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THE EFFECTS OF DEOXYNIVALENOL (DON) ON THE GUT MICROBIOTA, MORPHOLOGY AND IMMUNE SYSTEM OF CHICKEN – A REVIEW

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Abstract

Feed contamination is a major cause of diseases outbreak in the poultry industry. There is a direct relationship between feeding, the intestinal microbiota and how the immune system responds to disease infestation. Cereals which form the bulk of poultry feed are mostly contaminated by mycotoxins of Fusarium origin. Adequate knowledge of mycotoxins and their effects on animals is necessary. Deoxynivalenol (DON) is a major contaminant of poultry feed. DON has the ability to bind with a large number of eukaryotic ribosomal subunits because of the presence of an epoxide group and these disrupt the activity of peptidyl transferase and the elongation or shortening of peptide chains. Deoxynivalenol has varying effect ranging from acute, overt diseases with high morbidity and death to chronic disease, decreased resistance to pathogens and reduced animal productivity. Deoxynivalenol also impairs the intestinal morphology, nutrient absorption, barrier function, and the innate immune response in chickens. This review highlights the impacts of deoxynivalenol on the immune system, intestinal microbiota composition and the morphology of chicken.

Key words: deoxynivalenol, microbiota composition, immune system, intestinal morphology, mycotoxins

The purpose of every poultry industry is to ensure high productivity and improve upon quality at a low cost. This, coupled with increase in the human population and its corresponding demand for poultry meat and products, has necessitated that there should be constant, efficient and goal-oriented healthcare to prevent the development of diseases leading to loss in the industry. One major cause of diseases in the poultry industry is contamination of feed. There is a direct relationship between feeding, the intestinal microbiota and how the immune system responds to disease infestation (Wise and Siragusa, 2007; Kohl and Dearing, 2012; Oakley et al., 2013). One major mode of contamination of plant products is by mycotoxins of Fusarium origin (Pinton et al., 2008). These plant products are mostly used in the production of food and feed (Martins, 2018; Reddy et al., 2018), of which cereals account for a large part of these plants products in the preparation of human and animal diets (Stuper-Szablewska et al., 2016). To ensure that feed is not contaminated, knowledge about mycotoxins and their effect on animals is very important (Gajęcka et al., 2017; Liew and Mohd-Redzwan, 2018). Among the mycotoxins, the commonest are deoxynivalenol (DON), zearalenone (ZEN) and its metabolites, α-zearalenol (α-ZEL) and β-zearalenol (β-ZEL), with 58% and 41,157 μg/kg, for deoxynivalenol, and 46% and 3049 μg/kg for zearalenone, respectively (Schatzmayr and Streit, 2013; Lee and Ryu, 2017). The mycotoxin deoxynivalenol is a polar organic compound with formula 12,13-epoxy-3α,7α,15-trihydroxy-trichothec-9-en-8-one (Maresca and Fantini, 2010), having a ketone group on the C8 which is a characteristic feature of type B trichothecenes. The number and location of hydroxyl groups and acetyl esters can also determine the compound's relative toxicity inside cells (Pestka, 2004). DON has the ability to bind with a large number of eukaryotic ribosomal subunits because of the presence of an epoxide group (Pestka, 2010) and this disrupts the activity of peptidyl transferase and the elongation or shortening of peptide chains. Deoxynivalenol (DON) is a mycotoxin produced by Fusarium species. It is found mostly in cereals such as corn, barley, wheat, rye and sometimes in rice and sorghum and it is considered as one of the most important trichothecenes. Trichothecenes are the main and chemically most diverse group of the three major classes of Fusarium mycotoxins (Summerell and Leslie, 2011). They represent a large family of chemically related toxins produced by fungi in taxonomically unrelated genera, such as Fusarium, Myrothecium, and Stachybotrys and present a potential threat to animal health throughout the world (Li et al., 2011). They are classified into four groups (A, B, C and D) based on their substitution pattern, all containing a common 12,13-epoxytrichothecene group which is responsible for their cytotoxicity and a 9,10 double bond with various side chain substitutions. Deoxynivalenol (DON) and its 3-acetyl and 15-acetyl derivatives is a type B and contains a keto (carbonyl) function at C-8 and includes fusarenon-X and nivalenol (NIV). The occurrence of deoxynivalenol is associated primarily with *Fusarium graminearum* (*Gibberella zeae*) and *F. culmorum* (Alassane-Kpembi et al., 2015). Mycotoxins of Fusarium origin often contaminate cereal grains which constitute the bulk of feed for poultry. Several researchers have investigated the effects of DON mycotoxin on the functions of the immune system ranging from immunosuppression to immunostimulation and reported that these impact is dependent on the concentration, duration and time of exposure (Bondy and Pestka, 2000; Pinton et al., 2010; Becker et al., 2011). Pestka (2003) reported that concentrations of DON (less than 5 mg/kg feed) seem to be responsible for stimulation of immunity and high concentrations seem to suppress the immune responses. Desjardins (2006) also reported that chronic DON intoxication at high concentrations lead to injuries of rapidly and actively dividing cells of immune organs and mucosa of the gastrointestinal tract. The toxin binds to the 60S subunit of ribosomes thereby inhibiting the synthesis of protein. This induces a stress response and mitogen activated protein kinases (MAPKs) are activated, due to ribosomal conformational changes affecting the peptidyl transferase activity of ribosomes. An important activity of MAPKs is their effect on transcription factors. Higher expression of nuclear factor κB (NF-κB) induces the expression of pro-inflammatory cytokines affecting immune reactions in animals (Rocha et al., 2005). The important role being played by the intestinal microbiota of broiler chickens in ensuring optimum growth performance and good health of birds cannot be underestimated (Bjerrum et al., 2006). The influence of these microbiota are particularly important at the young stage since it would still be in the process of development (Gong et al., 2015). The interaction of intestinal growth, digestive functions, and diet is critical during the post-hatching period when birds switch to solid feed nutrition. Among the numerous functions of the microflora populations in the digestive tract of chicken is the promotion of immune system development and function, nutrition and function, metabolism and pathogen exclusion (Guarner and Malagelada, 2003; Noverr and Huffnagle, 2004; Macpherson and Harris, 2004; Backhed et al., 2005; Guarner, 2006; Round and Mazmanian, 2009). Several researches have reported that the balance and regulation of helper T cells (Th1, Th2, Th17), in helping protect the host from the invasion of enteric pathogens is greatly influenced by intestinal microbiota (Ivanov et al., 2008). Ley et al. (2006) also found that germ-free chicken lacking microbiota have few plasma cells, decreased IgA levels, and under-developed Peyer's patches in the small intestine, resulting in increased susceptibility to enteric pathogens. The gut of birds is colonized by environmental microbes immediately after hatching. Several factors such as nutrient composition of diet, age, medication and stress account for the composition of the gut microbiota (De La Cochtiere et al., 2008; Claesson and O'Toole, 2010; Claesson et al., 2011). For the complete maintenance of animal health, there must be homeostasis. In the absence of homeostasis, the animals are predisposed to several diseases. The gut microbiota composition is readily changeable (Jia et al., 2008); depending on the environmental condition prevalent and the nutrient composition of feed. Although some are beneficial to the growth of the animal, others are harmful. It is therefore imperative that the safety of the total environment and the nutrient composition and state of the feed must be greatly taken into consideration to ensure optimum performance (Claesson and O'Toole, 2010). The aim of this review is to assess the impact of deoxynivalenol (DON) on the gut microbiota, morphology and subsequently its effect on the immune system of chicken.

Deoxynivalenol (DON) in poultry feed

Deoxynivalenol (DON), also called vomitoxin, is a major contaminant of feedstuffs worldwide, produced by *Fusarium graminearum* (*Gibberella zeae*) and *F. culmorum* (Romers Lab Guide, 2000). It is found in cereal grains (wheat, maize, barley, oat and rye and less often in rice and sorghum) which form the bulk of feed for livestock. *Fusarium graminearum* and *F. culmorum* can survive in the leaves of the cold season and be a source of infection for the new crop. Cool temperatures and high humidity are the environmental conditions that favor the fungal development in the field (Dersjant-Li et al., 2003; Richard, 2007). If grains are not properly stored after harvesting, and are exposed to high moisture conditions, it gives rise to the fungal infestation. After infection of grains, *F. graminearum* infestation results in the disease known as ear rot in corn or head blight in wheat and barley (Richard, 2007). One sign associated with deoxynivalenol contamination is when corn kernels ripen prematurely, unevenly and have a blanched appearance. The natural occurrence of DON in grains used for poultry is normally between 0 and 5 mg/kg, although concentrations can be higher (Dersjant-Li, 2003). However, improved storage conditions (<14% moisture) will minimize further elaboration of DON. Fusarium mycotoxins have the property of exerting both acute and chronic toxic effects and this characteristic makes them a major cause of broad varieties of toxic effects in animals. These fungal compounds have varying effect ranging from acute, overt diseases with high morbidity and death to chronic disease, decreased resistance to pathogens and reduced animal productivity. Kanora and Maes (2009) reported that even when low levels of toxins are ingested, the metabolic, physiological and immunological properties of the animal are compromised, with symptoms associated with mycotoxicosis being evident. Since it is a common practice to use multiple grain sources in animal diets, the risk of exposure to several mycotoxins increases with diet complexity (Grenier and Applegate, 2013). The hemical structure of DON is shown in Figure 1.

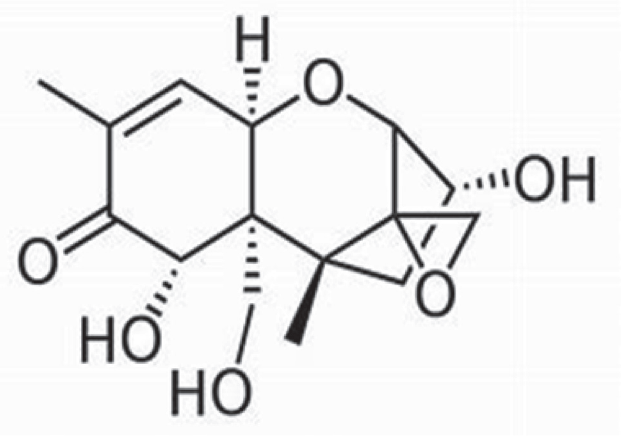

Figure 1. The chemical structure of deoxynivalenol

The gut microbiota, morphology and deoxynivalenol (DON)

The gut microbiota is very important in ensuring the health of the animal is not compromised. Among the numerous roles it plays are the modulation of the gut epithelial barrier, responding to inflammations, synthesis of vitamins, dietary fiber fermentation and providing protection against pathogen colonization (Maslowski and Mackay, 2011; Kogut and Arsenault, 2016). *Bacteroidaceae*, *Ruminococcaceae*, *Lachnospiraceae* and *Clostridiaceae* are the dominant bacterial taxa in chicken and they are highest in the ceca (Oakley et al., 2014). Moreover, the longer retention time of digesta in the ceca allows for a more complete microbial breakdown of complex fiber and enhances short-chain fatty acid (SCFA) production compared to the other gut sites (Oakley et al., 2014). Cereals form the bulk of poultry feed but there is the likelihood of it being contaminated by the Fusarium toxin deoxynivalenol (DON) which is very harmful for animal health (Escrivá et al., 2015), and causes substantial economic losses in poultry production (Awad et al., 2013). Andretta et al. (2011) reported that chickens are sensitive to moderate DON levels that compromise feed intake, growth performance and functioning of the immune system. The current guidance value of The European Union's standard for DON in poultry feed is 5 mg DON/kg feed (12% moisture) (2006/576/EC, 2006). When consumed, DON impairs the intestinal morphology, nutrient absorption, barrier function, and the innate immune response in chickens (Awad et al., 2011 b; Osselaere et al., 2013; Lucke et al., 2017 b). The gastrointestinal mucosa among other functions serves as a dynamic barrier, regulating uptake of nutrients and water, while excluding potential pathogens and toxicants (Eriksen and Pettersson, 2004). These functions are impaired upon ingestion of contaminated feed (Desjardins, 2006). Lipopolysaccharides (LPS) are immune-stimulatory compounds which are released by the gut microbiota (Saadia et al., 1990; Ge et al., 2000; Ghareeb et al., 2016; Lucke et al., 2017 a). These compounds are part of the outer membrane of Gram negative bacteria and may suppress growth performance in poultry by diverting energy for an elevated immune response (Ghareeb et al., 2016). Problems associated with LPS include damage to the gut mucosal tissue (Wu et al., 2013), modifying mucus secretion and composition *in vitro* (Dohrman et al., 1998; Smirnova et al., 2003; Cornick et al., 2015; Zhang et al., 2017). Moreover, evidence suggests that LPS can interfere with the response to other xenobiotic agents. Trichothecenes are small, amphipathic molecules that can move passively across cell membranes. They are easily absorbed via the integumentary and gastrointestinal systems, allowing for a rapid effect of ingested trichothecenes on rapidly proliferating tissues (Pinton and Oswald, 2014). Trichothecenes are toxic to animals and its exposure has been linked to reproductive disorders in domestic animals (Cortinovis et al., 2013). Damage to the gut barrier in duodenum and jejunum may modify intestinal nutrient flows with consequences for the microbial composition and metabolism in the ceca. Robert et al. (2017) reported that DON and other mycotoxins target the mucus and microbiota composition of their hosts, causing damage to the tissue of the gut, shortening the height of the villi, stop differentiation of gut cells and destabilize the composition of the gut (Suzuki and Iwahashi, 2015). The gastrointestinal tract (GIT) exhibits several characteristics such as chemical, physical, immunological and microbiological, all geared towards ensuring that its function of serving as a barrier against toxins and contaminants is not compromised (Bouhet et al., 2004). The villi, the minute membranes lining the mucous membrane of the small intestine serve as a site for the absorption of nutrients. Upon exposure of the villi to DON contaminated diets, there is atrophy of the villi in broilers (Awad et al., 2004, 2006, 2011). The structures of duodenal and jejunal mucosa villi are also affected and they become thinner and shorter on exposure to DON (Awad et al., 2011). This adversely affects the digestive and absorptive functions of the intestines. To maintain and ensure proper mucosal integrity, the gut barrier function of the epithelial cell layer needs to be in the best of shape. The integrity is mostly provided by the tight and adherence junctions of the epithelial cells which are known to be affected by fungal toxins (Bouhet et al., 2004). There are negative effects when the immune organs, liver and the small intestines are exposed to DON (Feinberg and McLaughlin, 1989). A research conducted on Peking ducks showed that feeding with an increasing proportion of DON contaminated wheat (6–7 mg DON/kg and 0.05–0.06 mg ZEN/kg) led to a decrease of the relative weight of the bursa of Fabricius (Dänicke et al., 2004), which in turn may decrease the production of antibodies. It was also discovered that in ducks, higher weights were recorded for the heart, liver and pancreas after feeding of DON (Cheng et al., 2004), while in broilers, gizzard, heart and bursa of Fabricius were having a higher weight (Kubena et al., 1985; Kubena et al., 1997). DON also had an irritant effect on the gizzard mucosa and a decrease in the weight of the small intestine of laying hens when fed a concentration of 3.4 and 9.9 mg/kg Fusarium mycotoxin (Dänicke et al., 2002). DON causes a disruption in the synthesis of protein thereby influencing the rate of passage across cell membrane (Lun et al., 1989; Waśkiewicz et al., 2014), affects the role of enzymes in metabolism in the cytoplasm, changes in affinity for an active binding site (Pinton and Oswald, 2014). These properties enable DON to influence specific tissues and organs. For the mycotoxin to take effect, it has to be released from the food matrix and absorbed from the intestines (Pinton et al., 2012) into the bloodstream, whereby it can affect the structural properties of intestinal mucosa and animal productivity.

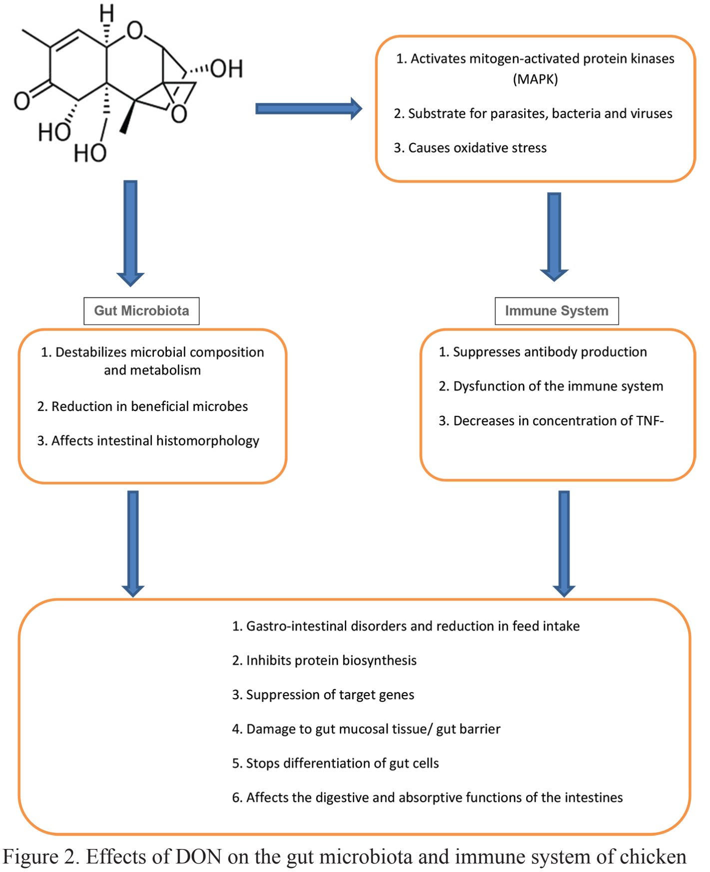

Figure 2. Effects of DON on the gut microbiota and immune system of chicken

The immune system and deoxynivalenol (DON)

The immune system is composed of interacting cells, tissues and proteins that form two distinct arms: the innate and adaptive immune responses. The innate immune system is the first line of defense and is rapid and non-specific but lacks memory of pathogens; therefore, it does not need prior experience of a pathogen to mount an attack, but subsequent challenges by the same pathogen result in a similar response to that of the first exposure (Lun et al., 1986). Adaptive immunity, however, is very slow to reach protective levels upon an initial exposure to a pathogen, but class switching occurs and the memory B cells generated are stored, which permits a rapid and specific defense against subsequent exposures to the same pathogen. At hatching, birds are quite vulnerable to environmental pathogens, as the immune system had not matured. At this early stage of life there is a strong reliance on maternal antibodies and innate immune function (Levy, 2007) whilst the adaptive immune system gradually develops in response to microflora colonization (Klasing and Leshchinsky, 1999; Klasing, 2004). The immune system serves among other functions to recognize foreign substances and organisms (antigens) that are able to enter the body and thereby initiate and manage appropriate physiological responses to neutralize and eliminate these organisms and substances. In a bid to achieve this goal, several mechanisms come into play, including inactivation of biological agents, lysis (rupture) of foreign cells, agglutination (clumping) or precipitation of molecules or cells, or phagocytosis (engulfing and inactivating) of foreign agents. There is varying literature regarding the impact of feeding DON on the health and performance traits in poultry. This notwithstanding, it is established that there is a dysfunction of the immune system of birds when exposed to DON, predisposing the birds to infectious diseases (Lun et al., 1986; Oswald et al., 2005). Ghareeb et al. (2012) and Dänicke et al. (2002) reported that birds that were exposed to DON had suppressed antibody response to infectious bronchitis vaccine (IBV) and Newcastle disease virus. DON decreased the concentration of tumor necrosis factor alpha (TNF-α) in plasma of broiler chickens (Awad et al., 2012). TNF-α is an important cytokine involved in systemic inflammation and stimulates the acute phase reaction. DON, therefore, can interfere with production of TNF-α from macrophages. DON also has adverse effect on the intestinal histomorphology, electrophysiology, absorption and barrier function in chickens (Awad et al., 2004, 2006 a, 2006 b; Girgis et al., 2010). The negative effects of DON on the health and growth performance of broiler chickens have been documented (Yunus et al., 2012; Antonissen et al., 2015). Because of its potential of serving as a protein inhibitor, it is able to initiate apoptosis by activating mitogen-activated protein kinases. This leads to a variety of lesions and symptoms including growth retardation, feed refusal and gastrointestinal disorders (Awad et al., 2006; Awad et al., 2012). Mycotoxins undergo the same processes as drugs (absorption, distribution, metabolisation and excretion). Mycotoxins sometimes act as substrates, inhibitors or inducers to these metabolizing enzymes. Several experiments done *in vivo* and *in vitro* showed absorption of DON mostly occurs from the stomach to the proximal jejunum, leading to inhibition of protein synthesis and suppression of various target genes, including amino acid transporters (Goyarts and Dänicke, 2006; Dänicke et al., 2006). Immune homeostasis can also be maintained by the intestinal epithelial cells (IEC) when they come into contact with commensal bacteria, and the most crucial key to coexistence of commensal bacteria and IECs is the ability to segregate host cells from microorganisms. This notwithstanding, disruptions occurring in the intestinal epithelial barrier pose risk of infection and inflammatory responses (Yan et al., 2013). In broiler chickens, T-2 causes reduced feed intake and body weight gain, but also severe oral lesions and immunological dysfunction (Devegowda and Murthy, 2005). Clinical signs depend on the exposure time and on the dose of the toxin. Moreover, this toxin causes oxidative stress that alters the cell cycle and induces apoptosis *in vitro* and *in vivo* (Islam et al., 1998; Chen et al., 2008). Ghareeb et al. (2006) reported that feeding 10 mg DON/kg to chicken altered the humoral immune response to viral vaccine, decreased the level of alanine transaminase (ALT), increased serum cholesterol concentration and the amount of circulating triglycerides. Moreover, Chen et al. (2017) verified that DON may cause a disturbance to the immune system and alter the intestinal barrier in Taiwan country chickens, and may also lead to irregularities in growth performances in a dose- and sex-dependent manner (Chen et al., 2017). For an immune response to be effective, the right mechanism, or combination of mechanisms, must be activated. However, for each species there are many diseases for which immunity does not exist. Also, under certain circumstances, these normally protective responses can result in significant tissue damage, which leads to immune-mediated diseases. The summary of the effects of DON on the gut microbiota and immune system of chicken is presented in Figure 2.

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