EFFECTS OF FUMONISIN B1 ON THE GASTROINTESTINAL TRACT FUNCTIONALITY – A REVIEW

YARSMIN YUNUS ZEEBONE – KOVÁCS MELINDA – HALAS VERONIKA

SUMMARY

Fumonisins (FB) are majorly produced by *Fusarium verticilloides* and *F. proliferatum* and are frequently present in maize and maize-based products. Fumonisin B1 (FB_1) is the most toxic among the existing congeners and its post-absorptive effects have been well documented as opposed to the gastrointestinal tract (GIT) functionality. The GIT is the primary point of contact to any ingested FB_1-contaminated food/feed and therefore, predisposed to high concentrations of this fungal metabolite. Furthermore, studies suggest that major mycotoxins typically target high protein turn-over and activated cells; such as the gastro-epithelial cells. In this regard, studies on gastrointestinal health have been fast-growing in recent years. This review dissertates on the toxicity of FB_1 in relation to GIT functionality. With the published data garnered, key morphological and functional alterations induced by FB_1 in the aspects of gut barrier functions, digestive and absorptive functions, immune status and microbial composition of the GIT are presented in this review. With respect to the latter, the potential mechanisms through which FB_1 acts is largely unknown and yet to be fully investigated.

ÖSSZEFOGLALÁS

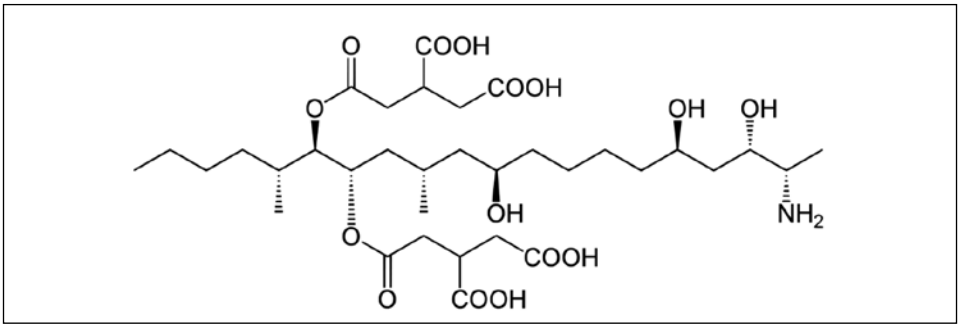
Zeebone, Y.Y. – Kovács, M. – Halas, V.: A FUMONIZIN B1 HATÁSA A TÁPCSATORNA MŰKÖDÉSÉRE – IRODALMI ÁTTEKINTÉS

A fumonizinek (FB), amelyeket főként a *Fusarium verticilloides* és *F. proliferatum* penészgombák termelnek, gyakran szennyezik a kukoricát és a kukoricaalapú termékeket. A fumonizinek között a fumonizin B1 (FB1) a legtoxikusabb származék, amelynek általános hatását jól ismerjük szemben a emésztőszervekre kifejtett károsító hatásaival. Pedig a bél a táplálékkal / takarmánnyal a szervezetbe jutó mikotoxinok első expozíciós szerve. A legtöbb mikotoxin károsítja a gyorsan osztódó sejteket, ilyenek tipikusan a bélhámsejtek is. Mindezek magyarázzák azt, hogy a mikotoxinok emésztőtraktus működését befolyásoló hatásának vizsgálata előtérbe került. Ez az összefoglaló közlemény erre a kérdésre fókuszál. Szakirodalmi adatok alapján bemutatja a FB1 által az emésztőrendszerben előidézett morfológiai és funkcionális változásokat, a FB1 hatását a bél integritására, barrier funkciójára a bélhám áteresztőképességére, az emésztésre és felszívódásra, a helyi immunválaszra, valamint a mikrobióta összetételére.

INTRODUCTION

Mycotoxins are low molecular weight (approximately 700MW) secondary metabolites of moulds that contaminate most agricultural products and present critical health risks to both humans and animals globally (*Binder*, 2007). The *Fusarium verticillioides* (Sacc.) is one of the most prevalent mycotoxin found in corn and corn products intended for both human and animal consumption. A family of foodborne mycotoxins, fumonisins (FB) were first isolated in 1988 from cultures of *F. verticillioides* strain MRC 826 by *Gelderblom and co-workers* in South Africa (*Gelderblom et al*., 1988). Among the 15 existing isolates, fumonisin B1 (FB_1) (*Figure 1.*) has been extensively studied due to its profound toxic activities.

Figure 1. *Chemical structure of FB_1 (https://en.wikipedia.org/wiki/Fumonisin_B1)*



1. ábra A FB1 kémiai szerkezete

Albeit bioavailability of FB is poor in a variety of examined animal species, exposure to this fungal metabolite may induce several animal and human disorders. These include equine leukoencephalomalacia (ELEM); pulmonary edema (PPE) and hydrothorax of swine; hepatotoxic and nephrotoxic in rats, rabbits, lambs, and calves (*Bane et al*., 1992; *Hascheck et al*., 1992; *Edrington et al*., 1995; *Smith et al*., 1996; *Howard et al*., 2001); human oesophagal cancer and some neural tube defects (NTDs) in some parts of the world (*Gelineau-van Waes et al*., 2009; *Islami et al*., 2009). The latter led the International Agency for Research in Cancer (IARC) to describe FB_1 as possibly carcinogenic; IARC classification of FB_1 (group 2B) (*IARC*, 2002). The initial mechanism of FB_1 toxicity is to disrupt the enzyme ceramide synthase (CerS) activity due to the structural resemblance of FB_1 and the sphingoid bases, sphinganine (Sa) and sphingosine (So). What follows is an array of cellular disturbances in cell growth and differentiation, cell survival, and apoptosis (*Merrill et al.,* 2001). Although its toxicity at the cellular level is well documented, data on the effects of FB on the gastrointestinal tract (GIT) is not fully understood. It is often overlooked that the GIT is the first to come into contact with any ingested mycotoxin such as FB and exposed to significantly higher concentrations relative to other tissues (*Grenier and Applegate,* 2013). In addition, emerging studies have highlighted the GIT as a new target for mycotoxins deleterious activities. Yet, as at the year 2013, only 83 studies have been garnered and this included all *in vitro*, *in vivo* and *ex vivo* studies (*Grenier and Applegate,* 2013).

The GIT is well designed to defend against pathogenic invasions to about 70% of the immune defences of an organism and in addition, maintains the indigenous microflora present in the gut (*Grenier and Applegate,* 2013). *Conway* (1994) describes gut health as a function of 3 main components; diet, mucosa and commensal microbiota. *Grenier and Applegate* (2013) further visualize these three components as a "Ménage a Trois" where each component interacts with each other to maintain intestinal harmony. The devastation to either of these three could result in gut health insults. Whenever the intestinal mucosa's integrity is compromised, the absorption of nutrients decreases. In addition, an increased proportion of nutrients absorbed is intended to repair the damaged area and supports the immune system until the intestinal damage is eliminated (*Lorenzoni,* 2010).

FB and their adverse effects are gaining a great deal of interest in mycotoxicology since it emerged that FB provokes poor intestinal health. This review is to summarize and illustrate key structural and morphological changes of the GIT and microbiota potentially induced by FB.

FUMONISIN B1 POTENTIALLY ALTERS GUT BARRIER FUNCTION

The epithelium lines the entire length of the GIT and it is essential to provide barrier function to the gut. It consists of a thin layer of cells that lines the lumen of the intestine and contains enterocytes, enteroendocrine, goblet cells at the villi, and the Paneth cells under the crypts (*Fink and Koo,* 2016). The epithelium acts as a barrier to noxious substances such as pathogens, toxins and foreign antigens that have been ingested. Epithelia cells are bridged with desmosomes, tight junctions (TJ), and adherens junctions (AJ). The mechanical linkage of adjacent cells is the responsibility of AJ and desmosomes. Whereas, the TJ control the intercellular space and regulate selective paracellular ionic solute transport (*Capaldo et al.,* 2014). The TJ are composed of the transmembrane and cytoplasmic scaffolding proteins. At the apical-lateral membrane of the epithelial cells, transmembrane TJ proteins such as occludin (OCLN), claudins (CLDN), junctional adhesion molecules (JAM) and tricellulin form a parallel barrier (*Chiba et al.,* 2008; *Schneeberger and Lynch,* 2004; *Tsukita et al.* 2001). A distortion to this parallel barrier is consequential to a defective gut barrier integrity.

To investigate the integrity of epithelial barrier in both *in vitro* and *ex vivo* assays, the transepithelial electric resistance (TEER) is the frequent marker utilized. This instrumentation basically follows the cycle of cell differentiation and, standard values for a completed non-permeable barrier are established based on individual devices and sizes inserted (*Akbari et al.,* 2017). Direct approaches include the use of paracellular flux probes and the assessment of the expression of TJ proteins together with histological approaches that illuminates alterations in the intestinal architecture, and into epithelial cell damage (*Bischoff et al.,* 2014). Impairment of the intestinal barrier integrity induced by FB_1 has been shown in different *in vitro*, *ex vivo* and *in vivo* studies which is summarized in *Table 1*.

Sphingolipids and lipid rafts play a major role in establishing and maintaining TJ (*Lambert et al.,* 2007). Indeed, FB_1 alters the intestinal barrier function by influencing sphingolipid metabolism, as demonstrated by an increase in the amount of free sphingoid bases, a depletion of glycolipids in the plasma membrane and

an increase in trans-epithelial flux (*Bouhet et al.,* 2004; *Loiseau et al.,* 2007). *Yamazoe et al.* (2017) reported accumulation of sphinganine (Sa) altered glycoprotein distribution in the jejunum which caused an increase in the transepithelial passage of FB_1. The increase in intestinal permeability in turn, promotes translocation of pathogenic bacteria (*Kelly et al.,* 2015). In contrast, although others (*Burel et al.,* 2013) found a change in the ratio of Sphingosin (So) and Sa in specific pathogen free piglets receiving 11.8 ppm FB_1, which in reference to the above findings can alter intestinal functions, the extent of change of the sphingoid bases observed in their work was described insufficient to induce any abnormalities in gut barrier function. Similarly, despite the effects observed for immune and oxidative stress markers, *Kim et al.* (2019) observed no noticeable effects on the TJ proteins OCLN, CLDN, or zona occludens-1 in piglets receiving a combination of aflatoxin (AF), FB_1 and deoxynivalenol (DON) in the concentrations of 180 μg/kg, 9 mg/kg and 1 mg/kg, respectively.

Table 1.

A summary of the effects of FB_1 on intestinal barrier integrity

Experimental model (1)	Dosage (2)	Exposure period (3)	Effects on barrier function (4)	Reference
Caco-2 cells	1–100 μM	7 days	A reduction in TEER values Decrease in transcript level of CLDN3, CLDN4 and OCLN (5)	Romero et al. (2016)
IPEC-1 Cells	50–200 μM	16 days	A reduction in TEER values Increase in permeability of FB_1 (6)	Loiseau et al. (2007)
IPEC-1 Cells	20–200 μM	4 hours	Increase in translocation of pathogenic Escherichia coli (strain 28C) (7)	Bouhet and Oswald (2007)
IPEC-1 Cells	50–500 μM	28 days	A reduction in TEER values (8)	Bouhet et al. (2004)
Porcine jejunal explants	10 μM	2 hours	Increase in TEER values Increase in permeability of HRP (9)	Lalles et al. (2009)
Piglets	3 mg/kg feed	5 weeks	Decrease in protein expression of OCLN in ileum (10)	Bracarense et al. (2012)
Piglets	0.5 mg/kg BW	7 days	Increase in translocation of pathogenic Escherichia coli (strain 28CNalr) (7)	Oswald et al. (2003)

TEER- transepithelial electrical resistance, CLDN- claudins, OCLN- occludin, HRP- horse radish permeability, IPEC-Intestinal porcine enterocyte cell.

1. táblázat A FB1 hatása a bél integritására

kísérleti modell (1); dózis (2); expozíciós idő (3); a barrier funkcióra gyakorolt hatás (4); a TEER (transzepiteliális elektromos rezisztencia) csökkenése, a CLDN3, CLDN4 (claudin) és OCLN (occludin) transzkripciójának csökkenése (5); TEER csökkenés, FB1 permeabilitás nő (6); a patogén E. coli transzlokációja nő (7); TEER csökkenés (8); TEER növekedés (9); OCLN expresszió csökkenés az ileumban (10)

FUMONISIN B1 MAY ALTER DIGESTIVE AND ABSORPTIVE PROCESSES OF NUTRIENTS

In the small intestine, crypts are responsible for the turnover of villus cell while villi are responsible for the absorption of nutrients. High villus is an indicator of a substantial absorption surface while flat crypts mean normal villus cell turnover. Both are worthwhile, and this is designated by high villus to crypt ratio (V:C) (*Gao et al.,* 2008). Cells from the intestinal crypts are responsible for enterocyte renewal and crypt depth is positively related with proliferative rate that can be measured by Ki-67 staining (*Willing and Van Kissel,* 2007).

Rauber et al. (2013) found morphologic changes in the small intestine of broilers receiving 100 or 200 mg/kg FB_1 diet for 28 days, and this was exhibited by the significant reduction on villus height (VH) and villus-to-crypt ratio (V:C), but no changes in crypt depth (CD). A 42-day trial involving weanling piglets exposed to 30 mg/g FB_1 resulted in intestinal villous fusion and atrophy (*Piva et al.,* 2005). Furthermore, it was demonstrated that ingestion of 6 ppm of FB_1 induced morphological and histological alterations in the intestine, with atrophy and fusion of the villi, decreased villi height and cell proliferation in the jejunum, and reduced numbers of goblet cells and lymphocytes (*Lalles et al.,* 2009; *Bracarense et al.,* 2012). A very recent study also reported a reduction in VH which in turn, reduced the percentage of cells positive to Ki-67 staining when nursery piglets were exposed to a combination of 180 μg/kg AF, 9 mg/kg FB_1 and 1 mg/kg DON for 48 days. The authors of this study explained this out-turn as the mycotoxins' potentiality to impair crypt cell proliferation (*Kim et al.,* 2019). Interestingly, others found a rather increment in ileal VH following a 9-day exposure of piglets to FB_1-rich diet which unfortunately, the authors could not explain (*Lessard et al.,* 2009).

The Ussing Chamber (UC) is used to study all epithelial tissues electrophysiologically, and some of the parameters that can be investigated are transepithelial electrical potential or short-circuit current (Isc). The Isc is induced by sodium absorption (Na^+) and chloride (Cl^-) ion secretion. Isc measurement is a remarkable indicator of the transport of sugar or amino acid, as many nutrients are transported by carrier systems and are normally transported with Na^+ (*Grenier,* 2013). *Lessard et al.* (2009) in their work, demonstrated how FB_1 can modulate some aspects of jejunal absorptive and secretory physiology without necessarily altering epithelial barrier function. The authors found a delayed increase in basal Isc of jejunal mucosa in UC for FB_1-treated pigs relative to the controls. This was explained by the increase in spontaneous trans-mucosal net ion transport, for example by Na^+ and (or) Cl^- channel processes (*Li et al.,* 2004).

Digestive enzymes are crucial for digesting dietary nutrients such as starch, fat, and proteins and any interference to the production of enzymes and/or activity is consequential to GIT dysfunctions. Again, *Lessard et al.* (2009) highlighted a significant reduction of alkaline phosphatase and aminopeptidase N enzyme activity and suggested this may have interfered with the digestion of proteins and peptides in the FB_1-rich (*in vitro* culture of the high-FB_1-producing *F. verticillioides* strain NRRL 34281) extract group. These changes can be a key factor attributable to villi morphology (*Grenier,* 2013). Details of this phenomena was however not shown in their work. Moreover, it was theorized that the intake of FB_1-rich extract

may result in alterations in the regulation of sodium-dependent glucose absorption and the basal and induced secretory properties of the intestinal mucosa. Although no alterations were evidence in barrier function of the pigs, the authors did not rule out such an occurrence should the exposure period be longer than 9 days as in this experiment (*Lessard et al.,* 2009).

Due to their distinctive ability to inhibit sphingolipid metabolism, FB_1 alters the function of cell membrane and lipid packing (*Ferrante et al.,* 2002). Exposure of pigs to FB_1 (1.5 mg/kg BW) for 7 days resulted in a significant increase in the concentration of Sa and So and a decrease in the total glycolipid content as well as alteration in the jejunal glycolipid composition, whereas no changes were observed in the duodenum and ileum (*Loiseau et al.,* 2007).

It is evidenced that animal growth is not always or, only moderately impaired by the presence of mycotoxins in the gut. However, it has to be pointed out that interference of these fungal metabolites with key processes of digestion and absorption often results in impaired intestinal functions (*Grenier,* 2013). On the whole, FB_1 still remains a crucial fungal toxin whose toxic activities on the digestive and absorptive functions of the GIT must be well investigated.

FUMONISIN B1 INTERFERES WITH IMMUNE STATUS OF THE GIT

The immune system of animals is made up of the gut-associated lymphoid tissues (GALT; Peyer's patches, mesenteric lymph nodes, caecal tonsils) in specific tissues where cells that have immunocompetence can effectively produce a specific immune response. Concomitantly, early and immediate responses are provided locally along the length of the intestinal tract where mucus, intraepithelial immune cells and intestinal epithelial cells (IECs) play essential role as sentries and defenders (*Grenier,* 2013). Cytokines, as generally referred, are a class of signaling molecules that transmit and control innate and acquired immunity and, inflammation and repair. They consist of a large group of proteins, glycoproteins or peptides produced by specific cells of the immune system to effect immune response via autocrine, endocrine and paracrine pathways (*Chung,* 2001). Mycotoxins, as stated early on, target the intestinal epithelium by affecting the proteins and peptides that serve vital functions in the immune system and host metabolism (*Grenier,* 2013).

It has been stressed that FB_1 has a controlling influence on animals by increasing interleukin (IL)-10 (IL-10) and IL-4 mRNA levels in the spleen of Balb/c mice alongside a decrease in mRNA levels of interferon (IFN)-gamma (IFN-γ) and tumor necrosis factor- alpha (TNF-α) relative to animals in the control group (*Abbès et al.,* 2016). In poultry species, FB_1 could significantly inhibit the expression of IL-1β, IL-2, IFN-α and IFN-γ when broilers were exposed to 15 mg FB_1 per kg for 3 weeks (*Cheng et al*. 2016). Whether or not in combination with aflatoxin B1 (AFB1), FB_1 increased levels of IL-4 and decreased levels of IL-10 in spleen mononuclear cells (SMC) in an *in vivo* studies performed with rats (*Theumer et al.,* 2002, 2003). Furthermore, other studies have shown how FB affect the functions of monocytes, morphological and functional changes of macrophages and enhancing susceptibility to infectious diseases (*Qureshi and Hagler,* 1992; *Dugyala et al.,* 1998; *Meli et al.,* 2000). In addition, *Ferrante et al.* (2002) showed in an *in vitro* studies performed with macrophages J774A.1 how FB_1 decreased microviscosity by increasing

membrane fluidity. The authors in further detail reported IFN-γ alone inhibited the fluid-phase endocytosis in J774A.1 cells and was able to exert its effect also in the presence of FB_1. It has already been reported elsewhere that IFN-γ inhibits both fluid-phase and receptor-mediated endocytosis in mouse peritoneal macrophages (*Konopski et al.,* 1995; *Montaner et al.,* 1999). Furthermore, *Tavasoly et al.* (2013) found that FB_1 can induce inflammation and infiltration of inflammatory cells such as lymphocytes in gastric gland parenchyma and attributed this to the chemotactic effects of necrotic cells and activated inflammatory cells.

Interleukin-8 (IL-8) is known to play an essential role in lymphocyte and neutrophil infiltration to the regional inflammation site (*Dinarello,* 1997). In both *in vivo* and *in vitro* studies on ileal samples, it was shown that FB_1 could decrease IL-8 expression at the mRNA and protein level in a dose-dependent manner (*Bouhet et al.,* 2006). Other works have affirmed this phenomenon (*Mahmoodi et al.,* 2012; *Minervini et al*., 2014). In fact, reduction and inhibition of IL-8 expression suggest that FB_1 in the host intestine can reduce lymphocyte and polymorph cell migration to the inflammatory regions. Such reduction could be responsible for a low number of polymorphonuclear leukocytes (PMNs) engaged in modulating infection sites, thus leading to the ineffective elimination of pathogens from the gut (*Brazil et al.,* 2013). Furthermore, *Sharma et al.* (2006) showed that FB_1 could increase the mRNA expression of TNF- α and IL-1α in mice peripheral blood. On another account, *Bhandari et al.* (2002) demonstrated that subcutaneous injection of FB_1 in mice could increase TNF-α and IL-1β in kidney and liver tissues.

Inhibitors of CerS activity have been shown to suppress T-dependent immune response (cluster of differentiation (CD) 3 (CD3), CD4, CD8, CD45), which inhibits DNA synthesis, also modifying T-lymphocyte surface antigen expression (*Martinova,* 1998). *Piva et al.* (2005) revealed severe infiltration of lymphocytes and monocytes; moderate infiltration of eosinophils and presence of submucosal nodular lymphoid aggregates in weanling piglets exposed to 30ppm dose of FB_1 over a period of 42 days. In another study, *Devriendt et al.* (2009) showed that FB_1 is capable of reducing the induction of an antigen-specific intestinal immune response following oral F4 fimbriae (surface protein of Enterotoxigenic *Escherichia coli*, ETEC) immunization. The authors indicated how key steps involved in immune response were altered in the intestines of FB_1-exposed piglets. They highlighted impairment in the T-cell stimulatory capacity and attributed this to the effects on antigen-presenting cells (APC). APC are essential in connecting innate and acquired immune responses via uptake of antigen in the lamina propria, maturation and migration to GALT, and interaction in these areas with T-cells. In their study, the ineffectiveness of MHC-II (Major Histocompatibility Class-II), CD80/86, and IL-12p40 expression might explain the low response of intestinal APC from FB_1-exposed animals to F4 stimulation. Out-turn of this was the ineffectiveness of AP cells to communicate and stimulate intestinal T-cells which ultimately may have resulted in defective production of specific immunoglobulin (*Grenier,* 2013).

Furthermore, it is evidenced that extraintestinal pathogenic *Escherichia coli* (ExPEC) under normal conditions can persist in the large intestine of pigs but can colonize the gut and translocate to internal organs following a defective immune response. Thus, the impaired immune response observed after FB_1 exposure in the work of *Devriendt et al.* (2009) may be attributable to the translocation of ExPEC to lungs, liver and spleen.

FUMONISIN B1 POTENTIALLY ALTERS THE INDIGENOUS MICROBIAL COMMUNITY OF THE GIT

The extensive efforts over the years to investigate the ecology of the gastrointestinal microbiota (GIM) are undoubtedly due to the tremendous benefits these organisms confer on their hosts (*Luckey,* 1972). The GIM represents an ensemble of microorganisms including bacteria, viruses and fungi that harbor the GI tracts of living organisms and play key role in host's nutrient absorption, immune system and epithelium development. These microbes serve as natural defense against pathogen colonization and guarantee good animal health (*Zoetendal et al.,* 2004). Valuable studies have shown that the GIM could influence many metabolic steps and affect many aspects of host physiology, including nutritional status (presence of mycotoxins) and stress responses (*Lankelma et al.,* 2015). An important factor in maintaining animal health is an adequate composition of the intestinal microbiota, as well as the quantitative and qualitative integrity of the gut ecosystem. Data on the effects of mycotoxins on the GIM are reported to be lacking. For the most part, FB_1 have been gaining considerable interest in mycotoxicology latterly.

Bacterial counting of aerobic and anaerobic cultivable-indicators can be used to determine the impact of mycotoxins on the microbiota. In a growing pig for instance, the GIT is colonized by a highly diverse consortium and about 90% of the bacterial community OTUs (Operational Taxonomic Units) are of the phyla Firmicutes and Bacteroidetes; dominated by the Lactobacillaceae, Lachnospiraceae, Ruminococcaceae and Prevotellaceae families and, *Lactobacillus, Prevotella* and *Blautia* genera (*Mateos et al.,* 2018). Utilizing the capillary electrophoresis single-stranded conformation polymorphism (CE-SSCP), *Burel et al.* (2013) reported that chronic exposure to 11.8 ppm of FB (FB_1+FB_2) transiently affected the balance of the digestive microbiota of pigs. The authors showed that FBs could reduce the fecal microbiota SSCP profiles of treated animals compared to untreated animals. Besides, after the co-contamination of FB_1 and Salmonella, the authors described what happened next as transient, but faster and more intense than that observed in the exposed group.

In a recent 4-week experiment to investigate the dynamic effects of FB_1 (12 mg/kg feed) exposure to young weaned pigs' fecal microbiota, *Mateos et al.* (2018) discovered pronounced effects of FB_1 on fecal microbiota and, it occurred after 22 days of exposure in the diet. After 29 days, the effect was alleviated albeit differences existed in the taxa relative abundance in both the treated and control groups. In addition, there was a significant increment or abundance of *Lactobacillus*, which was also the case of an *in vitro* study to investigate the interaction between FB_1 and caecal microorganisms in pigs (*Dang et al.,* 2017). Recently, some researchers found *Lactobacillus brevis*, *L. plantarum*, *L. pentosus* and some yeasts can degrade FB_1 (*Zhao et al.,* 2016; *Tuppia et al.,* 2017). *Zhao et al.* (2016) explain the underlying mechanism of *Lactobacillus* to remove FB_1 as a process of physical adsorption involving differing constituents of cell wall. Further with the aspect of degradation, *Kim et al.* (2019) reported an increase of Lactobacillaceae family proportion in the intestinal microbiome of mycotoxin-fed (AF, FB_1 and DON) pigs as well as an increase of gram-positive bacteria (known to effectively degrade DON) such as *Turicibacter sanguinis* and *Clostridium* sp. when yeast cell wall enzyme

(YCWE) was added to the diets of the pigs. These observations were explained as a sign of induced adaptation of the microbiome and of the pigs themselves to better handle mycotoxin insults. Although this latter study involves a combination of FB_1 and two other major mycotoxins, it still provides a decent amount of evidence that FB_1 potentially modifies the host's control of its symbiotic microbial community. By the way, co-contamination of mycotoxins in agricultural products is not uncommon and continues to pose a huge threat to food/feed safety and health of humans and animals.

CONCLUSION

This review has highlighted some crucial effects that FB_1 can have on key aspects of GIT functionality. As discussed above, it is apparent that FB_1 is capable of interfering with the gut barrier functions, digestive and absorptive functions, immune functions and the composition of the gut microbiome of the GIT. With respect to the latter, there is significant knowledge gap regarding FB_1 potential adverse effects. With this realization, it is dire for researches to be geared towards these key aspects of GI functionality; to better understand how, and to what extent toxicity of FB/FB_1 especially influence the microbial population and diversity of the host and certainly, the overall GIT functionality.

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A szerzők címe: *Zeebone Y. Y.[1,2] – Kovács M.[1,2] – Halas V.[1]*
[1]Kaposvári Egyetem Agrár- és Környezettudományi Kar
[2]MTA-KE-SZIE Mikotoxinok az élelmiszerláncban Kutatócsoport
Authors' address: [1]Kaposvár University, Faculty of Agricultural and Environmental Sciences
[2]MTA-KE-SZIE Mycotoxins in the Food Chain Research Group
H-7400 Kaposvár, Guba S. u. 40.
yarsminyunuszee3@gmail.com