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Review

Unravelling the impact of mycotoxins on gut health: implications for inflammatory bowel disease

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Consumption of mycotoxin-contaminated food is considered a main alimentary risk, with grave consequences on gastrointestinal function. Inflammatory bowel disease (IBD) is a complex, heterogeneous disorder of the gut, leading to severe abdominal pain, diarrhoea, and malnutrition. Similar indicators have been observed in foodborne mycotoxicosis. This review aims to elucidate the adverse effects of mycotoxin exposure on gut homeostasis and their correlation with IBD. We discuss latest research substantiating a role for mycotoxins in the pathogenesis of IBD, collating evidence of a crosstalk between mycotoxin-activated pathways and pathomechanisms of IBD. Considering the burden posed by IBD worldwide and the accelerating mycotoxin occurrence in global food commodities, we also propose future research directions to mitigate the harmful impact of mycotoxins on gut health.

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Contextual framework

Pathogenesis and epidemiology of inflammatory bowel disease

Inflammatory bowel disease (IBD) is a complex, heterogeneous disorder characterised by prolonged and recurrent inflammation of the gastro-intestinal tract, leading to immune-mediated intestinal mucosal damage. Disease complexity arises from the presence of multiple subtypes, with ulcerative colitis (UC) and Crohn's disease (CD) being the major ones, and a multi-factorial aetiology, involving individual genetic vulnerability, disruption of the intestinal mucosal barrier (IMB), dysregulated immune responses, abnormal intestinal microbiota (dysbiosis), environmental factors, lifestyle, and diet.

The annual incidence (per 100 000 people) of IBD varies by region (0–39.4 in North America, 0.9–37.0 in Europe, and ~1.4 in Asia), representing the fourth cause of gastrointestinal deaths in 2017 [1].

Although the clinical symptoms vary between subtypes, a constant feature of IBD is the abnormal interaction between the innate immune system and the gut microbiome. Both UC and CD are characterised by a compromised function and viability of intestinal epithelial cells (IECs), facilitating intramucosal bacterial colonisation and leading to overactivation of inflammatory and immune responses. While the main affected cells in UC are mucin-secreting goblet cells (GCs), resulting in abnormal mucus production and reduced protection from microbial invasion and toxin exposure, CD is often associated with Paneth cell (PC) dysfunction. PCs engage in the enteric innate mucosal system by secreting antimicrobial peptides and inflammatory cytokines; therefore, their loss is a primary cause of gut inflammation and dysbiosis.

Other nonimmune cells in the intestinal mucosal subepithelium involved in the pathogenesis of IBD are stromal cells, including fibroblasts, myofibroblasts, smooth muscle cells, endothelial cells, and perivascular pericytes. Enteric epithelial and stromal cells are directly involved in the activation of immune responses against microorganisms by releasing inflammatory and immunoregulatory chemokines. Through interaction with the gut microbiome and its metabolites, they regulate proper immune development, function, and homeostasis [2,3]. Balanced innate and adaptive immune responses are instrumental to support microbiome stability and limit pathogenic development. Alterations in the function of IECs or stromal cells can lead to abnormal

immune responses against the gut microbiota, causing severe IMB dysfunction and promoting chronic inflammatory states. Dysregulations in $CD4^+$ T cell populations, with an increase in T helper 17 cells (Th17) and a decrease in regulatory T cells (Tregs) [4], also contribute to pro-inflammatory over immunosuppressive pathways, with activation of autoinflammatory and autoimmune mechanisms [5].

Dysbiosis is another critical concurrent cause of persistent intestinal inflammation. IBD patients often show an overall reduction in microbial diversity and loss of gut homeostasis, accompanied by expansion of intestinal pathobionts or decreased *Firmicutes*/*Bacteroidetes* (F/B) ratio [6]. These changes decrease beneficial short-chain fatty acid synthesis, promote bacterial invasion of epithelial and immune cells, and the release of toxins or other harmful compounds [7].

Finally, diet also plays a key role in regulating gut microbiome and inflammatory responses. Fibre-deficient diets and food contaminants are known to negatively influence the gut microbiota, promoting dysbiosis and aggravating IBD.

Mycotoxins and food safety

Mycotoxins are low-molecular-weight (0.3–0.7 kDa), highly stable secondary metabolites produced by filamentous fungi belonging to *Aspergillus*, *Fusarium*, and *Penicillium* genera. These compounds show a wide array of chemical structures and toxicities, posing significant health risks, including teratogenic, mutagenic, carcinogenic, nephrotoxic, hepatotoxic, and immunotoxic effects.

Mycotoxins can lead to chronic and continuous poisoning, often unrecognised due to absence of clear clinical symptoms and lack of connection to known aetiological agents. Globally, it is estimated that 60% to 80% of crops are contaminated with mycotoxins throughout the entire food chain [8]. Furthermore, co-contamination with other poisonous substances and pollutants can aggravate mycotoxin toxicity. For instance, both cadmium and acrylamide have been reported to enhance Ochratoxin A (OTA)-mediated impairment of the IMB function [9,10]. Additionally, plant defence mechanisms can conjugate mycotoxins into less toxic biopolymers (masked mycotoxins), which can be converted back into their toxic forms by the gut microbiota. Therefore, the real extent of mycotoxin exposure and impact on gut health are underestimated on a global scale.

Indeed, chronic mycotoxin exposure can trigger oxidative stress and have genotoxic consequences. While aflatoxin B1 (AFB1) is the only mycotoxin recognised as a genotoxic carcinogen, OTA also exhibits genotoxic properties, although its carcinogenic classification remains under review. To protect consumer health from the effects of mycotoxins, health-based guidance values (HBGVs) for certain nongenotoxic mycotoxins are established as the maximum daily intake levels that can be sustained over a lifetime without significant health risks (Table 1). These values are typically originated from toxicological studies that determine a no-observed-adverse-effect level (NOAEL) or a lowest-observed-adverse-effect level. Uncertainty factors (UFs) are applied to account for interspecies extrapolation (animal to human) and intraspecies variability (human population differences). A conventional approach involves applying a 100-fold UF, including a 10-fold factor for interspecies differences (animal–human) and a 10-fold factor for human variability (human–human) [11]. However, UF magnitudes vary across regulatory agencies, depending on adverse effect nature, exposure duration, NOAEL confidence, and variability extent. HBGVs are typically set for individual mycotoxins, neglecting potential synergistic effects of co-occurring mycotoxins in food. While mycotoxin regulations exist, dietary differences lead to varying individual exposures. The long-term health impacts of low-dose (subclinical) mycotoxin exposure remain poorly understood and should not be underestimated.

The interplay between IBD and mycotoxins is a complex and emerging area of study [19,20]. While a direct correlation between mycotoxin exposure and IBD aetiology has not been proved yet, several studies have recently demonstrated how certain classes of mycotoxins can alter the IMB by changing the composition of the mucosal layer, influencing the microbiome and activating immunology and inflammatory pathways involved in both onset and progression of IBD (Figure 1).

Surveying current findings on mycotoxin-induced damage in cellular and animal models to elucidate the potential association between mycotoxin exposure and the pathogenesis of IBD shows critical need for further research. Understanding the mechanisms by which mycotoxins affect gut integrity and microbiome composition, particularly in vulnerable populations such as IBD patients, is essential to mitigate their harmful impacts on intestinal health (Figure 2).

Mycotoxins interactions with the gut: mechanistic implications in inflammatory bowel disease

Mycotoxins and gut microbiota

The human gut microbiota is a complex and diverse community of microorganisms with symbiotic and mutualistic relationship with the host [21]. Its diversity depends on several factors, including diet, human lifestyle, age, and environment [22,23]. In the environment,

Table 1

HBGVs and EU maximum levels for mycotoxins in food.

Mycotoxin	HBGV (μg/kg bw)	End point	Authoritative reports
AFB1	ALARA principle	Hepatotoxicity — leading to liver carcinogenicity, a $BMDL_{10}$ of 0.4 μg/kg bw/day was utilised for Margin of Exposure calculations (male Fischer rat study).	[12]
AFM1	ALARA principle	Hepatotoxicity — leading to liver carcinogenicity, a NOAEL was determined at 0.1 mg total intake over 21 months (male Fischer rat study).	[12]
OTA	ALARA principle	Nephrotoxicity-leading to kidney carcinogenicity in rats	[13]
PAT	PMTDI: 0.4	Combined reproductive toxicity, long-term toxicity/ carcinogenicity study in Wistar rats. NOAEL: 0.1 mg/kg bw (administered three times weekly; equivalent to 43 μg/kg bw/ day), (UF = 100).	[14]
Sum T-2 & HT-2	PMTDI (T2+HT2): 0.06 TDI (T2+HT2): 0.1 ARfD: 0.3 for T2 or HT2	Sub-acute (3 weeks) (leukopenia/reduced antibody production) LOEL; 0.029 mg/kg bw/day in pigs (UF = 500). Acute (emesis); $BMDL_{10}$ of 2.97 μg/kg bw/day calculated for emetic effects in mink for ARfD; 0.3 μg T2 or HT2/kg bw	[15]
DON & the sum of DON+ 3-Ac DON+ 5-Ac DON + DON-3-glc	TDI: 1	Chronic (growth retardation) NOAEL; 0.1 mg/kg bw day in mice (UF = 100)	[16]
	ARfD: 8 for DON and acetylated forms	Epidemiological data from mycotoxicoses NOAEL of 26 μg DON/kg bw per eating occasion for vomiting (default UF = 3.16 for toxicokinetic differences in the human population was needed)	
ZEN and its modified forms*	TDI: 0.25	EDC (pituitary adenomas) in male B6C3F1 mice. $BMDL_{10}$ of 6.39 mg/kg bw/day. NOAEL 10.4 μg/kg bw/day (UF = 40)	[17]
FB1 & the sum of FB_{1-4}	TDI (FB2+FB3+FB4): 1	Hepatotoxicity: $BMDL_{10}$ of 0.1 mg/kg bw/day calculated for megalocytic hepatocytes in mice (UF = 100).	[18]

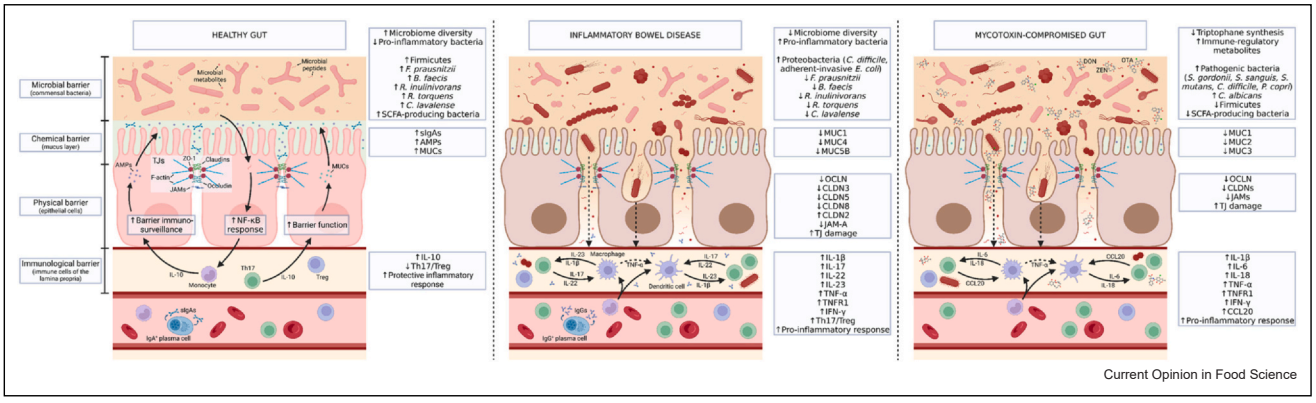
T-2: T-2 Toxin; HT-2: HT-2 Toxin (a metabolite of T-2 toxin); 15-Ac DON: 15-Acetyl-Deoxynivalenol; 3-Ac DON: 3-Acetyl-Deoxynivalenol; FBs: Fumonisins (including FB1, FB2, and FB3); ZENGlcs, ZEN Sulfs; α α-ZEL; α-ZELGlcs; α-ZELSulfs; β-ZEL, β-ZELGlcs; β-ZELSulfs; ZAN; ZANGlcs and ZANSulfs; α-ZAL; α -ZALGlcs; α-ZALSulfs; β-ZAL, β -ZALGlcs; b-ZALSulfs; cis-ZEN; cis-ZENGlcs and cis-ZENSulfs; cis- α-ZEL; cis- α-ZELGlcs and cis- α-ZELSulfs; cis- β -ZEL; cis-β-ZELGlcs and cis- β-ZELSulfs (Glc: glucose; Sulf: sulphate). Relative potencies factor for phase I and Phase II ZEN metabolites are also proposed by the EFSA COMTAM Panel. ALARA: as low as reasonably achievable (principle to minimise exposure); $BMDL_{10}$: benchmark dose lower confidence limit for a 10% response (used in risk assessment); PMTDI: provisional maximum tolerable daily intake; TDI: tolerable daily intake; ARfD: acute reference dose; LOEL: lowest observed effect Level; EDC: endocrine-disrupting chemical; SCF: Scientific Committee on Food (European Commission).
* References: [12–18].

mycotoxins have been described as antimicrobial agents in addition to their inhibitory effects on bacterial quorum-based communication. To date, studies have reported that mycotoxins influence the microbial community, but their impact on the human gut microbiome is still poorly defined.

Several studies showed that AFB1 (5–400 μg/kg bw) decreases phylogenetic diversity in rats/mice, deoxynivalenol (DON; 2–120 μg/kg bw) alters microbiota composition affecting the F/B ratio, ochratoxin A (OTA; 70–210 μg/kg bw) and zearalenone (ZEN; 1000 μg/kg bw) decrease microbiota diversity and changed dominant phyla, and fumonisin B1 (FB1) and B2 (FB2) induce microbiota imbalance in pigs [24]. At high doses, Patulin (PAT) also negatively impacts on the abundance of beneficial bacteria, such as *Lactobacillus*, *Dubosiella*, *Muribaculaceae*, *Burkholderia-Caballeronia-Paraburkholderia*, *Escherichia-Shigella*, *Akkermansia*, *Muribaculum*, *Delftia* and *Streptococcus*, favouring an increase in pathogenic *Mycoplasma*. PAT has also been linked to disruption of tryptophan metabolism and dysbiosis through reduction of tryptophan-degrading bacteria like *Bacteroides* and *Lactobacillus* [25]. Furthermore, DON-contaminated diet favours overgrowth of *Enterobacteriaceae* in rats with exacerbated symptoms of colitis [26].

Sensitivities to mycotoxins vary across species and age groups, with young individuals being more sensitive due to incomplete organ development. As an example, interaction of the gut microbiota with OTA can alter its absorption rate between species, ranging from 56% in rabbits to 66% in pigs [27] and 98% in humans [28]. While ruminants show certain resistance to mycotoxins due to the detoxifying role of the microbial population in the rumen [28], monogastric species are more susceptible to the toxic effects of mycotoxins in the gut microbiota. In children, exposure to AFs has been associated with gut dysbiosis, characterised by the dominance of the phylum *Firmicutes* over *Actinobacteria* [29]. Nevertheless, while the association between dysbiosis and IBD is clear, a causative role for mycotoxin–gut microbial interactions has not been determined yet.

Figure 1



Representation of healthy gut microbiota (left), IBDs (middle), and mycotoxin compromised gut (right) on the intestinal barrier, immune responses, and pathogen translocation. Healthy gut (left): an intact intestinal barrier, comprising a diversified gut microbiota, tightly packed IECs with intact TJs, and balanced immune cells (monocytes, T reg and T helper cells) is responsible for maintaining the immune tolerance and preventing intestinal inflammation. **IBDs (middle):** the inflamed intestinal barrier has a shift in microbiota composition leading to dysbiosis, MUC synthesis is reduced, IECs show disruption in TJ, an increased presence of pro-inflammatory cells (Th17, macrophages, dendritic cells) and cytokines, and paracellular and transcellular permeability. Decreased levels of TJ proteins (OCLN -3, -5, -8, and JAM-A) and increased levels of CLDN-2 lead to a weakened and more permeable barrier, allowing pathogens and antigens to penetrate the IMB. **Mycotoxin-compromised gut (right):** mycotoxins decrease the expression of MUC, and TJ proteins (CLDNs, OCLNs, JAMs, ZO-1) increasing intestinal permeability and the levels of pro-inflammatory cytokines and chemokine. Mycotoxins affect the microbiota causing overgrow of pathogenic bacteria. Abbreviations: SCFA: short-chain fatty acid; sIgA: secretory immunoglobulin A; Th17: T helper 17 cell; AMP: antimicrobial peptide; OCLN: occludin; CLND: claudin; JAM: junctional adhesion molecule; ZO-1: Zonula Occludens-1; F-actin: filamentous actin; IFN: interferon; TNF: tumour necrosis factor; IL: interleukin; CCL20: Chemokine (C-C motif) ligand 20; MUC (mucin). ↓indicates downregulation, and ↑ indicates upregulation. The figure was created with BioRender.com.

Mycotoxins and gut permeability

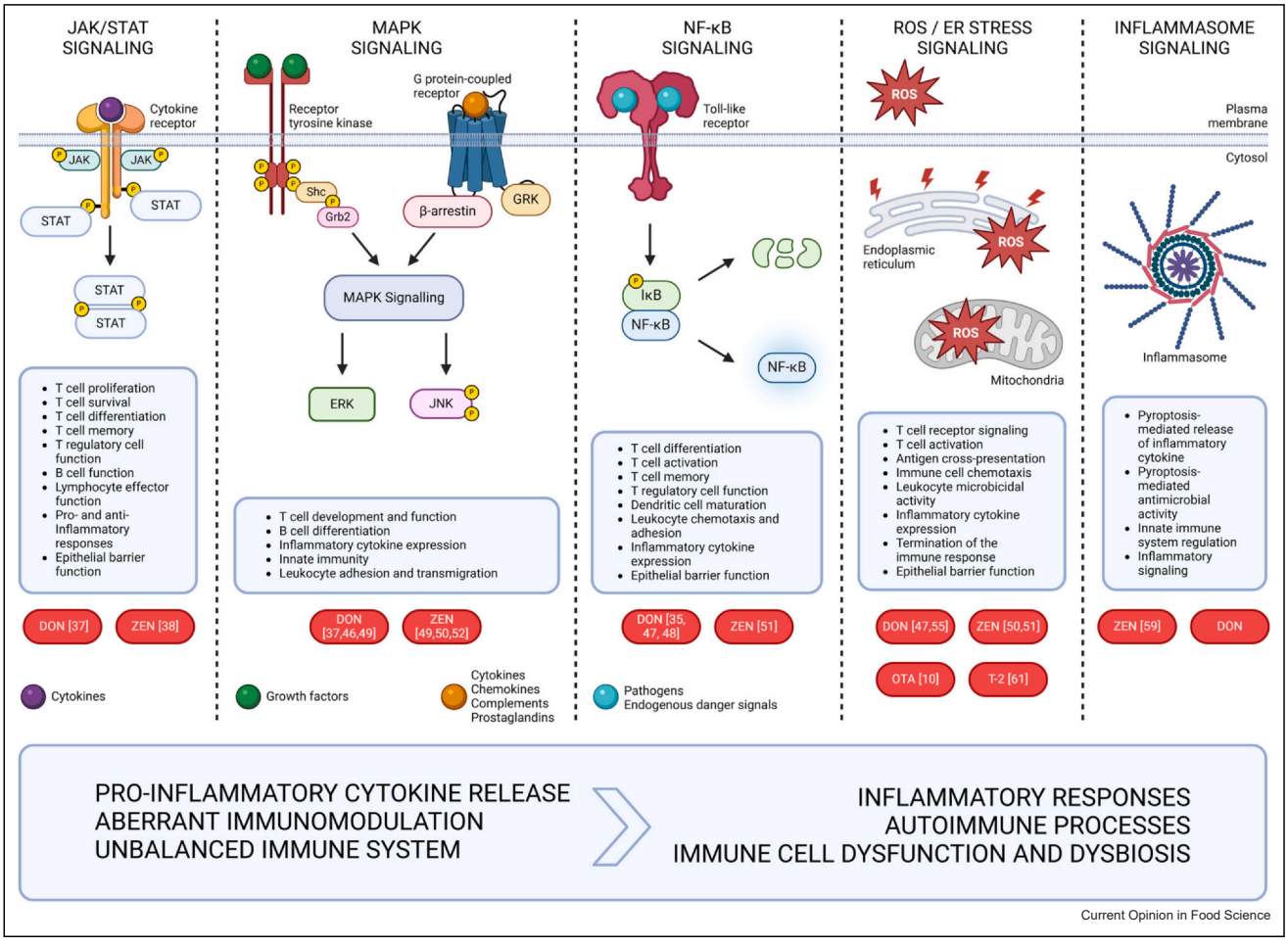
The intestinal epithelium selectively absorbs dietary nutrients, electrolytes, and water while preventing harmful substances from entering the body (Figure 1). IECs are interconnected by tight junctions (TJs), which regulate paracellular and transcellular transport, and secrete mucin, which prevent stress-induced damage and pathogen adhesion and invasion. Dysregulation of TJ proteins (e.g. claudins, occludin) and mucin depletion are hallmarks of IBD and are often accompanied by reduced GC numbers, permeability defects, and uncontrolled translocation of toxins and pathogens, exacerbating disease progression [30,31].

Recent reviews have examined the impact of single mycotoxin exposure on the intestinal physical and chemical barriers, highlighting their significant impact on IECs proliferation and viability, negatively affecting gut permeability [19,32,33] (Table 2). Exposure to AFB1, FB1, T2, and OTA significantly reduced cell viability in human colorectal adenocarcinoma cells, with varying cytotoxicity levels (IC_{50} values: 5.4, 9.4, 14.8, and 21.2 μM, respectively) [19]. Beyond cytotoxicity, OTA, PAT, DON, and ZEN have been reported to induce apoptosis by promoting mitochondrial reactive oxygen species (ROS) generation [19], implicating oxidative stress as a key driver of mycotoxin-induced intestinal damage. Most mycotoxins decrease transepithelial electrical resistance (TEER) in a time- and concentration-dependent manner, except for aflatoxin M1 (AFM1), which was tested at lower concentrations (up to 12 μM) [19,32]. Notably, most mycotoxins reduce TJ protein expression and distribution at low doses [32], although the specific mechanisms by which mycotoxins regulate TJ turnover and IEC integrity remain unclear.

Li et al. [34] suggested that DON (2 μM) induces endocytosis and degradation of claudins (CLDNs), occludins (OCLNs), and zonula occludens-1 (ZO-1) via cytoskeleton-dependent (CLDN-1, CLDN-3 and ZO-1) and cytoskeleton-independent pathways (OCLNs) (REFs). Moreover, subchronic exposure to AFM1 (0.0152–6.095 μM) seems not to affect cell morphology and viability after 24-hour exposure, although TEER values decrease in a time and concentration-dependent way, enhancing cell mechanical stress, intestinal permeability, chronic inflammation, and tissue damage [35]. Interestingly, when exposed to plasma from CD patients, Caco-2 shows increased paracellular permeability via ZO-1/OCLN downregulation [36], mirroring mycotoxin effects; however, to the best of our knowledge, mycotoxin in plasma of IBD patients has never been quantified.

Most of the studies on the impact of mycotoxins on gut health have primarily focused on *Fusarium* toxins in animals [19], reporting significant intestinal damage (DON, 2 mg/kg feed for 28 days), oxidative stress (ZEN,

Figure 2



Crosstalk between mycotoxin and immunomodulatory/inflammatory signalling pathways activated in IBD. Different mycotoxins can interfere with both intestinal epithelial and immune cell function, activating or disrupting immunomodulatory and inflammatory pathways. This can lead to imbalanced immune responses and triggers gut inflammation. Some of these pathways also play a role in the pathogenesis of IBD. The JAK/STAT signalling pathway acts downstream of cytokine receptors and regulates all aspects of gut immunity, from supporting proper immune cell development and differentiation, to immune tolerance, inflammatory processes, and IMB function. The ERK and JNK pathways are regulated by receptor tyrosine kinases (RTKs) and G protein–coupled receptors (GPCRs) following binding of multiple ligands, including growth factors, chemokines complements, and prostaglandins. MAPK pathways control immune cell differentiation and function, from expression of pro-inflammatory cytokines to chemotaxis, adhesion, and bactericidal activity. NF-κB takes part in various signalling pathways, including responses to pathogens and endogenous danger molecules mediated by Toll-like receptors. NF-κB activation can also occur downstream of the JAK/STAT and MAPK pathways. The NF-κB pathway has a crucial role in immunity and inflammation by controlling immune cell differentiation and activation, chemotaxis and adhesion, production of inflammatory cytokines and IMB functions. ROS can have direct cytotoxic effects by activating harmful oxidative reactions damaging proteins, lipids, and nucleic acids. On the other hand, they engage in intracellular signalling cascades and play a key role in immune cell function by regulating immune cell receptor signalling, antigen presentation, chemotaxis, and cytokine production, as well as immune response termination and IMB function. Inflammasome assembly is an essential process in innate immunity. It activates macrophage pyroptosis in response to pathogens or during inflammatory reactions, leading to release of pro-inflammatory cytokines and antimicrobial molecules. It is also involved in inflammatory signalling. By inducing aberrant activation or function of all these signalling pathways, mycotoxins can exacerbate various pathomechanisms of IBD, contributing to the onset of chronic inflammation, autoimmune processes, immune cell dysfunction, and dysbiosis. The figure was created with BioRender.com.

0.5–1.5 mg/kg feed for 10 days), TEER reduction (FB1, 6 mg/kg feed for 9 days), and alterations in GC number (DON, 1.5 mg/kg feed for 28 days; FB1, 6 mg/kg feed for 35 days). In contrast, low doses of DON and ZEN (< 1 mg/kg feed) exhibited no observable effects. *Fusarium* mycotoxins also elicit dose-dependent alterations in intestinal permeability and epithelial integrity in piglets, though their effects on mucin synthesis and GC dynamics remain unclear.

In addition to affecting TJ integrity, mycotoxins modify both composition of mucin monosaccharides and expression of intestinal mucins in a dose-dependent fashion, further compromising the IMB [33,37]

Table 2

Effects of mycotoxins on intestinal cell viability, permeability, and mucin expression.

Mycotoxin	Cell model	Concentration		Exposure Duration (hours)	Effects			
		(μM)	(μg/ml)		Cell viability	TEER and permeability	TJ Proteins	Mucin expression
AFB1	Caco-2	0.032–100	0.01–31.23	24, 48, 72	Significant ↓, IC_{50} = 5.4 μM	TEER ↓, permeability (LY & FITC-dextran 4 & 40 kDa) ↑	ZO-1, Occludin, Claudin-3, Claudin-4 ↓; altered distribution	–
AFM1	Caco-2, HT29-MTX	0.00152–12.2	0.0005–4	48	12 μM ↓ viability	No significant TEER change	–	MUC2, MUC5AC mRNA and protein expression altered (study dependent)
OTA	Caco-2, HT-29-D4, Caco-2/HT29-MTX, IPEC-J2	0.001–160	0.0004–64.65	6, 12, 24, 48	Significant ↓, IC_{50} = 20 μM; apoptosis at 10 μM	TEER ↓	ZO-1, Occludin, Claudin-3, Claudin-4 ↓; altered distribution	MUC2, MUC5B ↑ at low conc., ↓ at high conc.
PAT	Caco-2, HCT116	0.7–150	0.14–30.3	24	IC_{50} = 25 μM, ↓ viability, apoptosis	TEER ↓	ZO-1↓, Claudin-1, Claudin-3, Claudin-4; altered distribution	–
T-2	Caco-2	1–100	0.48–48.6	24	IC_{50} = 14.8 μM, ↓ viability	TEER ↓	Claudin-3, Claudin-4 ↓	Mucin layer and MUC2 protein expression ↓
DON	Caco-2, T84, HT-29-DR	0.1–100	0.03–29.63	24, 48, 72	Significant ↓ 1.7 μM apoptosis	TEER ↓, permeability (FITC-dextran 4 & 40 kDa) ↑	Occludin, Claudin-3, Claudin-4 ↓	MUC1, MUC2, MUC3 transcription ↓; MUC5AC and MUC5B contradictory
ZEN	IPEC-J2, IEC-1, HCT116, Caco-2	0.1–320	0.03–101.88	12, 24, 48	↓ viability, apoptosis	–	–	MUC5AC mRNA expression ↓
FBs	Caco-2, HT-29	1–100	0.78–78.4	24	IC_{50} = 9.4 μM, ↓ viability	TEER ↓	Occludin, Claudin-3, Claudin-4 ↓	–

T-2: T-2 Toxin; LY: Lucifer Yellow; FITC: Fluorescein Isothiocyanate.
↓ Decrease or downregulation; ↑ Increase or upregulation; – No significant effect observed or not studied.

(Table 2). Notably, inconsistencies between mucin mRNA levels and protein abundance suggest the involvement of post-transcriptional regulatory mechanisms, such as protein degradation pathways or translational inhibition. Collectively, these findings demonstrate that mycotoxins disrupt the IMB function by modulating mucin gene expression, protein synthesis, and compositional integrity [33,37].

Furthermore, co-exposure to multiple mycotoxins (e.g. AFM1+OTA, DON+OTA, T2+HT2) seems to amplify cytotoxicity and IMB disruption compared to single toxins [38-40]. This information highlights the potential risks of mycotoxin co-occurrence through diet, which can aggravate the disruption of IMB integrity in individuals with compromised epithelial function.

Mycotoxins and immune/inflammatory responses

Mycotoxins can play a significant role in the aggravation of intestinal symptoms in individuals with IBD. Recent studies on *Fusarium* toxins showed their potential to exacerbate inflammation- and immune-mediated epithelial damage by altering multiple disease pathways activated in IBD. Among them is Janus kinase (JAK) and signal transducer and activator of transcription (STAT) signalling, which controls immune and stromal gut cell homeostasis. In this regard, DON (3 μg/mL) has been linked to apoptosis activation through inhibition of the JAK2/STAT-3 signalling axis, promoting inflammation in porcine IECs (IPEC-J2) [376. Furthermore, ZEN (5 mg/kg feed for 14 days) was shown to trigger severe colon damage via the STAT and interferon stimulated gene 15 (ISG) pathway in rats [41]. Interestingly, overexpression of ISG15 has been observed during active intestinal inflammation in IBD patients [42]. Additionally, variants in genes of the JAK/STAT family have been associated with increased risk of IBD [43,44].

Other immunomodulatory pathways frequently dysregulated in IBD are the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and the mitogen-activated protein kinase (MAPK) pathways [45–47]. Activation of both pathways was observed in IPEC-J2 cells in response to DON (0.5–3 μg/ml), leading to dysregulated cytokine production [39,48–51]. Corroborating the adverse effects of *Fusarium* toxins on intestinal immune homeostasis, overactivation of the NF-κB and MAPK signalling pathway was also confirmed by *in vivo* studies. Increased extracellular signal-regulated kinase (ERK) and c-Jun N-terminal kinase (JNK) protein levels have been correlated with impaired T cell function in mice treated with either 20 μM ZEN or 1 μM DON [52]. Activation of JNK was also detected in *Drosophila melanogaster* upon chronic exposure to 20 μM ZEN, along with intestinal inflammation and mucosal damage [53]. Furthermore, short-term administration of ZEN (40 mg/kg feed for 12 days) was linked to inflammation and elevated NF-kB expression in the intestine of treated mice [54], while chronic exposure to ZEN (3 mg/kg feed for 32 days) was shown to induce upregulation of the B cell receptor signalling pathway, acting upstream of both ERK and NF-κB in piglets [55].

Another important pathomechanism in IBD concerns activation of oxidative stress-mediated signalling pathways, promoting dysbiosis and mucosal release of inflammatory mediators [56,57]. Emerging evidence advocates for a correlation between ROS exposure and inflammation in IECs. Chronic exposure to mycotoxins can participate in the pathogenesis of IBD by altering intestinal redox homeostasis. A study conducted in IPEC-J2 cells demonstrated how DON-mediated inflammation is intimately linked to elevation in cellular ROS levels [50]. Similarly, oxidative stress–dependent prostaglandin and pro-inflammatory cytokine release was observed in human colorectal adenocarcinoma cell lines upon exposure to 1 μM DON and 5 μM OTA [10,58]. Furthermore, impaired intestinal ROS detoxification was reported in ZEN-treated *D. melanogaster* [53].

Mycotoxins also exhibit bidirectional immunotoxicity, whereby low doses can stimulate immunity and cause inflammatory processes, while high doses can impair immune function [59]. Studies highlighted their direct involvement in immune dysregulation, which poses people with pre-existing chronic inflammatory conditions at elevated risk of symptom aggravation and disease progression. Although little is still known about mycotoxin-induced immunotoxicity in the context of intestinal immunity and IBD, fusarotoxins have been reported to disrupt both adaptive and innate immune responses, which can have grave consequences on maintenance of the homeostatic environment across the gut. Payros et al. [26] uncovered a link between exposure to DON (8 mg/kg feed for 28 days), alteration in the Th17/Treg balance and exacerbation of dextran sulphate sodium–induced colitis in a rat model of UC, favouring intestinal and systemic inflammation and a significant reduction in the Th17/Tregs ratio, a common feature of preclinical IBD [4,60,61]. Disrupted activated T cell proliferation and immune-related function were also reported in mice treated with 20 μM ZEN and 1 μM DON, with extensive reduction in the number of anti-inflammatory Treg [52]. Lee et al. [62] found that ZEN can inhibit innate immune responses by impairing macrophage immune function through repression of inflammasome activation, which can compromise the intestinal defences against enteric pathogens and opportunistic pathobionts [63]. Another fusarotoxin, T-2, has been linked to intestinal toxicity and inflammation in mice (0.5 mg/kg T-2 exposure for 28 days) through activation of Endoplasmic Reticulum stress and the inositol-requiring enzyme type 1 (IRE1)/X-box binding protein 1 (XBP1) pathway [64]. Interestingly,

Endoplasmic Reticulum stress is a recognised contributing factor in intestinal inflammation [65,66]. Activation of the IRE1/XBP1 pathway, in combination with increased mitochondrial ROS levels and oxidative stress, has also been shown to play a key role in induction of cytokine production by group 3 innate lymphoid cells [67], which are dysregulated in IBD [68].

Conclusions and future directions

IBD pathogenesis is characterised by IMB dysfunction, dysbiosis and dysregulated immune responses, which synergistically drive disease progression. Emerging evidence implicates mycotoxins as potential exacerbating factors in IBD through their capacity to disrupt gut barrier integrity, modulate the composition of the intestinal microbiota, and trigger aberrant immune and inflammatory responses. Collectively, the reviewed studies offer mechanistic insights into their potential role in the exacerbation of IBD. However, a direct correlation between mycotoxin exposure and IBD aetiology has yet to be properly established. Therefore, future research should focus on elucidating the mechanisms by which mycotoxins influence gut health, the role of diet in modulating these effects, and dietary interventions or therapeutic approaches to protect against mycotoxin-induced damage. Furthermore, there is a need for standardised protocols to assess the harmful effects of mycotoxins on gut homeostasis and facilitate comparison across studies. Additionally, it is essential to assess the impact of low-dose mycotoxin exposure and co-contamination to mimic real-world chronic exposure scenarios more accurately.

This is of relevance considering the global rise in mycotoxin occurrence in food products documented in the past decade, which places mycotoxin exposure as a significant threat to food safety and public health. Considering the challenges in producing mycotoxin-free food, protective strategies are also essential. Probiotics, prebiotics, and postbiotics are known to support gut health, with postbiotics offering antioxidant, immunomodulatory, and epithelial barrier-enhancing effects [69], as well as ability to inactivate potential mycotoxins through biotransformation or cell wall absorption [24], as developed for piglets [70]. Anti-mycotoxin additives are frequently used in animal feed to reduce exposure, while probiotics and mycotoxin-degrading enzymes show potential for human gut health due to their specificity and minimal nutritional impact [71]. Antioxidant phytochemicals could also help mitigate mycotoxin-induced gut damage. To date, over 30 plant-derived bioactive compounds have been shown to scavenge ROS and boost antioxidant enzyme synthesis [72], making them promising dietary interventions for those at risk of chronic inflammatory conditions. Integrating these approaches into preventive strategies holds significant promise for mitigating mycotoxin-induced damage and supporting overall intestinal health in both humans and animals.

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Data Availability

No data were used for the research described in the article.

Declaration of Competing Interest

All authors contributed equally to the concept and design of the work. All authors have read and agreed to the published version of the manuscript.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
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