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Review

Modified mycotoxins: An updated review on their formation, detection, occurrence, and toxic effects

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ABSTRACT

Modified mycotoxins are metabolites that normally remain undetected during the testing for parent mycotoxin. These modified forms of mycotoxins can be produced by fungi or generated as part of the defense mechanism of the infected plant. In some cases, they are formed during food processing. The various processing steps greatly affect mycotoxin levels present in the final product (free and modified), although the results are still controversial regarding the increase or reduction of these levels, being strongly related to the type of process and the composition of the food in question. Evidence exists that some modified mycotoxins can be converted into the parent mycotoxin during digestion in humans and animals, potentially leading to adverse health effects. Some of these formed compounds can be even more toxic, in case they have higher bioaccessibility and bioavailability than the parent mycotoxin. The modified mycotoxins can occur simultaneously with the free mycotoxin, and, in some cases, the concentration of modified mycotoxins may exceed the level of free mycotoxin in processed foods. Even though toxicological data are scarce, the possibility of modified mycotoxin conversion to its free form may result in a potential risk to human and animal health. This review aims to update information on the formation, detection, occurrence, and toxic effects caused by modified mycotoxin.

1. Introduction

Mycotoxins are toxic secondary compounds synthesized under specific conditions by certain fungal species capable of growing in a wide variety of foods. The most common mycotoxins are: aflatoxins; ochratoxin A (OTA); citrinin; patulin; trichothecenes: deoxynivalenol (DON), T2 toxin (T2) and HT2 toxin (HT2); fumonisins and zearalenone (ZEN). These metabolites are produced mainly by fungi of the genera *Aspergillus*, *Fusarium*, *Penicillium*, and *Alternaria* (Anfossi et al., 2016).

Several fungal species can produce the same mycotoxin, and one single species can synthesize more than one mycotoxin. However, the growth of the toxigenic fungi does not necessarily imply mycotoxin production. Similarly, the absence of mycotoxin is not ensured by the elimination of fungi, as it may have been produced before the inactivation of the fungi (Turner et al., 2009).

The growth of toxigenic fungi and mycotoxin production can occur at all stages of production and processing (Yogendrarajah et al., 2014). Their growth is largely dependent on environmental factors such as microbial competition, nutrient availability and substrate structure, activity water, pH, temperature, relative humidity, presence of insects, and application of fungicides and pesticides (Anfossi et al., 2016; Hameed et al., 2013). However, such factors have a different influence on fungal growth and mycotoxin production. Despite this, it is known that these factors are usually stricter for mycotoxins production than for fungal growth (Garcia et al., 2009). Therefore, it is difficult to describe a set of environmental conditions that will foster both fungal growth and mycotoxin production (Cast, 2003).

Mycotoxins are commonly found in cereals, fruits, and spices. However, because they are stable compounds, mycotoxins tend to remain in the final product. As such, mycotoxins are found in processed products such as beer, breads, juices, chocolate, and wine, due to the use of contaminated raw materials (Kabak, 2009; Turner et al., 2009). Two or more mycotoxins can co-occur in foods, rising the total levels of mycotoxin present and negatively affecting human and animal health

Abbreviations: 15-ADON, 15-Acetyl-deoxynivalenol; 3-ADON, 3-Acetyl-deoxynivalenol; AME, alternariol monomethyl ether; AOH, alternariol; D3G, deoxynivalenol-3-glucoside; DOM-1, de-epoxy deoxynivalenol; DON, deoxynivalenol; DON-15-GlcA, deoxynivalenol-15-glucuronide; DON15S, deoxynivalenol-15-sulfate; DON-3-GlcA, deoxynivalenol-3-glucuronide; DON3S, deoxynivalenol-3-sulfate; DON-GlcA, deoxynivalenol-glucuronide; FB1, fumonisin B1; FHB, Fusarium head blight; HFB, hydrolyzed fumonisins; HT2, HT2 toxin; HT2-3G, HT2 toxin-3-glucoside; LC-MS/MS, Liquid chromatography tandem-mass spectrometry; MS/MS, tandem-mass spectrometry; NIV-3G, Nivalenol-3-glucoside; OTA, ochratoxin A; T2, T2 toxin; T2-3G, T-2 toxin-glucoside; TCA, trichloroacetic acid; TFA, trifluoroacetic acid; ZEN, zearalenone; ZEN-14G, zearalenone-14-glucoside; ZEN-16G, zearalenone-16-glucoside; α-ZEL, α-zearalenol; α-ZEL-14G, α-zearalenol-14-glucoside; β-ZEL, β-zearalenol; β-ZEL-14G, β-zearalenol-14-glucoside

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Table 1
Major mycotoxin found in food and their modified forms.

Free mycotoxin	Major producing fungi	Matrix	Effects on health	modified mycotoxin
DON	*Fusarium culmorum; Fusarium graminearum* (Richard, 2012; Bottalico, 1998)	feed (Zhao et al., 2015), oat (Fredlund et al., 2013), cereals (Soleimany et al., 2012a), maize (Souza et al., 2008)	In animal: reduced growth and weight gain, feed refusal and emesis, affects system immune and intestinal functions. In human: nausea, diarrhea and vomiting (Bryden, 2012; Pinton et al., 2012; Pinton et al., 2009; WHO, 2002)	DON-3-glucoside; DON-Hexitol; DON-S-cysteine; DON-S-cysteinyl-glycine; DON-glutathione; DON-di-hexoside; "DON-2H"-glutathione; DON-malonylglucoside; 15-acetyl-DON-3-glucoside; 3-Acetyl-DON; DON-3-sulfate; DON-15-sulfate; 3-epimer-DON; norDON A, B and C; norDON-3-glucoside A, B, C and D; DON-3-glucoside-lactone; de-epoxy DON; DON-glucuronide; de-epoxy DON-3-sulfate; de-epoxy DON-15-sulfate;
ZEN	*Fusarium culmorum; Fusarium graminearum; Fusarium heterosporum* (Gajecka et al., 2011; Hussein and Brasel, 2001)	feed (Zhao et al., 2015), cereals (Soleimany et al., 2012b), breakfast cereals (Ibáñez-Vea et al., 2011), maize (Souza et al., 2008)	precocious pubertal changes, fertility problems and hyper estrogenic (Minervini and Dell'Aquila, 2008; Binder, 2007; IARC, 1993)	ZEN-16-O-β-glucoside; ZEN-14-O-β-glucoside; α-zearalenol; β-zearalenol; α-zearalenol-glucoside; β-zearalenol-glucoside; ZEN-4-glucoside; ZEN-4-sulfate; malonyl-glucosides (ZEN-MalGlc, α-ZEN-MalGlc, β-zearalenol-MalGlc); di-hexose- (ZEN-DiHex, α- zearalenol-DiHex, β-zearalenol-DiHex); hexose–pentose disaccharides (ZENHexPent, α-zearalenol-HexPent, β-zearalenol-HexPent); tri-hexose conjugate (β-zearalenol-TriHex); α-zearalenol-Sulfate; α-zearalenol; β- zearalenol
OTA	*Aspergillus* and *Penicillium* genera (Freire et al., 2017; Passamani et al., 2012; Serra et al., 2006)	wine (Freire et al., 2017), coffee (Leong et al., 2007), cocoa (Mounjouenpou et al., 2008), grapes (Lasram et al., 2007), cereals (Lee and Magan, 2000)	Immunosuppressive effects (Rossiello et al., 2008), teratogenic (Balasaheb et al., 2007), carcinogenic (Brown et al., 2007), mutagenic (Palma et al., 2007), neurotoxic (Sava et al., 2006) and genotoxic (Tozlovanu et al., 2006).	ochratoxin α; 4S-hydroxyochratoxin A; 4R-hydroxyochratoxin A; hydroxyochratoxin A-β-glucoside; ochratoxin A methyl ester; Ochratoxin α amide; 14-decarboxy-ochratoxin A;. Ochratoxin A mono- and disaccharide esters
T2 e HT-2	*Fusarium sporotrichioides* (Cast, 2003; Brown et al., 2001)	beer (Rubert et al., 2013), corn, wheat, barley, oats (Cast, 2003)	Inhibition protein synthesis and effects immunotoxins (WHO, 2002; Richard, 1991; Niyo et al., 1988).	HT2 toxin-3-glucoside; T-2 toxin-α-glucoside; T-2 toxin-β-glucoside; 15-acetyl-T2-tetraol-glucoside; hydroxy-HT2-glucoside; hydroxy-HT2-malonyl-glucoside; T2-triol-glucoside; dehydro-HT2-glucoside; HT2-diglucoside; HT2-malonyl-glucoside; 3-acetyl-HT2; 3-acetyl-T2; feruloyl-T2; HT2-sulfate
Fumonisin	*Fusarium proliferatum; Fusarium verticillioides; Aspergillus niger* (Varga et al., 2010; EFSA, 2005; Scott, 1993)	feed (Zhao et al., 2015), beer (Matumba et al., 2014), chili (Yogendrarajah et al., 2014), cereal (Soleimany et al., 2012a)	hepatotoxic, nephrotoxic (Binder, 2007), immunosuppressive (Marin et al., 2006), pulmonary edema in swine and leukoencephalomalacia in horses (IARC, 2002)	hidden fumonisins; N-(carboxymethyl) fumonisina B1; N-Acyl hydrolyzed fumonisin B1; bound hydrolyzed fumonisins