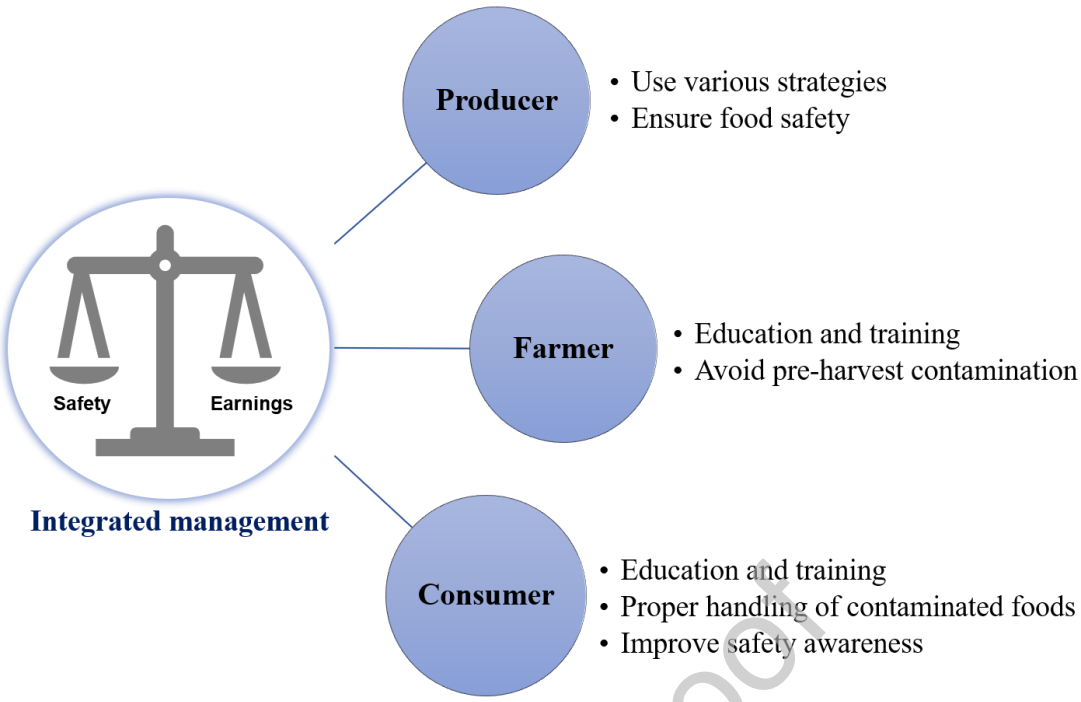


Figure 6. Integrated management for mycotoxins prevention and control in foods

All of authors declare no conflict of interest.