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Invited Review

Role of oxidative stress in Deoxynivalenol induced toxicity

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ABSTRACT

Deoxynivalenol (DON) is a *Fusarium* toxin that causes a variety of toxic effects with symptoms such as diarrhoea and low weight gain. To date, no review has addressed the toxicity of DON in relation to oxidative stress. The focus of this article is primarily intended to summarize the information associated with oxidative stress as a plausible mechanism for DON-induced toxicity. The present review shows that over the past two decades, several investigators have documented the generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) in oxidative stress as a result of DON treatment and have correlated them with various types of toxicity. The evidence for induction of an oxidative stress response resulting from DON exposure has been more focused on *in vitro* models and is relatively lacking in *in vivo* studies. Hence, more emphasis should be laid on *in vivo* investigations with doses that are commonly encountered in food products. Since DON is commonly found in food and feed, the cellular effects of this toxin in relation to oxidative stress, as well as effective measures to combat its toxicity, are important aspects to be considered for future studies.

Contents

Abbreviations: AIFM1, apoptosis inducing factor mitochondrion associated 1; AF, aflatoxin; C, catechin; CAT, catalase; CoQ10, Coenzyme Q_{10}; DON, deoxynivalenol; EC, European Commission; EGC, epigallocatechin; EGCG, epigallocatechin gallate; ECG, epicatechin gallate; ERK, extracellular-signal regulated kinase; GGT, gamma-glutamyltransferase; GSH, glutathione; GST, glutathione S transferase; GPx, glutathione peroxidase; GR, glutathione reductase; G6PDH, glucose-6-phosphate dehydrogenase; HMOX-1, heme oxygenase-1; HSP-70, heat shock protein-70; HT, hydroxytyrosol; ICDH, isocitrate dehydrogenase; IARC, International Agency for Research on Cancer; JAK/STAT, Janus kinase/Signal transducer and activator of transcription; JECFA, Joint FAO/WHO Expert Committee on Food Additives; JNK, c-Jun N-terminal kinase; LA, leontopodic acid; LPO, lipid peroxidation; MAPKs, mitogen-activated protein kinase; MDA, malondialdehyde; MMP, mitochondrial membrane potential; NO, nitric oxide; NF-κB, nuclear factor-kappaB; PMTDI, provisional maximum tolerable daily intake; ROS, reactive oxygen species; RNS, reactive nitrogen species; SOD, superoxide dismutase; TAS, total antioxidant status; TEMPO, 2,2,6,6-tetramethylpiperidine-1-oxyl; Trx-1, Thioredoxin-1; US-FDA, United States – Food and Drug Administration; ZEN, zearalenone; 8-OhdG, 8-hydroxy-2′-deoxyguanosine.

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1. Introduction

Trichothecenes are a group of mycotoxins that frequently contaminate food and feed globally (Pestka and Smolinski, 2005). Deoxynivalenol (DON, vomitoxin) is a type B trichothecene predominantly produced by *Fusarium graminearum* and *Fusarium culmorum* group of species contaminating basic grains such as wheat, maize, barley, and oats. DON is mainly produced in the field conditions, however secondary contamination may occur during storage (Ma and Guo, 2008). Structurally DON is a polar compound, containing 3 free hydroxyl groups (–OH), which are primarily associated with its toxicity (Nagy et al., 2005). Several reports suggest that the presence of DON in human food raises serious health concerns, particularly anorexia and vomiting (Pestka and Smolinski, 2005). DON has been shown to disrupt cell signaling, differentiation, growth, and macromolecular synthesis, which is associated with broad spectrum effects such as gastrointestinal homeostasis, growth, neuroendocrine function, and immunity (Pestka and Smolinski, 2005). Considering its global occurrence, DON seems to be one of the most important trichothecenes mycotoxins in cereal contamination (European Commission, 2003).

Two major outbreaks of human gastroenteritis in Japan and Korea were linked to *Fusarium* infected foods, where people suffered from nausea, diarrhea and vomiting as their primary symptoms (Yoshizawa, 1983). These findings indicate that DON was the possible causative agent. In a similar report from China, gastroenteritis outbreaks during 1984–1991 were associated with DON and other trichothecene-infected cereals affecting 130,000 people (Luo, 1994). In Kashmir Valley of India, several thousand individuals consuming rain-damaged moldy wheat products suffered from severe gastroenteritis where DON was reported to be present in the range of 0.34–8.4 mg/kg (Bhat et al., 1989).

Due to wide occurrence of DON in food crops, together with its potential toxicological implications in animal models as well as in humans, DON has attracted significant public health attention over the last few years. Several national and international food safety organizations and expert groups have highlighted the need for risk assessments of DON in food. Considering the toxicity of DON, European Commission (EC) introduced maximum permissible limits of 1250 μg/kg in unprocessed cereals other than durum wheat, oats and maize, 1750 μg/kg in unprocessed durum wheat and oats, 750 μg/kg in finished products (cereals intended for direct human consumption, cereal flour, bran and germ as end product), 500 μg/kg in bread (including small bakery wares), pastries, biscuits, cereal snacks and breakfast cereals and 200 μg/kg in processed cereal-based foods and baby foods for infants and young children, to reduce the risk to the consumer (EC, 2006). The US Food and Drug Administration (US-FDA) has established advisory guidelines for DON in food and feed with a permissible limit of 1000 μg/kg in finished wheat products (e.g., flour, bran, and germ) for human consumption (FDA, 2010). Reviewing the toxicological data and toxicokinetics studies on DON, the Joint FAO/WHO Expert Committee on Food Additives (JECFA, 2010) has established a provisional maximum tolerable daily intake (PMTDI) of 1 μg/kg bw.

It is well established that on acute exposure, DON induces serious dysfunction in animals and humans. The main toxic effect of DON at the cellular level is due to the inhibition of protein and nucleic acid synthesis (Shifrin and Anderson, 1999; Ueno et al., 1973) via binding to the ribosome and by activating cellular kinases, Mitogen-activated protein kinase (MAPKs) including p38, c-Jun N-terminal kinase (JNK), and extracellular-signal regulated kinase (ERK) (Shifrin and Anderson, 1999). DON has been reported to cause MAPKs mediated upregulation of proinflammatory cytokine and chemokine expression as well as apoptosis (Islam et al., 2006; Shifrin and Anderson, 1999; Zhou et al., 2003). *In vitro* studies suggest that at low to moderate concentrations (<500 ng/ml) DON selectively induces gene expression, but upon prolonged exposure to high concentrations (>500 ng/ml), the toxin causes cell death due to apoptosis (Pestka, 2008). A recent study in macrophages has demonstrated that the activation of Janus kinase/Signal transducer and activator of transcription JAK/STAT signaling pathway may be a critical mediator to induce the inflammatory response and apoptosis (Wang et al., 2012).

There has been considerable focus for the past several years over the potential of DON to induce oxidative stress. *In vitro* studies conducted on several cell lines have suggested the possible role of oxidative stress on DON-induced cytotoxicity and apoptosis (Braicu et al., 2009; Costa et al., 2009; Sahu et al., 2008; Zhang et al., 2009). Oxidative stress is a phenomenon which occurs in a cell when the concentration of reactive oxygen species (ROS) exceeds the antioxidant capacity (Sies, 1991). ROS can initiate the process of lipid peroxidation in the lipid membrane causing damage to phospholipids and lipoprotein of the cell membrane, and damage to DNA by propagating a chain reaction (Braca et al., 2002). Results suggest that ROS may play an important role in the induction of DON-induced damage to proteins, lipids and DNA, thus altering the antioxidant status which may result in toxicity. To date, there are reviews on DON-induced toxicity, apoptosis, and carcinogenesis (Ma and Guo, 2008; Pestka, 2008, 2010), but none of the reviews have focused attention on oxidative stress. The scope of this review is primarily intended to summarize the evidence associated with a role of oxidative stress as a plausible mechanism for DON-induced toxicity. A list of studies related to DON-induced toxicity under *in vitro* and *in vivo* conditions is provided in Tables 1 and 2, respectively. The present review shows that over the past two decades, several investigators have documented the generation of oxidative stress as a result of DON treatment, which has been correlated with various types of toxicity.

2. Generation of reactive oxygen and reactive nitrogen species

Oxidative stress is initiated by reactive oxygen species (ROS) such as superoxide anion (O-2), perhydroxy radical (HOO^{-}) and hydroxyl radical ($HO^{\cdot}$) and by reactive nitrogen species (RNS) including nitric oxide. Increased production of ROS leads to oxidative stress that affects the endothelial and vascular function, and contributes to vascular disease (Cai and Harrison, 2000). Nitric oxide (NO) is also a principal determinant of normal endothelial and vascular function. During the process of inflammation, NO production may increase considerably and in association with other ROS may contribute to oxidative stress (Kojda and Harrison, 1999). One of the fundamental reasons for large amounts of ROS and RNS production in cells is due to the involvement in host defenses that kill or destroy invading microorganisms, however if the cellular homeostasis is altered, these reactive species may damage tissue structures. Basically, it is the imprecise targeting of ROS and RNS that can induce oxidative stress in normal cells leading to enhanced toxicity (Cerutti et al., 1992).

DON-dependent production of ROS has been reported in several cell culture studies; however DON (25–250 ng/ml) has been reported to have negligible effects on the production of NO (Ji et al., 1998). Cellular oxidative stress was reported in rat liver clone-9 cells where DON (0.1 μg/ml) was reported to induce ROS generation (Sahu et al., 2008), which was further linked with hepatotoxicity. A study conducted by Costa et al. (2009) revealed that DON at 80 and 160 μM concentrations caused a significant increase in ROS levels in U937 cells thereby causing cell damage. During this process DON was also able to enhance glutathione peroxidase (GPx) activity, but this effect was not able to protect against cell death (Costa et al., 2009). In yet another study, a single dose of