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Review article

An update on T2-toxins: metabolism, immunotoxicity mechanism and human assessment exposure of intestinal microbiota

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ABSTRACT

Mycotoxins are naturally produced secondary metabolites or low molecular organic compounds produced by fungus with high diversification, which cause mycotoxicosis (food contamination) in humans and animals. T-2 toxin is simply one of the metabolites belonging to fungi trichothecene mycotoxin. Specifically, Trichothecenes-2 (T-2) mycotoxin of genus fusarium is considered one of the most hotspot agricultural commodities and carcinogenic compounds worldwide. There are well-known examples of salmonellosis in mice and pigs, necrotic enteritis in chickens, catfish enteric septicemia and colibacillosis in pigs as T-2 toxic agent. On the other hand, it has shown a significant reduction in the Salmonella population's aptitude in the pig intestinal tract. Although the impact of the excess Fusarium contaminants on humans in creating infectious illness is less well-known, some toxins are harmful; for example, salmonellosis and colibacillosis have been frequently observed in humans. More than 20 different metabolites are synthesized and excreted after ingestion, but the T-2 toxin is one of the most protuberant metabolites. Less absorption of mycotoxins in intestinal tract results in biotransformation of toxic metabolites into less toxic variants. In addition to these, effects of microbiota on harmful mycotoxins are not limited to intestinal tract, it may harm the other human vital organs. However, detoxification of microbiota is considered as an alternative way to decontaminate the feed for both animals and humans. These transformations of toxic metabolites depend upon the formation of metabolites. This study is complete in all perspectives regarding interactions between microbiota and mycotoxins, their mechanism and practical applications based on experimental studies.

1. Introduction

Fungal biochemical or metabolic pathways yield various metabolites or compounds and intermediates that don't play significant role in the physiochemical properties and these metabolites are refer as secondary metabolites. These compounds or metabolites have wide range of adverse effects on biological system such as potent poison known as mycotoxins. The mycotoxin-producing fungi genera are these such as *Penicillium, Alternaria, Aspergillus, Fusarium, Phomopsis, Cephalosporium, Emericella, Trichoderma, Myrothecium, Neopetromyces, Trichothecium, Claviceps, Byssochlamys,* and also *Neotyphodium.*

Mycotoxins have been categorized as specialized low molecular weight organic compounds or secondary metabolites or all-natural items of microfungi or molds or filamentous fungi (Pathogenic fungi), especially fungi belongs to category Penicillium, Fusarium and Aspergillus [1]. The huge number of about >300 mycotoxins have been reported that show toxicological impacts and significant effects in animals and plants. Previous agriculture toxicological surveys forecasted that around world's 25% of agriculture products were annually infected with mycotoxins [2, 3]. Considering that the exploration of first ever reported mycotoxin aflatoxin was recognized in year 1965 as feed and food commodities. At early age of mycotoxins research, aflatoxin have been considered as primary human health hazards due to having potential carcinogenic, mutagenic and genotoxic effects. Mycotoxins effect human health badly in many ways. These effects may be both acute and chronic that provoke many health issues including cancer, loss of immunity, gangrene, aberrations in normal metabolism and severe respiratory problems [4].

Recent studies put awareness related to different mycotoxins that show negative physiological impacts on intestinal microbiota, susceptibility of intestinal anatomy and alter the intestinal cellular permeability

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[5]. The intestinal permeability or mucosal barrier feature are related to luminal epithelial integrity, luminal pathogens allergen translocation, and non-specific inflammatory feedback and additionally hyper-activation of natural immune system. The most primary highlighted and well-studied example of mycotoxin includes trichothecene, deoxynivalenol and mediated intestinal permeability dysfunction that have demonstrated as pro-inflammatory and immunomodulatory effects [6]. Nonetheless, most recently in vitro and in vivo studies described that mycotoxin have negative impact on gut permeability. Previous research findings were ineludibly revealed that mycotoxin studies have deliberately addressed at concentration prevailed and higher manifestation due to its potential agriculture commodities and medical relevancies [7].

The mycotoxins production is closely undergoing the metabolic pathway that utilized the primary metabolites such as fatty acid and amino acid. Mycotoxins biosynthesis and contamination of feed and food, goods and agricultural exposure are based upon ecological factors particularly commercial or physiochemical properties of substrate, temperature and humidity [8]. Among all of the above stated mycotoxins, the most important mycotoxins are T-2 toxins that have potential worldwide health hazards particularly in agriculture [8]. T-2 have ring structure of by-products substances that are termed as trichothecenes. T-2 toxins are a large group member of chemically derived and manufactured toxic substances produced by fungal taxonomical genera such as *Stachybotrys, Myrothecium*, and *Fusarium* [9]. There are naturally taking place more than 20 isomeric compounds synthesized by fusarium types like fusaron X, T-2 toxins, nivalenol deoxynivalenol, diacetoxyscirpenol and HT-2 toxin. This review is most likely to elaborate and talk about the impact of T-2 toxins on intestinal tract immune-modulatory effects and microbiota [10].

2. Chemical structure of T-2 toxins

T-2 mycotoxin as a stable organic and water insoluble compound has a low molecular weight (MW 466.52) and some organic solvents like ether, petroleum exceptionally soluble in chloroform, dimethyl sulphoxide, acetone, methanol, ethanol, ethyl-acetate and propylene glycol [11]. It shows high resistant to UV light and high temperature (>151.5 °C) [5, 12]. It remained activated during food processing and heat sterilization through autoclaving. The inactivation of T-2 toxic takes place by heating it between 200 °C and 210 °C for 30–40 min or via absorbing method by NaOCl sodium hypochlorite and (NaOH) sodium hydroxide for a minimum of 4 h [13]. T-2 toxin can be purified by few microbes including molds and mildews [6, 12]. These basic structure of T-2 is tetracyclic, accompanied by a sesquiterpenoid 12, 13 epoxytri-choth ec-9-ene ring framework [14]. The chemical composition was depicted by a hydroxyl (OH) at the C-3 placement, acetyloxy (- $OCOCH_3$) groups at C-4 as well as C-15 orders, hydrogen atom at C-7 position as well as an ester connected isovaleryl [$OCOCH_2CH(CH_3)_2$] at the C-8 position (Figure 1) [15].

In this figure, chemical structure of T-2 toxin is explained. A tetracyclic sesquiterpenoid ring system containing 12, 13 epoxytrichothene ring is present in its structure. T-2 toxins mainly contain epoxy ring in their chemical structure. These epoxy rings are attached with many acetyl and hydroxyl groups that are present in its side chains as shown above in these figures. These side chains molecules mainly show biological activity of T-2 toxins that make them more toxic. Although 12, 13 epoxy rings show toxic behavior [16]. Mycotoxins work by inhibiting protein synthesis that ultimately damage the macrophage system and increase sensitivity for other endotoxins. In this way, they inhibit clearance of particles in lungs and cause respiratory syndromes. Although, the primary mechanism of action of T-2 toxins is to modify the DNA templates to alter the transcription process or inhibit the protein synthesis by impairing the translation process. In such cases these toxins have to react directly or indirectly with enzymes or proteins [17]. Both T-2 toxins and DON enter in cells via endocytosis, by crossing the plasma membrane. These lipophilic nonpolar molecules get dissolve in lipid bilayer and ultimately dissolve in lipid bilayer and enters in cytoplasmic region of the host.

3. Physiochemical properties and toxic effects of T-2 toxins

3.1. Occurrence of T-2 toxins

In tropical as well as subtropical regions, the global incidence of T-2 toxin and its associated mycotoxins have been predominantly reported. Sultry (warm and humid) climate facilitates the *Fusarium spp.* infection in plants. On the other hand, inadequate and improper handling, carrying and storage conditions of grain with high moisture can be principal cause of T-2 contamination [18, 19]. For this reason, one of the most critical factors that show impact and enhance the T-2 toxic manifestation is weather conditions, dampness and grain handling (13–22 %) [3]. T-2 toxin has been generated at the temperature between 0 and 32 °C, and maximum synthesis occurs at temperatures <15 °C [20]. The optimum temperature of *F. sporotrichosis*, among *Fusarium spp.*, for T-2 toxin synthesis is comparatively low with other spp (6–12 °C). Even it can synthesize mycotoxin at freezing conditions under snow cover in field and at storage places [21].

3.2. Poisoning of the T-2 toxin

The trichothecene family includes vast range of mycotoxins, along with T-2 is one of the most studied and earlier reported toxins with intense lethality and high rate of toxicity as compare to the other members. The deleterious and toxic effects of T-2 determined by different factors that includes the exposure time; lethal dose concentration and administration,

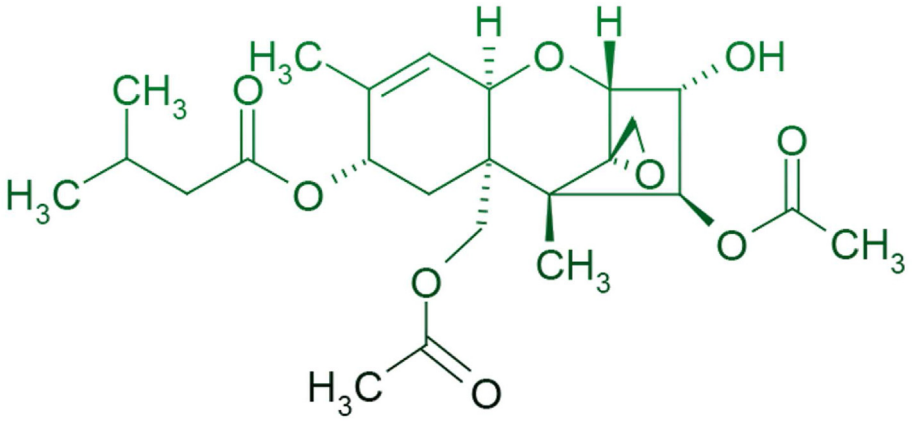

Figure 1. T-2 Toxin and its chemical structure.

the age, gender and health status of person as well as co-occurrence of other toxins [22, 23]. Feeding on grain, hay and straw, being out during winter along with co-occurrence with *F. poae* along with *F. sporotrichiella* typically results in toxication. Therefore, *F. poae* and *F. sporotrichiella* are considered as main causative agents of alimentary toxic aleukia. This condition mainly refers for humans and is characterized by diarrhea, vomiting, skin inflammation and sometimes results in death.

The toxins synthesized and excreted by fungi (T-2 and diacetoxyscirpenol) have local allergic or irritating effects and cause some fatal diseases including necrosis and ulceration in GIT, heart, kidney, brain, hemorrhagic inflammation, and dystrophy in liver. Damaging effects are also provoked in hemorrhagic diathesis and blood vessel walls [24]. The induction of cytotoxic and deteriorative effects on immature Leydig cells (TM3) in mouse model are other toxic effects [25]. The alteration of different organs (thymus, kidney, spleen, and liver) metabolism have been reported in Wistar rats after constant and long-term exposure with T-2 toxin [26].

The proposal of glutathione disulfide and 3-hydroxybutyrate with their increased elevation T-2 toxin induced the oxidative stress in body organ systems and generated the free radicals. Furthermore, the urinary l-methylmalonate and 1-ethyl nicotinamide diminution can arise throughout cysteine biosynthesis [27]. T-2 contaminant induced dysregulation of citrate and succinate in urine and also decreased the level of fumarate inside the liver, abided by an elevated level of NAD+ in rats after exposure with T-2. Previous studies revealed that T-2 decrease the rate of the tricarboxylic acid (TCA) cycle. The concise illustration can look at Figure 2, suggesting the T-2 toxin safe design and toxic flow down pattern [28].

This figure demonstrate two behaviors of T-2 toxins. In general terms, toxic effects of T-2 toxins on agriculture, cattle and humans results in enhanced mortality rate. Reactive oxygen species such as silver ions, copper ions, zinc ions and many more are responsible for its toxic mechanism. When T-2 toxins react with reactive species, they ultimately transform into apoptosis that cause death in cattle and humans. On the other hand, prophylaxis by using herbal strategies results in decontamination of environment and many more therapies. All these therapeutic strategies favors in survival of agriculture, cattle and humans [29].

3.3. Severe toxicological effects

As detail discussed earlier, the toxic effects can be found out through multifarious route of exposure. Due to distinctive physiochemical nature, it has most efficient absorptive and deleterious properties among its family members that might be taken in straight employing the skin [23]. The primary illustrative signs and symptoms of T-2 toxicity include emesis, vomiting, loss of appetite, skin blistering and weight loss.

Experiments were designed to review acute poisoning levels in diverse speculative versions including mice, pigeons and rats that provided the T-2 toxic substance utilizing unique exposure paths viz intratracheal, intravenous, intraperitoneal, subcutaneous and also intragastric [30]. It was perceived that rats administered with the T-2 toxin revealed the elevated level of serotonin and tryptophan in brain that produced a surge in dopamine and as a result 3,4-dihydroxyphenylacetic acid levels declined [21]. Furthermore, it's reported that the dopamine concentration was enhanced, and level of epinephrine was reduced in response to induced toxins. This sequel action shows that T-2 generates and improves the production of indole amine levels inside the brain that results in alteration of animal feeding patterns. So, it was concluded that uptake of T-2 toxin disturb the feeding pattern in animals by disturbing the gut microbiota [31].

Nevertheless, HT-2 and T-2 mycotoxin combined effects in laboratory animals fed an industrial commodity would indeed not be found. If the elevated levels were amongst 250–2000μg/kg body weight [32]. In a research, the acute poisoning was investigated; a rabbit model demonstrated histopathological and pathological adjustments inside the bone marrow as well as lymphocytes and gastrointestinal system. In contrast, subacute poisoning validated catarrhal gastritis with the issues of a stubborn belly lining infection, hypertrophy as well as adrenal cortex emaciation [33].

3.4. Persistent toxicological effects

In female rats which were imperiled to the T-2 toxin identified via a boost in serotonin and tyrosine level in the cerebellar area. Besides, cortical tryptophan titer was elevated and suggesting that different mode of T-2 toxin activity varies in terms of chronic impacts than it performs in

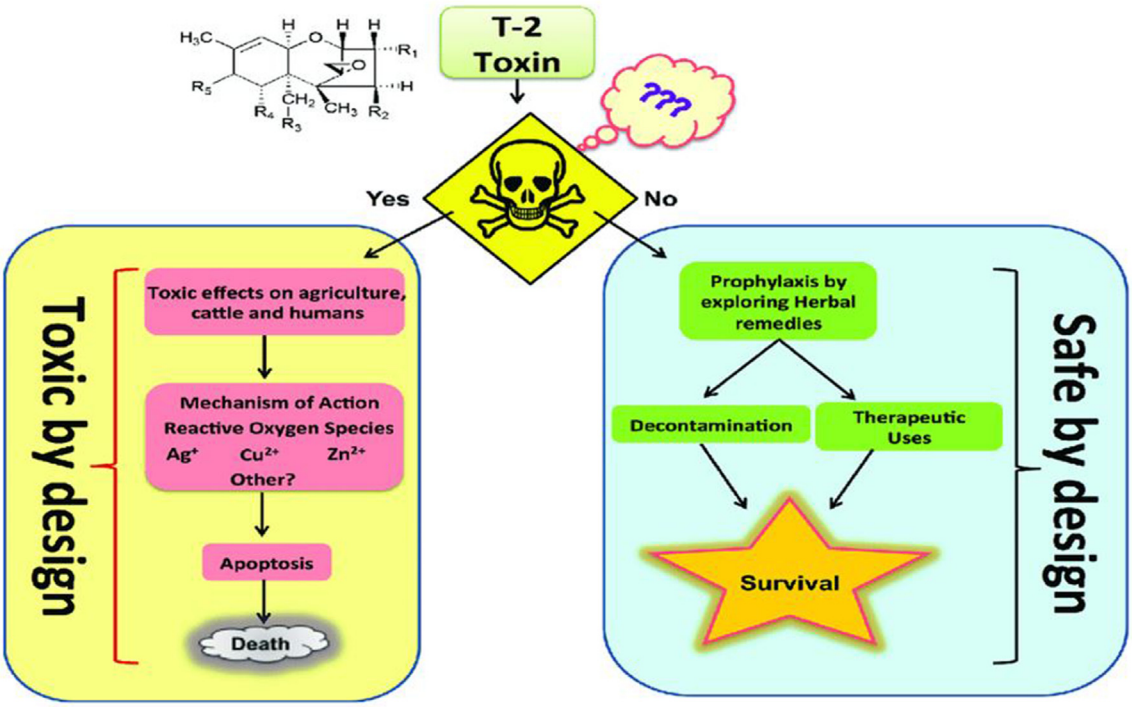

Figure 2. Toxic and safe design schematic illustration of T-2 toxin [24].

regards to acute behavior of administration [34]. However, a severe treatment of T-2 raised levels of tryptophan, serotonin levels in the brainstem and decreased in cerebellar areas [35]. Various other indicators that are connected to chronic toxicity in rabbit include lymphoid tissue necrosis, emaciation and also subacute catarrhal gastritis [36]. T-2-contaminated feed has revealed to reduce egg production, weight gain and hatching capability in poultries. Many research studies have prevailed significant decreases in serum cholesterol and total protein level, along with increase concentration of uric acid and lactate dehydrogenase in serum sample [37, 38].

Another study shown that T-2 toxicity in poultry can have phenotypic alteration the in young chicks especially change the feather follicle and patter [39]. T-2 toxicity has also been demonstrated in a research study conducted on white ducks which exhibited an important reduction in weight gain capability as T-2 contaminant doses were increased [40]. There have likewise been significant deficiencies in blastogenic lymphocytic feedback to particular and non-specific mitotic proteins or mitogens [41]. In addition to these, weight-loss, reduced levels of blood cells, leucocytes and lower degrees of plasma glucose have been observed in T-2 mycotoxin treated animals and a few pathological and lining effects improvements were all observed. The T-2 was also linked to a raised swelling rate, damage to DNA and apoptosis. Both T-2 toxin and deoxynivalenol (DON) favors the formation of cellular reactive oxygen species (ROS) that lead to further induction of lipid peroxidation and aberrant changes in DNA. All these damaged DNA results in cell apoptosis in multiple types of various cells [42].

3.5. Mechanism of action

In T-2 toxin, the thiol group has enable the compound a potential transcription and translational inhibitor [43]. It likewise prevents lymphocyte proliferation by altering the physiology of membrane, impairing the antibody production and change the dendritic cell growth [44]. Artificial insemination, the T-2 contaminant that triggers programmed cell death (apoptosis) in human U937 cells, liver cells, HL-60 cells, Vero, and Jurkat cells [45].

Previous in-vivo study exhibits the deleterious effects have been reported. In this study T-2 was injected subcutaneously and results unveiling the apoptotic effects on different tissues and organs such as bone marrow, brain, kidney and skin [5]. Moreover, the T-2 toxic has been effect and dysregulate the immune system [46]. The T-2 toxin is thought to be binding and inactivating the peptidyl-transferase function at the transcription site [47], leading to protein synthesis restraint [6]. The 60S ribosomal system is the most well-known molecular target of trichothecenes especially T-2 and blockage of polypeptide chain initiation [31]. The inhibitory effects of T-2 at transcription and translation level that prominently effect the growing cells for instance gastrointestinal tract mucosal lining cells, bone marrow, hemopoietic stem cells, skin and erythroid cells [48]. In addition, T-2 mycois supposed to interrupt the functions of DNA polymerases, terminal monoamine oxidase and deoxynucleotidyl transferase. Moreover, proteins play an important role in coagulation pathway [49]. Salmonella colonization in pigs has revealed to be lowered by this toxics [50].

An earlier research work focused on the T-2 toxin as it involves in the activation process of cellular immunity. This study has shown that T-2 mycotoxin activates the macrophages via “extracellular signal regulated kinase” (ERK1/2) and “mitogen activated protein kinase” (MAPK) pathway. As a result, *Salmonella* uptake by macrophages and also induce the membrane ruffles and reorganization. The T-2 mechanism of action with subcellular structures develops disturbance of mitochondrial morphology, rough endoplasmic reticulum and various other membrane layers [5, 51]. They protect against the metabolically active and vivacious enzymes like succinic dehydrogenase, blocking mobile energetics by lowering the malate, pyruvate and succinate that causes oxidation of molecules and hinders the healthy and balanced synthesis of protein in mitochondria [52]. The trichothecenes family's ability to go across the placenta and damage the mouse fetuses by triggering the apoptosis in the immune system of a body and numerous other cells was also reported [21].

Nevertheless, l-carnitine can minimize oxidative stress in rat hepatocytes which is induced by the T-2 toxin [53]. In granulosa cells of rat ovarian, it also controls the secretion of steroid hormones by using the cAMP-PKA pathway [54]. T-2 toxic substance binds to thiol group and as a result, converting it into the DNA synthesis inhibitor as well as potential protein [33]. T-2 toxin can enable to disturb antibody production [55], modify the membrane function [56], lymphocyte progression [57] and also dendritic cell growth [58]. T-2 toxic induced single strand DNA breaks in lymphoid cells such as vitro and vivo. In addition, in vitro T-2 toxin triggers apoptosis in a variety of cells including U937, Jurkat, HL60 [59], human hepatoma cells [60] and Vero cells [20]. In vivo, apoptosis has observed in splenic and thymic lymphocytes in addition to various other mouse tissues including skin [22, 60], bone marrow, intestinal epithelial cells [61], brain [62] and kidney [63]. In the toxicity of several mycotoxins, oxidative damage is considered as the major indicator. Essential biomolecules include proteins, nucleic acid sand lipids that are usually the targets of oxidative damage [64]. Most of the trichothecenes family especially T-2 bind to subcellular frameworks that cause functional disability and interfere with mitochondrial oxidative properties, rough endoplasmic reticulum functions, myofibers elasticity, as well as membrane morphology [65]. They prevent succinic dehydrogenase activity that cause reduced succinate, pyruvate and malate oxidation that are restraint of mitochondrial healthy protein synthesis which affects cellular energetics [27]. T-2 toxic substance therapy causes apoptosis in a cell types selection using non-mitochondrial and mitochondrial mechanisms [66, 67]. Moreover, trichothecenes have revealed for enhanced apoptosis in the mouse fetus after going across the placenta [68].

Besides these oxidative damage mostly trigger these cells that indicate and target macro biomolecules such as proteins, lipids, and nucleic acids. Hydrogen peroxide, hydroxyl radicals, and superoxide particles tend to be the significant ROS connected with the oxidation of healthy proteins, lipids, and DNA. Mycotoxin-induced ROS generation is also believed to be moderated by mitochondrial complex I and CYP450 [9].

3.6. Toxicokinetics

In general, T-2 toxin adversely effects human, animals, plants, invertebrates, birds and eukaryote cells in different ways. The primary exposure signs and symptoms of T-2 toxin rely on the dosage and thrashing of the exposure [69]. T-2 is taken in quickly after ingestion in many animal species and it does not need any transporter protein and assistant for distribution in body and to reach at any specific organs. Maximum concentration of toxin in plasma would reach after 30 min of exposure in rats. After 4 h, it is administered intravenously to pigs, 15–24 % of the radioactivity labelled was traced in the gastrointestinal system and 4.7–5.2 % in the tissues, liver and mainly muscle. T-2 toxin has a plasma shelf-life that is around less than 20 min. T-2 toxic substance is quickly metabolized and show no vital accumulation of T-2 that is detected after it has been secreted in the in vivo tested animals (e.g. guinea pig, livestock, dog) [70].

4. Toxic and pathological effects of T-2 toxin on intestinal microflora

The mycotoxins’ effect on the gut microorganisms resemble to alter the digestive tract microbial populace. These modifications can take place at the species, genus and phylum levels. This alteration can be the direct effect of mycotoxins and their antimicrobial properties or it can be secondary to the toxic consequences of mycotoxins on the intestinal cells, as well as release of antimicrobial substances [71, 72]. Considering that the emphasis of T-2 mycotoxins in the various gastrointestinal parts varies dramatically because of absorption as well as likewise biliary excretion.

Nonetheless, the microbiota on T-2 mycotoxins is also due to the microbiome, along with the fact that the microbiome differs in structure, relying on a component of an intestine that is being evaluated. Fusarium mycotoxins generally develop interactions with wide range of animal host species such as salmonellosis in mice and pigs, necrotic enteritis in chickens, catfish enteric septicemia, and colibacillosis in pigs. The likelihood of developing adverse effects by exposing fungus trichothecene mycotoxins depends on toxin dose, purity and duration of exposure. This fungus develop infection in host animal species by affecting their alimentary canal. It is challenging to characterize and its consequences may differ with the speculative layout of the research perspective [73, 74]. T-2 toxin may have adverse impacts on almost entirely cellular progressions that occurs in the gastrointestinal system. Even digestive tract mucosa can be damaged by a toxin with minimum quantity and it also impairs the nutrient reabsorption. Necrosis has been spotted in the gizzard cells, oral cavity, mucosa of GIT system and liver [75].

Necrotic lesions follows the "white-yellowish mucosal lump" such as caseous-necrotic materials in the intestine, [76]. T-2 toxin and co-toxins of trichothecenes family is swiftly absorbed in the gut, metabolized, as well as removed practically entirely (80–90%) within two days [77]. Nevertheless, their dangerous result can be improved by enterohepatic recirculation [78]. Despite the erudite tract lesions triggered by T-2 toxin [79], the impacts of T-2 toxic on gastrointestinal integrity have hardly been checked out.

Nevertheless, in a study Goossens et al. [80] found that T-2 toxic affects the barrier integrity, occurring at a concentration of 21 nM, which is detected by a reduction in TEER (Trans-epithelial electrical resistance) values and also results in increasing the concentration and passage of the antibiotic agents, including "doxycycline and paromomycin" across the IPEC-J2 cells. Further this research showed that a direct contact of mice with T-2 toxin dose 3.3 mg/kg body weight for 24 days improves the translocation of Mycobacterium consumption [81]. Also, a substantial increase in the *Salmonella typhimurium* translocation throughout IPEC-J2 cell monolayer currently arises 30 min after T-2 toxin has a direct exposure with a low dose concentration as 2.1 nM [82]. Unexpectedly in the same research study, TEER value persisted for 24h after exposure to the T-2 concentrations ranging between 1.6 and 10.7 nM [83].

In a recent work, it has been shown that the TEER value that is exponentially down in T-2 toxin shows the Caco-2 cells at concentration ~100 μM for 7 days. It has conveyed the substantial reduction in the transcription rate of protein coding genes such as CLDN4, CLDN3, and OCLN [84]. The similar mechanism underlying the intestinal barrier dysfunction caused by combined effects of T-2/and HT-2 toxin are under investigation and would certainly invite researchers for further studies [85]. Gratz et al. (2017) [86] revealed that human digestive tract microbiota released incognito T-2 toxic as a parent mycotoxin and, therefore, helped thermycotoxin exposure. Moreover, T-2 mycotoxins induce the ribotoxic stress and efficiently inhibit eukaryotic 28S rRNA.

Schmeits et al. [87] proposed that T-2 toxic had not effects on protein synthesis and growth in theoretical aspects. Nonetheless, this contrasts that has been shown in a research conducted by Tenk et al. [37]. This study demonstrated that the T-2 mycotoxin supervision for a week was sufficed in creating a high number of aerobic bacteria in the intestine of rates and swine. At the same time, the microbial populations have been shown to be extensively influenced by T-2 and a mechanism that causes the discomposure of bacterial colonies stays to be clarified [88].

4.1. Colibacillosis

The *E. coli* as a gram-negative belongs to *Enterobacteriaceae.* This bacteria is deliberately considered as normal flora of intestine because it causes the intestinal infections in animals and human [89]. A unique selection of these stress bearing and particularly a combinations of virulence strains enable them to create illness. Scientific disorders developing from infection with these patho-types consist of enteric and diarrheal conditions, urinary system infections and meningitis/sepsis. The pathogenicity process of *E. coli* infections differs depending upon the histology. Still, it may be trying to conquer the gastrointestinal system mucosa, escaping innate immunity, regeneration and triggering host problems [90]. T-2 can take part in the *E. coli* infections' development in various organisms by enhancing proliferation in gut and efflux while still disrupting the immune response.

Pigs have nourished a diet tainted with a reduced rate of FB1, which improved digestive tract translocation and evacuation of a "septicemic *E. coli* infection" (SEPEC) pressure from the gastrointestinal tract to the body system. Due to increase in the mesenteric lymph nodes by bacterial invasion, mucosal lining and lungs were proliferated after FB1 therapy [91].

Previous study has proposed that DON () play role to increase SEPEC translocation through the IPEC-1 (intestinal epithelial cell monolayer) in vitro [92]. Calf sensitivity to Shiga toxic or vero toxin-producing *E. coli* (STEC) and associated hemorrhagic enteritis is increased by mycotoxins. Currently, Baines et al. found that introducing juvenile calf bodies to a mixture of *Fumonisins* and aflatoxin stimulated STEC-associated hemorrhagic enteritis [93]. Pig's mucosal immune responses was observed to be impaired after enterotoxigenic *E. coli* contaminated feed (ETEC). However, retro-effect have been observed in case of feeding with FB1-contaminated diet. Devriendt et al. [94] documented a long-term *E. coli* infection in pigs who had been provided 10 days Fumonisins and then screened with $F4^{+}$ ETEC *E. coli.*

APCs (Antigen-presenting cells) play an essential part in the gut-associated lymphoid tissue or mucosal immune system, affixing the inherent as well as adaptive immune response by antigen uptake in the respiratory tract, maturation, lamina propria and also translocation to GALT and contact with T cells. The FB1 has adverse effects on the intestinal tract APCs function by reducing the transcription of the relevant major histocompatibility complex II (MHC-II), IL-12p40 cytokine and cell of differentiation (CD) 80/6 genes [58]. As a result, the *E. coli*-induced adaptable immune response can be affected by APCs' migrating function [95]. In comparison, after intravenous (IV) administration of moniliformin and FB1, systemic *E. coli* clearance was restrained in turkeys and broiler [96]. This current study on gastro infection can be fruitful and open new window for medical research because gastrointestinal tract of human and pig are nearly similar to each other. The "entero pathogenic *E. coli*" (EPEC) instigates the infant diarrhea that is significant concern and emergency health issue in less developed countries. For example "entero hemorrhagic *E. coli*" (EHEC) infections have become challenging to global health and has many threats [97].

4.2. Salmonellosis

Salmonellosis is caused by *Salmonella* a Gram-negative bacteria, which is a facultative intracellular and facultative anaerobic, bacterium of the Enterobacteriaceae family. Salmonella and its host interaction are multifaceted, in which bacteria use array of mechanism to conquer the host defense mechanisms. However, Enteric fever and Gastroenteritis induced by typhoidal and non-typhoidal i. e, *Salmonella serovars* are divided into two critical disease manifestation respectively [98]. There are three steps of a Salmonella infection: the first step involves the adhesion to the intestinal surface; the second step is the infiltration of the intestinal mucosal wall; and third strep is to disseminate the mesenteric lymph nodes and other visceral organs.

Salmonella infects digestive epithelium through microbial endocytosis, and the bacteria are then contained to the intracellular phagosomal region namely "the Salmonella-containing vacuole" (SCV). The bacteria is typically located in macrophages in the surrounding tissues after passing the epithelial barrier [99]. The gastrointestinal phase of *Salmonella typhimurium* infection is induced by T-2 mycotoxin treated pigs. Non-cytotoxic concentration of T-2 promotes Salmonella penetration in the bowel and *Salmonella Typhimurium* migration through the epithelial cells [100]. *Salmonella Typhimurium* diffusion was unaffected by frequent high contact of pathogen-free livestock to usually

Mycotoxin-contaminated diet [101]. The normal immune response is activated when Salmonella enters the digestive system epithelium, and the porcine digestive system begins to produce many cytokines [102]. Both *Fusarium* mycotoxins, especially T-2 and DON, and *Salmonella* create an effect on the body natural immune system. Vandenbroucke et al. [83] discovered that lowering DON levels would enhance the early immune responses to *Salmonella typhimurium* infection in the digestive tract. Its close contact with the intestinal tract resulted in enhanced production of many cytokines, including those that stimulate proinflammatory cytokines (TNF-α) and T-lymphocyte stimulatory cytokines (IL-12). As immune responses of body are stimulated by host immune cells. These immune cells such as monocytes, neutrophils, eosinophils and basophils are considered as molecular and cellular targets for immunotherapy. All these immune cells have proteins, surface receptors and cytokines for immunostimulation, immunomodulation and immunoactivation. These modulatory immune cells provide better approaches to treat infectious cells. The researchers speculated that the increased inflammatory bowel disease (IBD) or intestine inflammation was caused by DON-induced Salmonella typhimurium infiltration into and translocation across the gut mucosal epithelium [83].

Fusarium mycotoxins especially T-2 are assisting the *Salmonella typhimurium* infection to infect the systemically in pigs. Post intestinal infection phase of *Salmonella* typhimurium, it can cause septicemia (*Salmonella* typhimurium bloodstream invasion) and via macrophages it can reach visceral organs (lymphatic tissues of the small intestine, spleen, liver). But systematic invasion research study on *Salmonella* typhimurium to infect the organs other than gastrointestinal tract is still poorly understood and very limited data is available [103].

Salmonella can persist and even duplicate in host cells after microbial ingestion by the macrophage. Direct contact of macrophages to the non-cytotoxic concentration of DON and T-2 stimulates *Salmonella typhimurium* endorsement. Salmonella's entry into host body cells necessitates a complex set of actin cytoskeletal modifications [83]. T-2 mycotoxin improves *Salmonella typhimurium* engulfment in vitro [83].

Since low concentrations of T-2 modulates the reconstruction of macrophage cytoskeleton by ERK1/2 F-actin and results in an increased Salmonella uptake in "porcine alveolar macrophages" (PAM). In porcine macrophages, the non-cytotoxic target of Fusarium mycotoxins (DON and T-2) have no effects on *Salmonella typhimurium* intracellular growth. Additionally, they have adverse impacts on the host defense due to *Salmonella typhimurium* infection, as Fusarium mycotoxins act to regulate the metabolic rate of bacterium [104].

T-2 enhanced inflammatory effects are more likely due to the mycotoxin devastating impact on the digestive system instead of on the pathogen [83]. The bacterial expression of regulatory bodies of SPI-1 (Salmonella pathogenicity island-1) and SPI-2, respectively. Just a high concentration of T-2 enhances *ssr*A and *hil*A. SPI-1 genetics express critical intracellular replication systems, while SPI-2 genetics encode microbial secretion systems required for breach [105]. T-2 toxin's effects on the bacterium are likely to be even more noticeable as compare to the host body cells that mediates effects and result into the in-vivo reduction of emigration in pigs [101]. Decreased Salmonella mobility is caused by the low dose of T-2 and a normal down-regulation of genetics linked to the ribosomal proteins, Salmonella metabolism and SPI-1 genetics [104].

Very little is known about the communication between *Salmonella* infection and *Fusarium* mycotoxins in animals is readily available. Recently available literature has mainly focused on T-2 propagation and an intensity of the infection. *Salmonella typhimurium* related body organ lesions or death is observed in T-2-challenged mice and broiler chicken [106, 107]. When mice were infected with *Salmonella typhimurium*, they develop a bacterial infection and shown similar symptoms as people infected with *Salmonella typhi* [107]. At the lateral stage of murine salmonellosis, the combined effects of microbial lipopolysaccharide (LPS) along with T-2 can co-assist to develop the increased mortality [108]. In healthy human cells, cellular toxicity of T-2 toxin has been observed by the pathologists. They have examined functions of salmonellosis infection more clearly in hematopoietic cells and in those tissues that contain infiltrating lymphocytes. Furthermore, DON eliminates tolerance to *Salmonella enteritidis* dental infection in mice by fostering *Salmonella* migration to the "mesenteric lymph node" (MLN), spleen and liver [109]. The use of mouse and pig variants to inspect the infectious disease, mycotoxins effect and their combination on animal safety and health is significant [110] (Figure 3).

Salmonella typhimurium infection in mice is an imperative "host-pathogen interaction model" to study the consequences of typhoid fever in humans. T-2 has been presented to increase *Salmonella* induced death rate (mortality) at low to high toxin concentrations [111]. In terms of anatomical as well as physiological attributes, including kidney size, function, structure, lung vascular bed anatomy, breathing rates, cardiovascular anatomy, coronary artery circulation, digestive physiology and immunological reaction, the pig is extremely comparable to humans and has actually been used to investigate various diseases [110]. The association between *Salmonella typhimurium* and T-2 mycotoxins which has been examined in a porcine infection model, offers us with significant finding about the effect of this interaction of human IBD and immune response [83].

To summarize, it is hard to limit the accurate representation of co-exposure to *Salmonella typhimurium* and T-2 mycotoxins. . The newly released information gives an insight of direct mycotoxin contact with bacteria, host-pathogen and host cells interaction. This study depicts the harmful effects of T-2 toxins in low or relevant concentration in case of bacterial infection caused by *Salmonella typhimurium* bacteria. And when we discuss about role of T-2 toxins in bacterial infection and immunotoxicity, animals treated with fusarium T-2 toxins develop leukopenia and show decreased activity in their lymphocytes. Basically, T-2 toxins has capability to initiate hypoxia in cells that lead to activation of hypoxia-inducible factors. This activation ultimately leads to release the exosomes involved in immunotoxicity. Based on mycotoxin direct disclosure physiognomies, one of these outcomes would be the product of T-2 mycotoxins and *Salmonella* contact [112].

Gastrointestinal tract (GI) is mainly affected by taking contaminated food and feed. Generally, intestinal epithelial barriers are present in GI tract that function as filter for harmful mycotoxins. These macrophages help in engulfing of these toxins, present in lamina propria. After engulfing of salmonella by macrophages it results in activation of actin. These actin activation and reorganization events help in activation of transcriptional system. Mitogen activated protein kinase pathway (MAPK) extracellular signal regulated kinases pathway (ERK) and all salmonella pathogenicity island-1 (SPI-1) effector proteins react with DON site and activate the other proteins for neutralization of toxins, in macrophages [113].

4.3. Necrotic enteritis in broilers

The Gram-positive *Clostridium perfringens* as a primary cause of "Necrotic enteritis" (NE) and ailment affects broiler. This spore-forming bacterium is naturally occurring in soil, food and digestive tracts of animals and particularly chickens [114]. As earlier mentioned that NE is multifaceted and multifactorial ailment with various factors prompting the manifestation and duration of the episodes. The mucosal damage is one of the well-known predisposing factors that is caused by *coccidial* pathogen [115]. In broiler, only *C. perfringens* tension revealing NetB pollutants will trigger NE. Since *C. perfringens* is auxotrophic or autotrophic for various amino acids, the extensive and close accessibility of these amino acids will help wide spreading of bacterial proliferation [116]. Consumption of T-2 toxin feed is a highly risk factor due to the advancement of fatal enteritis in broiler chicks and its adverse impacts on the epithelial barrier and food accessibility for *clostridial* spread in the digestive system. Recently, researchers experimentally have proven subclinical NE infection variance showing that chicks fed with T-2-contaminated diet for 3 weeks and were more likely growing the NE lesions than chicks fed with controlled and specific diet. Therefore,

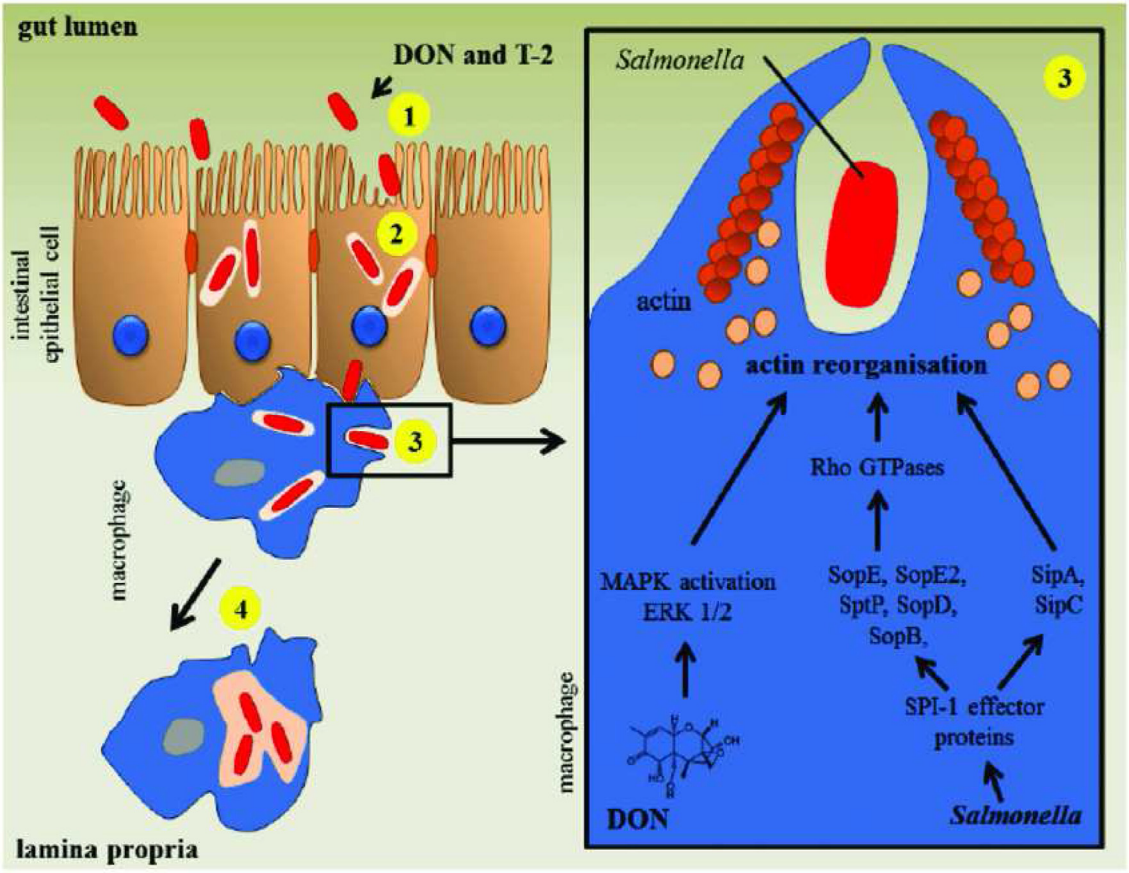

Figure 3. T-2 mycotoxins and its impacts on the human intestinal gut region against infection by salmonella [50].

adverse impacts of T-2 on the small intestine or intestinal membrane may result in food digestion impairment and leakage of plasma amino acids into the gastro intestinal lumen. As a result, *C. perfringens* start proliferation in the presence of the essential growth substrate [117].

4.4. T-2 mycotoxins as an aqueduct for quorum sensing

A mechanism known as quorum sensing enables bacteria and fungus to control the developmental programs. These programs consist of biofilm development and expression of virulence proteins. In addition to these the earlier mentioned mechanism also manages the alteration in expression pattern of genes that are based upon population densities. Many studies revealed the mechanism of microbes and their metabolic products to hinder in quorum sensing properties. T-2 mycotoxins are related to interrupting bacterial quorum signaling [118]. T-2 Mycotoxins works as a quorum quencher of acyl homo-serine lactone fragments at low concentrations versus the bio-control representative *Pseudomonas* chorographic. At higher concentrations, T-2 mycotoxins impedes the production of the antifungal metabolite phenazine-1-carboxamide by the microorganism [119]. Additionally, two different other mycotoxins, *zearalenone and fumonisins*, have actually been revealed to prevent quorum sensing in the bacteria *Chromobacterium* violaceum. Diketopiperazines derived from gram-negative bacteria have actually been shown to manage quorum-dependent phenotypes [120], possibly linking diketopiperazine-like mycotoxins (gliotoxin, roquefortines to name a few) as extra quorum regulating molecules [121].

4.5. Edwardsiella ictaluri infection in catfish

The Gram-negative microbe *Edwardsiella ictaluri* belongs to the *Enterobacteriaceae* family. "Bacillary Necrosis of Pangasianodon" (BNP), which is infected by *E. ictaluri,* is one of the common infectious diseases in catfish (*Ictalurus punctatus*). Aside from Vietnamese lakes, pounds etc (freshwater) processing. The business of American network catfish (*Ictalurus punctatus)* still suffers greatly by this microbe infections, as refer as Catfish "Enteric Septicemia" (ESC). BNP is recognized by multifocal uneven white spots of different sizes on a variety of body organs, such as kidney, spleen, and liver [122]. In the network catfish, ESC can manifest as an extreme form of septicemia and enteritis and fast mortality rate [123]. Mortality got in touch with fusarium mycotoxins' co-existence as well as likewise *E. ictaluri* is hard to anticipate in a juvenile network catfish. T-2 elevated the *E. ictaluri*-associated death [124]. At the same time, the restrained contamination of T-2 enhanced the endurance of the network catfish. The susceptibility to mycotoxin varies by fish species. . For example, rainbow trout are particularly sensitive to T-2, while network catfish are impervious. Significant information about the mycotoxin's poisoning of microorganisms is missing. To determine the end result, further work in term of interactions between *E. ictaluri* and *Fusarium* mycotoxins would be needed [125].

4.6. Coccidiosis

Protozoa of the gastrointestinal tract that include *coccidia* (*Cryptosporidium*, *Sarcosporidia* and *Eimeria*, *Isospora*) and having flagella, are essential transmittable causative agents. *Coccidiosis* in chicken refers to a health condition triggered by the Eimeria bacteria. This is a highly one of the most serious enteric problems that disturb the performance. The oral-fecal life cycle of these obligate intracellular parasites alternates between evolving stages in outside and inside the host. "*Eimeria brunetti, Eimeria optimums, Eimeria acervulina, Eimeria praecox, Eimeria tenella, Eimeria mitis* and *Eimeria necatrix",* have all been detected in chickens [126]. The physio-biological traits such as pathogenicity and immunogenicity are

species specific. Eimeria Immunity is multifaceted and predisposed by both the parasite and the host [127].

The cellular immune component is mainly mediated by lymphocytes of the intra-epithelial lymphocytes (IEL) and lamina propria, Macrophages, IEL, and $CD4^+$ T-lymphocytes, are primary component exposed against Eimeria infection, Whereas IFN and $CD8^+$ T-lymphocytes are essential for scavenger defensive immunity against Eimeria infection [128]. As in innate immune response, production of cytokines and chemokines is increased to diagnose inflammatory condition. Continuous secretion of cytokines and chemokines help in activation of immune cells such as neutrophils and macrophages. Girgis et al. [129] revealed that diet contained with T-2 mycotoxins had a detrimental effect on the cellular immune response to coccidiosis in broiler chickens. T-2 mycotoxins lower the number of $CD8^+$ and $CD4^+$ T-cells count in the duodenum mucous membranes accompanying Eimeria infection of broiler. Additionally, consuming a mycotoxin-contaminated diet reduced CD8+ T-cells and also monocyte count in the blood, which may indicate increased infiltration of immune cells at the gastrointestinal site of coccidial infection [129, 130].

Furthermore, feeding plan of Eimeria-challenged bird a diet contaminated with T-2 mycotoxin induced over-expression of IFN-γ gene in the cecal tonsils without being connected to deceptive resistant to coccidial infection in relation to improvements in the oocyst yield. The lymphoid tissues represent cecal tonsils in the cecum that originally comes from GALT. To fight with the Eimeria infection associates with the expression of a number of interleukins (ILs) rather than just IFN-γ, and enhance the gene expression isn't necessarily associated with functional secretion [131]. Furthermore, mild levels of T-2 mycotoxins were shown to have a detrimental impact on GIT morphology and affect the recovery of the intestinal tract from an infection of enteric coccidial, as shown by theevident villus region with the lower villus height. T-2 mycotoxins were seen to inhibit the Eimeria-induced immune proposed by Girgis et al., but no consequence was shown on fecal oocyst counts [129].

Correspondingly, Békési et al. [132] study reported that a T-2 mycotoxin diet has minor effect on *Cryptosporidium baileyi* oocyst discharge in broiler. Researchers are trying to investigate the mycotoxin induce animal susceptibility towards the infectious diseases mainly concerns is to disclosure with single major mycotoxins. There is limited information in the literature to show the effects of co-occurrence of mycotoxin as well as plant metabolite interaction. Nonetheless, Girgis et al. [130] revealed that the combinatorial impact of T-2, ZEN, DON Fumonisins, 15-acetylDON (15-AcDON) change the Eimeria-induced immune responses. Surprisingly, broiler feed is contaminated by mycotoxin and also reduces the effectiveness of the anti-coccidial therapy. Activation of CD4+ and CD8+ on naïve T cells in response to foreign stimulus lead to regulation of immunity. In conclusion, Fusarium mycotoxins have a detrimental impact on the immune responses (innate and adaptive) against Eimeria, but do not affect the oocyst yield. In order to determine the mycotoxins impact on the infection status, more information about medical coccidiosis lesion scoring is also needed [133].

5. Genotoxic and cytotoxic effects of T-2 toxins in humans and animals

In eukaryotic cells, T-2 toxic inhibits the synthesis of proteins, DNA and RNA. As a result, cell cycle is disturbed and induces the cell death in vitro and in vivo [134]. Both molecular and chemical structures of T-2 toxin have a vital function to determine the kind and mode of target action, due to this specificity it can interact with protein molecules. Hence T-2 toxic like diacetoxyscirpenol and HT-2 toxin truncate the initiation of a polypeptide chain. On the other hand, trichothecenes influence the elongation and termination processes [135]. This mechanism of action is similar to the activity of specific antibiotics such as “streptogramins, macrolide antibiotics and lincosamides” on microbial cells [136]. Moreover, the cytotoxic effects of T-2 toxin are observed in lymphoid cells, while DNA strand breaks the induction dysfunction of a body's immune system. The harmful effects of mycotoxins on human health have studied and observed in both acute and chronic form. These adverse effects ultimately lead some serious problems such as liver cancer, gangrene, respiratory problems and some other immune disorders. Mycotoxins including T-2 toxins impose serious threat for both humans and livestock [1]. Surprisingly, T-2 toxin are proactively worked reported in mitotic active cells (gastrointestinal tract cells, lymph nodes, spleen, bone marrow and hepatic cells) [135]. Mycotoxins ingested by animals and humans produce a toxic response known as mycotoxicosis. Different type of cancers, alimentary toxic aleukia, nephropathy and neurological disorders have been reported as most common diseases caused by mycotoxins [50]. Furthermore, direct exposure of mycotoxins in humans seems more dangerous even in very minute quantity. However, chronic diseases progress due to continuous and prolonged exposure of mycotoxins with humans either in direct or indirect way. Aflatoxins, trichothecenes, fumonisins and ergot alkaloids are well known studied mycotoxins that are threat for humans by causing fatal diseases in them [137].

T2's cytotoxic radiomimetic results have been reflected by the truncated protein synthesis and inhibition of DNA and RNA synthesis [138]. Additionally, in-vivo T-2 toxins can initiate the polyploidy in *Allium cepa*, sex-linked recessive lethal mutation in *Drosophila melanogaster* [139]. The single strand of DNA manifests the breaks in thymus and spleen of BALB/c. The chromosomal aberrations in Chinese hamster bone marrow, along with DNA damages in peripheral lymphocytes of chicken [140]. Previous studies' results about genotoxicity have shown that in vitro, T-2 toxicity triggers the DNA single-strand breaks are analysed as in primary thymic and hematocytes and spleen lymphocytes of BALB/c mouse. The this triggering effects are seen in the development of micronucleus, hereditary anomalies and sister chromatid swapping in Chinese hamster V79 fibroblasts [141]. The literature also showed the spontaneous DNA synthesis in human fibroblasts, as well as disorder of intercellular communication in Chinese hamster V79 cells [142]. Furthermore, in vitro studies confirmed that T-2 and other co-mycotoxins can induced and promote apoptosis [143] and in vivo in hematopoietic cells, liver, spleen and digestive system Chinese hamster. In poultry, apoptosis were reported in the thymus, but not yet seen in the spleen. The apoptosis that rely on the activation of p38 MAP kinases and JNK are triggered by T-2 toxin. However, no specific and consistent mechanism has been proposed for a clear description [144].

6. Immuno-toxic effects of T-2 toxin

T-2 mycotoxin with the immunomodulatory activity can activate (immune-stimulator) or stop (immune-suppressor) the working of the immune system. Beside with inhibitory effects of T-2 toxin in immune system, some studies shows that expression pattern of mycotoxins is observed in favorable prognosis in different type of infectious diseases. Because of its co-stimulatory action, it has potential to control stimulatory mechanisms for the treatment of diseases. But still its mechanism of action as co-stimulatory signal molecule is under investigation. An immunomodulatory function of T-2 is mainly dependent on time and dose. Immuno-suppression is due to high dose of toxin that induce damages to the lymph nodes, spleen, bone marrow, digestive system mucosa and thymus, leucopenia, and subsequently enhanced the chances of getting infected with microbes (Salmonella sp. and Listeria monocyte genes) [145]. Likewise, immune system activation is prompted by low dose of the toxin and demonstrated by elevated level of serum IgE and IgA antibodies as a result of quick and short-term triggering of genes in charge of the function of the body immune system together with gene important for inflammatory response [146]. The toxicity level of type A-trichothecene (T-2 toxin) is reported higher in the literature than B-trichothecenes.

Nonetheless, T-2 toxin can deplete lymphoid and necrosis cells in the spleen, thymus and lymph nodes in poultry animals and pullets [134]. Current study of health institutes support that T-2 toxin show its

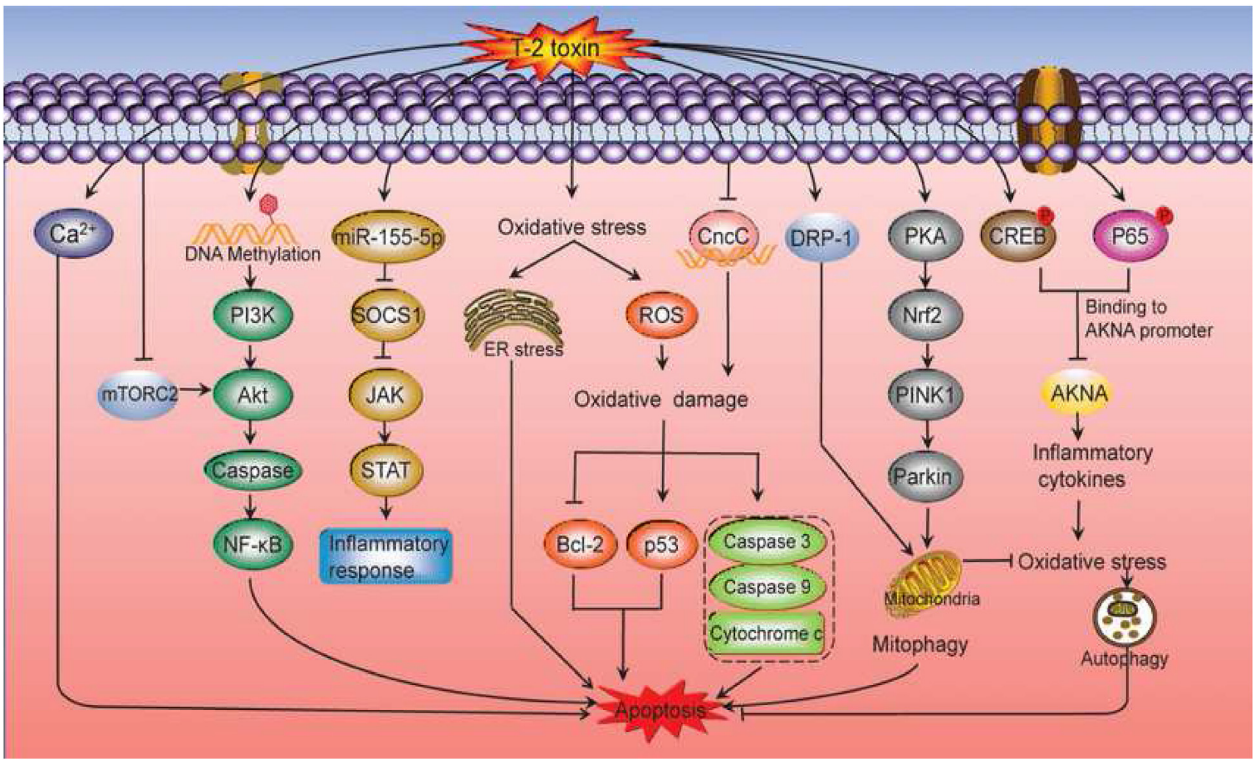

Figure 4. A schematic illustration of the proposed T-2 toxin immune-toxicity mechanism in animals and humans [150].

expression as immune inhibitor on T lymphocytes, tumor cells and myeloid cells. This expression suppress T cell's activation, cell division and production of cytokines [134]. Salmonella infection can enhance the mortality rate by the interaction of T-2 toxin with chicken [147]. It also reduced the antibody titers against Newcastle and infectious bursal diseases [148]. Molecular and cellular mechanism of T-2 toxin are not similar to the mechanisms of other mycotoxins. Immunosuppressive effects result from direct or indirect inhibition of protein synthesis. Most of the research work on T-2 toxin and its impacts have been undertaken by evaluating the laboratory animals, and still we need to investigate possible outcomes on chicken in future research [149] Figure 4.

This figure proposed a T-2 toxin immune toxicity mechanism in animals and humans. Release of Ca ions, DNA methylation induced by several proteins, inflammatory response as a result of different pathways including JAK and STAT are activated via stress. All these activations results in apoptosis that is pivotal for cell survival. While another group of researchers have studied oxidative stress, ER stress and reactive oxygen species responsible for oxidative damage that leads to apoptosis. In addition to these PKA, CREB and P65 proteins bind to their respective promoters that activate the inflammatory cytokines in response to oxidative stress and lead to apoptosis by mitophagy and autophagy [151].

7. Treatment of toxic manifestation because of T-2 toxin

There is no particular antidote apart from detoxifying with all-natural substances and bringing back lipids, nutrients, enzymes, amino acids, probiotics and controlled diet plan. Super-activated charcoal needs to be given by mouth if the toxin is ingested [152]. On extreme and emergency situation, radical treatment such as prescriptions like antifungal therapy may be required if all-natural therapy is inefficient [153]. Super-activated charcoal adsorbs and eliminate the toxic from the GI system, and protect further cellular stress. Dosage for adult is 1 g/kg PO/NG; repeat dose of 20–50 g q 2–6 h can be administrated and dosage for pediatric <1 year: 1 g/kg PO, for 1–12 years: 25–50 g PO and also for teenagers: 25–100 g PO repeat does in children not given; half initial dosage advised [154, 155].

Mycotoxins as toxic secondary metabolites are causative agents for disease and death in both animals and humans. Among trichothecene mycotoxins, T-2 toxin is unique in producing cytotoxicity as it effect cellular immune system in animals. Basically T-2 mycotoxin interfere with immune system by blocking protein synthesis followed by inhibition of RNA and DNA synthesis. The harmful effects of T-2 toxin in different organs and systems such as liver, skin, gastrointestinal tract, intestinal mucosa, bone marrow, spleen and lymphoid cells are reported. Although, mycotoxins belonging to *Fusarium sp.* are common and show less harmful effects on human health. *Salmonellosis* and *colibacillosis* species are studied for humans that produce toxins in various infections by hindering the cellular immune system of host.

The molecular characterization of microbiota involved in antitoxic effects help us in development of probiotics. Less absorption of mycotoxins in intestinal tract results in biotransformation of toxic metabolites into less toxic variants. In addition to these, effects of microbiota on harmful mycotoxins are not limited to intestinal tract, it may harm the other human vital organs. However, detoxification of microbiota is considered as an alternative way to decontaminate the feed for both animals and humans. These transformations of toxic metabolites depend upon the formation of metabolites. This study is complete in all perspectives regarding interactions between microbiota and mycotoxins, their mechanism and practical applications based on experimental studies.

8. Conclusions

The interactions between mycotoxins and microbiota of the intestine were discovered earlier. A safety outcome of the microbiota versus mycotoxin toxicity explained a couple of the variations in susceptibility level in different animals. This result was linked to the fragments that are being degraded into less harmful metabolites and decrease in mycotoxin absorption oraly.

In recent studies, immunotoxicity mechanism of T-2 toxin and human T-2 toxin is discussed. In general terms, the microbiota have potential benefit on mycotoxins toxicity, an adverse finding in the form of conjugated/masked mycotoxins hydrolysis was recently discovered. This hydrolysis that is linked to digestive enzymes and stomach acidity resulted in the secretion of mycotoxins in the GIT system, especially stomach, along with non-conjugated forms led to the general toxicity of contaminated food and feed. Nevertheless, the communications between mycotoxins and intestinal microbiota are not restricted to influences of the microbiota on mycotoxins. Additionally, a boosting variety of investigates are determining results of mycotoxins on the microbiota. The initial work mainly concerned with the disturbed and barrier effects; which were mainly provided by the digestive system and consequences of microbial translocation. On other hand, the digestive tract barrier is the product of a balance between three barriers/mechanisms: (1) the first mechanism is to create a physical-chemical barrier from the secretions of epithelial cells; (2) the second barrier or mechanism is attached to the microbiota that colonizes the digestive system; and (3) the third one is the immune threat.

Moreover, modified forms of T-2 toxins exerts immunotoxic effects by effecting JAK/STAT signaling pathways. Infections related to mycotoxins disturb the gut microbiota that results in autophagy and disturb the normal functioning. Oxidative stress and transcriptional changes lead to apoptosis that enhance the immunity against mycotoxins. At high dose of toxin, as revealed in a study is a high risk of bacterial invasion. It naturally comes from the mycotoxin toxicity to the immune system and gut cells.

This study found that mycotoxins disrupt microbiota in intestines by changing relative abundance of species, genus and phylum levels. From literature study, it has been found that interactions between mycotoxins and gut microbiota vary at specie, genus and phylum level. This has been confirmed by analysis of the effects of the microbiota present between metabolism of mycotoxins and the toxicokinetics [156]. As a result, many innovative approaches were proposed to study the impacts of mycotoxins on human health. Mycotoxins as toxic secondary metabolites are causative agents for disease and death in both animals and humans. Among trichothecene mycotoxins, T-2 toxin is unique in producing cytotoxicity as it effect cellular immune system in animals. Basically T-2 mycotoxin interfere with immune system by blocking protein synthesis followed by inhibition of RNA and DNA synthesis. The harmful effects of T-2 toxin in different organs and systems such as liver, skin, gastrointestinal tract, intestinal mucosa, bone marrow, spleen and lymphoid cells are reported. Although, mycotoxins belonging to *Fusarium sp.* are common and show less harmful effects on human health. *Salmonellosis* and *colibacillosis* species are studied for humans that produce toxins in various infections by hindering the cellular immune system of host. While research works on the communications between mycotoxins and intestine microbiota that occur due to a low doses is still in progress. Therefore, more research studies need to be undertaken before concluding the actual impacts on human health since innovative approaches are key to address the open health challenges.

Declarations

Author contribution statement

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Declaration of interest's statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

References

[1] M.E. Zain, Impact of mycotoxins on humans and animals, J. Saudi Chem. Soc. 15 (2) (2011) 129–144.
[2] J. Fink-Gremmels, N. Georgiou, Risk Assessment of Mycotoxins for the Consumers. Residues of Veterinary Drugs and Mycotoxins in Animal Products, NL-Wageningen Press, Wageningen, 1996, pp. 159–174.
[3] D.L. Sudakin, Trichothecenes in the environment: relevance to human health, Toxicol. Lett. 143 (2) (2003) 97–107.
[4] N. Benkerroum, Chronic and acute toxicities of aflatoxins: mechanisms of action, Int. J. Environ. Res. Publ. Health 17 (2) (2020) 423.
[5] L. Afsah-Hejri, et al., A review on mycotoxins in food and feed: Malaysia case study, Compr. Rev. Food Sci. Food Saf. 12 (6) (2013) 629–651.
[6] R. Krska, et al., Determination of T-2 and HT-2 toxins in food and feed: an update, World Mycotoxin J. 7 (2) (2014) 131–142.
[7] G.O. Adegoke, P. Letuma, Strategies for the prevention and reduction of mycotoxins in developing countries, Mycotoxin and food safety in developing countries (2013) 123–136.
[8] P. Rafai, et al., Effect of dietary T-2 fusariotoxin concentrations on the health and production of white Pekin duck broilers, Poultry Sci. 79 (11) (2000) 1548–1556.
[9] V.S. Mary, et al., Reactive oxygen species sources and biomolecular oxidative damage induced by aflatoxin B1 and fumonisin B1 in rat spleen mononuclear cells, Toxicology 302 (2-3) (2012) 299–307.
[10] R. Pósa, et al., Interaction of Bordetella bronchiseptica, Pasteurella multocida, and fumonisin B1 in the porcine respiratory tract as studied by computed tomography, Can. J. Vet. Res. 75 (3) (2011) 176–182.
[11] R. Kachuei, et al., Determination of T-2 Mycotoxin in Fusarium strains by HPLC with fluorescence detector, Journal of Applied Biotechnology Reports 1 (1) (2014) 38–43.
[12] A. Kanora, D. Maes, The role of mycotoxins in pig reproduction: a review, Vet. Med. 54 (12) (2010) 565–576.
[13] A.R. Hesketh, et al., Biosynthesis of trichothecene mycotoxins: identification of isotrichodiol as a post-trichodiene intermediate, Phytochemistry 30 (7) (1991) 2237–2243.
[14] H.G. Kalantari, M. Zong, I.-M. Chang, Assay of T-2 toxin contamination in domestic and imported agricultural products in Korea, JSM Mycotoxins 1989 (30) (1989) 32–34.
[15] H. Kalantari, A. Hematti, Antidote for T-2 toxin from medicinal plants in mice, Hakim Research Journal National Research Center of Medical Science IR 4 (2000).
[16] H. Kalantari, M. Mousavi, Review on T-2 Toxin, 2010.
[17] A. Medina, et al., Biocontrol of mycotoxins: dynamics and mechanisms of action, Curr. Opin. Food Sci. 17 (2017) 41–48.
[18] J.J. Park, E.B. Smalley, F.S. Chu, Natural occurrence of Fusarium mycotoxins in field samples from the 1992 Wisconsin corn crop, Appl. Environ. Microbiol. 62 (5) (1996) 1642–1648.
[19] G. Diaz, et al., Individual and combined effects of T-2 toxin and DAS in laying hens, Br. Poultry Sci. 35 (3) (1994) 393–405.
[20] C. Bouaziz, et al., Different apoptotic pathways induced by zearalenone, T-2 toxin and ochratoxin A in human hepatoma cells, Toxicology 254 (1-2) (2008) 19–28.
[21] Y. Li, et al., T-2 toxin, a trichothecene mycotoxin: review of toxicity, metabolism, and analytical methods, J. Agric. Food Chem. 59 (8) (2011) 3441–3453.
[22] J. Shinozuka, et al., T-2 toxin-induced apoptosis in hematopoietic tissues of mice, Toxicol. Pathol. 26 (5) (1998) 674–681.
[23] J. Wu, et al., Autophagy and apoptosis interact to modulate T-2 toxin-induced toxicity in liver cells, Toxins 11 (1) (2019) 45.
[24] M. Adhikari, et al., T-2 mycotoxin: toxicological effects and decontamination strategies, Oncotarget 8 (20) (2017), 33933.
[25] D. Huang, et al., Nitric oxide mediates apoptosis and mitochondrial dysfunction and plays a role in growth hormone deficiency by nivalenol in GH3 cells, Sci. Rep. 7 (1) (2017) 1–14.
[26] Z. Zhang, et al., Protective Effect of Selenomethionine on T-2 Toxin–Induced Rabbit Immunotoxicity, Biological Trace Element Research, 2021, pp. 1–11.
[27] J. Holme, et al., Mechanisms involved in the induction of apoptosis by T-2 and HT-2 toxins in HL-60 human promyelocytic leukemia cells, Cell Biol. Toxicol. 19 (1) (2003) 53–68.
[28] Y. Chen, et al., Oxidative stress and apoptotic changes in broiler chicken splenocytes exposed to T-2 toxin, BioMed Res. Int. 2019 (2019).
[29] G.J.A. Speijers, M.H.M. Speijers, Combined toxic effects of mycotoxins, Toxicol. Lett. 153 (1) (2004) 91–98.

[30] A. Ling, et al., Individual and combined cytotoxic effects of T-2 toxin and its four metabolites on porcine Leydig cells, Food Chem. Toxicol. 139 (2020), 111277.
[31] M. Devreese, P. De Backer, S. Croubels, Different methods to counteract mycotoxin production and its impact on animal health, Vlaams Diergeneeskundig Tijdschrift 82 (4) (2013) 181–190.
[32] E. Binder, et al., Worldwide occurrence of mycotoxins in commodities, feeds and feed ingredients, Anim. Feed Sci. Technol. 137 (3-4) (2007) 265–282.
[33] K. Horvatovich, et al., Dose-related genotoxic effect of T-2 toxin measured by comet assay using peripheral blood mononuclear cells of healthy pigs, Acta Vet. Hung. 61 (2) (2013) 175–186.
[34] O. Rocha, K. Ansari, F. Doohan, Effects of trichothecene mycotoxins on eukaryotic cells: a review, Food Addit. Contam. 22 (4) (2005) 369–378.
[35] L. Kubena, et al., Cecal volatile fatty acids and broiler chick susceptibility to Salmonella typhimurium colonization as affected by aflatoxins and T-2 toxin, Poultry Sci. 80 (4) (2001) 411–417.
[36] A.V. Nathanail, et al., Metabolism of the Fusarium mycotoxins T-2 toxin and HT-2 toxin in wheat, J. Agric. Food Chem. 63 (35) (2015) 7862–7872.
[37] I. Tenk, E. Fodor, C. Szathmáry, *The effect of pure Fusarium toxins (T-2, F-2, DAS) on the microflora of the gut and on plasma glucocorticoid levels in rat and swine.* Zentralblatt für Bakteriologie, Mikrobiologie und Hygiene. 1. Abt. Originale. A, Medizinische Mikrobiologie, Infektionskrankheiten und Parasitologie 252 (3) (1982) 384–393.
[38] Z. Wang, J. Feng, Z. Tong, Human toxicosis caused by moldy rice contaminated with fusarium and T-2 toxin, Biomed. Environ. Sci.: BES (Biomed. Environ. Sci.) 6 (1) (1993) 65–70.
[39] Q.-H. Wu, et al., Oxidative stress-mediated cytotoxicity and metabolism of T-2 toxin and deoxynivalenol in animals and humans: an update, Arch. Toxicol. 88 (7) (2014) 1309–1326.
[40] W. Wu, et al., Comparison of anorectic potencies of the trichothecenes T-2 toxin, HT-2 toxin and satratoxin G to the ipecac alkaloid emetine, Toxicol Rep 2 (2015) 238–251.
[41] L. Yang, et al., Cytotoxicity and apoptosis induced by mixed mycotoxins (T-2 and HT-2 toxin) on primary hepatocytes of broilers in vitro, Toxicon 129 (2017) 1–10.
[42] J.C. Young, et al., Degradation of trichothecene mycotoxins by chicken intestinal microbes, Food Chem. Toxicol. 45 (1) (2007) 136–143.
[43] C. Nyangi, et al., Assessment of pre-harvest aflatoxin and fumonisin contamination of maize in Babati District, Tanzania, Afr. J. Food Nutr. Sci. 16 (3) (2016) 11039–11053.
[44] K. Obremski, et al., The effect of T-2 toxin on percentages of CD4+, CD8+, CD4+ CD8+ and CD21+ lymphocytes, and mRNA expression levels of selected cytokines in porcine ileal Peyer's patches, Pol. J. Vet. Sci. (2013).
[45] Y. Ueno, et al., Induction of apoptosis by T-2 toxin and other natural toxins in HL-60 human promyelotic leukemia cells, Nat. Toxins 3 (3) (1995) 129–137.
[46] F.T. Guilford, J. Hope, Deficient glutathione in the pathophysiology of mycotoxin-related illness, Toxins 6 (2) (2014) 608–623.
[47] W.B. Henghold 2nd, Other biologic toxin bioweapons: ricin, staphylococcal enterotoxin B, and trichothecene mycotoxins, Dermatol. Clin. 22 (3) (2004) 257–262.
[48] R. Rai, et al., Analysis of feed ingredients for Afla and T-2 mycotoxins by ELISA in rural areas of Uttar Pradesh, Ind J Vet Pathol 35 (2011) 238–240.
[49] H. Johnsen, et al., Cytotoxicity and effects of T2-toxin on plasma proteines involved in coagulation, fibrinolysis and kallikrein-kinin system, Arch. Toxicol. 61 (3) (1988) 237–240.
[50] G. Antonissen, et al., The impact of Fusarium mycotoxins on human and animal host susceptibility to infectious diseases, Toxins 6 (2) (2014) 430–452.
[51] M. Norlia, et al., Molecular characterisation of aflatoxigenic and non-aflatoxigenic strains of Aspergillus section Flavi isolated from imported peanuts along the supply chain in Malaysia, Toxins 11 (9) (2019) 501.
[52] S. Stoev, et al., Special Pathology and Diagnostics of Mycoses, Mycotoxicoses, Parasitoses, Intoxications and Avitaminoses, Publishing House CD Contrast, 2010, pp. 1–239.
[53] M. Moosavi, et al., l-carnitine protects rat hepatocytes from oxidative stress induced by T-2 toxin, Drug Chem. Toxicol. 39 (4) (2016) 445–450.
[54] J. Wu, et al., T-2 toxin regulates steroid hormone secretion of rat ovarian granulosa cells through cAMP-PKA pathway, Toxicol. Lett. 232 (3) (2015) 573–579.
[55] M. Li, et al., T-2 toxin impairs murine immune response to respiratory reovirus and exacerbates viral bronchiolitis, Toxicol. Appl. Pharmacol. 217 (1) (2006) 76–85.
[56] D.L. Bunner, E.R. Morris, Alteration of multiple cell membrane functions in L-6 myoblasts by T-2 toxin: an important mechanism of action, Toxicol. Appl. Pharmacol. 92 (1) (1988) 113–121.
[57] P. Kamalavenkatesh, et al., Immunopathological effect of the mycotoxins cyclopiazonic acid and T-2 toxin on broiler chicken, Mycopathologia 159 (2) (2005) 273–279.
[58] N. Hymery, Y. Sibiril, D. Parent-Massin, In vitro effects of trichothecenes on human dendritic cells, Toxicol. Vitro 20 (6) (2006) 899–909.
[59] P. Huang, et al., T-2 toxin initially activates caspase-2 and induces apoptosis in U937 cells, Toxicol. Lett. 170 (1) (2007) 1–10.
[60] C. Bouaziz, et al., Cytotoxicity and related effects of T-2 toxin on cultured Vero cells, Toxicon 48 (3) (2006) 343–352.
[61] S.M. Albarenque, et al., T-2 toxin-induced acute skin lesions in Wistar-derived hypotrichotic WBNIIILA-Ht rats, Histol. Histopathol. 14 (2) (1999) 337–342.
[62] J.M. Grizzle, et al., Determination of the acute 50% lethal dose T-2 toxin in adult bobwhite quail: additional studies on the effect of T-2 mycotoxin on blood chemistry and the morphology of internal organs, Avian Dis. 48 (2) (2004) 392–399.
[63] S. Sehata, et al., Morphological and microarray analysis of T-2 toxin-induced rat fetal brain lesion, Food Chem. Toxicol. 42 (11) (2004) 1727–1736.
[64] F. Atroshi, et al., Significance of apoptosis and its relationship to antioxidants after ochratoxin A administration in mice, J. Pharm. Pharmaceut. Sci. 3 (281) (2000) e291.
[65] J. Pace, M. Watts, W. Canterbury, T-2 mycotoxin inhibits mitochondrial protein synthesis, Toxicon 26 (1) (1988) 77–85.
[66] M.M. Alam, et al., Thymocyte apoptosis by T-2 toxin in vivo in mice is independent of Fas/Fas ligand system, Biosci. Biotechnol. Biochem. 64 (1) (2000) 210–213.
[67] G.-H. Yang, et al., Apoptosis induction by the satratoxins and other trichothecene mycotoxins: relationship to ERK, p38 MAPK, and SAPK/JNK activation, Toxicol. Appl. Pharmacol. 164 (2) (2000) 149–160.
[68] N. Ishigami, et al., Apoptosis in mouse fetuses from dams exposed to T-2 toxin at different days of gestation, Exp. Toxicol. Pathol. 52 (6) (2001) 493–501.
[69] R.A. Corley, et al., Disposition of T-2 toxin, a trichothecene mycotoxin, in intravascularly dosed swine, J. Agric. Food Chem. 34 (5) (1986) 868–875.
[70] S.C.o. Food, Opinion of the Scientific Committee on Food on Fusarium Toxins. Part 6: Group Evaluation of T-2 Toxin, HT-2 Toxin, Nivalenol and Deoxynivalenol, 2002, pp. 1–12.
[71] F. Berthiller, et al., Rapid simultaneous determination of major type A-and B-trichothecenes as well as zearalenone in maize by high performance liquid chromatography–tandem mass spectrometry, J. Chromatogr. A 1062 (2) (2005) 209–216.
[72] H. Tanaka, et al., Development of a liquid chromatography/time of flight mass spectrometric method for the simultaneous determination of trichothecenes, zearalenone and aflatoxins in foodstuffs, Rapid Commun. Mass Spectrom: An Int. J. Dev. Rapid Dissem. Up-to-the-Min. Res. Mass Spectro. 20 (9) (2006) 1422–1428.
[73] M. Pascale, M. Haidukowski, A. Visconti, Determination of T-2 toxin in cereal grains by liquid chromatography with fluorescence detection after immunoaffinity column clean-up and derivatization with 1-anthroylnitrile, J. Chromatogr. A 989 (2) (2003) 257–264.
[74] C.M. Maragos, Measurement of T-2 and HT-2 toxins in eggs by high-performance liquid chromatography with fluorescence detection, J. Food Protect. 69 (11) (2006) 2773–2776.
[75] M. Sokolović, V. Garaj-Vrhovac, B. Šimpraga, T-2 toksin-pojavnost i toksičnost u peradi, Arh. Hig. Rad. Toksikol. 59 (1) (2008) 43–52.
[76] R. Robert, M. Paterson, N. Lima, Toxicology of mycotoxins, in: E. Luch (Ed.), Molecular, Clinical and Environmental Toxicology, Clinical Toxicology, 2010, pp. 31–63.
[77] N. Ishigami, S. Sehata, T-2 toxin-induced toxicity in pregnant mice and rats, Int. J. Mol. Sci. 9 (11) (2008) 2146–2158.
[78] R. Segal, et al., Trichothecene-induced hemolysis: I. The hemolytic activity of T-2 toxin, Toxicol. Appl. Pharmacol. 70 (3) (1983) 343–349.
[79] P. Pinton, et al., Toxicity of deoxynivalenol and its acetylated derivatives on the intestine: differential effects on morphology, barrier function, tight junction proteins, and mitogen-activated protein kinases, Toxicol. Sci. 130 (1) (2012) 180–190.
[80] J. Goossens, et al., Porcine intestinal epithelial barrier disruption by the Fusarium mycotoxins deoxynivalenol and T-2 toxin promotes transepithelial passage of doxycycline and paromomycin, BMC Vet. Res. 8 (1) (2012) 1–10.
[81] K. Kanai, E. Kondo, Decreased resistance to mycobacterial infection in mice fed a trichothecene compound (T-2 toxin), Jpn. J. Med. Sci. Biol. 37 (2) (1984) 97–104.
[82] E. Verbrugghe, et al., A modified glucomannan mycotoxin-adsorbing agent counteracts the reduced weight gain and diminishes cecal colonization of Salmonella Typhimurium in T-2 toxin exposed pigs, Res. Vet. Sci. 93 (3) (2012) 1139–1141.
[83] V. Vandenbroucke, et al., The mycotoxin deoxynivalenol potentiates intestinal inflammation by Salmonella typhimurium in porcine ileal loops, PLoS One 6 (8) (2011), e23871.
[84] A. Romero, et al., Mycotoxins modify the barrier function of Caco-2 cells through differential gene expression of specific claudin isoforms: protective effect of illite mineral clay, Toxicology 353 (2016) 21–33.
[85] T. Sadler, et al., Prevention of fumonisin B1-induced neural tube defects by folic acid, Teratology 66 (4) (2002) 169–176.
[86] S.W. Gratz, et al., Masked trichothecene and zearalenone mycotoxins withstand digestion and absorption in the upper GI tract but are efficiently hydrolyzed by human gut microbiota in vitro, Mol. Nutr. Food Res. 61 (4) (2017), 1600680.
[87] P.C. Schmeits, et al., DON shares a similar mode of action as the ribotoxic stress inducer anisomycin while TBTO shares ER stress patterns with the ER stress inducer thapsigargin based on comparative gene expression profiling in Jurkat T cells, Toxicol. Lett. 224 (3) (2014) 395–406.
[88] E.J. van Opstal, S.R. Bordenstein, Rethinking heritability of the microbiome, Science 349 (6253) (2015) 1172–1173.
[89] E.M. Binder, Managing the risk of mycotoxins in modern feed production, Anim. Feed Sci. Technol. 133 (1-2) (2007) 149–166.
[90] J.B. Kaper, J.P. Nataro, H.L. Mobley, Pathogenic escherichia coli, Nat. Rev. Microbiol. 2 (2) (2004) 123–140.
[91] I.P. Oswald, et al., Mycotoxin fumonisin B1 increases intestinal colonization by pathogenic Escherichia coli in pigs, Appl. Environ. Microbiol. 69 (10) (2003) 5870–5874.

[92] P. Pinton, et al., The food contaminant deoxynivalenol, decreases intestinal barrier permeability and reduces claudin expression, Toxicol. Appl. Pharmacol. 237 (1) (2009) 41–48.
[93] D. Baines, et al., Aflatoxin, fumonisin and shiga toxin-producing Escherichia coli infections in calves and the effectiveness of Celmanax®/Dairyman's Choice™ applications to eliminate morbidity and mortality losses, Toxins 5 (10) (2013) 1872–1895.
[94] B. Devriendt, et al., The food contaminant fumonisin B1 reduces the maturation of porcine CD11R1+ intestinal dendritic cells, resulting in a reduced efficiency of oral immunisation and a prolonged intestinal ETEC infection, in: 11th International Symposium on Dendritic Cells in Fundamental and Clinical Immunology, 2010.
[95] B. Grenier, T.J. Applegate, Modulation of intestinal functions following mycotoxin ingestion: meta-analysis of published experiments in animals, Toxins 5 (2) (2013) 396–430.
[96] Y. Li, et al., Effects of moniliformin on performance and immune function of broiler chicks, Poultry Sci. 79 (1) (2000) 26–32.
[97] Y. Li, et al., The individual and combined effects of fumonisin B1 and moniliformin on performance and selected immune parameters in Turkey poults, Poultry Sci. 79 (6) (2000) 871–878.
[98] H.L. Andrews-Polymenis, et al., Taming the elephant: Salmonella biology, pathogenesis, and prevention, Infect. Immun. 78 (6) (2010) 2356–2369.
[99] M.E. Ohl, S.I. Miller, Salmonella: a model for bacterial pathogenesis, Annu. Rev. Med. 52 (1) (2001) 259–274.
[100] V. Vandenbroucke, et al., The mycotoxin deoxynivalenol promotes uptake of Salmonella Typhimurium in porcine macrophages, associated with ERK1/2 induced cytoskeleton reorganization, Vet. Res. 40 (6) (2009) 1.
[101] C. Burel, et al., Effect of low dose of fumonisins on pig health: immune status, intestinal microbiota and sensitivity to Salmonella, Toxins 5 (4) (2013) 841–864.
[102] K. Skjolaas, et al., Effects of Salmonella enterica serovars Typhimurium (ST) and Choleraesuis (SC) on chemokine and cytokine expression in swine ileum and jejunal epithelial cells, Vet. Immunol. Immunopathol. 111 (3-4) (2006) 199–209.
[103] F. Boyen, et al., Non-typhoidal Salmonella infections in pigs: a closer look at epidemiology, pathogenesis and control, Vet. Microbiol. 130 (1-2) (2008) 1–19.
[104] E. Verbrugghe, et al., T-2 toxin induced Salmonella Typhimurium intoxication results in decreased Salmonella numbers in the cecum contents of pigs, despite marked effects on Salmonella-host cell interactions, Vet. Res. 43 (1) (2012) 1–18.
[105] Y. Hara-Kudo, et al., Effects of deoxynivalenol on Salmonella enteritidis infection, Jsm Mycotoxins 1996 (42) (1996) 51–55.
[106] D. Vidal, S. Mavet, In vitro and in vivo toxicity of T-2 toxin, a Fusarium mycotoxin, to mouse peritoneal macrophages, Infect. Immun. 57 (7) (1989) 2260–2264.
[107] H.W. Mittrücker, S.H. Kaufmann, Immune response to infection with Salmonella typhimurium in mice, J. Leukoc. Biol. 67 (4) (2000) 457–463.
[108] J. Tai, J. Pestka, Synergistic interaction between the trichothecene T-2 toxin and Salmonella typhimurium lipopolysaccharide in C3H/HeN and C3H/HeJ mice, Toxicol. Lett. 44 (1-2) (1988) 191–200.
[109] H. Rothkötter, E. Sowa, R. Pabst, The pig as a model of developmental immunology, Hum. Exp. Toxicol. 21 (9-10) (2002) 533–536.
[110] F. Meurens, et al., The pig: a model for human infectious diseases, Trends Microbiol. 20 (1) (2012) 50–57.
[111] J.-H. Tai, J. Pestka, T-2 toxin impairment of murine response to Salmonella typhimurium: a histopathologic assessment, Mycopathologia 109 (3) (1990) 149–155.
[112] D. Bréa, et al., The pig as a model for investigating the role of neutrophil serine proteases in human inflammatory lung diseases, Biochem. J. 447 (3) (2012) 363–370.
[113] J. Hernández-Ramírez, et al., The effect of moderate-dose aflatoxin B1 and Salmonella Enteritidis infection on intestinal permeability in broiler chickens, Mycotoxin Res. 36 (1) (2020) 31–39.
[114] A.J. Barbara, et al., Necrotic enteritis-producing strains of Clostridium perfringens displace non-necrotic enteritis strains from the gut of chicks, Vet. Microbiol. 126 (4) (2008) 377–382.
[115] R. Williams, Intercurrent coccidiosis and necrotic enteritis of chickens: rational, integrated disease management by maintenance of gut integrity, Avian Pathol. 34 (3) (2005) 159–180.
[116] A.L. Keyburn, et al., NetB, a new toxin that is associated with avian necrotic enteritis caused by Clostridium perfringens, PLoS Pathog. 4 (2) (2008) e26.
[117] G. Antonissen, et al., Deoxynivalenol predisposes for necrotic enteritis by affecting the intestinal barrier in broilers, International Poultry Scientific Forum (2013).
[118] A.J. Martín-Rodríguez, et al., Inhibition of bacterial quorum sensing by extracts from aquatic fungi: first report from marine endophytes, Mar. Drugs 12 (11) (2014) 5503–5526.
[119] E.T. van Rij, et al., Influence of fusaric acid on phenazine-1-carboxamide synthesis and gene expression of Pseudomonas chlororaphis strain PCL1391, Microbiology 151 (8) (2005) 2805–2814.
[120] C.W. Bacon, D.M. Hinton, T.R. Mitchell, Is quorum signaling by mycotoxins a new risk-mitigating strategy for bacterial biocontrol of Fusarium verticillioides and other endophytic fungal species? J. Agric. Food Chem. 65 (33) (2017) 7071–7080.
[121] J. Bao, et al., New furanone derivatives and alkaloids from the co-culture of marine-derived fungi Aspergillus sclerotiorum and Penicillium citrinum, Chem. Biodivers. 14 (3) (2017) e1600327.
[122] M. Crumlish, et al., Identification of Edwardsiella ictaluri from diseased freshwater catfish, pangasius hypophthalmus (sauvage), cultured in the mekong delta, vietnam, J. Fish. Dis. 25 (12) (2002) 733–736.
[123] H. Ferguson, et al., Bacillary necrosis in farmed pangasius hypophthalmus (sauvage) from the mekong delta, vietnam, J. Fish. Dis. 24 (9) (2001) 509–513.
[124] B.B. Manning, et al., Exposure to feedborne mycotoxins T-2 toxin or ochratoxin A causes increased mortality of channel catfish challenged with Edwardsiella ictaluri, J. Aquat. Anim. Health 17 (2) (2005) 147–152.
[125] B.B. Manning, et al., The effect of feeding diets containing deoxynivalenol contaminated corn on channel catfish (I ctalurus punctatus) challenged with E dwardsiella ictaluri, Aquacult. Res. 45 (11) (2014) 1782–1786.
[126] H.S. Lillehoj, E.P. Lillehoj, Avian Coccidiosis. A Review of Acquired Intestinal Immunity and Vaccination Strategies, Avian diseases, 2000, pp. 408–425.
[127] H.D. Chapman, et al., A selective review of advances in coccidiosis research, Adv. Parasitol. 83 (2013) 93–171.
[128] H. Lillehoj, W. Min, R. Dalloul, Recent progress on the cytokine regulation of intestinal immune responses to Eimeria, Poultry Sci. 83 (4) (2004) 611–623.
[129] G.N. Girgis, et al., Immunomodulatory effects of feed-borne Fusarium mycotoxins in chickens infected with coccidia, Exp. Biol. Med. 233 (11) (2008) 1411–1420.
[130] G.N. Girgis, et al., Effects of feed-borne Fusarium mycotoxins and an organic mycotoxin adsorbent on immune cell dynamics in the jejunum of chickens infected with Eimeria maxima, Vet. Immunol. Immunopathol. 138 (3) (2010) 218–223.
[131] G. Girgis, et al., Morphologic changes in the intestine of broiler breeder pullets fed diets naturally contaminated with Fusarium mycotoxins with or without coccidial challenge, Avian Dis. 54 (1) (2010) 67–73.
[132] L. Békési, et al., Effect of F-2 and T-2 fusariotoxins on experimental Cryptosporidium baileyi infection in chickens, Int. J. Parasitol. 27 (12) (1997) 1531–1536.
[133] I. Varga, A. Ványi, Interaction of T-2 fusariotoxin with anticoccidial efficacy of lasalocid in chickens, Int. J. Parasitol. 22 (4) (1992) 523–525.
[134] Y. Saif, et al., Diseases of Poultry 11thed, Iowa State University Press, 2003, p. 56.
[135] P.K. Venkatesh, et al., Induction of apoptosis by fungal culture materials containing cyclopiazonic acid and T-2 toxin in primary lymphoid organs of broiler chickens, Mycopathologia 159 (3) (2005) 393–400.
[136] A. Jimenez, D. Vazquez, Quantitative binding of antibiotics to ribosomes from a yeast mutant altered on the peptidyl-transferase center, Eur. J. Biochem. 54 (2) (1975) 483–492.
[137] A. Barac, Mycotoxins and human disease, in: Clinically Relevant Mycoses, Springer, 2019, pp. 213–225.
[138] D. Corrier, Mycotoxicosis: mechanisms of immunosuppression, Vet. Immunol. Immunopathol. 30 (1) (1991) 73–87.
[139] M. Sorsa, et al., Evaluation of the mutagenicity of epoxytrichothecene mycotoxins in Drosophila melanogaster, Hereditas 92 (1) (1980) 163–165.
[140] M. Sokolovic, et al., Chicken nucleated blood cells as a cellular model for genotoxicity testing using the comet assay, Food Chem. Toxicol. 45 (11) (2007) 2165–2170.
[141] C. Hsia, et al., Natural occurrence and clastogenic effects of nivalenol, deoxynivalenol, 3-acetyl-deoxynivalenol, 15-acetyl-deoxynivalenol, and zearalenone in corn from a high-risk area of esophageal cancer, Cancer Detect. Prev. 13 (2) (1988) 79–86.
[142] C. Jone, et al., Effect of biological toxins on gap-junctionai intercellular communication in Chinese hamster V79 cells, Cell Biol. Toxicol. 3 (1) (1987) 1–15.
[143] J.J. Pestka, et al., Cellular and molecular mechanisms for immune modulation by deoxynivalenol and other trichothecenes: unraveling a paradox, Toxicol. Lett. 153 (1) (2004) 61–73.
[144] A. Poapolathep, et al., Nivalenol-induced apoptosis in thymus, spleen and Peyer's patches of mice, Exp. Toxicol. Pathol. 53 (6) (2002) 441–446.
[145] G.S. Bondy, J.J. Pestka, Immunomodulation by fungal toxins, J. Toxicol. Environ. Health B Crit. Rev. 3 (2) (2000) 109–143.
[146] Z.W. Jaradat, B. Vilà, R.R. Marquardt, Adverse effects of T-2 toxin on chicken lymphocytes blastogenesis and its protection with vitamin E, Toxicology 225 (2-3) (2006) 90–96.
[147] D. Konjević, et al., A pathological condition possibly caused by spontaneous trichotecene poisoning in Brahma poultry: first report, Avian Pathol. 33 (3) (2004) 377–380.
[148] C. Girish, G. Devegowda, Efficacy of glucomannan-containing yeast product (Mycosorb®) and hydrated sodium calcium aluminosilicate in preventing the individual and combined toxicity of aflatoxin and T-2 toxin in commercial broilers, Asian-Australas. J. Anim. Sci. 19 (6) (2006) 877–883.
[149] M. Sokolović, V. Garaj-Vrhovac, B. Šimpraga, T-2 toxin: incidence and toxicity in poultry, Arh. Hig. Rad. Toksikol. 59 (1) (2008) 43–52.
[150] Q. Wu, et al., An Update on T-2 Toxin and its Modified Forms: Metabolism, Immunotoxicity Mechanism, and Human Exposure Assessment, Archives of Toxicology, 2020, pp. 1–25.
[151] M. Agrawal, A. Bhaskar, P. Rao, Involvement of mitogen-activated protein kinase pathway in T-2 toxin-induced cell cycle alteration and apoptosis in human neuroblastoma cells, Mol. Neurobiol. 51 (3) (2015) 1379–1394.
[152] M. Chaudhari, et al., Oxidative stress induction by T-2 toxin causes DNA damage and triggers apoptosis via caspase pathway in human cervical cancer cells, Toxicology 262 (2) (2009) 153–161.
[153] H. Kalantari, Medical Aspects of Chemical and Biological Terrorism, House of the union of scientists in Bulgaria, 2005, pp. 333–343.
[154] J.-h. Chen, et al., T-2 toxin-induced apoptosis involving Fas, p53, Bcl-xL, Bcl-2, Bax and caspase-3 signaling pathways in human chondrocytes, J. Zhejiang Univ. - Sci. B 9 (6) (2008) 455–463.
[155] A.M. Haig, Chemical Warfare in Southeast Asia and Afghanistan: Report to the Congress, US Department of State, Bureau of Public Affairs, Office of Public, 1982.
[156] P. Guerre, Mycotoxin and gut microbiota interactions, Toxins 12 (12) (2020) 769.