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An overview of mycotoxins, their pathogenic effects, foods where they are found and their diagnostic biomarkers

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Abstract

Mycotoxins are products of the secondary metabolism of fungi, which can be present in food as contaminants. According to Food and Agriculture Organization (FAO), these substances, making them relevant to global health, contaminate approximately 25% of all food worldwide. The occurrence of exposure to these mycotoxins is more common in developing countries, where their effects are more harmful to health due to the high rate of malnutrition in these places. The damage caused by them can manifest acutely or chronically, and among them stand out hepatotoxicity, nephrotoxicity, immunogenicity, carcinogenesis, mutagenesis, and teratogenesis and are associated with particularly dangerous nutritional disorders in children from poorer regions. This review focuses on aflatoxins, fumonisins, zearalenone, deoxynivalenol and ochratoxins, with special attention to their impacts on human and animal health, based on experimental studies and case reports. The biomarkers most used in the detection of these substances based on their metabolism are also discussed.

Keywords: mycotoxin biomarkers; fungi; toxicity; carcinogenesis.

Practical Application: Control of food contamination by mycotoxins.

1 Introduction

Mycotoxins are secondary products of fungal metabolism, with a high capacity to cause damage to human and animal health (Bennett & Klich, 2003).

Fungi can naturally proliferate in food and are very commonly found in grains used for animal and human food. The growth is mainly favored by humidity and temperature. Inadequate harvesting and storage practices contribute to fungal contamination (Batatinha et al., 2008).

The presence of fungi in food does not necessarily indicate that they are contaminated with mycotoxins; similarly, the elimination of the fungi does not guarantee that the mycotoxin has been removed because they have high stability (Turner et al., 2009).

In Brazil, mycotoxins can be found in isolation or in combination in foods such as peanuts, grains, cereals, corn, wheat and animal foods such as milk, eggs and meat. The fact that these mycotoxins can be found in various foods makes them of great importance in public health, in addition to causing negative impacts on the economy (Maziero & Bersot, 2010; Calori-Domingues et al., 2016).

There are several mycotoxins produced by different types of fungi. Sometimes a single fungus species can produce different mycotoxins, making the discussion about the toxic potential of association between them relevant (Sweeney & Dobson, 1998; Marin et al., 2013).

The ingestion of food contaminated by mycotoxins can cause damage to human and animal health and can lead to death, depending on the mycotoxin and the amount ingested (Peraica et al., 1999). Among the harmful effects caused by mycotoxins, hepatotoxicity, nephrotoxicity, carcinogenesis, immunosuppression, and mutagenicity stand out (Rocha et al., 2014). In addition, some mycotoxins, such as aflatoxins and fumonisins, have teratogenic potential and may cause bone malformation and poor development in fetal organs, as demonstrated in previous studies with experimental models (Fetaih et al., 2014; Abdel-Wahhab et al., 2004).

There are several methods that aim to detect mycotoxins in food samples and biological samples. Among the techniques stand out are immunoenzymatic assays and chromatography that can isolate molecules (Chauhan et al., 2016; Pimpitak et al., 2020). Chromatography becomes more effective when associated with mass spectrometry, as it allows a greater amount of information about the analyte to be obtained, making its identification more assertive (Chiaradia et al., 2008; Medina et al., 2019). Fluorescence methods can also be used to detect food contamination, mainly by aflatoxins (Raota & Giovanela, 2016). Currently, the most commonly used techniques for determining mycotoxin exposure are high-performance liquid chromatography with fluorescence detection (HPLC-FLUO) and high-performance liquid chromatography coupled with sequential mass spectrometry (LC-MS/MS) (Al-Jaal et al., 2019).

Residues and metabolites of mycotoxins, such as aflatoxin, can be identified in humans and animal viscera and excreta, and these are important markers of poisoning by these substances (Ramalho et al., 2018; Jager et al., 2016).

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An important point in the study of poisoning by mycotoxins is that food contamination is intended for the consumption of farm animals, culminating in animal products contaminated with metabolites of these substances, which contributes to human exposure to mycotoxins (Dias, 2018).

Chronic exposure to small amounts of mycotoxins in food is a major global health problem due to the ability of these substances to lead to the development of various pathologies, which makes monitoring mycotoxins in foods important for generating new technologies. Detection and elimination of these substances aim at reduction of exposure and therefore of the diseases caused by them (Smith et al., 1995; Maziero & Bersot, 2010).

Studies indicate that the presence of mycotoxins in food is more common in developing countries, and the population of these countries will often be exposed to food contaminated with one or more mycotoxins (Bryden, 2007).

It is estimated that approximately 25% of the entire world's food is contaminated by mycotoxins (Bennett & Klich, 2003). Due to the importance of mycotoxins for public health, legislation defines the maximum permitted amount of these substances in food. In Brazil, these quantities are stipulated in RDC No. 7/2010 of the national health surveillance agency (ANVISA).

The purpose of this review is to discuss the following mycotoxins: aflatoxins, fumonisins, zearalenone, deoxynivalenol and ochratoxins, raising the main topics about their impact on human and animal health and the biomarkers used to evidence exposure to these substances.

2 Mycotoxins

2.1 Aflatoxins

Aflatoxins are mycotoxins of common occurrence in Brazil and are produced by fungi of the genus *Aspergillus spp.*, mainly *A. flavus, A. parasiticus* and *A. nomius* (Caldas et al., 2002). The group of aflatoxins has many representatives among fungal metabolism products and metabolic products of these substances in the body. The toxins B1, B2, G1 and G2 stand out due to their toxicological importance, and aflatoxin B1 is the most important due to its carcinogenic potential. Aflatoxin B1 is classified by the International Agency for Research on Cancer (IARC) as a group 1 carcinogen, which means that aflatoxin B1 (AFB1) is part of the group of substances with the greatest carcinogenic potential (International Agency for Research on Cancer, 2002).

The products of hepatic metabolism of aflatoxins are responsible for their toxic effects (Batatinha et al., 2008). These metabolites cause acute liver damage when ingested in large quantities or express a high potential carcinogenic when ingested continuously, causing damage in DNA through adduct formation and interfering with protein metabolism (Wild & Turner, 2002).

The ingestion of aflatoxins is especially relevant in developing countries, where contact with these substances occurs, from the development embryo, into adulthood (Gong et al., 2002). One of its effects would be the impairment in the development of children, in addition to the association with nutritional disorders such as Kwashiorkor (McMillan et al., 2018).

Poor diets, from the nutritional point of view, seem to be related to the increase in the toxic and carcinogenic effects of aflatoxins, a fact that may be related to the low intake of substances with antioxidant potential such as vitamins, a common condition in the poorest populations of countries under development (Rogers & Newberne, 1971).

In some countries, mainly in Africa and Asia, children become fed almost exclusively with potentially contaminated grain, and after being weaned, this is due to the economic condition. It was shown that the increase in serum concentration of aflatoxin in these children is also related to dwarfism (Alamu et al., 2020).

Experimental studies in rats demonstrate that exposure to AFB1 during the period of embryonic development can lead to genotoxic changes, favoring the development of neoplasms in adulthood (Chawanthayatham et al., 2015). In addition, the mutagenic effect of aflatoxins during embryonic development can lead to a series of morphological and behavioral changes, which may lead to reproductive disability and even death (Fetaih et al., 2014; Supriya & Reddy, 2015).

When high doses of aflatoxin are ingested, they usually cause acute poisoning; although acute poisoning outbreaks are not so common, they usually go with anorexia, general malaise, low fever, and may progress with emesis, severe abdominal pain, acute hepatitis and death (Azziz-Baumgartner et al., 2005).

The biomarkers used to determine exposure to aflatoxins are metabolites of AFB1, such as aflatoxin M1 (AFM1), aflatoxin P1 (AFP1), aflatoxin Q1 (AFQ1), aflatoxin-albumin, AFB-N7 guanine and aflatoxicol (AFL), present in biological fluids (Bando et al., 2007). AFB1 and metabolites can be detected in the blood, urine and feces of humans and animals, which is an important tool for assessing the exposure of individuals to aflatoxins (Fernandez et al., 1997; Mykkänen et al., 2005). For the monitoring of these biomarkers, analytical techniques that are sensitive, specific and that can be applied to many samples are necessary (Groopman & Kensler, 1999).

Free AFB1 can be found in the blood, but its levels are high for a short time after intake, making it not a good exposure marker, as aflatoxin-albumin is found in blood samples for up to 20 days after exposure (Jager et al., 2016).

AFM1 can be found in urine, feces and milk, and in the case of lactating women and animals, with high toxic potential, this metabolite is especially important in the contamination of children during breastfeeding and in commercial milk from animals (Diaz & Sánchez, 2015; Giovati et al., 2015; Hajmohammadi et al., 2019; Ahmadi, 2020). AFM1 is further classified by IARC as agent 2B for its carcinogenic potential in humans (International Agency for Research on Cancer, 1993). The assessment of AFM1 levels in urine can also be used as a biomarker to determine the effectiveness of methods that aim to decrease exposure to AFB1 (Mitchell et al., 2013).

Another important biomarker is AFB-N7-guanine, a lead product of AFB1 epoxide with a guanine of the DNA molecule that is excreted in urine. AFB-N7-guanine is a biomarker that shows, in addition to exposure to AFB1, DNA damage, the

main factor in the development of hepatocellular carcinoma (Dohnal et al., 2014).

The search for AFB1 biomarkers in hair and nail samples is relevant, as it may indicate exposure that has occurred for a longer time (Mupunga et al., 2017).

2.2 Fumonisins

Fumonisins are a group of mycotoxins produced mainly by fungi of the genus *Fusarium spp.*. These mycotoxins are found in foods such as corn and forages and are associated with liver damage and some types of neoplasms. The variant of greater importance is fumonisin B1 (FB1), classified by IARC as a 2B group member with carcinogenic potential for humans (International Agency for Research on Cancer, 1993). The mechanism of action of FB1 consists of the interruption of sphingolipid synthesis by inhibiting sphingosine-N-acetyltransferase, inducing oxidative stress, altering DNA methylation, and modulating autophagy and stress of the endoplasmic reticulum (Voss & Riley, 2013; Liu et al., 2019).

Among the diseases caused by fumonisins in animals are leukoencephalomalacia of the horse and pulmonary edema in swine (Marasas et al., 1988; Harrison et al., 1990). In addition, FB1 has been shown to cause hepatotoxicity and nephrotoxicity in rats (Voss & Riley, 2013). In humans, fumonisins are constantly found in places with a high incidence of esophageal cancer, which is therefore a sign that these toxins may play a role in the development of this neoplasm (Come et al., 2019).

In underdeveloped countries where maize and derivative feeding rates are high, the fumonisins present in these foods seem to be related to impaired child development (Chen et al., 2018).

The experimental administration of FB1 is related to malformations in the closing of the neural tube in mice (Gelineau-van Waes et al., 2009). Skeletal anomalies are also observed in rats, as well as failure to develop the organs and even decrease the number of pups per litter (Abdel-Wahhab et al., 2004).

In rats, liver damage caused by FB1 can lead to an imbalance in the mineral composition of bones, leading to decreased bone strength (Rudyk et al., 2019).

The toxic action of fumonisins occurs mainly by inhibiting the function of the enzyme ceramide synthase, leading to a decrease in the production of sphingolipids and, therefore, accumulation of sphinganine (Sa) and sphingosine (So). Sphingosine and sphinganine in serum, tissues, urine, and feces can be used as biomarkers of exposure to fumonisins (Van der Westhuizen et al., 1999).

In rats, the rates of Sa, So and free FB1 in the urine remain high for a longer time when compared to serum, so the urinary determination of Sa/So is more effective for determining exposure to fumonisins (Cai et al., 2007).

High amounts of free FB1 have been found in the urine of people who have eaten contaminated corn in China, indicating free urinary FB1 as a potential biomarker of human exposure to fumonisins (Xu et al., 2010). The Sa/So ratio can be used to determine the degree of exposure to fumonisins; in addition, men have a greater amount of Sa and So in the urine when exposed to FB1 (Qiu & Liu, 2001).

Fumonisins can still be identified in human and animal hair, which is an important tool in detecting exposure to these mycotoxins in populations, and the toxicokinetic mechanism that explains the presence of fumonisins in the hair has yet to be elucidated (Sewram et al., 2003; Souto et al., 2017).

2.3 Zearalenone

Zearalenone (ZEN) is a nonsteroidal estrogenic mycotoxin produced mainly by fungi of the genus *Fusarium spp*. ZEN can be produced in colder climates and can be found in various foods, mainly in corn. This mycotoxin acts in the body as an estrogenic substance, and its mechanism consists of binding to receptors for 17β estradiol, leading to hyperestrogenism and reproductive disorders (Batatinha et al., 2008).

The metabolites of ZEN, α and β-zearalenol have higher affinity for estradiol receptors and are therefore primarily responsible for the mechanism of action (Fitzpatrick et al., 1989).

The ingestion of food contaminated with ZEN leads to endocrine disorders due to its similarity to naturally produced estrogenic hormones, and constant hormonal stimulation can lead to the development of hormone-dependent neoplasms (Kowalska et al., 2016).

In Tunisia, significant amounts of ZEN and metabolites in the urine of patients with breast cancer have been identified, indicating a possible role of this mycotoxin in the development of this neoplasm (Belhassen et al., 2015). The association between ZEN and carcinogenesis is the subject of discussion, considering that experimental studies demonstrate the ability of this substance to decrease the possibility of the development of malignant neoplasms in rats in the prepuberty period (Hilakivi-Clarke et al., 1999). Other experimental studies also evaluated whether ZEN is related to the progression of breast cancer through inhibition of apoptosis mechanisms and promotion of cell proliferation mechanisms (Yu et al., 2005).

Experimental studies also demonstrate that exposure to ZEN can lead to the death of Sertoli cells in mice by inducing reactive oxygen species and the ATP/AMPK pathway (Zheng et al., 2018). Other mechanisms that induce apoptosis by ZEN are due to the stress of the endoplasmic reticulum and the activation of autophagy, as demonstrated with immortalized Leydig cells from goats (Yang et al., 2017).

In humans, consumption of food contaminated with ZEN during pregnancy can expose the fetus to this mycotoxin and its metabolites (Warth et al., 2019). Experimental studies in rats indicate that gestational exposure to ZEN blocks the fetal development of Leydig cells, which is an important indicator that this exposure leads to anomalies in the development of the male reproductive tract (Pan et al., 2020).

Estimates of exposure to ZEN in humans have shown that a large part of the population consumes safe amounts of this mycotoxin; however, in different parts of the world, exposure has not been reported and may present different results in populations exposed to potentially contaminated food (Maragos, 2010).

The biomarkers used for the detection of zearalenone are ZEN free and its metabolites α and β zearalenol (α-ZEL and β-ZEL) and α and β zearalanol (α-ZAL and β-ZAL), in addition to the conjugates with glucuronic acid as β-zearalenol-14-glucuronide (Frizzell et al., 2015).

In humans, urine samples are the main way to assess exposure to ZEN, with α-ZOL found in greater quantities, followed by ZEN and finally β-ZOL (Ali & Degen, 2018).

2.4 Deoxynivalenol

Deoxynivalenol (DON) is a mycotoxin produced by fungi of the genus *Fusarium spp.* that can be found in several grains and products of animal origin. The main damage to human and animal health occurs mainly in an acute form leading to nausea, emesis, diarrhea, abdominal and head pain, dizziness, and fever, which can evolve to death depending on the amount ingested. The chronic effects are mainly on the immune, reproductive, and gastrointestinal systems. This toxin acts mainly on the neuroendocrine system, inhibiting the growth hormone cascade and stimulating inflammatory responses. In addition, it acts on the gastrointestinal tract, inhibiting gastric emptying and causing imbalance in the intestinal mucosa, consequently affecting the absorption of nutrients. (Fioramonti et al., 1993; Pestka, 2010; Sobrova et al., 2010).

Ingestion of DON, in addition to its acute effects, can lead to genotoxicity on human lymphocytes, probably resulting from the decrease in antioxidant substances, leading to DNA damage by oxidative stress (Yang et al., 2014). Furthermore, DON seems to have a genotoxic effect on *E. coli* strains present in the human intestine, which is a possible indicator of its participation in intestinal carcinogenesis, although previous studies have ruled out that DON may play some role in the development of neoplasms (Pestka, 2010; Payros et al., 2017). DON seems to cause emetic effects in humans, and when its effects are evaluated in animals, it is possible to observe effects on the immune system, anorexia and loss of nutritional efficiency as well as adversely affect reproductive capacity (Pestka & Smolinski, 2005).

Reviews carried out in cell lines of human intestinal mucosa suggest that DON acts by modulating the activity of intestinal transporters, thus acting on nutrient absorption, and the main mechanism of injury occurs by the inhibition of protein synthesis and the decrease in intercellular junction constituents (claudina-4). (Maresca et al., 2002; Van de Walle et al., 2010).

The toxicity of d to DON varies according to the species affected, as well as other mycotoxins, and pigs are more sensitive and ruminants are the most resistant (Pestka, 2007).

Experimental studies demonstrate that DON may have teratogenic potential related to disorders of bone and cartilage development; however, such findings are open to discussion, considering that other studies do not show changes in embryonic development, which is a point to be clarified in the future (Khera et al., 1982, 1986; Debouck et al., 2001).

The main route of DON metabolism includes conjugation with glucuronic acid to free DON and conjugation with glucuronic acid, for example, DON-Glucuronide (DON-GlcA), the most commonly used way to measure exposure. In addition to free DON and DON-GlcA, de-epoxy deoxynivalenol (DOM-1) is another metabolite present in body fluids associated with microbiota (Al-Jaal et al., 2019).

Free DON can be used as a biomarker to investigate the exposure of farm workers who handle grain or silage, showing satisfactory results in humans (Turner et al., 2010a). Among the conjugates with glucuronic acid, DON-15-Glycuronide is found in greater quantity in urine and is therefore a good biomarker of exposure to DON (Warth et al., 2012).

DON-1 is the metabolite found in lesser amounts in human urine samples (Turner et al., 2010b; Ali et al., 2016). DON-1 is found in greater proportion in animal samples and is a less toxic metabolite of DON derived from the metabolism of the intestinal microbiota. The low levels of DON-1 in humans may indicate a greater sensitivity to the toxic effects of DON (Turner et al., 2011).

2.5 Ochratoxins

Ochratoxins are secondary metabolic products of fungi of the genus *Aspergillus spp. and Penicillium spp.* found mainly in nuts, dried fruits, grapes and grapes-derived drinks (Rocha et al., 2014). It has a structure similar to that of phenylalanine, which makes this mycotoxin act to inhibit protein synthesis. Its effects include nephrotoxicity, hepatotoxicity, immunosuppression and teratogenesis (Al-Jaal et al., 2019). Within the group of Ochratoxins, the most important is Ochratoxin A (OTA), due to its ability to cause damage to human and animal health, being categorized by the International Agency for Research on Cancer (1993) as a potential carcinogen for humans, remaining in group 2B.

The most prominent damage caused by ingestion of OTA is due to nephrotoxicity, which can cause edema, necrosis and changes at the cellular level, such as karyomegaly and apoptosis, in several species. (Huff et al., 1975; Maaroufi et al., 1999). In humans, OTA has been identified at high levels in areas with a high incidence of endemic Balkan nephropathy and malignant neoplasms of the urinary tract (Simon, 1996; Castegnaro et al., 2006). The mechanism by which OTA causes nephrocarcinogenesis is still the subject of discussion. Considering the mechanism of adducts formation with DNA, hypotheses are raised that a series of epigenetic mechanisms are related to the carcinogenic potential of OTA. (Marin-Kuan et al., 2008; Pfohl-Leszkowicz & Manderville, 2012).

As shown in experimental studies, OTA, which is metabolized in the liver via cytochrome P450, acts on hepatic metabolism, inducing changes in its metabolic pathways, thus leading to the development of liver diseases over time (Qi et al., 2014). The mechanisms by which OTA operates in the liver are mostly increased production of reactive oxygen species in hepatocytes, followed by lesions in DNA and stimulation of intrinsic apoptosis pathway activation (Gayathri et al., 2015).

OTA metabolites can be found in human and animal breast milk, which shows the risk of contamination during breastfeeding

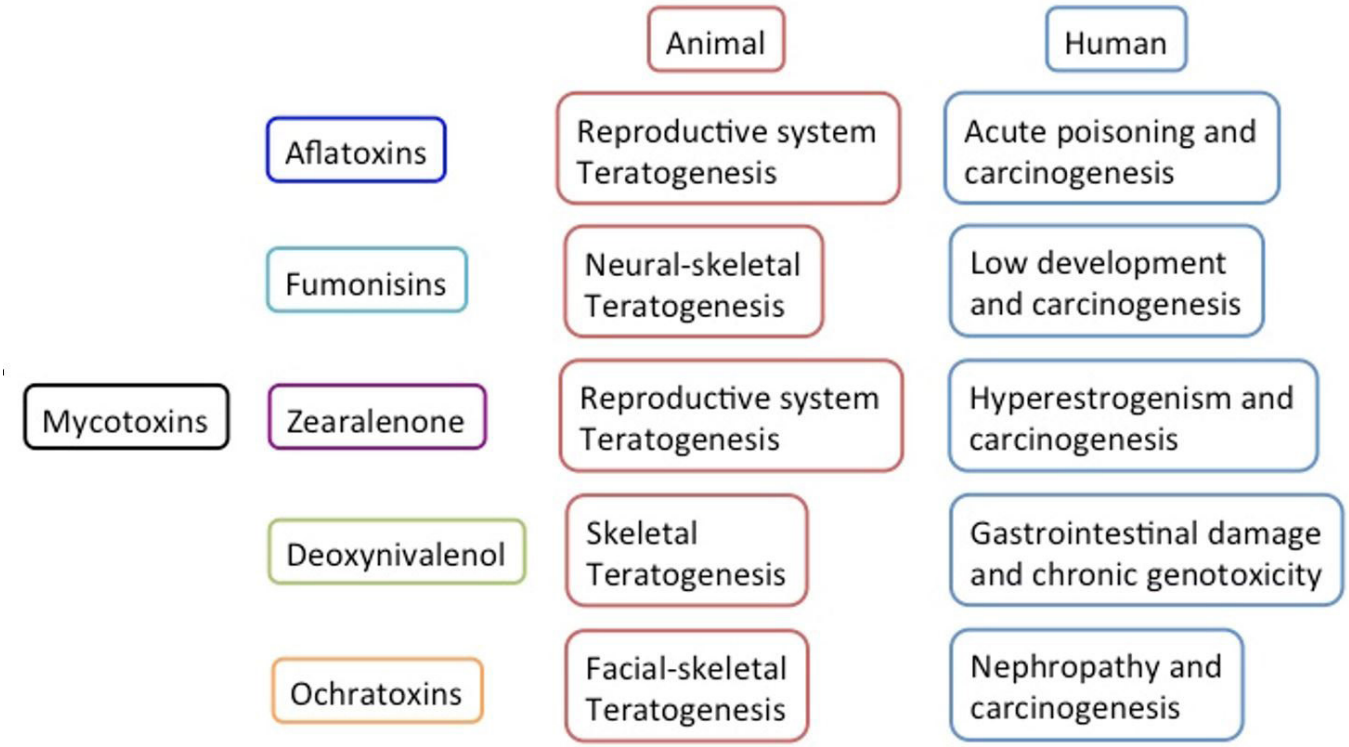

Figure 1. The main impact of aflatoxins, fumonisins, zearalenone, deoxynivalenol and ochratoxins on human and animal health.

and in dairy products (Breitholtz-Emanuelsson et al., 1993; Skaug, 1999; Skaug et al., 2001).

Experimental studies also suggest a great teratogenic potential of OTA. When evaluated for its effects in rats and mice, OTA has been related to increased prenatal mortality and decreased weight of puppies, bone, eye, and face malformations. When delivered in high doses, it leads to the death of fetuses (Hayes et al., 1974; Brown et al., 1976). A study conducted on perfused human placenta demonstrated ineffectiveness in transferring OTA, going against the results obtained in animals, and this is a point to be investigated in the future (Woo et al., 2012).

The most commonly used biomarkers for the diagnosis of exposure to OTA is OTA, ochratoxin α and β (OTα and OTβ), which are the products of hydrolysis by carboxypeptidases, and finally 4-R-hydroxyocratoxine (4-OH-OTA), which results from hydroxylation processes by enzymes of the cytochrome P450 family and peroxidases. All can be found in serum, plasma, and human and animal urine (Rocha et al., 2014; Al-Jaal et al., 2019). OTA can still be evidenced in milk, although the levels of biomarkers in urine indicate a better source to assess exposure (Scott, 2005).

A study conducted in adult Germans showed a greater amount of OTα in urine samples when compared to OTA, an inverse situation in the assessment of plasma levels of these biomarkers; the studies in this case indicate a greater amount of OTA in the blood when compared to OTα (Ali et al., 2017, 2018). Figure 1 summarizes the main damages of mycotoxins on human and animal health.

Finally, the improved detection of fungal biomarkers is also important for the investigation of alternatives that can minimize the presence of mycotoxins in foods, or at least neutralize their toxic and teratogenic effects. For example, the use of polymers with three-dimensional and specific sites (Bodbodak et al., 2018), as well as the biofilm of *Lactobacillus rhamnosus* (Assaf et al., 2019) for binding with AFM1, can reduce the presence of this mycotoxin in milk. The use of some lipid compounds has also been shown to be promising because in addition to having a mycostatic effect, they have antioxidant capacity, decreasing fungal toxicity (Bemvenuti et al., 2019; Villegas-Rascón et al., 2018).

3 Conclusions

Mycotoxin contamination of food is very relevant from a global health point of view, and understanding its mechanisms of action makes it increasingly possible to associate it with several diseases. To establish more precisely how these substances are associated with various pathologies, the measurement of exposure of populations based on their biomarkers is essential, which makes it important to know in detail the biotransformation of these substances and define the best markers to identify them. Another very important point is the chain reaction that can take place when the feed of farm animals is contaminated and then their products such as meat, milk and eggs become contaminants. Thus, due to its close correlation with human health, procedures for feeding farm animals should be optimized, with the rapid identification of pathogens, as well as the proposition of measures to reduce these damages.

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