Mycotoxin-induced toxicity; an updated mini-review on the current concepts

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Abstract

Since the secondary fungal metabolites, mycotoxins, are easily the most widespread, hence, it is difficult to delete them. On the other hands, mycotoxins are acutely and chronically toxic to animals and humans. Mycotoxins contamination induced oxidative stress and apoptosis; consequently, they involved in the regulation of gene expression. Additionally, challenging with mycotoxins caused the prevalence of many health problems especially for humans including genotoxicity, immunotoxicity, hepatotoxicity, neurotoxicity as well as nephrotoxicity.

Introduction

Molds produce more than 400 different mycotoxins that are toxic to humans (1). Mycotoxins are considered to be the secondary metabolites of fungi that produce in crops and foods in either pre-harvest or post-harvest (2). The most common fungi produced mycotoxins, are Aspergillus families (3) including A. flavus, A. parasiticus and A. ochraceus, Fusarium species (4), and also Fumonisin moniliforme (5). Mycotoxins have been increasingly attracting the concern of health organizations due to their ubiquitous nature of fungi; thus, their occurrence in feeds cannot be ignored (6). Interestingly, it has been estimated that 25% of the world’s crop such as nuts, cereals and rice is contaminated by mould and fungal growth, as reviewed by according to the United Nations Food and Agriculture Organization (7) and the World Health Organization (8). The effects of mycotoxins on human health depend on dosage, length of exposure, type of mycotoxins, and physiological and nutritional status (9). There are several health problems including gastrointestinal pain, diarrhea and liver cancer (10), as well as retarded growth and development in livestock and humans being (11), as evidenced by several studies. Furthermore, mycotoxins serve as potent immunosuppressive agents negatively affecting immune cells (12).

Materials and Methods

This mini-review article discusses the physiological mechanism responsible for cisplatin nephrotoxicity. For this review, we used a variety of sources by searching through Web of Science, PubMed, EMBASE, Scopus, EBSCO and directory of open access journals (DOAJ). The search was performed using combinations of the following key words and or their equivalents such as mycotoxins, immunotoxicity, hepatotoxicity, genotoxicity and nephrotoxicity.

Key Point

Mycotoxins, the secondary metabolites of fungi, are easily widespread. They negatively affect many organs and systems including liver, immune and nervous systems and also even at the cell “gene”. They, therefore, could bind to DNA and consequently produce DNA adducts.

Mycotoxins

Mycotoxins consisted of aflatoxins (13), fumonisin (5), ochratoxins (14), zeralenon (15) and also deoxynivalenol (16). There are five subfamilies of aflatoxins including B1, B2, G1, G2, and M1 (17), but aflatoxin B1 is considered to be the most mutagenic and carcinogenic metabolites amongst aflatoxins (18). The toxic effects of mycotoxins on human and animal health are known as mycotoxicosis (19). Fungal secondary metabolites, mycotoxins, have been well known as “silent killers”, “invisible thieves”, “unavoidable contaminants”, and “natural toxicants” (20).

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Humans are exposed to mycotoxins via intake of plants and human products contaminated with mycotoxins (2). For instance, a proportion of aflatoxins including M1 and M2 is hydroxylated and excreted in milk, when aflatoxins B1 and B2 are consumed by lactating cows (21). In addition, humans fed on the high levels of deoxynivalenol in China showed gastrointestinal pains (22). Additionally, the outbreak of gastrointestinal problems was observed in people consumed wheat contaminated with deoxynivalenol in India (23). Notably, exposure to mycotoxins elevated the outbreak of infection diseases, which resulted from bacteria, viruses and other fungi, in animals (24).

With respect to several studies, mycotoxins contamination led to the outbreak of immunotoxicity, genotoxicity, hepatotoxicity, nephrotoxicity and neurotoxicity (Figure 1). Evidence showed that membrane-active properties of mycotoxins manifest their toxicity; because alterations of fatty acid composition in the membrane lead to detrimental effects (25). Since mycotoxins has the detrimental effects on human health and on the other hand, amongst all adverse effects of mycotoxins, immunotoxicity is known to be the most widespread consequence of mycotoxicosis (12), so, the aim of this study was to evaluate the effects of mycotoxins on health and highlighted immunotoxicity effects.

**Hepatotoxicity**

Liver is considered to be biologically active organs in metabolism, excretion and detoxification (26,27). When mycotoxins absorb in the gastrointestinal tract, they transfer to liver; thereby, injuring the liver (28). Hepatocellular carcinoma is known to be the most common disease and the forth cause of death (29). It was reported that there is high correlation between the occurrences of hepatocellular carcinoma and aflatoxin B1 challenge (13). Notably, it is estimated that 5%-30% of liver cancer is caused by aflatoxin intake (30). The highest outbreak of liver cancer approximately 40% is reported to be in Africa (30). In this regard, the incidence of hepatocellular carcinoma is logarithmically raised as the level of aflatoxins intake is elevated (13,31).

Furthermore, some studies have been showed that exposure to mycotoxins induced hepatic histopathology alterations including bile duct proliferation, periductal fibrosis and cholestasis (32). In this case, Bakeer et al (33) studied the effects of mycotoxins (aflatoxin, and ochratoxin) on hepatic histopathology in broilers. They found that aflatoxin challenge induced Kupffer cells activation, sinusoidal dilation and periacinar hepatic necrosis and hepatocellular vacuolations in broiler chicks. Additionally, Ortatatlci et al (31) reported that feeding diets containing 100 ppb aflatoxin displayed hydropic degeneration and fatty vacuoles in hepatocytes when compared to control. Also, Krishnamoorthy et al (34) exhibited pale, enlarged liver, hepatocytes necrosis and also bile duct hyperplasia in chicks exposed to T-2 toxin.

**Nephrotoxicity**

Many studies have been demonstrated that long time exposure to mycotoxins is account for nephropathies and urinary tract tumors (35). High levels of ochratoxin A in the serum is an indicative of chronic nephropathy (36). Ochratoxin A binds to a serum macromolecule of low relative molecular weight accounting for the nephrotoxic effects in mammals due to its accumulation in the kidney (37). Ali and Abdu (38) studied the effect of ochratoxin A on rats’ kidney. They found that ochratoxin A treatment caused the declines in kidney weight and its relative weight and the increases in serum urea and creatinine levels. Furthermore, animal study reported that ochratoxin A treatment increased renal disease followed by proximal tubular atrophy and also cortical interstitial fibrosis (39).

**Genotoxicity**

Mycotoxins seem to interact with DNA and other macromolecules; as the consequence, mycotoxins are referred to be carcinogenic, mutagenic, teratogenic (40). Combinations of T-2 toxins and aflatoxin B1 are the strongest mutagens (41). Sehata et al (42) studied the alterations in gene expression induced by T-2 toxin in the fetal brain of pregnant rats. In this case, 2 mg/kg T-2 toxin are orally administrated in rats on day of 13 of gestation. They found that 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 pro-

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**Figure 1.** Major mechanisms of mycotoxin toxicity (adapted from References 12 and 26).
tein 3 were upregulated by T-2 toxin treatment. Islam et al (43) searched the effects of the deoxynivalenol on expression of interleukin-8 gene in cloned human monocytes and peripheral blood mononuclear cells. They showed that deoxynivalenol treatment (250–1000 ng/mL) caused an increase in interleukin 8 mRNA abundance. Luhe et al (44) found the increased apoptosis, inflammation and oxidative stress gene expressions in rat kidney as the consequence of ochratoxin A treatment.

**Immunotoxicity**
The immune system is considered to be a crucial defensive mechanism against invading pathogenic bacteria and foreign cells (45). The specialized cells of immune system interact with each other to produce the desired consequences (45).

It has been found that the effect of mycotoxins on immune system is either suppressive or stimulator depending on the time, duration and dose of exposure (46). Previous study has been found that there is a potent association between aflatoxins contamination and immunosuppression, reflecting that intake of aflatoxins increased the susceptibility of humans to infections (47). Girish and Smith (48) found that mycotoxins induce immunosuppression through several mechanisms, as evidenced by the decreased antibody production against antigens, the retarded hypersensitivity response, the decreased systemic bacterial clearance, the depressed lymphocyte proliferation, the suppressed macrophage phagocyte activity, the altered CD4+/CD8+ ratio, and also the decreased immune organ weights. Many studies have indicated that mycotoxins especially aflatoxin B1 interact with biomolecules namely DNA; in turn, altering their actions (40). Mycotoxins always inhibit protein synthesis; consequently, they adversely influence immune cell proliferation (49). In addition, mycotoxins are cytotoxic especially lymphocytes due to their impacts on membranes (50). Immune cells have the high level of polyunsaturated fatty acids on their membrane and receptors; thus, free radicals-induced by mycotoxins impose these cells to damage (50). On the other hand, mycotoxins negatively affect the receptors on the surface of macrophages, neutrophils and lymphocytes; as the results, they induce miscommunication between immune cells resulting in immunosuppression (20).

It has been also demonstrated that the susceptibility of immune system to immunotoxicity resulted from mycotoxins is probably related to the sensitivity of immune cells to proliferation and differentiation that interfere with immune-mediated activities and consequently affect cellular and humoral immunity (51). Mycotoxins not only are cytotoxic to macrophage, but also they suppress humoral immunity (51). In this regards, ochratoxin A is considered to suppress natural killer cell activity via inhibition of interferon production (52). Gliotoxin is known to inhibit the lymphocyte stimulation, cytotoxic T cell activation and gamma interferon production (53). Deoxynivalenol exposure causes the inhibition in protein biosynthesis and consequently the alteration in pro-inflammatory cytokine production (54). Deoxynivalenol intoxication predisposed the animals to infectious diseases (54). Moreover, deoxynivalenol challenge negatively affects the production of TNF-α from the macrophages (55). Chronic exposure to 10 mg deoxynivalenol/kg feed suppressed the plasma TNF-α level responsible for inflammation (55). The levels of mRNA of interleukins 1β, 6 and 12 were increased after oral challenge with 5 to 25 mg of deoxynivalenol/kg body weight (56).

**Conclusion**
Taken together, mycotoxins are widespread and their controls are approximately impossible due to their natures. Many studies have indicated that mycotoxins have several adverse effects (including immunotoxicity, hepatotoxicity, nephrotoxicity and also genotoxicity) on animal and human health. Amongst mycotoxins toxicities, immunotoxicity is more dangerous than other their effects.

**Author’s contribution**
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**Ethical considerations**
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