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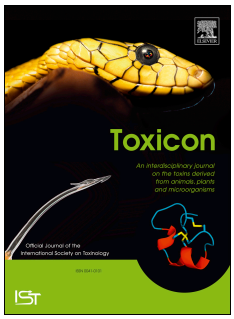

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Genotoxic Effects of Mycotoxins

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Abstract

Fungi produce mycotoxins in the presence of appropriate temperature, humidity, sufficient nutrients and if the density of the mushroom mass is favorable. Although all mycotoxins are of fungal origin, all toxic compounds produced by fungi are not called mycotoxins. The interest in mycotoxins first started in the 1960s, and today the interest in mycotoxin-induced diseases has increased. To date, 400 mycotoxins have been identified and the most important species producing mycotoxins belongs to *Aspergillus, Penicillium, Alternaria* and *Fusarium* genera. Mycotoxins are classified as hepatotoxins, nephrotoxins, neurotoxins, immunotoxins etc. In this review genotoxic and also other health effects of some major mycotoxin groups like Aflatoxins, Ochratoxins, Patulin, Fumonisins, Zearalenone, Trichothecenes and Ergot alkaloids were deeply analyzed.

Key Words: Mycotoxin, Aflatoxins, Ochratoxin A, Patulin, Fumonisins, Zearalenone, Trichothecene, Ergot alkaloids, genotoxicity, health effect

1. Introduction

Of the 14,000 fungal species identified in nature, nearly 2000 are known to be safe for consumption and about 700 have important pharmacological properties (Kalac 2016). Fungi produce mycotoxins in the presence of appropriate temperature, humidity, sufficient nutrients and if the density of the mushroom mass is favorable (Gürbüzel et al. 2015). Mycotoxins have no significant effect on the growth and development of fungi, and these compounds are a product of primary metabolic activities. Low-weight fungal metabolites are not considered mycotoxins (Bennett & Klich, 2003). The interest in mycotoxins first started in the 1960s, and today the interest in mycotoxin-induced diseases has been increased. To date, 400 mycotoxins have been identified and the most important species producing mycotoxins belongs to Aspergillus, Penicillium, Alternaria and Fusarium genera (Jahanian, 2016). Mycotoxins are classified according to the affected tissue as hepatotoxins, nephrotoxins, neurotoxins, immunotoxins by clinicians. In fact, none of these classifications accurately reflects the correct classification. For example, Aflatoxin is a hepatotoxic, mutagenic, carcinogenic Aspergillus toxin (Bennett and Klich, 2003).

Mycotoxins can adversely affect many organs and systems such as liver, kidney, immune, reproductive and developmental systems, and can also lead to cancer with their genotoxic and carcinogenic properties (Becit et al., 2017). The severity of the damage caused by mycotoxins in the body may vary depending on factors such as vitamin deficiency, energy deprivation, alcohol use and infectious disease status. Although the negative effects of mycotoxins vary depending on individual factors, it becomes pathogenic in the use of antibacterial, chemotherapeutic or immunosuppressive drugs, in the presence of human immunodeficiency virus infection and other predisposing factors. Also, mycotoxins act as potent immunosuppressive agents that negatively affect immune cells (Jahanian, 2016). Complications caused by mycotoxins are generally similar to pathologies caused by pesticides or heavy metal residues. Mycotoxins worsen the effects of malnutrition and can

synergistically interact with other toxins by increasing vulnerability to microbial diseases. Although Fink-Gremmels et al. (1999), describes several methods of treatment for mycotoxin exposure and few evidence regarding some Lactobacillus strains effectively bind dietary mycotoxins (El-Nezami et al., 1998; El-Nezami et al., 2002), there are almost no methods of treatment for mycotoxin exposure out of supportive therapy (diet, hydration). Although the number of people affected by mycotoxins is less than the number of people affected by bacteria, protozoan and viral infections, the exact number of affected people is still unknown. However, according to the United Nations Food and Agriculture Organization (FAO, 2001) and the World Health Organization (WHO, 2000), 25% of crops such as hazelnuts, grains and rice in the world are polluted by the growth of mold and fungi and therefore it is thought that there may be chronic mycotoxin exposure in larger than estimated number. It has been determined that chronic mycotoxin exposure causes genotoxicity by oxidative stress, protein synthesis inhibition, creating DNA addition products, changing DNA methylation and lipid peroxidation (Wen et al, 2016). Therefore, determination of genotoxic effects of chronic mycotoxin exposure and measuring possible risks are important. In this article, the genotoxic effect of major mycotoxins was evaluated alphabetically, avoiding mycotoxin classifications.

2. Material and Methods

This work reviews the published literature about the genotoxic and other health effects of Aflatoxins, Ochratoxins, Patulin, Fumonisins, Zearalenone, Trichothecenes and Ergot alkaloids.

2.1. Inclusion and exclusion criteria

This systematic review included all studies investigating the genotoxic and health effects of mycotoxins. The results were restricted to articles written in English.

2.2. Information sources

Owing to the medical nature of the question, the search was confined to Pubmed, Scopus, Web of Science, and Google Scholar. Over 300 abstracts published from 1989 to March 2020 including studies in bio-monitoring, animals, humans and in vitro were found. The search terms included combination of mycotoxin, Aflatoxins, Ochratoxins, Patulin, Fumonisins, Zearalenone, Trichothecenes, Ergot alkaloids, genotoxicity, genotoxic effects, genetic effects, DNA damage, bio-monitoring, chromosomal aberrations, sister chromatid exchanges, micronuclei, comet, health effect.

3. Results

All results about genotoxicity of following mycotoxins are summarized in Table 1.

3.1 Aflatoxins

Aflatoxins, produced mainly by *Aspergillus flavus* and *Aspergillus parasiticus*, are hypertoxic secondary metabolites and generally found in cereals, milk, tree nuts and oilseeds. Aflatoxins are slightly solubile in water, insoluble in nonpolar solvents, soluble in strong polarity organic solvents such as, chloroform and methanol. There are 18 different types of Aflatoxins (B1,

B2, G1, G2, M1, M2, P, Q, etc.) and their molecular weights are between 312-346 g/mol. Aflatoxins are named according to their ability to color in ultraviolet light. While AFB1 and AFB2 give blue color, AFG1 and AFG2 give green color (Peng et al., 2018). AFM1 and AFM2, on the other hand, are encoded with the letter "M" due to the fact that mammals that consume food contaminated with aflatoxins are especially in the milk secretion and are hydroxylated derivatives of AFB1 (Abdallah et al., 2015). Although aflatoxin can be found at a certain rate in the milk secretion of mammals, it is stated that the aflatoxin exposure amount of fetuses and infants is much lower than the rate after weaning (Khlangwiset et al., 2011).

Aflatoxins show acute toxicity at high doses and chronic toxicity at sub-lethal doses. AFB1, the most naturally occurring carcinogen, is defined as group 1 carcinogen according to IARC (IARC, 2012). It is stated that AFB1 is clastogenic agent and participates in the extrahepatic cycle, leading to chromosomal abnormalities, micronucleus formation, sister chromatid exchange, unscheduled DNA synthesis and DNA strand breaks (Corcuera et al., 2015). The most important target organ of AFB1 is the liver, where the toxin is metabolised mainly by CYP1A2 and CYP3A4 and causes numerous mutations, particularly in the p53 tumor suppressor gene (Theumer et al., 2018). AFB1, which is also metabolized via prostaglandin H synthase, causes oxidative stress in *in vitro* (Parveen et al., 2014) and *in vivo* (Guindon et al., 2007) conditions independent of enzymatic bioactivation, leading to mutagenic and genomic instability therefore it poses a risk of genotoxicity. Chronic exposure to AFB1 has been identified as an important risk factor in the development of hepatocellular carcinoma (HCC), especially in hepatitis B and C infected individuals (Rushing & Selim, 2018; Hamid et al., 2013). It has also been noted that aflatoxins can play a causal role in 5-28% of HCC cases worldwide (Liu & Wu, 2010).

Detoxification of AFB1in metabolism completed by combining hydroxylated metabolites with sulfate and glucuronic acid, turning into sulfate or glucuronide esters and finally excreted in urine and bile. During biotransformation, a very reactive form occurs as a result of the epoxidation of the double bond in the bifuran ring in aflatoxins. It is stated that among these compounds, the epoxy form of Aflatoxin B1 combines with DNA to form the AFB1-N7-Gua complex that is responsible for the carcinogenic and genotoxic effects in the cells. While epoxide radical of AFB1 causes molecular (increase apoptosis, decrease p53 protein level), biochemical (decrease mitochondrial activity, increase reactive oxygen species, decrease cell viability), and morphological (deterioration in cell communication, cell membrane damage) changes (Reddy and et al., 2006), exoepoxide form of AFB1 causes mutation in p53 tumor suppressor gene and induces cancer (Groopman & Kensler, 2005).

Aflatoxin contamination in cereals containing corn and peanuts is still a public health problem, especially in African countries. Recently, 37.6% of the cereal samples have been reported to be positive for at least one aflatoxin type and the largest amount was found in rice (Andrade and Caldas, 2015). Gamma radiation and ozone applications offer great potential for detoxification of aflatoxins in some food matrices, although most of the physical and chemical methods for aflatoxin detoxification can affect the nutritional properties of food. In fact, biological methods based on the removal or degradation of aflatoxins by bacteria and yeasts have good perspectives, further research is needed to clarify the detoxification mechanisms by microorganisms and potential effects of their existence in food products (Ismail et al. 2018). Nowadats, studies have been focused on reducing aflatoxin concentration in foods by using some nutritional components. Rushing and Selim (2018) stated that

applying acidic arginine solution prepared with organic acids (citric acid and phosphoric acid) to contaminated foods, resulted decrease in AFB1 concentration up to >99% and it turned into AFB2a-Arg complex. When the toxicokinetic effects of the AFB2a-Arg complex were evaluated, it was determined that the product was highly stable in biological fluids, it was not metabolized by P450 enzymes, it had poor intestinal permeability/high intestinal flow compared to AFB1, and did not have a mutagenic effect in same AFB1 mutagenic concentrations. These results show that the conversion of AFB1 to AFB2a-Arg is a potential strategy for detoxifying contaminated foods. It is stated that the genotoxic effects of aflatoxins, which show great resistance to traditional processes applied to food or feed processing, including pasteurization, sterilization and other thermal applications, can also be suppressed by some dietary changes. Li et al. (2019) reported that curcumin supplementation decreased mutagenic effect of AFB1 by reducing levels of reactive oxygen species (ROS) and 8-hydroxy-2'- deoxyguanosine (8-OHdG), also activates the Nrf2 signaling pathway. Therefore, curcumin should be considered a potential agent for the prevention of AFB1-induced toxicity. In another study, it was found that curcumin was protective against genotoxicity created by AFB1 in liver (Abdel-Wahhab et al., 2016). It is stated that a key factor for reducing AFB-induced carcinogenesis in experimental animals may results of enhancing detoxification enzymes such as certain glutathione-S-transferases regulated by the Keap1-Nrf2-ARE signal path. Drugs that are a prototypical inducer of antioxidant response, such as “Ditiolthione” and “Oltipraz”, and dietary components such as “Sulforafan” are also effective inducers of this pathway in rodent models (Gross-Steinmeyer and Eaton, 2012). Sulforafan is a compound in the isothiocyanate group of organosulfur compounds, and it is stated that garlic with high sulfur component is also protective against genotoxicity caused by AFB1 (Guyonnet et al., 2002). It is stated that vegetables in the Apiaceous and Brassica families may be protective against genotoxicity caused by aflatoxins by inhibiting CYP1A2 activity and by changing the expression of liver enzymes involved in oxidation of aflatoxins, respectively (Gross-Steinmeyer & Eaton, 2012). Although it is stated that lactic acid bacteria also play an antigenotoxic role by removing genotoxins like AFB1 and AFM1 from the environment, this protective role may differ between species and even strains. Therefore, studies are underway to identify strains with superior potential protection against Aflatoxin-induced genotoxicity (Kurhan & Çakır, 2017).

3.2 Ochratoxins

Ochratoxins are produced by *Penicillium* and *Aspergillus* fungi and are generally found in products such as cereals, coffee, cocoa, spices, beer, wine, dried fruit and animal feed (EFSA, 2006) and have more than 10 derivatives. Ochratoxin A (OTA) is the most common and toxic mycotoxin. OTA is at least ten times more toxic than ochratoxin B, ochratoxin C or citrine, and has been identified by IARC as a possible human carcinogen in Group 2B. Although the maximum OTA limit for unprocessed grains and processed grain products has been set by many countries and organizations, no limit has yet been set for OTB and OTC (Qileng et al., 2018). OTA is generally produced during storage in the presence of suitable humidity, temperature and other environmental conditions (Bondy et al., 2015). Compared to other foods, contaminated grain-based foods are the most important cause of OTA exposure in humans (Kuiper-Goodman et al., 2010). It has been reported in various studies that OTA is also found out of cereal-based foods such as coffee. Tafuri et al. (2004) found that 50% of cocoa powder samples contain OTA in the range of 0.22 to 0.77 µg/kg, Petkova-Bocharova et al. (1985) stated that 16.7% of bean samples contain OTA in the range of 25-27 µg/kg, 27.3%

of corn samples were in the range of 25-35 μg/kg, and 9% of wheat flour samples were in the range of 10–25 μg/kg. However, OTA exposure poses a risk not only for adults but also for infants. In Portugal, it has been reported that OTA is found in baby foods and in a significant number of processed cereal-based foods produced for children (Alvito et al., 2010; Assunção et al., 2016). Kamali et al. (2017), reported that OTA was detected in 84 human milk samples at concentrations ranging from 0.11 to 7.34 ng/mL, while 14 samples were found to have risky rates (> 3 ng / mL). Babies are more sensitive to the effects of mycotoxins because of their higher metabolic rate, lower body weight, limited ability to detoxify genotoxic compounds and the development of certain tissues and organs. For this reason, it is important to prevent contaminated food consumption of mothers. On the other hand, it is stated that exposure to intrauterine OTA may increase the risk of cancer later in life (Woo and El-Nezami, 2016).

While exposure to OTA has been associated with a number of diseases that affect the kidney, both in animals and humans, it has also been reported to be associated with stomach, esophagus and testicular cancer (Pfohl Leszkowicz and Manderville, 2007). In addition to nephrotoxicity, neurotoxicity, immunotoxicity, myelotoxicity, reproductive toxicity and teratogenicity was also reported (Costa et al., 2016). OTA has also been shown as the cause of Balkan Endemic Nephropathy, a chronic progressive kidney disease associated with upper urothelial system tumors in humans (Pfohl-Leszkowicz, 2009).

OTA is structurally similar to phenylalanine and therefore inhibits many enzymes that use phenylalanine as a substrate, such as phenylalanine-tRNA synthetase. In addition, it contributes formation of reactive oxygen specieses by inhibiting activation of protein-1, Nrf2 activation, glutathione-S-transferase and cytoprotective enzymes, and damages the cell membrane by increasing lipid peroxidation (Marin-Kuan et al., 2011). These effects are the mechanisms underlying the carcinogenic effects of OTA. In addition; inhibition of protein synthesis, mitochondrial respiration and ATP formation, disruption of calcium homeostasis are other factors explaining its genotoxic activity (Gupta et al., 2018; Costa et al., 2016). Cell-based analysis, transcriptomic analysis of renal tissues and cultured cells shows that OTA can disrupt post-translational protein modifications (Jennings et al., 2012). In a study to investigate the genotoxic effect of OTA, authors reported that it leads structural and numerical changes in chromosomes by inhibiting histone-acetyl-transferase (HAT) enzyme, disrupting DNA repair, cell cycle control and mitosis error repair (Bouslimi, 2008). It has also been reported in different studies that OTA causes karyomegaly, genetic instability and tumorigenesis by HAT inhibition (Czakai et al., 2011; Mally 2012). Studies have been conducted to suppress the oxidative effect of OTA with nutritional components, using antioxidants (vitamin E), phenolic compounds (catechins and quercetin), melatonin and zinc, showed that these antioxidants have not always altered the OTA toxicity (Sorrenti et al. 2013). Meki and Hussein (2001) reported that melatonin did not change the level of lipid peroxidation products but increased the level of glutathione peroxidase, glutathione reductase and glutathione-S-transferase. In a study evaluating the effectiveness of vitamin E for OTA and citrine genotoxicity, it was reported that it reduces ROS levels and cytotoxicity in HepG2 cells, but genotoxic damage cannot be prevented completely (Gayathri et al., 2015). Zheng et al. (2013), reported that zinc reduced the cytotoxicity of OTA by inhibiting DNA damage and regulating the expression of zinc-related genes. This study also showed that zinc helps maintain DNA integrity through DNA strand breaks, 8-hydroxy-2deo-deoxyguanosine (8-OHdG) formation and reduction of DNA hypomethylation. In a study evaluating the

effectiveness of polyphenols (luteolin, chlorogenic acid and caffeic acid) against DNA damage caused by OTA, it was found that these polyphenols reduced DNA damage and the most positive effect was found by chlorogenic acid (Cariddi et al., 2015). In another study, epigallocatechine gallate and epicatechin gallate were decreased the level of increased reactive oxygen species (Costa et al., 2007). Fusi et al. (2010) stated that α-tocopherol reduces OTA-induced cytotoxicity and DNA damage in fibroblast cells. In addition, quercetin has been reported to prevent OTA-induced oxidative stress and apaptosis, inhibit caspase cascade activation leading to DNA fragmentation, and exhibit antigenotoxic potential by relieving DNA damage and micronucleus (MN) formation (Ramyaa and Padma, 2013).

3.3 Patulin

Patulin (Raistrick, 1943), first isolated from *Penicillium griseofulvum* by Harold Raistrick in 1943, is a mycotoxin produced mainly by Aspergillus and Penicillium and is found in fruits such as grapes, pears and peaches, especially in apples. It is in Group 3 according to IARC's carcinogenic risk classification. The World Health Organization has determined the safety level for patulin in apple juice to be 50 µg/L (WHO, 2005) and this amount complies with FDA and European Union recommendations (FDA, 2005; EU, 2002). In addition, this limit is 10 µg/L for apple-based foods produced for children and babies. In a study conducted in Qatar, it was stated that apple-based baby products are found to have products above these limits (Hammami et al., 2017). In a study conducted in China, it was stated that 17.5% of 137 products examined PAT level was at doses above 50 µg/kg (Ji et al., 2017). Although high PAT levels affect all races, genders and age groups, there is an increased risk for infants and babies. Even Patulin exposure below the tolerable daily level of mothers who are breastfeeding, it can lead to exposure above the tolerable level for babies and infants (Saleh and Goktepe, 2019).

Patulin is highly toxic to liver, kidneys, gastrointestinal tract and immune system. In addition, in many cell-based and animal-based studies, PAT has been reported to be a risk factor for genotoxicity, embryotoxicity, cytotoxicity, neurotoxicity, immunotoxicity, carcinogenicity and teratogenicity (Ramalingam et al., 2018). Patulin can react with aminoacids such as cysteine, lysine, histidine, and make covalent additions with electrophilic chemicals. These properties cause PAT toxicity (Saleh and Goktepe, 2019). In addition to these toxicity mechanisms, it activates the Rpn4 transcription factor, causing overexpression of the Rpn4 gene and shows genotoxic effect. Its overexpression leads to protein breakdown and proteotoxicity (Guerra-Moreno, 2017). In another study on the mutagenic effect of PAT, it was found that it stimulates the expression of pro-apoptotic protein ATF3 and thus causes reduction in cell growth (Kwon et al., 2012). PAT increases the expression of some autophagy markers (LC3-II and LC31), causing autophagic system activation. Autophagic system activation involves selective cleavage of cytoplasmic organelles as well as bulk degradation of some cytoplasmic proteins and causes DNA damage (Lee et al., 2012). PAT is highly reactive to the thiol groups of proteins and glutathione (GSH), and therefore it has been reported that patulin causes mutagenic effects, especially in cells with low glutathione levels, lead to chromosome damage and increase micronucleus formation. (Puel et al., 2010). In a study conducted to evaluate the effects of GSH on Patulin-induced DNA damage, N-acetylcysteine (NAC), which is a GSH precursor, showed prevention for chromosomal

damage. These results show that GSH plays an important role in cellular defense against PAT-induced genotoxicity (Zhou et al., 2009). In studies to reduce oxidative stress and chromosomal abnormalities induced by PAT, it is stated that substances showing antioxidant and antigenotoxic activities can correct these negative effects. *Rhodotorula mucilaginosa* (Li et al., 2019) and *Rhodosporidium paludigenum* (Zhu et al., 2015) are important species that can suppress negative effects of PAT. It is stated that plant polyphenols can be protective against PAT-induced genotoxicity like other mycotoxins. Song et al. (2014) found that green tea polyphenols are protective against hepatotoxicity and genotoxicity of PAT. In another study, it was observed that oxidative stress and apaptotic damage caused by PAT decreased with green tea components (Jayashree et al., 2017).

3.4 Fumonisins

Fumonisins (Fumonisin B1 (FB1), Fumonisin B2 (FB2) and Fumonisin B3 (FB3)) are carcinogenic and genotoxic secondary metabolites found in corn-based foods worldwide and are produced by *Fusarium verticillioides* and *F. proliferatum* (Khan et al., 2018). Among these species, the most known and toxic species is FB1 and it was isolated from the culture of *F. verticillioides* MRC 826 in 1988 by Gelderblom et al. (1988). In the following years, it was found that there was a strong positive correlation between fumonisins related eusophageal tumor incidence and contaminated corn consumption (up to 155 ppm, FB1) (Chu and Li, 1994; Van der Westhuizen et al., 2010) and liver cancer and neural tube defects (Radić et al., 2019). Fumonisins enter the food chain by corn and groundwater consumption (Waśkiewicz et al., 2015). Industrial food production is seen as an effective tool for preventing and reducing food contamination by FB1. Therefore, FB1 concentrations in maize-based foods are generally low in western countries, where industrial food production and consumption is more intense. In contrast, corn grown in South America, and Africa is more often infected by fungi producing fumonisin due to unfavorable climatic conditions and improper planting and storage conditions (Dutton, 2009). FB1 is defined by IARC as a possible human carcinogen in Group 2B, and shows genotoxic activity via oxidative stress, DNA damage, cell cycle arrest, apoptosis, inhibition of mitochondrial respiration and deregulation of calcium homeostasis (Radić et al., 2019). However, the question of whether fumonisins have genotoxic effects is still controversial, and data in the literature do not fully support the assumption that FB1 is a genotoxin. It has been stated in some studies that FB1 is a genotoxic compound (Domijan et al., 2015) and the underlying reason is oxidative stress-increasing effect (Mary et al., 2012). In addition, it is stated that it may have genotoxic effects with changes in DNA methylase/demethylase balance and epigenetic mechanisms such as DNA hypomethylation. Other physiopathological features of fumonisins are that they inhibit ceramide synthase activity and cause imbalances in cell lipid metabolism. It is also estimated that the deterioration of FB1-induced sphingolipid metabolism plays a key role in FB1 toxicity. Ceramide and sphingosine-1-phosphate (S1P) play opposite roles in mammalian cells, and their relative levels can affect the final destiny of the cell. Fumonisins change apoptosis balance by causing ceramide depletion, accumulation of sphing and high sphingosine 1-phosphate (S1P) production (Claudino-Silva et al., 2018). However, it is stated that the apoptotic effects of fumonisins are still controversial. It was defined as pro-apoptotic (Ribeiro et al. 2010; Jones et al. 2001) or anti-apoptotic (Boppana et al., 2014; Mullen et al., 2012). However, it has been suggested that decreased ceramide or increased production of S1P may result increased tumor formation in cancer cells and the development of drug resistance mechanisms in these cells (Bondy et al., 2012). One of the most prominent features of FB1-

borne tumors is their aggressive growth characteristics and their high metastasis potential (Müller et al., 2002).

It is stated that these negative effects of fumonisins can be reduced/prevented with some probiotics and herbal extracts. Lactic acid bacteria (*Lactobacillus paracasei* BEJ01) (Abbès et al., 2016) and gingseng extract (Hassan et al., 2015) suppress increased DNA fragmentation and increase antioxidant enzyme levels. Extracts of *Aquilegia vulgaris* L. have also been found to be protective against FB1-induced oxidative stress and cytotoxicity (Hassan et al., 2010).

3.5 Zearalenone

Zearalenon (ZEA), a macrocyclic resorcyclic acid lactone, is a non-steroidal estrogenic mycotoxin produced by Fusarium fungi. The European Union stated that the maximum ZEA level for unprocessed grains should be 100 µg/kg (EC, 2007). ZEA is found in barley, rice, corn and other grains on almost all continents and can also be classified as xeno-estrogen due to its chemical similarity to estrogen. ZEA's estrogen-like nature (shows 17β-estradiol-like activity) allows it to bind to estrogen receptors and causes biological accumulation. Although ZEA and its metabolites (α-ZOL and β-ZOL) are excreted through feces and urine as both free compounds and glucuronide conjugates, their bioaccumulation can lead to disruption of the hormonal balance of the body and, as a result, they may cause numerous reproductive system diseases such as prostate, ovarian, cervical or breast cancer. It is also stated that ZEA can cause phagolysosomal damage in the kidneys (Gao et al., 2013). The mutagenic activity of ZEA, which is also stated to cause genotoxic activity by causing micronucleus and chromosome aberrations, DNA strand breaks and DNA addictions, is still a matter of debate. ZEA, listed as a Group 3 carcinogen by IARC, has been reported to induce spontaneous breast tumors, hepatocarcinoma, and esophageal cancer incidence, increase cell proliferation in MCF-7 breast cancer cells and neuroblastoma SK-N-SH cells (Abassi et al., 2016). In addition, it has been stated that exposure to ZEA in embryonic kidney cells (HEK293) causes DNA strand breaks dose dependently (Gao et al., 2013).

There is evidence that the negative effects of ZEA, which exhibit high stability during storage and do not deteriorate when exposed to high temperatures, can be eliminated by some nutritional components and probiotic bacteria. Belgacem et al. (2019) stated that ZEA causes an increase in the frequency of polychromatic erythrocyte and chromosomal abnormalities in bone marrow cells, and they also showed that *Lactobacillus plantarum* MON03 strain prevents this increase and consequently may be protective against DNA fragmentation and genotoxic activity. In a study on colorectal carcinoma cells (HCT-116), kefir was found to be protective against increased cell proliferation and oxidative stress caused by ZEA (Golli-Bennour et al., 2019). The protective role of plant secondary metabolites against the adverse effects of ZEA has also been frequently investigated. It is stated that 4-methylthio-3-butenyl isothiocyanate extracted from *Raphanus sativus* may be protective against the genotoxic and clastogenic effects of ZEA (Salah- Abbès et al., 2009). Vitamin E has also been found to be protective against increased ZEA induced unscheduled DNA synthesis and chromosomal aberrations (Ben Othmen et al., 2008).

3.6 Trichothecenes

Trichothecenes (C-4, C-15) are divided into macrocyclic and non-macrocyclic trichothecenes and are generally found in barley, wheat, rye, corn and oats. More than 180 trictothecene mycotoxins have been identified in the last 40 years, and its epoxy group (C-12, C-13) is thought to be responsible for toxic effects. Clinical signs of exposure to trichothecenes are; emesis, weight loss, immunomodulation, coagulopathy, bleeding and cellular necrosis of mitotically active tissues (intestinal mucosa, skin, bone marrow, ovary, testicle, spleen) (Mostrom and Raisbeck, 2007). The most toxic members of trichothecene, which are classified in four groups as A, B, C and D, are T-2 toxin from group A and Deoxynvalenol (DON) toxin from group B. It is stated that T-2 toxin, which belongs to class A of trichothecene, is frequently detected in cereal samples taken from EU member countries (Escriva et al., 2015). T-2 toxin inhibits protein synthesis and subsequently disrupts DNA and RNA synthesis. In addition, exposure to this toxin is associated with leukopenia in lymphoid organs, inhibition of erythropoiesis in the bone marrow and spleen. The genotoxic mechanism of T-2 toxin, which has an immunosuppressant feature that disrupts the maturation process of dendritic cells by reducing the proliferative response of lymphocytes, is not fully known. However, it is thought that genotoxic activity of T-2 due to neutralizing glutathione, inducing lipid peroxidation, disrupting DNA and RNA synthesis. The tolerable maximum level of T-2 toxin and its major metabolite HT-2 toxin, was determined as 100 ng/kg/bw (EFSA, 2011).

DON, one of the best known trichothecenes and classified as group 3 carcinogen, inhibits protein synthesis by interfering with the active peptidyl transferase region in ribosomes. In addition, binding of DON to the ribosome in eukaryotic cells creates a "ribotoxic stress response" involving phosphorylation of mitogen-activated protein kinases (MAPKs). MAPKs activation modulates the expression of genes associated with immune response, chemotaxis, inflammation and apoptosis (Escriva et al., 2015). The maximum tolerable daily intake has been set at 1μg/kg/bw by FAO/WHO (JECFA, 2011).

It was found that DON increased DNA damage by 46.8% in chicken lymphocytes and it was stated that consuming DON-contaminated diets in combination with low protein feed may induce DNA damage (Awad et al., 2012). Yang et al. (2014) stated that DON causes chromosome and DNA damage, reduces cell viability, increases lipid peroxidation, 8-OHdG and reactive oxygen species. In addition to the oxidative stress caused by DON's genotoxic activity, it has been shown to reduce the expression of HO-1 protein and prevent DNA repair.

Although it is stated that NIV from another B group trichothecene induces chromosomal aberration in fibroblast cells, it is stated that data obtained from sister chromatid exchange test, chromosomal abnormality test and Comet test are contradictory and a definitive assessment cannot be made about the genotoxic effect of NIV (Becit et al. 2017). Satratoxin H from group D trichothecene has structurally similar to T-2 toxin but 5 times more toxic than T-2. It has been reported that NIV caused apoptosis, increased DNA fragmentation and strand breaks in pheochromocytoma cells (PC-12) (Nusuetrong et al., 2012). Studies on protective compounds that are thought to reduce the genotoxic effect of trichothecenes are ongoing. It is stated that Silymarin and inulin nanoparticles decreased high liver enzyme activity, chromosomal damage, DNA fragmentation, oxidative stress and negative histological changes in liver tissue (Abdel-Wahhab et al., 2018).

3.7 Ergot Alkaloids

Claviceps purpurea can synthesize about 40 Ergot alkaloids (EAs) with various chemical structures, and these alkaloids can turn into lysergic acid, which is toxic to humans and animals. EAs may be an agonist or antagonist to noradrenaline, dopamine and serotonin neurotransmitters because compounds derived from D-lisergic acid are structurally similar to these neurotransmitters. The most known EAs are Ergometrin, Ergokornin, Ergokristin, Ergokriptin, Ergosin and Ergotamin. These toxins are mostly found in cereal products such as rye, wheat, barley, corn, triticale, oats, millet and sorghum (Bryla et al., 2019). Although there are no regulations regarding maximum EAs limits in unprocessed grain or corn products in the European Union, the concentration of ergot sclerotia in unprocessed grains is legally limited to 0.5 g/kg/bw. However, it is stated that this limit may threaten human health due to the presence of significant amount of EAs in cereal samples containing less than 0.5 g/kg/bw ergot sclerotia (Bryla et al., 2018).

Ergot poisoning can cause physiological problems such as vasoconstriction/vasodilation, diarrhea, gangrene, miscarriage, internal bleeding, uncontrolled muscle contractions, as well as psychological problems (hallucinations). Another feature of these alkaloids is that their cytotoxic effects. In a study evaluating the cytotoxic effect of Ergometrin, Ergokornin, Ergokristin, Ergokriptin, Ergosin and Ergotamin, it was determined that EAs except Ergometrin showed cytotoxic effect and caused apoptosis (Mulac and Humpf 2011). Studies on the genotoxic activity of EA's are very limited. In EFSA's report (2012), it was stated that genotoxicity studies related to EAs' except ergotamine are insufficient. Studies evaluating the genotoxic and mutagenic effects of ergotamine revealed different results. In the study of Roberets and Rand (1977), it was stated that ergotamine can induce chromosomal abnormalities in human lymphocytes and leukocytes. Seifried et al. (2006) found that Ergotamine does not show mutagenic effects in mouse lymphoma cells. In another study, it has been reported that ergotamine and ergometry are inducers of sister chromatid change in ovarian cells, ergocristine is slightly inductive and ergocriptine is not effective (Dighe and Vaidya, 1988). Further studies are need to evaluate genotoxic and mutagenic efficacy of EAs.

4. Conclusion

According to the Food and Agriculture Organization, World Health Organization and some scientific data, a significant part of the edible foods in the world, especially cereals, are contaminated with mold and fungi. Therefore, a significant part of the world population is exposed to chronic mycotoxin exposure. Many studies have reported that chronic mycotoxin exposure causes genotoxicity by triggering oxidative stress, inhibiting protein synthesis, creating DNA addition products, altering DNA methylation, causing lipid peroxidation. Therefore, it is essential to develop measures to reduce or prevent genotoxic effects of chronic mycotoxin exposure.

Compliance with ethical standards

Conflict of interest The author declares that there are no conflicts of interest regarding the publication of this paper.

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Mycotoxin	Biological sample/ Cell line	Damage	Ref.
AFB1	HepG2 cells, Huh7 cells, HCT116 cells	* The treatment of HepG2 hepatoma cells with mutation-inducing doses (3–5 mmol/l) of AFB1 induced DNA adducts, 8-hydroxyguanine lesions and DNA strand breaks. Persistent phospho-H2AX and 53BP1 foci were also detected, but cell growth was not affected. * AFB1-exposed HepG2 cells formed phospho-H2AX and 53BP1 foci, but failed to phosphorylate both Chk1 and Chk2. * AFB1-exposed cells did not show p53-dependent G1 arrest or a sustained G2/M arrest. *Genotoxic doses of AFB1 induce an incomplete and inefficient checkpoint response in human cells.	Yüzügüllü et al. 2011
AFB1, AFB2, AFG1, AFG2, AFM1	HepG2 cells, ACHN cells, LS-174T cells	* AFB1 and AFG1 demonstrated a genotoxic potential in all the cell lines tested with different potencies. * AFM1 was genotoxic only at the highest concentration tested (10 μM) and only in the LS-174T cells * AFB2 and AFG2 were not genotoxic whatever the cell line tested * Based on these results the genotoxic potencies of aflatoxins were in the following order: AFB1 and AFG1 > AFM1.	Theumer et al. 2018
AFB1	Grass carp (*Ctenopharyngodon idella*)	* The genotoxicity of AFB1 was only recorded in groups which were exposed to 75 ppb and 100 ppb AFB1 per kg of diet exhibiting micronuclei frequency percentage of 0.85 and 2.15% respectively. * The histopathological study revealed that higher concentrations of AFB1 were causing pathological changes in liver, kidney, intestine and gills tissue.	Khan et al. 2019
AFB1, T-2 toxin, Vomitoxin	Salmonella typhimurium	* Whereas the individual trichothecene mycotoxins (T-2 toxin, vomitoxin) did not show any mutagenic activity in the test systems mentioned, in combination with AFB1, or as a combination of all three mycotoxins, they showed a mutagenic effect significantly greater than AFB1 alone in the Ames test (in strain TA98 at all concentrations) as well as in the micronucleus test (combination of T-2 toxin with AFB1).	Smerak et al. 2001
AFB1, OTA	Fisher 344 rats (bonemarrow, liver and kidney cells)	* With regard to the micronucleus assay, positive results were obtained for AFB1 (0.25 mg/kg b.w.) and negative results were obtained for OTA (0.5 mg/kg b.w.). * In the comet assay, positive results were obtained for AFB1 in the liver and for OTA in the kidney.	Corcuera et al. 2015
OTA	Male Wistar rats (proximal tubule cells)	* Ochratoxin A treatment caused increased apoptosis, inflammation and oxidative stress gene expressions in rat kidney.	Luhe et al. 2003
OTA	Vero-E6 cell line	* OTA modestly increased the % of DNA in tail, revealing the presence of oxidative DNA lesions.	Costa et al. 2016
OTA, PAT	Caco-2 human colon cancer cells	* Cells exposure to several OTA concentrations induced neither a significant level of DNA damage nor oxidative DNA damage. Likewise, PAT concentrations up to 6 μM did not increase the level of DNA breaks. However, the highest concentration of 12 μM caused a marked damaging effect on cells' DNA. * The combination of several PAT concentrations (0.7, 2 and 6 μM) with 120 μM of OTA produced a very high level of DNA damage	Assunção et al. 2019
OTA, FB1	Human peripheral blood lymphocytes	*Both mycotoxins, OTA (4 μmol/l) and FB1 (20 μg/ml), induced DNA damage in human peripheral blood lymphocytes already after 1 h exposure	Domijan et al. 2015
OTA, CTN	Balb/c male mice, Vero cells	* Cultured renal cells respond to OTA and CTN exposure by a moderate and weak inhibition of cell proliferation. However, when combined, they exert a significant increase in inhibition of cell viability. Similar results were found for the investigated genotoxicity end-points (DNA fragmentation and chromosome aberrations).	Bouslimi et al. 2008
PAT	Human hepatoma HepG2 cells	*A significant increase of the micronuclei frequency induced by PAT was found in human hepatoma HepG2 cells.	Zhou et al. 2009
PAT	Brain, kidney, liver and urinary bladder	* The effect of patulin was dose-dependent and the highest patulin dose (3.75 mg/kg intraperitoneally) induced DNA strand breaks in the brain, liver and kidneys.	De Melo et al. 2012
PAT	Bone marrow cell	*In bone marrow cell, PAT was found to induce micronucleus and chromosomal aberration formation	Song et al. 2014
FB1	HepG2 cells	*FB1 caused a pronounced dose-dependent genotoxic effect at exposure concentrations ≥ 25 μg/ml. FB1 is clastogenic in human derived cells and this mycotoxin may act as a genotoxic carcinogen in humans.	Ehrlich et al. 2002
FB1	Rabbit kidney cells	* Exposure to FB1 caused a significant increase in micronucleus frequency in a concentration- and in a time-dependent manner.	Rumora et al. 2002
FB1	Male Wistar inbred rats	*The DNA damage was found in 81.7% (comet assay) and in 7.0% (micronucleus technique) in group fed with contamined diet containing 100 ppm of FB1. FB1 caused oxidative stress mediated genotoxicity.	Theumer et al. 2010
FB1 FB2	A549 cells, THP-1 cells	* In A549 cells DNA damaging effect of FB1 was slightly higher than that of FB2. While no significant changes were observed in comet tail length.	Jakšić et al. 2018
FB1	Male fingerlings	*Fumonisins B1+B2 changed the expression of genes in apoptosis balance. As the period of consumption and level of fumonisin are increased, the numerical relationship between	Claudino-

FB2		SPL:CASP7 (sphingosine phosphate lyase:caspase 7) mRNA was also increased.	Silva et al. 2018
FB1 FB2 FB3	Human lymphocytes and *Allium cepa* (onion)	*Cytogenetic studies using FB1, FB2 and FB3 levels gave positive results for the higher concentrations (5 and 10 µg/g) with FB1. As regards the cytogenetic aspect of FB1, it is found that an increase in the incidence of genetic damage measured by chromosomal aberrations, sister chromatid exchange, micronuclei and chromosomal aberrations in Allium cepa. These results indicate that human lymphocytes cells and plants cells (Allium cepa) have a very sensitive cellular response to the mycotoxin fumonisin B1 as observed at the highest concentrations.	Lerda et al. 2005
ZEA	HEK293 cells	*Exposure of human embryonic kidney (HEK293) cells to ZEA (10 or 20 µM) resulted in a concentration dependent increase in DNA strand breaks measured with the comet assay.	Gao et al. 2013
ZEA	Ovarian somatic cells, porcine granulosa cells	* RT-qPCR, immunofluorescence and western blot analysis further confirmed the expression of DNA damage and repair related genes (γ- H2AX, BRCA1, RAD51 and PRKDC) were increased in ZEA exposed granulosa cells.	Liu et al. 2018
ZEA	Balb/c female mice (bone marrow cells)	*The results show that ZEN was cytotoxic and genotoxic to mice as indicated by the increase in frequencies of polychromatic erythrocytes micronucleated (PCEMN) and chromosomal aberrations in bone marrow cells. In the small intestine ZEN was increased DNA fragmentation, down regulated the expressions of caspase-3, caspase-9, and Bax as well as up-regulated the expression of Bcl-2 and their target proteins.	Belgacem et al. 2019
ZEA, α-ZOL, β-ZOL	Balb/c (bone marrow cells), HeLa cells	*ZEA as well as α - and β -ZOL increased the percentage of chromosome aberrations in mouse bone-marrow cells and in HeLa cells. In the two systems, ZEN and α -ZOL exhibited the same range of genotoxicity and both were more genotoxic than β -ZOL.	Ayed et al. 2011
T-2 toxin	Pregnant Wistar: Slc rats (liver, placenta and fetal liver)	* The expression of oxidative stress-related gene including heat shock protein 70 and apoptosis-related genes including caspase-2 and insulin-like growth factor-binding protein 3 were upregulated by T-2 toxin treatment.	Sehata et al. 2004
DON	Human monocytes and peripheral blood mononuclear cell	*Deoxynivalenol treatment (250-1000 ng/mL) caused an increase in interleukin 8 mRNA abundance.	Islam et al. 2006
DON	Chicken lymphocytes	* The diets contaminated with the mycotoxin DON at moderate levels in combination with low-protein feed are able to induce lymphocyte DNA damage in chickens.	Awad et al. 2012
DON	Human peripheral blood lymphocytes	*DON was able to decrease cell viability and cause damage to the membrane, the chromosomes or the DNA at all times of culture *The results of the RT-PCR and the Western Blot indicated that DON is able to enhance mRNA or protein expressions of DNA repair genes and HO-1 in 6 h and to inhibit these expressions in 24 h. DON potentially triggers genotoxicity in human lymphocytes.	Yang et al. 2014
DON	Sprague dawley rats (liver and bone marrow)	* DON increased the percentage of chromosomal aberration, DNA fragmentation and comet score	Abdel-Wahhab et al. 2018
Citrinin (CTN)	Human peripheral blood lymphocytes	* CTN caused a significant concentration-dependent increase in micronucleus (MN) frequency in human lymphocytes. * All the CTN concentrations (60µM, 80µM and 100µM)led to a clear decrease in the percentages of binucleated/mononucleated cells. *CTN at high concentrations is genotoxic in cultured human lymphocytes	Altuntaş et al. 2007
CTN	Human enterocyte-like Caco-2 cell-line	* For both toxins, a 3 h exposure did not cause any DNA damage, unlike after 24 and 72 h exposure in post confluent Caco-2 cells where DNA damage was significantly observed with a dose-dependent relationship. * In dividing cells, only FusX increases DNA strand breaks in the 0.01–0.05µM range after 72 h.	Bony et al. 2007

HepG2: Human hepatoblastoma cells; **ACHN**: Human renal adenocarcinoma cells; **LS-174T**: Human epithelial colorectal adenocarcinoma cells; **Huh7:** Human liver cell line; **HCT116:** Human colon cancer cell line; **A549:** Adenocarcinomic human alveolar basal epithelial cells; **THP-1:** Human leukemia monocytic cell line. **HEK293:** Human embryonic kidney cells; **Vero-E6:** The green monkey kidney cells

This is a review manuscript and did not need ethical approval

Declaration of interests (Aslı UÇAR)

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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