

Mycotoxins and oxidative stress: where are we?

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Abstract

Mycotoxins are the most common contaminants of food and feed worldwide and are considered an important risk factor for human and animal health. Oxidative stress occurs in cells when the concentration of reactive oxygen species exceeds the cell's antioxidant capacity. Oxidative stress causes DNA damage, enhances lipid peroxidation, protein damage and cell death. This review addresses the toxicity of the major mycotoxins, especially aflatoxin B₁, deoxynivalenol, nivalenol, T-2 toxin, fumonisin B₁, ochratoxin, patulin and zearalenone, in relation to oxidative stress. It summarises the data associated with oxidative stress as a plausible mechanism for mycotoxin-induced toxicity. Given the contamination caused by mycotoxins worldwide, the protective effects of a variety of natural compounds due to their antioxidant capacities have been evaluated. We review data on the ability of vitamins, flavonoids, crocin, curcumin, green tea, lycopene, phytic acid, L-carnitine, melatonin, minerals and mixtures of anti-oxidants to mitigate the toxic effect of mycotoxins associated with oxidative stress.

Keywords: antioxidants, mycotoxins, oxidative stress.

1. Introduction

Mycotoxins are secondary fungal metabolites often found as contaminants in agricultural commodities all over the world and pose a risk for human and animal health (Bennett and Klich, 2003; Wu *et al.*, 2014a). More than 400 different mycotoxins have been isolated and chemically characterised. Those of major medical and agricultural concern are aflatoxins, fumonisins, ochratoxins, trichothecenes, zearalenone (ZEA) and patulin (PAT) (Wu *et al.*, 2014a).

The molecular mechanisms behind the toxic effects of the major mycotoxins are established and oxidative stress and the generation of free radicals have been shown to be implicated in mycotoxin toxicity (Adhikari *et al.*, 2017; Wang *et al.*, 2016). Indeed, the imbalance between free radicals and the antioxidant defence systems can cause chemical damage to DNA, proteins and lipids, as observed upon exposure to mycotoxins (Assi, 2017).

As human and animal exposure to mycotoxins is unavoidable, effective ways to mitigate their harmful impacts are required. Several studies have demonstrated the beneficial effects of antioxidant substances in the prevention and treatment of various diseases (Li *et al.*, 2015). In this context, the use of natural antioxidants has been shown to mitigate and/or prevent the toxic effects of mycotoxins (Sorrenti *et al.*, 2013).

The aims of this review are first to describe the cellular mechanisms involved in the physiological control and imbalance of free radical generation; second to summarise the toxic effects of the major mycotoxins associated with oxidative stress; and third, to present the main natural antioxidants used to mitigate the toxic effects of these mycotoxins.

2. Oxidative stress: physiological control and damage caused by overproduction of free radicals

One consequence of aerobic conditions is activation of oxidative mechanisms and the subsequent generation of reactive oxygen species (ROS) (Droge, 2002). Cells have developed primary and secondary enzymatic systems to avoid ROS-induced damage (Valko *et al.*, 2007). Superoxide dismutase (SOD), catalase (CAT), glutathione reductase (GR) and glutathione peroxidase (GPx) are characterised as primary antioxidant enzymes that trigger the breakdown of free radicals or combine toxic compounds with glutathione (GSH). The mechanisms of action of these enzymes are diverse. SOD breaks down the superoxide anion radical into H_2O and O_2 , whereas CAT catalyses the decomposition of hydrogen peroxide (H_2O_2) into water and oxygen. GPx reduces hydrogen peroxide to water and GR can regenerate GSH (Droge, 2002). By contrast, glutathione S-transferase (GST), a secondary detoxification enzyme, acts by binding ROS to GSH (Hayes and Strange, 1995) or by detoxifying lipid peroxides (Pickett and Lu, 1989).

Other mechanisms, including cysteine and GSH, are also involved in physiological control of ROS generation (Droge, 2002). GSH interacts with multiple antioxidant enzymes, modulating the action of GR, GPx and GST (a decrease in GSH content reduces enzymatic activity).

A control mechanism also exists for the expression of enzymes with antioxidant activity. Control is regulated by antioxidant response elements (AREs) that are activated by nuclear factor erythroid 2-related factor 2 (Nrf2) (Jin *et al.*, 2014). Nrf2-ARE is considered to be an important signalling pathway associated with antioxidant activity. Cells subjected to oxidative stress induce Nrf2 translocation to the nucleus, thereby activating genes encoding antioxidant enzymes and detoxifying enzymes of phase II (e.g. SOD) through ARE binding. Interestingly, although high antioxidant induction is associated with Nrf2 when this pathway is activated by ROS, the response is limited because ROS also activates a cell death-signalling pathway (Jin *et al.*, 2014; Valko *et al.*, 2007).

Organelles such as peroxisomes and mitochondria provide membrane-limited compartments specialised in redox activities. Consumption of oxygen leads to the production of H_2O_2 , which oxidises some molecules. Furthermore, these organelles contribute to metabolic functions as they contain CAT, an enzyme that decomposes the H_2O_2 and prevents intracellular accumulation of this compound (Valko *et al.*, 2007). Cellular respiration in mitochondria creates one of the main superoxide production sites. During this process, ATP is produced by the electron transport chain and during energy transduction, free radical superoxide is formed,

which has been associated with the cell pathophysiology in several diseases (Droge, 2002; Valko *et al.*, 2007).

Generation of oxidative stress, free radicals, and damage to DNA, proteins and lipids

Cells in homeostasis may produce free radicals as a result of physiological reactions (cellular respiration, for example). A variety of exogenous factors can promote oxidative stress and overproduction of free radicals (Young and Woodside, 2001). Oxidative stress occurs in cells when the production of ROS, such as hydroxyl radical ($HO\cdot$), perhydroxyl radical ($HOO\cdot$), superoxide anion ($O_2^{\cdot-}$) and reactive nitrogen species (RNS) including nitric oxide (NO), exceeds the antioxidant capacity of a cell (Valko *et al.*, 2007). Changes in intracellular antioxidant systems or in the production of free radicals can result in oxidative stress (Halliwell and Whiteman, 2004). Increased ROS production alters and/or activates several intracellular mechanisms that promote oxidative damage to DNA, proteins and membrane lipids. Lipid peroxidation may also lead to cell death. The mechanisms involved in the induction of cell apoptosis caused by the generation of ROS include activation of p53, mitogen-activated protein kinases (MAPKs), caspases and changes in the Bcl-2/Bax expression (Farley *et al.*, 2006).

Cells in homeostasis are maintained in a redox state through the association of the iron and copper redox couple. However, in a situation of oxidative stress, when superoxide is overproduced, the 'free iron' (Fe^{2+}) is released into the cytoplasm. This release considerably increases the oxidative stress, and leads to the generation of other reactive radicals through the Fenton reaction. In this reaction, Fe^{2+} and H_2O_2 generate one of the most harmful radicals, the reactive hydroxyl ($Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + \cdot OH + OH^-$). Transition metal ions, mainly iron, have been implicated in the generation of highly reactive radicals leading to DNA and membrane damage. Cellular and organelle membranes are attractive targets for oxidation due to the polyunsaturated fatty acid residues of phospholipids (Birben *et al.*, 2012). Secondary ROS metabolites can be produced, including endoperoxides (cyclisation reaction) and malondialdehyde (MDA), the toxic final product of lipid peroxidation, which is potentially mutagenic (Birben *et al.*, 2012; Marnett, 1999).

The level of cytosolic calcium (Ca^{2+}) can be increased by ROS generation through an influx of extracellular Ca^{2+} or mobilisation of intracellular Ca^{2+} stores (Droge, 2002). This increase in the cytosolic Ca^{2+} level contributes to the activation of protein kinase C α and to the transcriptional induction of the activator protein 1 (AP-1), c-Fos and c-Jun (Maki *et al.*, 1992). MAPK signalling cascades are activated through a variety of membrane receptors (receptor tyrosine kinases, protein tyrosine kinases, receptors of cytokines and growth factors, and heterotrimeric G protein-coupled receptors) and are

regulated by phosphorylation and dephosphorylation on serine and/or threonine residues (Droge, 2002). The association between oxidative stress and the generation of free radicals can activate the MAPK pathway, mainly c-Jun N-terminal kinase (JNK) and p38, resulting in cell apoptosis (Allen and Tressini, 2000).

Another important free reactive radical produced in biological systems is NO. NO is a normal cellular metabolite with different functions in cells including neurotransmission, maintaining vascular tone, defence, smooth muscle relaxation and immune regulation (Bergendi *et al.*, 1999). Like with ROS, a nitrosative stress occurs following overproduction of RNS and disruption of the antioxidant system (Ridnour *et al.*, 2004). The mechanisms of cell damage induced by nitrosative stress include changes in protein structure (through nitrosylation reactions) leading to inhibition of their function (Valko *et al.*, 2007) and cell apoptosis. The induction of apoptosis by NO is associated with a decrease in the concentration of cardiolipin, an important component of the inner mitochondrial membrane. This molecule contributes to the optimal function of enzymatic systems involved in mitochondrial energy metabolism. A decrease in the cardiolipin level results in disruption of the electron transport chain, changes in mitochondria permeability and the release of cytochrome C into the cytosol (Droge, 2002). Furthermore, free radicals, such as superoxide anion and NO, are produced by phagocytic cells during the respiratory burst occurring in the inflammatory process. Together, these radicals can react to produce the peroxynitrite anion (ONOO⁻), a molecule that is a powerful oxidant and can cause DNA fragmentation and lipid oxidation.

The generation of free radicals can increase the expression of cyclooxygenase-2 (COX-2), and of arachidonic acid metabolism, promote the upregulation of proinflammatory cytokines, such as tumour necrosis factor (TNF), interleukin (IL)-1, IL-6 and IL-8, thereby inducing a chronic inflammatory response and the stimulation of more free radicals (Reuter *et al.*, 2010). Extensive data has shown that oxidative stress contributes to the inflammatory process, which, in turn, leads to overproduction of reactive radical species thereby promoting a harmful feedback process that increases cellular damage.

The primary function of the respiratory chain is to use the energy produced to transfer electrons into the mitochondrial intermembrane space. However, a small percentage of electrons escape from the mitochondrial space, producing superoxide (Birben *et al.*, 2012). In normal conditions, the production of superoxide is limited by SOD, which transforms the anion into hydrogen peroxide (Droge, 2002). Under oxidative stress, overproduction of superoxide occurs via activation of nicotine adenine dinucleotide phosphate (NADPH) and depletion of SOD

(Birben *et al.*, 2012). Under oxidative stress, some organelles including peroxisomes, mitochondria and endoplasmic reticulum (ER) are affected by the overproduction of free radicals, mainly associated with lipid peroxidation. The peroxisome damage leads to CAT depletion and intracellular accumulation of H₂O₂ (Valko *et al.*, 2007). The mitochondria are an important target for injury induced by oxidative stress caused via endogenous metabolic processes and/or exogenous oxidative influences (Guo *et al.*, 2013). The mitochondrial damage to DNA caused by oxidative stress can result in a decrease in proteins that are important for electron transport, leading to the generation of ROS and the dysregulation of organelles, which, in turn, activate cell apoptotic mechanisms (Van Houten *et al.*, 2006). Furthermore, radicals such as NO⁻ and ONOO⁻ are responsible for detrimental changes in the mitochondrial respiratory chain (Sas *et al.*, 2007). The structural changes in mitochondrial proteins result in altered function in which enzymatic systems of the electron-transport chain (nicotinamide adenine dinucleotide dehydrogenase, cytochrome-c-oxidase, and adenosine triphosphate synthase) are the main targets of the free radicals (Van Houten *et al.*, 2006).

ROS can also alter mitochondrial phospholipids resulting in lipid peroxidation, which, in turn, increases mitochondrial membrane permeability. The mitochondrial permeability transition pore (MPTP) can be induced by ROS generation due the oxidation of thiol groups on the adenine nucleotide translocator (part of the MPTP) (Valko *et al.*, 2007). ONOO⁻ can also affect mitochondrial homeostasis and energy production by inactivating enzymatic systems and promoting the release of mitochondrial Ca²⁺ (Douarre *et al.*, 2012). The intracellular elevation of the Ca²⁺ level also changes mitochondrial membrane potential (MMP) and induces the production of superoxide radicals, resulting in a vicious cycle (Douarre *et al.*, 2012). The mitochondrial excess of Ca²⁺ contributes with the formation of MPTP, to osmotic swelling and rupture of the outer mitochondrial membrane (Douarre *et al.*, 2012). These mitochondrial changes caused by oxidative stress can lead to cell apoptosis due to the release of cytochrome-c, changes in Bcl2/Bax expression (down-regulation of the Bcl2 protein and an increase in Bax expression), activation of MAPKs and casp-3 (Anuradha *et al.*, 2001; Farley *et al.*, 2006).

The ER is an organelle that regulates protein synthesis, drug detoxification, carbohydrate metabolism, lipid biosynthesis and Ca²⁺ homeostasis. Oxidative stress and ROS generation deregulate the ER functions and release Ca²⁺ into the cytosol (Minasyan *et al.*, 2017). The ER and mitochondria interact physiologically and functionally at sites called mitochondrial associated membranes. The damage to ER caused by oxidative stress results in mitochondrial dysfunction and cell apoptosis (Kim *et al.*, 2008).

3. Response to mycotoxins and oxidative stress: interaction in *in vitro*, *in vivo* and *ex vivo* models

The mycotoxins aflatoxin B₁ (AFB₁), deoxynivalenol (DON), nivalenol (NIV), fumonisin B₁ (FB₁), ochratoxin A (OTA), PAT and ZEA are the main contaminants of food and feed worldwide and have been extensively studied due their toxic effects on the human and the animal health (Wu *et al.*, 2014a). Several aspects of the intracellular action of mycotoxins have been elucidated: the induction of oxidative stress and ROS generation have become one of the major triggers of their lesional mechanisms, as observed in *in vitro*, *in vivo* and *ex vivo* studies. The oxidative stress mechanisms associated with AFB₁, DON, NIV, T-2 toxin (T-2), FB₁, OTA, PAT and ZEA are summarised in Figure 1 and 2.

Aflatoxin B₁

Aflatoxins are fungal metabolites mainly produced by *Aspergillus flavus* and *Aspergillus parasiticus* (Saini and Kaur, 2012). More than 10 forms of aflatoxins are known, among which the main ones are AFB₁, and aflatoxins B₂ (AFB₂), G₁ (AFG₁), G₂ (AFG₂), M₁ (AFM₁) and M₂ (AFM₂) (Kumar *et al.*, 2017). Aflatoxins are natural contaminants of cereals (maize, rice, oats, barley and sorghum), groundnuts, pistachio nuts, almonds, cottonseed and walnuts (Wu *et*

al., 2014a). Milk can be contaminated by AFM₁, which is a principal hydroxylated-AFB₁ metabolite biotransformed by hepatic cytochrome P450 in cows fed an AFB₁ contaminated diet (Bennet and Klick, 2003).

The toxicity of AFB₁ is mainly associated with the binding of bioactivated AFB₁-8,9-epoxide to cellular macromolecules, such as mitochondria, nuclear nucleic acids and nucleoproteins, with cytotoxic effects (Bennet and Klich, 2003).

Studies *in vitro* (Liu and Wang, 2016; Mary *et al.*, 2012; Wang *et al.*, 2017) and *in vivo* (Abdel-Wahhab and Aly, 2003; Shi *et al.*, 2015) demonstrated that oxidative stress plays a major role in the toxic effects of AFB₁. The main consequences of ROS generation induced by AFB₁ are damage to DNA (Wang *et al.*, 2017; Zhang *et al.*, 2015b) and mitochondrial lesions (Liu and Wang, 2016) as summarised in Figure 1. AFB₁ uncouples mitochondrial oxidative phosphorylation, reduces MMP and induces mitochondrial permeability (Liu and Wang, 2016; Shi *et al.*, 2015). The mitochondrial alterations associated with oxidative stress activate cytochrome C, modulate Bcl2/Bax gene expression and activate caspase 9 and caspase 3 (Liu and Wang, 2016; Mary *et al.*, 2017; Wang *et al.*, 2017) leading to cell apoptosis. Mary *et al.* (2017) also reported that hepatocytes treated with AFB₁ increase the expression

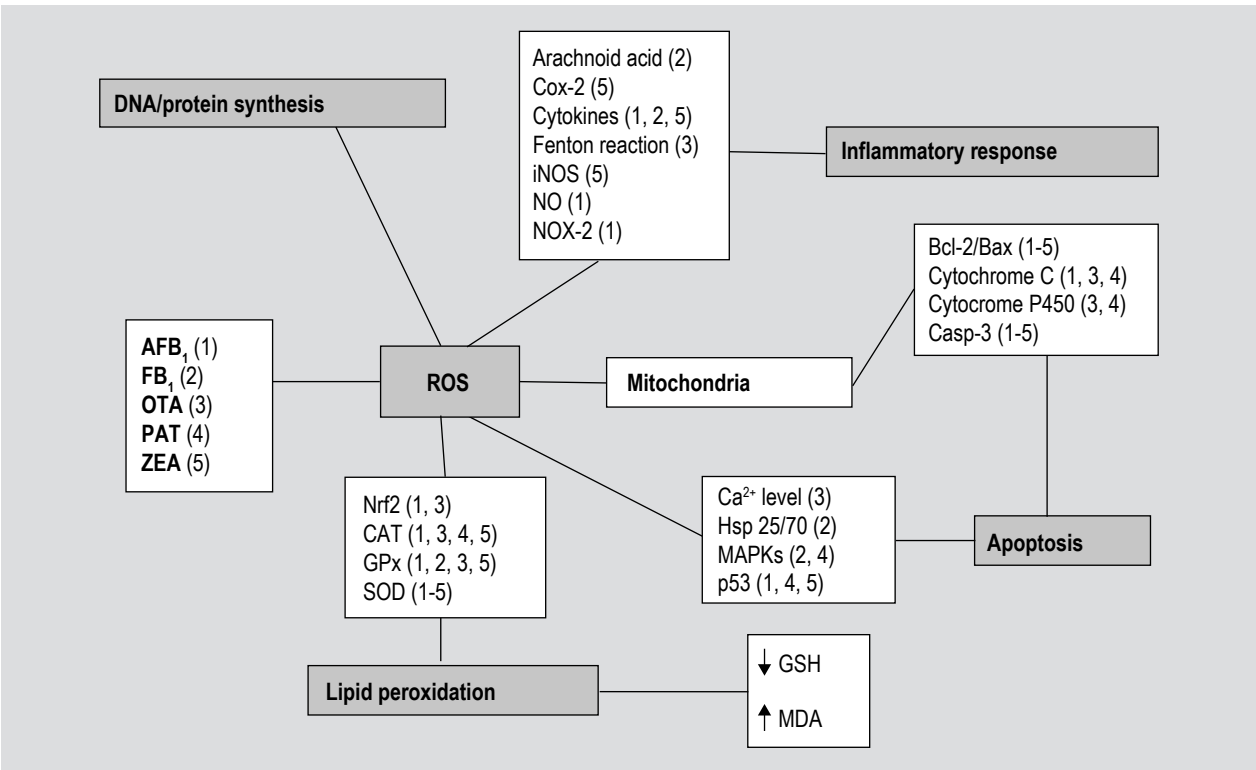


Figure 1. Summary of the intracellular lesions associated with oxidative stress induced by the main mycotoxins that contaminate food and feed. AFB₁ = aflatoxin B₁; FB₁ = fumonisin B₁; OTA = ochratoxin A; PAT = patulin; ZEA = zearalenone. The numbers between brackets indicate the mycotoxins involved in each process.

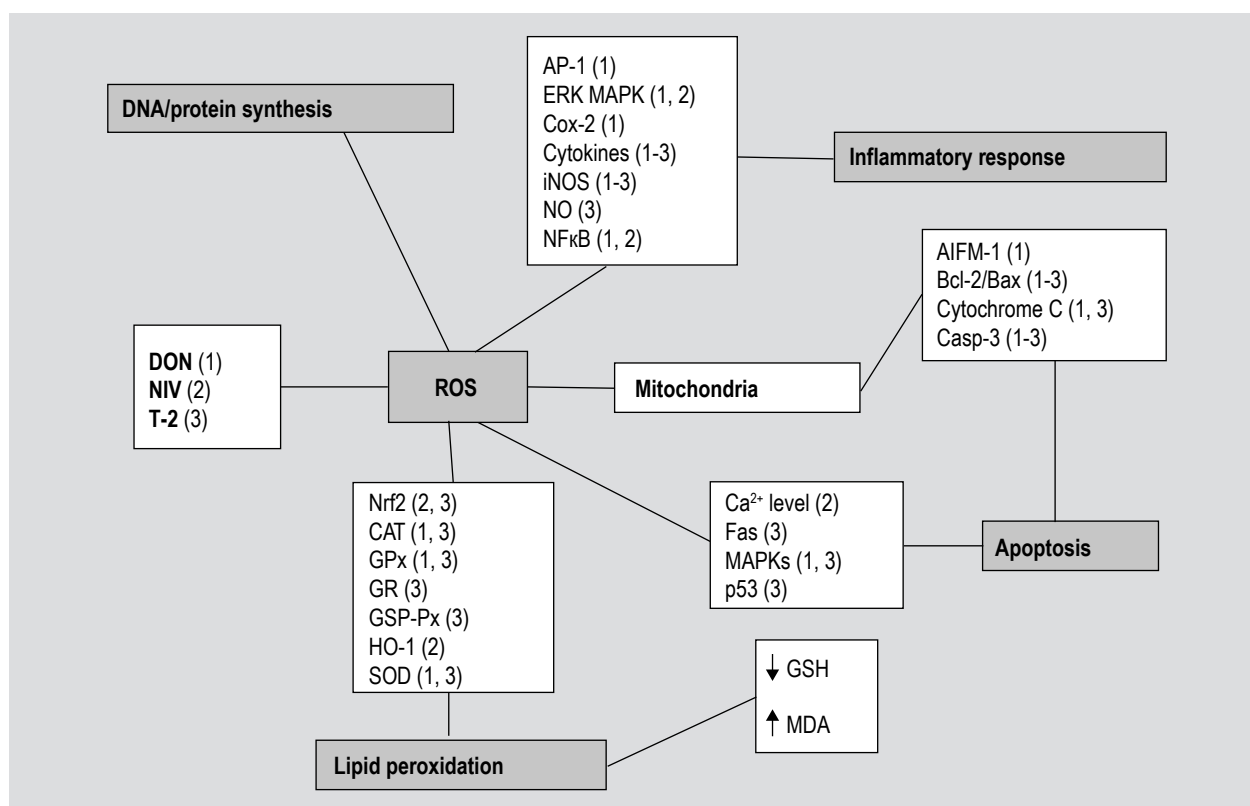


Figure 2. Summary of the intracellular lesions associated with oxidative stress induced by trichothecenes that contaminate food and feed. DON = deoxynivalenol; NIV = nivalenol; T-2 = T-2-toxin. The numbers between brackets indicate the mycotoxins involved in each process.

of the p53 gene, which was associated with an increase in cell apoptosis.

Recent studies have shown that AFB₁ causes changes in intracellular antioxidant mechanisms such as Nrf2, SOD, GPx and CAT expression (Liu and Wang *et al.*, 2016; Wang *et al.*, 2017), inhibiting antioxidant enzymes and causing an increase in lipid peroxidation (LPO) and a decrease in the level of GSH (Ma *et al.*, 2015; Maurya and Trigun, 2016). Moreover, ROS generation induced by AFB₁ modulates the inflammatory response through up-regulation of pro-inflammatory cytokines TNF- α , IL-1 α , IL-1 β and IL-6 and NO expression, by reducing anti-inflammatory cytokine IL-4 expression, inducing cytochrome P450 activity, increasing arachidonic acid metabolism, and activating the NADPH oxidase (NOX)-2 dependent signalling pathway, thereby promoting the autophagy of pro-inflammatory macrophages M1 (An *et al.*, 2017; Ma *et al.*, 2015; Meissonier *et al.*, 2007).

Deoxynivalenol

DON is a type B trichothecene predominantly produced by *Fusarium graminearum* and *Fusarium culmorum* (Bennet and Klich, 2003). Exposure to DON has been associated with alterations in the intestinal, immune, endocrine and

nervous systems in several animal species and in humans (Maresca *et al.*, 2013; Payros *et al.*, 2016; Pestka, 2010a). At a molecular level, DON causes ribotoxic stress, inducing MAPK phosphorylation, promoting apoptosis, resulting in changes in the inflammatory response and decreasing the expression of cell adhesion proteins (Pierron *et al.*, 2016; Silva *et al.*, 2014).

Studies *in vitro* (Li *et al.*, 2014; Yang *et al.*, 2014; Zbynovska *et al.*, 2013) and *in vivo* (Borutova *et al.*, 2008; Osselaere *et al.*, 2013) established the toxic effects of DON associated with oxidative stress and ROS generation as observed in the Figure 2. DON alters the intracellular antioxidant defence system in target tissues such as liver, kidney, lymphoid organs, intestine and blood/serum as demonstrated by an increase in MDA concentration (Li *et al.*, 2014) and a decrease in GSH, SOD, CAT and GPx levels (Hou *et al.*, 2013; Strasser *et al.*, 2013; Zbynovska *et al.*, 2013).

The oxidative stress signalling pathway induced by DON has been suggested to be one of the mechanisms behind DNA fragmentation, cell death and apoptosis (Frankic *et al.*, 2008; Zhang *et al.*, 2009) as well as the inhibition of protein synthesis and an increase in carbonyl content (Strasser *et al.*, 2013). Furthermore, alterations in the surface of lysosomal membranes lead to lysosomal fragility, a decrease

in the MMP, an increase in membrane permeability and consequent deregulation of Bcl-2/Bax expression (leading to release of cytochrome C and activation of caspase 3, 8, 9 and apoptosis inducing factor mitochondrion associated 1) have been associated with ROS generation induced by DON (Kouadio *et al.*, 2005; Li *et al.*, 2014; Sun *et al.*, 2015). It has also been established that the ribotoxic stress induced by DON can stimulate apoptosis via activation of the p38 MAPK (Pestka *et al.*, 2008).

In addition, DON-induced oxidative stress can modulate the inflammatory response through up-regulation of pro-inflammatory cytokines including IL-1 β , IL-2, IL-6, IL-8, TNF- α , down-regulation of anti-inflammatory IL-4 and IL-10, selective activation of ERK MAPK, NF κ B and AP-1, and increased and decreased expression of intracellular proteins involved in innate immunity, such as cyclooxygenase-2 (Cox-2) and inducible nitric oxide synthase (iNOS), respectively (Cano *et al.*, 2013; Graziani *et al.*, 2015; Pestka *et al.*, 2010b).

Nivalenol

NIV is another type B trichothecene and is generally a biologically active metabolite of DON, present in agricultural commodities (Bennet and Klich, 2003). NIV is not as prevalent as DON, but NIV showed higher acute toxicity than DON (Alassane-Kpembi *et al.*, 2015; Cheat *et al.*, 2015). Studies *in vivo* (Cheat *et al.*, 2015), *in vitro* (Alassane-Kpembi *et al.*, 2015; Del Regno *et al.*, 2015; Marzocco *et al.*, 2009) and *ex vivo* (Alassane-Kpembi *et al.*, 2017; Cheat *et al.*, 2015) reported that NIV, such as DON, induce inhibition of protein, DNA and RNA synthesis, mitochondrial damage, cell apoptosis, decreases cellular viability and modulate inflammatory response mainly due to ROS generation associated with induction of oxidative stress as demonstrated in Figure 2, affecting the gastrointestinal tract and organs of the immune system.

The oxidative stress induced by NIV promotes ROS release via the NADPH oxidase signalling pathway, decreases the GSH level, alters Ca²⁺ homeostasis and activates nuclear factor kappa beta (NF- κ B) (Del Regno *et al.*, 2015). This ROS generation induces DNA and mitochondrial damage, activation of extracellular regulated kinase (ERK) MAPK, changes in Bcl-2 expression, up-regulation of Bax gene and activation of caspase 3, thereby promoting cell apoptosis (Marzocco *et al.*, 2009). The oxidative stress induced by NIV stimulates the antioxidant intracellular mechanisms of defence through an increase in heme oxygenase-1 (HO-1) and activation of Nrf2 (Del Regno *et al.*, 2015). In addition, the NIV-induced oxidative stress modulates the inflammatory response by activation of NF- κ B, up-regulation of pro-inflammatory cytokines such as IL-8, IL-1 α , IL-1 β , IL-17A, IL-22, interferon (IFN)- α and an

increase in iNOS expression (Alassane-Kpembi *et al.*, 2017; Del Regno *et al.*, 2015; Marzocco *et al.*, 2009).

T-2 toxin

T-2 is a type A trichothecene produced by several *Fusarium* species, mainly *Fusarium sporotrichioides*, *Fusarium poae* and *Fusarium langsethiae*. Studies have demonstrated that T-2 affects the gastrointestinal tract, kidney, liver, heart, skin, the nervous, immunological, and reproductive systems, and embryogenic development in humans and animals (Agrawal *et al.*, 2012; Li *et al.*, 2011; Meissonnier *et al.*, 2008).

The main molecular target of trichothecenes is the ribosomal unit, affecting initiation of the polypeptide chain (Li *et al.*, 2011). Like other trichothecenes, T-2 binds and inactivates peptidyl transferase activity resulting in inhibition of protein synthesis and disruption of the mitochondrial morphology, ER and other membranes (Adhikari *et al.*, 2017). Studies *in vitro* (Chen *et al.*, 2008; Yang *et al.*, 2016; Zhang *et al.*, 2016) and *in vivo* (Chaudhari and Lakshmana, 2010) provided evidence that T-2-induced oxidative stress is associated with an increase in ROS generation and DNA, protein and lipid peroxidation leading to cell apoptosis.

The oxidative stress induced by T-2 promotes Fas up-regulation, p53 activation, down-regulation of Bcl-2 and up-regulation of the pro-apoptotic factor Bax causing cytochrome C release, caspase 3 activation and cell apoptosis (Chen *et al.*, 2008; Zhang *et al.*, 2018) (Figure 2). ROS generation causes a decrease in Nrf2 expression, changes in the intracellular antioxidant enzymes GPx, GR, SOD and CAT, promoting a decrease in GSH level and an increase in MDA level (Wu *et al.*, 2014b; Yang *et al.*, 2016).

Another apoptosis signalling pathway linked to oxidative stress induced by T-2 is through the activation of JNK1, p38 MAPK, increase in heat shock protein (Hsp) 70 expression, increase in iNOS activity and NO release, causing mitochondrial damage and activation of caspase 3 (Chaudhari and Lakshmana, 2010; Li and Pestka, 2008). In addition, studies have shown that T-2 can modulate the inflammatory response by increasing the expression of pro-inflammatory cytokines such as TNF- α , IL-6, IL-1 β and IL-11 (Agrawal *et al.*, 2012; Zhou *et al.*, 2014).

Fumonisin B₁

Fumonisin B₁ is a group of mycotoxins mainly produced by *Fusarium verticillioides* and *Fusarium proliferatum* (Voss *et al.*, 2001). At least 15 related fumonisin compounds have been identified so far, but FB₁ is the most significant fumonisin due to its toxicity and widespread occurrence (Voss *et al.*, 2007).

At cellular level, FB₁ inhibits ceramide synthase, blocking the synthesis of sphingolipids, a class of membrane lipids that play an important role in cell signalling transduction pathways and cell growth, differentiation, and death (Grenier *et al.*, 2012; Voss *et al.*, 2007). Ceramide synthase inhibition leads to reduced levels of ceramide and intracellular accumulation of sphingolipids (So) and sphinganine (Sa). These free sphingoid bases are pro-apoptotic, cytotoxic growth inhibitors and are immunotoxic (Loiseau *et al.*, 2007; Voss *et al.*, 2001, 2007).

Studies *in vitro* (Domijan *et al.*, 2015; Mary *et al.*, 2012) and *in vivo* (Abbes *et al.*, 2016; Hassan *et al.*, 2015) revealed the potential of FB₁ to induce oxidative stress with consequent ROS generation, cytotoxic effects and apoptosis. The action of FB₁ on ROS generation has been considered a consequence rather than a mechanism of its toxicity (Galvano *et al.*, 2002; Wang *et al.*, 2016). However, some studies showed that FB₁ was able to increase the rate of oxidation, promote the production of free radicals and accelerate the chain reactions associated with lipid peroxidation in membranes (Hassan *et al.*, 2015; Stockmann-Juvala and Savolainen, 2008). These changes were demonstrated in different animal models by alterations in GPx and SOD expression, increase in MDA production and decrease in the GSH level (Abbes *et al.*, 2016; Domijan *et al.*, 2007; Poersch *et al.*, 2014).

The increase in ROS production induced by FB₁ has also been associated with inhibition of DNA synthesis and DNA fragmentation (Kouadio *et al.*, 2005; Wang *et al.*, 2016), inhibition of protein synthesis (Domijan *et al.*, 2007), mitochondrial injury with consequent deregulation of calcium homeostasis and caspase 3 activation, induction of cytochrome P450 activity with an increase in arachidonic acid metabolism and modulation of inflammatory response (Abbes *et al.*, 2016; Domijan and Abramov, 2011; Mary *et al.*, 2017). Some studies have demonstrated that perturbations of the cellular redox state due the FB₁ exposition can activate MAPKs and Hsp 25/70. Both signalling pathways can affect cell survival and are involved in the regulation of apoptosis (Lalles *et al.*, 2010; Rumora *et al.*, 2007) (Figure 1).

Ochratoxin A

Ochratoxins are a group of mycotoxins produced by filamentous fungal species such as *Aspergillus* and *Penicillium* and occur in nature in three different isoforms: ochratoxin A, B and C. OTA is the most pathogenic to humans and animals, and is found in a wide range of foods and feed, including cereals, meat, dried fruits, nuts, coffee, wine and beer (Bennet and Klich, 2003; Limonciel and Jennings, 2014; Malir *et al.*, 2016).

Studies involving mammalian species *in vitro* (Bhat *et al.*, 2016; Gayathri *et al.*, 2015; Lautert *et al.*, 2014; Li *et*

al., 2015) and *in vivo* (Aydin *et al.*, 2003; Tanaka *et al.*, 2016) showed nephrotoxic, hepatotoxic, immunotoxic, enterotoxic, neurotoxic and teratogenic effects of OTA. The toxicity and carcinogenic mechanisms of OTA have been associated with induction of oxidative stress (Costa *et al.*, 2016), cell apoptosis (Ramya and Padma, 2013), cell autophagy/mitophagy (Gan *et al.*, 2017; Qian *et al.*, 2017) and protein synthesis inhibition (Mally and Dekant, 2009).

ROS generation has been reported to trigger OTA toxicity (Zhu *et al.*, 2017). Several oxidative stress mechanisms elicited by OTA have been proposed through *in vivo* (Abdel-Wahhab *et al.*, 2017; Gan *et al.*, 2017) and *in vitro* studies (Bhat *et al.*, 2016; Ramya *et al.*, 2014) (Figure 1). OTA can cause damage due to oxidative stress through the generation of hydroxyl radicals via the Fenton reaction, via flavoprotein NADPH-cytochrome P450 activation and inhibition of Nrf2 activation and gene transcription. In addition, OTA can decrease the expression of the intracellular antioxidant enzymes GPx, CAT, SOD and GR (Abdel-Wahhab *et al.*, 2017; Bhat *et al.*, 2016) as demonstrated by an increase in MDA levels.

ROS generation increased by OTA promotes the activation of the apoptosis signalling pathway through the mitochondrial lipid peroxidation, promoting loss of mitochondria membrane potential, increasing membrane permeability (Bhat *et al.*, 2016), activating JNK MAPKs (Zhu *et al.*, 2017) and affecting the ER calcium channels with consequent release of the calcium into cytosol (Sheu *et al.*, 2017). These lesional mechanisms promote changes in the Bcl-2 family, inducing the expression of Bax, facilitating the release of cytochrome C and the activation of caspase 3 in the cytosol.

Patulin

PAT is a mycotoxin produced by several fungal species of the genera *Penicillium*, *Aspergillus*, *Paecilomyces* and *Byssoschlamys* and is a common contaminant of apples and its products, rotten fruit, mouldy feed and stored cheese (Tannous *et al.*, in press).

The toxic effects of PAT have been described *in vitro* (Assunção *et al.*, 2016; Jayashree *et al.*, 2017; Zhang *et al.*, 2015a), *in vivo* (Boussabbeh *et al.*, 2016b; Lu *et al.*, 2017;) and *ex vivo* (Maidana *et al.*, 2016) mainly associated with ROS generation and activation of p53 protein and cleaved caspase 3 (Assunção *et al.*, 2016; Boussabbeh *et al.*, 2016b; Jayashee *et al.*, 2016; Jin *et al.*, 2016) (Figure 1).

PAT has a strong affinity for sulfhydryl groups (Tannous *et al.*, in press). Therefore, the rapid ROS generation observed in the PAT toxicity is likely due to its electrophilic attack of the intracellular antioxidant enzymes containing the sulfhydryl group, mainly GSH (Jin *et al.*, 2016). PAT

decreases SOD and CAT activity, promoting an increase in MDA levels (Zhang *et al.*, 2015a).

ROS generation also leads to lipid peroxidation, modulation of p38 MAPK expression, injury of cellular membranes and consequent DNA damage (Jin *et al.*, 2016). The activation of p53 is initiated by ROS generation that results in an increase in ROS generation (feedback loop) due to the increase in p53-induced gene 3 (PIG 3) expression that induces the inhibition of anti-oxidant enzyme CAT (Jin *et al.*, 2016). In addition, p53 activation induces mitochondrial damage and caspase 3 activation leading to cell apoptosis (Boussabbeh *et al.*, 2016b). PAT also modulates other mechanisms associated with apoptosis regulation: it decreases Bcl-2 expression and increases Bax, cytochrome C and P450 expression (Boussabbeh *et al.*, 2016b; Jin *et al.*, 2016). Some studies have demonstrated that the generation of ROS causes mitochondrial damage and activates caspase 3 due to ER stress induced by PAT (Boussabbeh *et al.*, 2015, 2016a).

Zearalenone

ZEA is a resorcylic acid lactone derived mycotoxin produced by *Fusarium* fungi and is a contaminant commonly found in unprocessed maize kernels. ZEA and its metabolites (α - and β -zearalenol) have structural analogy to oestrogens. The oestrogenic activity of ZEA and its derivative has been demonstrated both *in vivo* (Koraichi *et al.*, 2012) and *in vitro* (Frizzell *et al.*, 2011; Parveen *et al.*, 2009).

ZEA toxic effects can be induced by mechanisms that are not associated with its oestrogenic activity. ZEA affects the integrity of DNA and mitochondria, decreases cell proliferation and modulates the inflammatory response (Liu *et al.*, 2017; Marin *et al.*, 2015). These cytotoxic and genotoxic effects may be connected with oxidative stress generated by ZEA (Marin *et al.*, 2015). Some studies *in vivo* (Liu *et al.*, 2017; Marin *et al.*, 2015) and *in vitro* (Hassen *et al.*, 2007; Qin *et al.*, 2015) demonstrated the capacity of ZEA to induce ROS and lipid peroxidation, causing oxidative DNA and mitochondrial damage, apoptosis and modulation of pro- and anti-inflammatory cytokines as observed in Figure 1. The inhibition of protein and DNA synthesis caused by the oxidative stress was related to fragmentation of DNA, production of micronuclei and formation of DNA-adduct (Abid-Essefi *et al.*, 2004). Furthermore, the decrease in cell proliferation could be the result of cell arrest in the G2/M phase induced by ZEA (Abid-Essefi *et al.*, 2003).

The generation of ROS by ZEA exposure led to an increase in iNOS and Cox-2 expression, and up-regulation of pro-inflammatory and down-regulation of anti-inflammatory cytokines (Marin *et al.*, 2015). Studies *in vivo* (Liu *et al.*, 2017; Marin *et al.*, 2015) and *in vitro* (Hassen *et al.*, 2007; Qin *et al.*, 2015) showed that ZEA also increases MDA levels due to the modulation of intracellular antioxidant

mechanisms: decrease in GSH levels and SOD activity, increase in GPx and CAT activities. The latter enzymes are involved in intracellular antioxidant activity of the hydrogen peroxide conversion, consequently, the increase in GPx and CAT activities could be associated with an intracellular compensatory mechanism to scavenge ROS generation induced by ZEA (Marin *et al.*, 2015). Recent studies showed that ZEA-ROS generation increased the expression of p53, decreased MMP, promoting a decrease in anti-apoptotic Bcl-2 gene expression, leading to Bax expression and caspase 3 activation (Fan *et al.*, 2017). Therefore, the mitochondrial damage induced by the oxidative stress due to ZEA exposure can result in cell apoptosis.

4. Antioxidants and mycotoxins: does a protective effect exist?

Antioxidants are able to compete with other oxidisable substrates at relatively low concentrations, and thus to significantly delay or inhibit the oxidation of the substrates (Diplock *et al.*, 1998). The physiological role of antioxidants is to prevent damage to cellular components arising as a consequence of chemical reactions involving free radicals. In recent years, studies have demonstrated that the generation of oxidative stress and of free radicals, mainly ROS and RNS, plays an important role in the development of several diseases, including cancer (Reuter *et al.*, 2010; Zuo *et al.*, 2015). Similar protective action of antioxidants, mainly of natural origin, has been observed against the toxic effects of several mycotoxins (Sorrenti *et al.*, 2013).

The protective properties of antioxidants are probably due to their ability to act as free radical scavengers, thereby protecting DNA, cell proteins and lipids from mycotoxin-induced damage. Many natural substances have been used for their ability to modulate the oxidative stress caused by mycotoxins, including ascorbate (vitamin C), tocopherol (vitamin E), carotenoid (vitamin A) and the flavonoids (Diplock *et al.*, 1998; Sorrenti *et al.*, 2013; Strasser *et al.*, 2013). Several studies have also demonstrated the ability of crocin, curcumin, green tea, lycopene, phytic acid, L-carnitine, melatonin and minerals to modulate mycotoxin-induced oxidative stress (Meki *et al.*, 2004; Moosavi *et al.*, 2016; Salem *et al.*, 2016; Silva *et al.*, 2014; Verma and Mathuria, 2008; Zheng *et al.*, 2013).

Vitamins

Vitamins, mainly vitamins A, C and E, and their precursors act as free radical scavengers. These vitamins reduce oxidative stress and mycotoxin-induced damage to the cells (Strasser *et al.*, 2013). The main effects of vitamins A, C and E on the cellular oxidative stress induced by mycotoxins observed in *in vitro* and *in vivo* studies are listed in Table 1.

Table 1. Effects of antioxidant vitamins A, C and E in mycotoxin studies.

Mycotoxin ¹	Experimental model	Antioxidant effects ²	Reference
Vitamin A			
AFB ₁	<i>in vitro</i> : human lymphocytes	increase GSH, GPx and SOD; decrease MDA	Alpsoy <i>et al.</i> , 2009
	<i>in vitro</i> : microsomal enzymes	inhibit microsomal enzymes and reduce the bioactivation of AFB ₁	Wheeler <i>et al.</i> , 2006
	<i>in vitro</i> : HepG2 cells	decrease the bioactivation of AFB ₁ ; decrease apoptosis; inhibit p53 mutation	Reddy <i>et al.</i> , 2006
	<i>in vivo</i> : mice	decrease the mitotic and meiotic clastogeny	Sinha and Dharmshila, 1994
DON	<i>in vitro</i> : murine lymphoma cells	decrease the lipid (MDA) and protein peroxidation	Strasser <i>et al.</i> , 2013
OTA	<i>in vivo</i> : rats	increase GSH and GPx; decrease apoptosis	Palabiyik <i>et al.</i> , 2013
ZEA	<i>in vivo</i> : mice	decrease DNA adduct formation	Ghedira-Chekir <i>et al.</i> , 1998; Grosse <i>et al.</i> , 1997
Vitamin C			
AFB ₁	<i>in vitro</i> : woodchuck hepatocytes	decrease DNA adduct formation	Yu <i>et al.</i> , 1994
	<i>in vitro</i> : human lymphocytes	increase GSH, GPx and SOD; decrease MAD level	Alpsoy <i>et al.</i> , 2009
	<i>in vitro</i> : microsomal enzymes	inhibit microsomal enzymes and reduce the bioactivation of AFB ₁	Wheeler <i>et al.</i> , 2006
	<i>in vivo</i> : rats	increase AFB ₁ metabolism to AFM ₁	Gradelet <i>et al.</i> , 1998
	<i>in vivo</i> : guinea pig	decrease the GSH level; decrease the cytochrome P450 level	Netke <i>et al.</i> , 1997
	<i>in vivo</i> : rabbits	decrease the number of abnormal and dead sperms	Salem <i>et al.</i> , 2001
	<i>in vivo</i> : rohu (<i>Labeo rohita</i>)	increase serum lysozyme activity; enhance phagocytic ratio; immunostimulatory effect	Sahoo and Mukherjee, 2003
DON	<i>in vitro</i> : rat erythrocytes	decrease the haemolytic effect	Rizzo <i>et al.</i> , 1992
	<i>in vitro</i> : murine lymphoma cells	decrease the lipid (MDA) and protein peroxidation	Strasser <i>et al.</i> , 2013
	<i>in vivo</i> : rats	increase the CAT, SOD and GST activities; increase GSH level; decrease MDA level	Atroshi <i>et al.</i> , 1995; Rizzo <i>et al.</i> , 1994
OTA	<i>in vivo</i> : mice	decrease apoptosis	Atroshi <i>et al.</i> , 2000a
T-2	<i>in vitro</i> : rat erythrocytes	decrease the haemolytic effect	Rizzo <i>et al.</i> , 1992
	<i>in vivo</i> : rats	increase CAT, SOD, GST and GSH level	Atroshi <i>et al.</i> , 1995; Rizzo <i>et al.</i> , 1994
ZEA	<i>in vivo</i> : piglets	increase T-AOC, SOD and GPx; decrease MDA level	Shi <i>et al.</i> , 2017
	<i>in vivo</i> : mice	decrease DNA adduct formation	Ghedira-Chekir <i>et al.</i> , 1998; Grosse <i>et al.</i> , 1997
Vitamin E			
AFB ₁	<i>in vitro</i> : HepG2 cells	decreased p53 mutation; decreased DNA adduct formation; decreased apoptosis	Reddy <i>et al.</i> , 2006; Abdel-Hamid and Firgany, 2015
	<i>in vitro</i> : human lymphocytes	increased GST, GPx and SOD; decreased MDA level	Alpsoy <i>et al.</i> , 2009
	<i>in vitro</i> : microsomal enzymes	inhibited of microsomal enzymes and reduce the bioactivation of AFB ₁	Wheeler <i>et al.</i> , 2006
	<i>in vivo</i> : rats	increased the CAT, SOD and GST; decreased MDA level; decreased cytochrome P-450 activity	Cassandi <i>et al.</i> , 1993
	<i>in vivo</i> : mice	increased 3 β - and 17 β -hydroxysteroid dehydrogenases activities and serum testosterone levels	Verma and Nair, 2002
DON	<i>in vitro</i> : rat erythrocytes	decreased the haemolytic effect	Rizzo <i>et al.</i> , 1992
	<i>in vitro</i> : murine lymphoma cells	decreased the lipid (MDA) and protein peroxidation	Strasser <i>et al.</i> , 2013
	<i>in vivo</i> : piglets	decreased DNA damage	Frankic <i>et al.</i> , 2008
	<i>in vivo</i> : rats	increased the CAT, SOD and GST and GSH level; decreased MDA level	Atroshi <i>et al.</i> , 1995; Rizzo <i>et al.</i> , 1994
FB ₁	<i>in vivo</i> : rats	decrease DNA fragmentation; decreased the Ca ²⁺ nuclei; decreased the AST/ALT	Atroshi <i>et al.</i> , 1999
OTA	<i>in vitro</i> : porcine fibroblasts	decreased DNA fragmentation	Fusi <i>et al.</i> , 2010
	<i>in vitro</i> : HepG2 cells	decreased DNA fragmentation, Bax expression and casp-3 activation	Gayathri <i>et al.</i> , 2015
	<i>in vivo</i> : rats	increase the protein level; decreased the AST, ALT, AP and γ GT	Atroshi <i>et al.</i> , 2000b
	<i>in vivo</i> : mice	decreased apoptosis	Atroshi <i>et al.</i> , 2000a

Table 1. Continued.

Mycotoxin ¹	Experimental model	Antioxidant effects ²	Reference
Vitamin E			
PAT	<i>in vitro</i> : HepG2 cells	decreased p53 activation; decreased DNA damage	Ayed-Boussema <i>et al.</i> , 2013
T-2	<i>in vitro</i> : chicken lymphocytes	increased lymphocyte proliferation	Jaradat <i>et al.</i> , 2006
	<i>in vitro</i> : Vero cells	decreased Hsp 70 expression	El Golli <i>et al.</i> , 2006
	<i>in vitro</i> : rat erythrocytes	decreased the haemolytic effect	Rizzo <i>et al.</i> , 1992
	<i>in vivo</i> : chicken	decreased MDA level	Hoehler and Marquardt, 1996
	<i>in vivo</i> : rats	increased the CAT, SOD and GST and GSH level; increase the protein level; decreased MDA level, AST, ALT, AP and γGT.	Atroschi <i>et al.</i> , 1995, 2000a.; Rizzo <i>et al.</i> , 1994
ZEA	<i>in vivo</i> : mice	decreased DNA adduct formation	Ghedira-Chekir <i>et al.</i> , 1998; Grosse <i>et al.</i> , 1997

¹ AFB₁ = aflatoxin B₁; DON = deoxynivalenol; FB₁ = fumonisin B₁; NIV = nivalenol; OTA = ochratoxin A; PAT = patulin; T-2 = T-2 toxin; ZEA = zearalenone.
² ALT = alanine transaminase; AP = alkaline phosphatase; AST = aspartate transaminase; CAT = catalase; GPx = glutathione peroxidase; GSH = glutathione; GST = glutathione S-transferase; γGT = gamma-glutamyl transpeptidase; MDA = malondialdehyde, SOD = superoxide dismutase; T-AOC = total antioxidative capacity.

Vitamin A has three active forms: retinol, retinal, and retinoic acid (retinoids), which are essential for physiological functions, including reproduction, vision, growth, and maintenance of epithelial tissues. The antioxidative effects of vitamin A have been associated with inhibiting cytochrome P450-mediated metabolism of toxic substances and preventing mutagenic epoxies from binding to DNA, thereby forming epoxides and competing with mutagenic epoxides in reaction with DNA (Diplock *et al.*, 1998). The toxic effects of AFB₁, DON, OTA and ZEA have been shown to be reduced in interaction with vitamin A in *in vitro* and *in vivo* models. The beneficial effects include increased levels of antioxidant enzymes (GSH, GPx), a decrease in mycotoxin bioactivation and in cell death (Table 1).

Vitamin C or ascorbic acid is a lactone synthesised in the liver of many species. It is a first-line antioxidant that has beneficial effects including protecting cell membranes, proteins and nucleic acids from oxidation. Its biological action and antioxidant characteristic are associated with its ability to donate electrons. At physiological levels, vitamin C is a powerful scavenger of oxygen-derived free radicals such as superoxide radical anion, H₂O₂, the hydroxyl radical, and singlet oxygen in plasma and tissues (Diplock *et al.*, 1998). In addition, ascorbic acid is an efficient scavenger of reactive nitrogen oxide species, thereby avoiding nitrosative stress and cell damage (Rock *et al.*, 1996). Vitamin C also interacts with GSH, reducing GSH production, which, in turn, reduces oxidative stress. The main effects of vitamin C on mycotoxin induced-toxicity are reducing lipid peroxidation and increasing levels of antioxidant enzymes. These and other effects have been described for AFB₁, DON, OTA, T-2 and ZEA (Table 1). Reduced adduct formation, decreased

apoptosis and enhancement of phagocytosis have been reported for AFB₁ and ZEA (Ghedira-Chekir *et al.*, 1998; Sahoo and Mukherjee, 2003).

Vitamin E refers to a group of substances that includes tocopherols and tocotrienol derivatives. There are two forms of vitamin E, γ-tocopherol and α-tocopherol. α-tocopherol is the most biologically active form of vitamin E (Traber and Sies, 1996) and the major function is that of a peroxyl radical scavenger, interrupting the propagation of free radicals. In addition, vitamin E interacts with reactive nitrogen oxide species and singlet oxygen, thereby maintaining the integrity of polyunsaturated fatty acids in cell membranes (Rock *et al.*, 1996). Vitamin E has been shown to act favourably against seven mycotoxins (AFB₁, DON, FB₁, OTA, PAT, T-2 and ZEA) (Table 1). Its actions are similar to those of vitamins A and C, although decreased DNA fragmentation and damage of DON, FB₁ and OTA was also reported (Atroschi *et al.*, 1999; Frankic *et al.*, 2008; Gayathri *et al.*, 2015). In addition, reduced Hsp 70 expression and increased lymphocyte proliferation were described for T-2 (El Golli *et al.*, 2006; Jaradat *et al.*, 2006).

Flavonoids

The flavonoids are the most common hydroxylated phenolic substances that are synthesised by plants. Sources of flavonoids are citrus fruits, berries, red wine and tea (Diplock *et al.*, 1998). The function of flavonoids is associated with its structure, which includes a number of structurally different subgroups, including flavonols (quercetin, kaempferol, myricetin), flavanols (catechin and epicatechin), isoflavones (genistein), flavones (apigenin, hesperetin), flavanones

(naringenin, taxifolin) and/or anthocyanidins (cyanidin, malvidin) (Rice-Evans and Miller, 1996). The biological function of antioxidants is connected with their capacity to scavenger free radicals (peroxyl radical and hydroxyl radical), as well as chelating metals involved in the Fenton reaction (Rice-Evans and Miller, 1996).

The flavonol quercetin is one of the most effective polyphenolic substances linked to a reduction in the levels of ROS and reactive nitrogen species. In previous *in vivo* and *in vitro* studies, quercetin was shown to modulate the effects of oxidative stress caused by T-2, AFB₁ and OTA resulting in an increase in Nrf2 expression, SOD and GPx activity as well as total antioxidant status and GSH levels (Abdel-Wahhab *et al.*, 2017; Capcarova *et al.*, 2015; Choi *et al.*, 2010; Ramyaa and Padma, 2013; Ramyaa *et al.*, 2014). On the other hand, quercetin was associated with a decrease in ER oxidative stress, ROS generation, MAD level, P450 and NADPH activity, cytochrome C release, casp-3 activation cell apoptosis, Cox-2 and NO expression, TNF- α , IL-6 and IL-2 and a decrease in DNA damage (Abdel-Wahhab *et al.*, 2017; Ramyaa and Padma, 2013; Ramyaa *et al.*, 2014).

Recent studies demonstrated the antioxidant effects of other flavonoids on oxidative stress induced by mycotoxins. Proanthocyanidin increased Nrf2 expression, SOD, GPx, CAT activities, GSH level, and decreased MDA content, DNA damage and the expression of pro-inflammatory cytokines (IL-1 β , TNF- α , IL-6 and IFN- γ) in rats and mice subjected to AFB₁ (Long *et al.*, 2016c) and ZEA (Long *et al.*, 2016b) diets. Cyanidin decreased DNA damage, ROS production, lipid hydroperoxide and iNOS, and increased HO-1 activity and non-protein thiol groups in rats, in a pig kidney cell line (LLC-PK1), and in human fibroblasts exposed to OTA (Sorrenti *et al.*, 2012). Baicalein, wogonin and hesperidin increased cell viability and decreased genotoxicity and casp-3 activation in mice and neural crest cells exposed to AFB₁ (Nones *et al.*, 2013; Ueng *et al.*, 2001). Zhong *et al.* (2017) reported that the apigenin re-established MMP, increased Bcl-2 expression, decreased Bax, p53 activation and the cytochrome C release in human embryonic kidney cells 293 (HEK 293 cells) treated with PAT. With the addition of silymarin to their diet, mice subjected to FB₁ contaminated feed showed decreased TNF- α expression and casp-8 activation (Sozmen *et al.*, 2014).

Crocin, curcumin, green tea, lycopene and phytic acid

Crocin is a major bioactive compound and is mainly found in *Gardenia jasminoides* and saffron. Water and ethanol extracts of crocin displayed antioxidant activity against O₂⁻ and HO radicals (Xiao *et al.*, 2017). Curcumin is a hydrophobic polyphenol derived from turmeric, a compound extracted from the root of *Curcuma longa* L. rhizome. Curcumin has diverse biological functions and its structure, which is composed of methoxy groups and

phenols, is associated with its properties (Zheng *et al.*, 2017). The antioxidant action of crocin and curcumin on the molecular effects of mycotoxins *in vitro* and *in vivo* are summarised in Table 2.

Green tea is derived from *Camellia sinensis* leaves and contains a wide range of bioactive compounds of which one third are composed of polyphenols of which the majority are flavonoids. Catechins (GTCs) are one of the main flavonoids in green tea. GTCs have antioxidant capacity to scavenge ROS such as O₂⁻, H₂O₂ and HO radicals (Cooper *et al.*, 2005). Lycopene is the most abundant carotenoid (non-vitamin A) in orange fruits and vegetables, mainly tomatoes and derived products and is responsible for their bright red colour. Lycopene is a recognised antioxidant and has been considered the most efficient in scavenging single oxygen (Mordente *et al.*, 2011). Phytic acid (IP6) is a saturated cyclic acid commonly found in plant tissues and seeds; and its antioxidant effect is on ROS production mainly due its capacity to chelate iron, thereby inhibiting the Fenton reaction (Silva and Bracarense, 2016). The antioxidant effects of green tea, lycopene and IP6 on mycotoxin-induced oxidative stress *in vitro* and *in vivo* studies are listed in Table 3.

L-carnitine

L-carnitine is an endogenous mitochondrial membrane compound that plays a prominent role in facilitating the transport of long-chain fatty acids into mitochondria and the oxidation pathway (Adeva-Andany *et al.*, 2017). L-carnitine decreases oxidative stress, increases endogenous antioxidant defence capacity, protects mitochondria against lipid oxidation, and decreases apoptosis through the inhibition of mitochondrial swelling and cytochrome C release (Adeva-Andany *et al.*, 2017). L-carnitine has been shown to decrease ROS production, MDA level, casp-3 activation, DNA and protein damage, and to increase MMP and GSH levels in rats and quails subjected to AFB₁ or T-2 contaminated diets (Citil *et al.*, 2005; Moosavi *et al.*, 2016; Yatim and Sachan, 2001).

Melatonin

Melatonin is a hormonal product of the pineal gland that controls reproductive functions, modulates immune system activity, limits tumorigenesis and effectively inhibits oxidative stress (Reiter, 1997). Antioxidant effects of melatonin reported in rats exposed to AFB₁ and OTA contaminated diets included an increase in the GSH level and in the activity of CAT, GPx, GSH, GST, GR and SOD (Abdel-Wahhab *et al.*, 2005; Meki *et al.*, 2004; Sutken *et al.*, 2007), a decrease in MDA and LPO content (Abdel-Wahhab *et al.*, 2005; Sutken *et al.*, 2007; Yenilmez *et al.*, 2010) and decreased expression of NO, Hsp 70 and casp-3 (Meki *et al.*, 2001, 2004).

Table 2. Effects of antioxidant food compounds (crocin and curcumin) in mycotoxins studies.

Mycotoxin ¹	Experimental model	Antioxidant effects ²	Reference
Crocin			
AFB ₁	<i>in vivo</i> : rats	increase GSH level, GPx and GST activities; decrease DNA damage	Lin and Wang, 1986; Wang <i>et al.</i> , 1991
PAT	<i>in vivo</i> : mice	increase GSH level and Bcl-2 expression; re-establish the MMP; decrease p53 activation, Bax expression and cytochrome C release; decrease MDA content, Hsp 70 expression, casp-3 activation and CAT; decrease DNA damage	Boubassabbeh <i>et al.</i> , 2016a,b
ZEA	<i>in vitro</i> : HCT11 and HEK293 cells	decrease MDA content, ER stress and DNA damage	Ben Salem <i>et al.</i> , 2015b
	<i>in vivo</i> : mice	increase Bcl-2 expression; decrease Bax, Hsp 70 expression and p53 activation; decrease MDA content, CAT and SOD activities; decrease protein carbonyl generation	Ben Salem <i>et al.</i> , 2015a; Salem <i>et al.</i> , 2016
Curcumin			
AFB ₁	<i>in vitro</i> : human primary hepatocytes	decrease DNA damage	Gross-Steinmeyer <i>et al.</i> , 2009
	<i>in vivo</i> : broiler chickens	increase GSH level, CAT, GST and SOD activities; decrease cytochrome P450 expression; decrease IL-6 expression	Gowda <i>et al.</i> , 2009; Yarru <i>et al.</i> , 2009
	<i>in vivo</i> : mice	increase ATPase and SDH; increase GSH level, CAT, GPx and SOD activities; decrease DNA and protein damage	Mathuria and Verma, 2007a,b; Verma and Mathuria, 2008, 2009; Verma <i>et al.</i> , 2008
	<i>in vivo</i> : rats	increase GSH level, CAT, SOD, GPx and GST activities; increase Bcl-2 expression; decrease Bax expression; decrease casp-3 activation; decrease DNA and protein adduct formation	Abdel-Wahhab <i>et al.</i> , 2016; El-Bahr, 2015; Nayak and Sashidhar, 2010; Poapolathep <i>et al.</i> , 2015
ZEA	<i>in vivo</i> : rats	decrease MDA content; decrease DNA fragmentation	Ismail <i>et al.</i> , 2015
	<i>in vivo</i> : sow	increase GSH level, CAT and SOD activities	Qin <i>et al.</i> , 2015

¹ AFB₁ = aflatoxin B₁; PAT = patulin; ZEA = zearalenone.
² ATPase = adenosine triphosphatase; CAT = catalase; GPx = glutathione peroxidase; GSH = glutathione; GST = glutathione S-transferase; GST = glutathione S-transferase; MDA = malondialdehyde; MMP = mitochondrial membrane potential; SDH = succinate dehydrogenase; SOD = superoxide dismutase.

Minerals

Several minerals are dietary constituents involved in the antioxidant defence system, acting directly as antioxidants or promoting detoxifying enzymes (Sorrenti *et al.*, 2013). Antioxidant enzymes, such as GPx and SOD require a dietary supply of selenium (Se), copper (Cu) and zinc (Zn) (Wang *et al.*, in press).

Se is an essential micronutrient associated with Se-dependent enzymes, including GPx, thioredoxin reductases, iodothyronine diiodinases, and selenophosphate synthetases (Wang *et al.*, 2016). Se has been shown to increase the antioxidant function of CAT, GSH, GPx and SOD, decrease MDA content, increase the level of GSH and to modulate DON-induced immunosuppression in piglet lymphocytes and broiler chickens exposed to DON (Placha *et al.*, 2009; Wang *et al.*, in press). Long *et al.* (2016a,b) observed that Se increased GPx and SOD activities and Bcl-2 expression,

decreased MDA content, Bax and casp-3 expression in mice fed with ZEA.

Zn exerts its antioxidant activity either in an acute way or on a long-term basis. In the first form, zinc acts by stabilising protein sulfhydryl groups against oxidation and exchanging redox active metals (copper and iron) (Zheng *et al.*, 2013). In the second form, Zn induces the expression of metallothioneins, which act as electrophilic scavengers. Moreover, zinc is a co-factor of the SOD enzyme that catalyses superoxide anions into less toxic O₂ and H₂O₂ and modulates the activity of GPx and glutamylcysteine synthetase, through the activation of metal response transcription factor-1 (MTF-1) (Powell, 2000). Zheng *et al.* (2013) demonstrated the antioxidant effect of zinc as being an increase in SOD activity and a decrease in ROS generation and in DNA damage in HepG2 cells exposed to OTA.

Table 3. Effects of antioxidant food compounds (green tea catechin, lycopene and phytic acid) in mycotoxins studies.

Mycotoxin ¹	Experimental model	Antioxidant effects ²	Reference
Green tea catechin			
AFB ₁	<i>in vitro</i> : chicken hepatocytes	increase Bcl2-expression; increase SOD, CAT, GR activities; decrease MDA content; decrease Bax and NF-κB expression; decrease TNF-α, IL-1β and IL-6 expression	Oskoueian <i>et al.</i> , 2015
	<i>in vitro</i> : HepG2	decrease ROS production	Corcuera <i>et al.</i> , 2012
	<i>in vivo</i> : piglets	decrease the cytochrome 450 content	Tulayakul <i>et al.</i> , 2007
	<i>in vivo</i> : rats	decrease the cytochrome 450 content; decrease DNA damage; decrease cell proliferation (promotion phase cancer)	Ito and Ito, 2007; Qin <i>et al.</i> , 2000
FB ₁	<i>in vivo</i> : rats	increase GSH level	Marnewick <i>et al.</i> , 2009
OTA	<i>in vitro</i> : LLC-PK1 cells	increase cell viability; decrease ROS production; decrease DNA damage	Costa <i>et al.</i> , 2007
PAT	<i>in vivo</i> : mice	increase GSH level; decrease MDA content; decrease protein carbonyl formation; decrease p53 and casp-3 activation; decrease DNA damage	Jayashree <i>et al.</i> , 2017; Song <i>et al.</i> , 2014
Lycopene			
AFB ₁	<i>in vivo</i> : rats	decrease DNA adduct formation	Tang <i>et al.</i> , 2007
OTA	<i>in vivo</i> : rats	increase GSH level and GPx activity; decrease MDA content; decrease apoptosis; decrease DNA damage	Aydin <i>et al.</i> , 2013; Palabyik <i>et al.</i> , 2013
T-2	<i>in vivo</i> : chicks	increase GSH level; decrease MDA content	Leal <i>et al.</i> , 1999
ZEA	<i>in vivo</i> : mice	increase GSH level; increase CAT, GPx, GST, GR and SOD activities; increase IL-10 expression; decrease TNF-α, IL-1β, IL-2 and IL-6 expression	Boeira <i>et al.</i> , 2015
Phytic acid			
AFB ₁	<i>in vivo</i> : rats	increase GSH level; increase CAT and SOD activities	Abu El-Saad and Mahmoud, 2009
DON	<i>in vitro</i> : IPEC-1 cells	increase TEER	Pacheco <i>et al.</i> , 2012
	<i>ex vivo</i> : piglet intestine	decrease Cox-2 and casp-3 expression	Silva <i>et al.</i> , 2014
FB ₁	<i>ex vivo</i> : piglet intestine	decrease Cox-2 and casp-3 expression	Silva <i>et al.</i> , 2014

¹ AFB₁ = aflatoxin B₁; FB₁ = fumonisin B₁; OTA = ochratoxin A; PAT = patulin; T-2 = T-2 toxin; ZEA = zearalenone.

² CAT = catalase; GPx = glutathione peroxidase; GR = glutathione reductase; GSH = glutathione; GST = glutathione S-transferase; IL = interleukin; MDA = malondialdehyde; NF-κB = nuclear factor kappa beta; ROS = reactive oxygen species; SOD = superoxide dismutase; TEER = transepithelial electrical resistance; TNF-α = tumour necrosis factor alpha

Mixtures

Several studies have demonstrated that mixtures of natural substances reduce the oxidative stress lesions caused by mycotoxins. The combination of L-carnitine, vitamin E, selenium, melatonin, coenzyme Q10 and tamoxifen (Abidin *et al.*, 2013; Atroshi *et al.*, 2000; Sutken *et al.*, 2007; Yenilmez *et al.*, 2010) increased protective effects on DNA, proteins and lipids against OTA-induced toxicity compared to the individual effects of the compounds. Moreover, the combination of coenzyme Q10, L-carnitine, alpha-tocopherol and selenium, garlic and curcumin (El-Barbary, 2016), black tea and curcumin (Alm-Eldeen *et al.*, 2015) displayed potent antioxidant effects against the toxic effects of AFB₁. In T-2-induced oxidative stress experiments, the increase in the level of GSH and the decrease in DNA damage were more apparent in mixtures of coenzyme Q10, L-carnitine, alpha-tocopherol and selenium (Atroshi *et*

al., 1999) and tamoxifen, vitamin E, and Se (Atroshi *et al.*, 1997, 2000).

5. Conclusions

Oxidative stress, ROS and RNS generation induced by mycotoxins have been associated with their cytotoxic effects on DNA, protein synthesis and mitochondria. These effects have been confirmed in different assays on cell membranes, proteins or nucleic acids, but the mechanisms involved in the activation of the signalling pathways that results in cell death or increased permeability for the different mycotoxins remain uncertain. Which factors are involved in activation? Dose, duration of exposure, and animal species are some of the aspects that need to be investigated in addition to the molecular characteristics of mycotoxins. In addition, most available data were acquired in *in vitro* studies or mice/rat models. New data from other animal models, especially those of economic interest are still lacking.

Several antioxidants have demonstrated their beneficial effects in mitigating and/or preventing the toxic effects of mycotoxins in *in vitro*, *in vivo* and *ex vivo* experimental models, but again the mechanisms and pathways involved in these effects are still not fully understood, pointing to a wide range of research opportunities. Although numerous studies have demonstrated the protective and preventive effect of antioxidants on mycotoxins-induced oxidative stress, the choice of the most appropriate nutritional methods requires knowledge of the type of antioxidants in the diet, their bioavailability and food sources, and the exact intake required to achieve these protective effects.

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