Poultry Science

Pathological consequences, metabolism and toxic effects of trichothecene T-2 toxin in poultry

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ABSTRACT Contamination of feed with mycotoxins has become a severe issue worldwide. Among the most prevalent trichothecene mycotoxins, T-2 toxin is of particular importance for livestock production, including poultry posing a significant threat to animal health and productivity. This review article aims to comprehensively analyze the pathological consequences, metabolism, and toxic effects of T-2 toxin in poultry. Trichothecene mycotoxins, primarily produced by *Fusarium* species, are notorious for their potent toxicity. T-2 toxin exhibits a broad spectrum of negative effects on poultry species, leading to substantial economic losses as well as concerns about animal welfare and food safety in modern agriculture. T-2 toxin exposure easily results in negative pathological consequences in the gastrointestinal tract, as well as in parenchymal tissues like the liver (as the key organ for its metabolism), kidneys, or reproductive organs. In addition, it also intensely damages immune system-related tissues such as the spleen, the bursa of Fabricius, or the thymus causing immunosuppression and increasing the susceptibility of the animals to infectious diseases, as well as making immunization programs less effective. The toxin also damages cellular processes on the transcriptional and translational levels and induces apoptosis through the activation of numerous cellular signaling cascades. Furthermore, according to recent studies, besides the direct effects on the abovementioned processes, T-2 toxin induces the production of reactive molecules and free radicals resulting in oxidative distress and concomitantly occurring cellular damage. In conclusion, this review article provides a complex and detailed overview of the metabolism, pathological consequences, mechanism of action as well as the immunomodulatory and oxidative stress-related effects of T-2 toxin. Understanding these effects in poultry is crucial for developing strategies to mitigate the impact of the T-2 toxin on avian health and food safety in the future.

Key words: mycotoxin, chicken, poultry, T-2 toxin, trichothecene

2024 Poultry Science 103:103471
https://doi.org/10.1016/j.psj.2024.103471

INTRODUCTION

In the contemporary world, contamination of feed and food by various mold species is increasingly becoming a severe issue. As secondary metabolites, these fungi can produce chemicals that, while not essential for their survival, may profoundly impact the physiological status of the organism producing them. The presence of these molds in feed is common, but the quantity of secondary metabolites they release is not directly proportional to the level of fungal contamination. This discrepancy arises because molds spend a significant proportion of their life-cycle producing primary metabolites—less harmful molecules, necessary for their development and reproduction—under favorable living conditions (Zhao et al., 2021; Liu et al., 2022). However, during certain phases or due to sudden changes in temperature, nutrient availability, or oxygen levels, fungi begin synthesizing secondary metabolites (Edite Bezerra da Rocha et al., 2014). Such metabolites include for example, plant growth factors, chemicals combating microorganisms, specific pigments, as well as mycotoxins (Mukherjee et al., 2017; Janevska and Tudzynski, 2018; Keswani et al., 2019). The latter are toxic compounds, that can influence the metabolic and health status of animal cells, particularly protein and nucleic acid metabolism as well as other biochemical processes within cellular components. Recent research suggests that there are hundreds of poisonous compounds produced by fungi, although the number of mycotoxins relevant to animal feeding is substantially lower (Omotayo et al., 2019; Awuchi et al., 2022).

Extensive research on mycotoxin-related damage and their exact mechanism of action commenced in

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the 1960s. This discovery followed an unexplained and unknown ailment (turkey X disease), which led to the death of more than 100,000 turkeys in England, and was attributed to high levels of aflatoxin contamination in peanut meal in the feed (Bradburn et al., 1994). In contrast to less frequent acute mycotoxicoses, there is now a much higher incidence of low-level, longer-term mycotoxin contamination, leading to the development of chronic and less specific symptoms in animals (Bryden, 2012). Immunosuppressive effects of mycotoxins have been observed wherein even concentrations below the acute intoxication dose significantly increased the animals' susceptibility to complex multifactorial diseases (Awad et al., 2013; Pierron et al., 2016). Mold presence is often an unrecognized problem causing substantial economic damage to crops, livestock and food production globally. Recent surveys indicate that in Europe, approximately 60 to 70% of all crop samples are contaminated with mycotoxins. In some parts of Asia and America, the percentage exceeds 80% (Luo et al., 2021; Nešić et al., 2023; Sun et al., 2023). Only a fraction of this contaminated amount, that poses a severe risk, is destroyed, while the remainder is used as food or feed. The significance of mycotoxins for food hygiene and safety is underscored by their accumulation in animals, entering the food chain, and potentially causing harm to humans through the ingestion of animal-derived food (Hussain et al., 2010; Bansal et al., 2023).

Mold contamination does not invariably imply mycotoxin presence, as their production can be influenced by various external factors. These factors may include temperature, humidity, pH conditions, specific climatic elements, the fungi species infecting the feed, the timing of infection or the extent of damage to the grain. It is crucial to note that, depending on environmental factors, many fungal species may produce entirely different types of mycotoxins (Rodríguez and Núñez, 2020). Studies on mycotoxins in feed also suggest that higher levels of mycotoxin contamination can be expected under more extreme weather conditions (Van der Fels-Klerx et al., 2016). Grains most commonly contaminated with T-2 and HT-2 toxin include wheat, maize, barley, and oats. Detailed information of contaminated unprocessed grains according to recent European Food Safety Authority **(EFSA)** results are presented in Table 1 (European Food Safety Authority et al., 2017). The incidence of T-2 and HT-2 toxin varies greatly between depending on the geographical regions. According to recent results, prevalence of the toxin is the highest in oat samples. Examples for highly affected areas are southern Finland and northern Italy where dangerous amounts of contaminations were reported (Luo et al., 2021). T-2 and HT-2 toxins were found in more than 60% of oat samples in Finland, with average concentrations of T-2 and HT-2 as high as 60.1μg/kg and 159 μg/kg, respectively (Nathanail et al., 2015). Among the most contaminated samples, the sum of T-2 and HT-2

Table 1. Summary statistics of the levels of individual T2, HT2, and sum of the T2 and HT2 in unprocessed grain samples according to EFSA results.

			Concentration range (μg/kg)			
Commodity	N	%LC	Mean	Median	P75	P95
T-2 toxin						
Grains as crops, unspecified	1	100	0.00–19.0	0–19.0	0–19.0	–
Wheat grain crop	85	98	0.32–19.8	0–25.0	0–25.0	0–25.0
Barley grain	63	98	0.70–80.8	0–100	0–100	0–100
Corn grain	17	76	8.92–20.3	0–6.40	0–24.6	–
Rye grain	17	100	0.00–91.2	0–100	0–100	–
Spelt grain	3	100	0.00–2.00	0–2.00	0–2.00	–
Buckwheat grain	4	100	0.00–87.5	0–100	0–100	–
Millet grain	2	100	0.00–75.0	0–75.0	0–100	–
Oats, grain	91	87	1.52–33.7	0–50.0	0–50.0	10.4–150
Rice	191	100	0.00–93.2	0–100	0–100	0–100
HT-2 toxin						
Grains as crops, unspecified	1	100	0.00–47.5	0–47.5	0–47.5	–
Wheat grain crop	68	99.5	0.13–20.2	0–25.0	0–25.0	0–25.0
Barley grain	61	98	0.89–95.6	0–100	0–100	0–100
Corn grain	7	100	0.00–8.29	0–7.60	0–10.0	–
Rye grain	17	100	0.00–100	0–100	0–100	–
Spelt grain	3	100	0.00–0.00	0.00–0.00	0.00–0.00	–
Buckwheat grain	4	100	0.00–100	0–100	0–100	–
Millet grain	2	100	0.00–100	0–100	0–100	–
Oats, grain	91	74	11.1–65.4	0–70.0	2.8–100	90–250
Rice	191	100	0.00–100	0–100	0–100	0–100
Sum of T-2 and HT-2 toxins						
Grains as crops, unspecified	1	100	0.00–19.0	0–19.0	0–19.0	–
Wheat grain crop	150	98	1.32–35.8	0–50.0	0–50.0	0–50.0
Barley grain	14	100	0.00–113	0–22.8	0–75.0	–
Corn grain	14	64	40.3–52.5	0–25.0	35.0–35.0	–
Spelt grain	3	100	0.00–0.00	0.00–0.00	0.00–0.00	–
Oats, grain	49	90	13.4–109	0–75.0	0–75.0	–

N: number of analytical results; LC: left-censored data; P75: 75th percentile; P95: 95th percentile; LB: lower bound; UB: upper bound (European Food Safety Authority et al., 2017).

toxin (1,860 μg/kg) exceeded the current threshold applied by the European Commission (200 μg/kg) by 8 times (Luo et al., 2021). Similarly, durum wheat in Italy had T-2 values as high as 149 μg/kg and 486 μg/kg (Juan et al., 2016). These results emphasize the great importance of implementing comprehensive meteorological surveillance together with strict quality control measures to effectively decrease the health hazards connected to trichothecene exposure (Nada et al., 2022).

There is also increasing attention recently regarding the so-called masked and hidden mycotoxins in addition to their intact form. According to the currently accepted classification, the different mycotoxin derivatives can be divided into 3 groups. These are mycotoxins in their free form, mycotoxins bound to the so-called matrix and toxins that have been chemically modified for some reason. These latter derivatives are often also highly toxic, but their importance is increased by the fact that they can be converted back to their original structure or to other molecules that are significantly more toxic than the initial one. This can happen either by detoxification processes in humans or animals or as the result of metabolism by the intestinal microbiota (Berthiller et al., 2013; Rychlik et al., 2014; Tan et al., 2022).

General Characteristics of Trichothecenes Focusing on T-2 Toxin

Field fungi of the *Fusarium* genus, encompassing both saprobiontic and plant pathogenic species, are widely distributed and can inflict significant economic damage on agriculture globally, particularly in temperate climatic zones (Rampersad, 2020). Trichothecenes, produced by this genus, are relatively small, amphipathic sesquiterpene molecules. These compounds can passively traverse the cell membrane, and can be absorbed through the gastrointestinal tract, skin surface, or via inhalation, from the lungs (Adhikari et al., 2017; Huang et al., 2023). Additionally, other fungal species apart from *Fusarium*, such as *Cephalosporium, Trichotecium, Stachybotrys, Myrothecium*, or *Trichoderma* species also produce trichothecene mycotoxins, albeit with lesser significance (Song et al., 2023). This group comprises over 200 fungal toxins. Trichothecenes can be classified into subgroups A, B, C, and D based on their structure (Liu et al., 2023a,b). They share the common 12,13-epoxy ring as a fundamental structure and contain various substitution groups depending on the side chains of the specific toxin. According to the aforementioned classification, the T-2 toxin is categorized as a non-macrocyclic type-A trichothecene (Ji et al., 2019). It is an extremely stable molecule that primarily contaminates feed during storage, exhibiting high resistance to heat exposure and UV radiation. Consequently, it is not degraded during common food and feed production processes or even after autoclaving; approximately 30 to 40 min at around 200°C are required to inactivate the toxin (Chen et al., 2019a).

Metabolism of T-2 Toxin in Poultry

The precise mechanism of the toxin's degradation in the body is an area of intensive research. Following absorption, liver serves as the primary organ for toxin metabolism as trichothecenes are usually metabolized by the hepatic microsomal xenobiotic transforming enzymes (Bócsai et al., 2016). It is also important to mention, that in different animal species sometimes different enzymes might play a central role in the detoxification process. Consequently, there are also distinct avian-specific characteristics compared to mammals (Wu et al., 2020; Li et al., 2022). As the result of the complex degradation process, a total of 19 different metabolites were detected in the feces and bile of chickens. Moreover, approximately 80% of orally administered T-2 toxin is metabolized and eliminated in the excreta within 48 h (Li et al., 2022). Half-life of the toxin in blood plasma is generally short, primarily influenced by the mode of application, the ingested amount, and species-specific characteristics. In contrast to other mycotoxins such as aflatoxin, the ingested toxin does not accumulate significantly in the tissues (Kuca et al., 2008; Li et al., 2011).

In the complex degradation process, HT-2 toxin and thereafter neosolaniol **(NEO)**, T-2 triol and tetraol, as well as a number of further intermediates can be synthesized from T-2 toxin (Yang et al., 2017a). Major metabolic pathways of T-2 toxin involve hydrolysis, hydroxylation, and sulfate conjugation. De-epoxidation also stands as a crucial step in the detoxification (Yang et al., 2013). Major degradation pathways and hypothesized metabolism of T-2 toxin in chickens are presented in Figure 1 (Yang et al., 2017a).

There is considerable variability in the toxicity among different metabolites. HT-2 toxin, the primary metabolite of T-2 toxin, is considered highly toxic, while others are mainly less harmful molecules (Meneely et al., 2023). T-2 toxin is rapidly metabolized into HT-2 toxin, indicating that HT-2 toxin contributes at least partially to its toxic effects (Edwards et al., 2009). They are commonly found together in contaminated grains (Yang et al., 2017b).

Research to date has shown that besides carboxylesterase 1 (**Ces1**), members of the cytochrome P450 (CYP) enzyme family such as CYP1A4, CYP1A5, CYP2H1, CYP2C18, and CYP3A37 enzymes, play a pivotal role in the degradation process in chickens (Osselaere et al., 2013; Shang et al., 2013; Yuan et al., 2013; Lin et al., 2015; Dai et al., 2020). Additionally, the xenobiotic-transforming capacity of the liver cells can be altered by the toxin. This alteration may occur due to the inhibition of the microsomal monooxygenase enzyme system, including cytochrome P450 (CYP) enzymes, affecting physiological drug metabolism and causing changes in the withdrawal period of animal products following medication (Osselaere et al., 2013). It was hypothesized, that activation of farnesoid X receptor **(FXR)** also promotes T-2 toxin xenobiotic metabolism by increasing CYP3A37 expression. Therefore, its

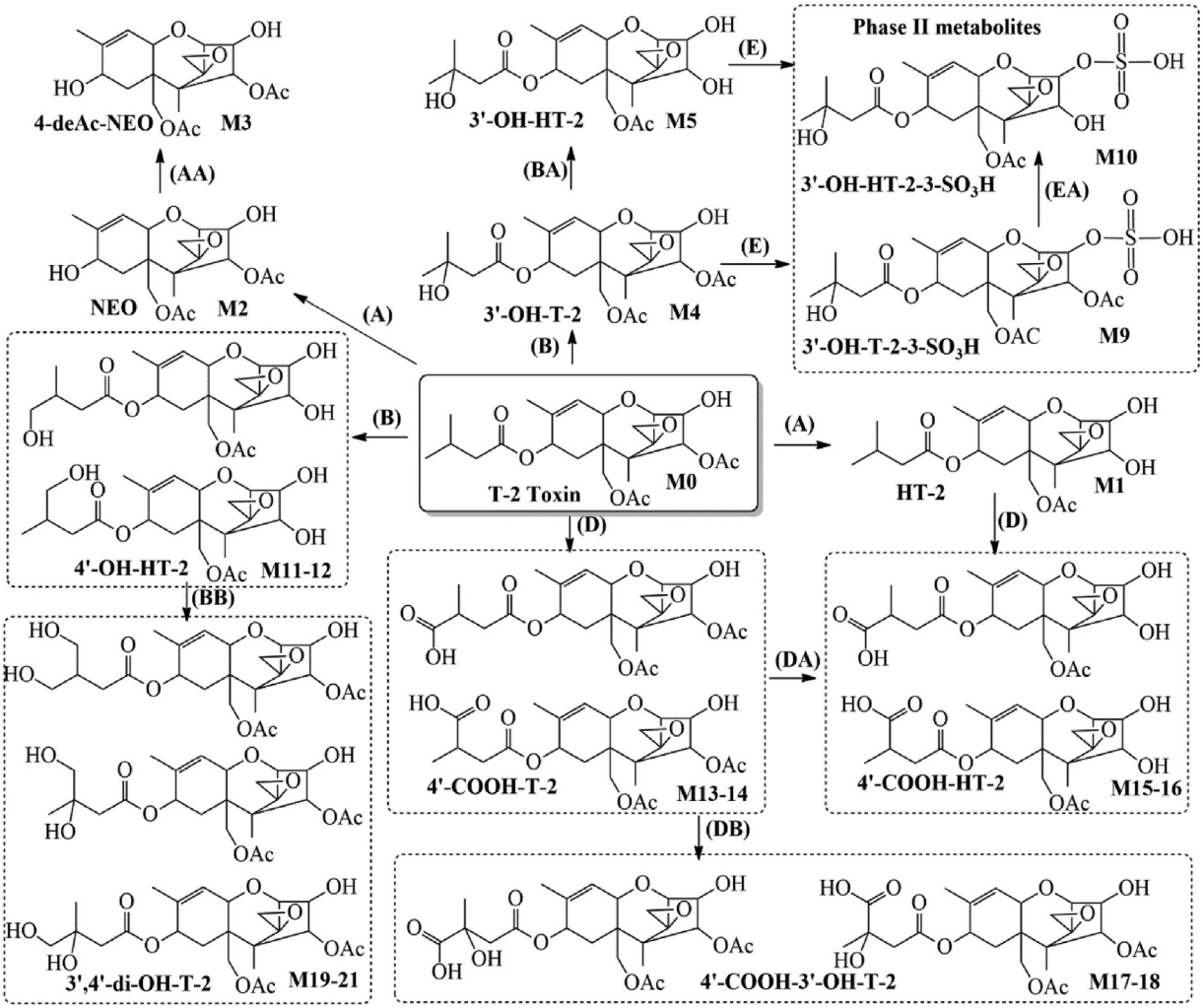

Figure 1. Degradation pathway and metabolism of T-2 toxin in chickens according to Yang et al. (2017). Major chemical reactions: hydrolysis (A); hydroxylation (B); carboxylation (D); and sulfation (E) (Yang et al., 2017a).

induction plays a cytoprotective role in liver injury induced by T-2 toxin through hydroxylation (Dai et al., 2020). Furthermore, the action of inducible CYPs may lead to protective or even toxic effects via the metabolism of their substrate or the production of reactive oxygen species (**ROS**), highlighting their complex role in the exertion of toxic effects related to xenobiotics (Nebert and Dalton, 2006). According to previous results, T-2 toxin also affects the expression and the activity of the aforementioned CYP enzymes by either upregulating or downregulating them in chicken hepatocytes. Expression was found to be mediated by aryl hydrocarbon receptors **(AhR)** in case of several CYP enzymes (Wang et al., 2011; Shang et al., 2013; Liu et al., 2019). AhR expression and its translocation into the nucleus is induced following T-2 toxin exposure which thereafter is attached to the proximal xenobiotic-responsive element **(XRE)** in the 5′-flanking region of CYP1A5. Since chicken CYP1A5 can be considered as the ortholog of human CYP1A2, effect of T-2 was found to be similar to other, already known inductor molecules like β-naphthoflavone **(BNF)**, 3-methylcholanthrene **(3MC)** and 2,3,7,8-tetrachlorodibenzo-p-dioxin **(TCDD)**. The mechanism affects the basal expression of CYP1A5 as well as leads to its induced transcriptional activation and results in the catalysis of T-2 toxin degradation into 3′-OH-T-2, which is an even more toxic metabolite (Liu et al., 2019). For this reason, activation of CYP1A5 is considered to increase the cytotoxic effects of T-2 toxin correlating with consequently reduced cell viability, increased DNA damage and oxidative stress, ultimately leading to apoptosis (Liu et al., 2019). There are also some species-specific characteristics regarding detoxification mechanisms comparing chicken with other poultry species; however, this field and the relationship with T-2 toxin metabolism is yet poorly understood (Grizzle et al., 2005).

General Pathologic Findings in Poultry Caused by T-2 Toxin

The most common symptoms of T-2 toxin consumption in poultry include reduced feed intake and growth rate, altered immune function, neurological and reproductive disorders, depigmentation of the skin of the feet, deterioration of feather quality and lesions on the mucous membranes of the digestive track (Sokolovic et al., 2008).

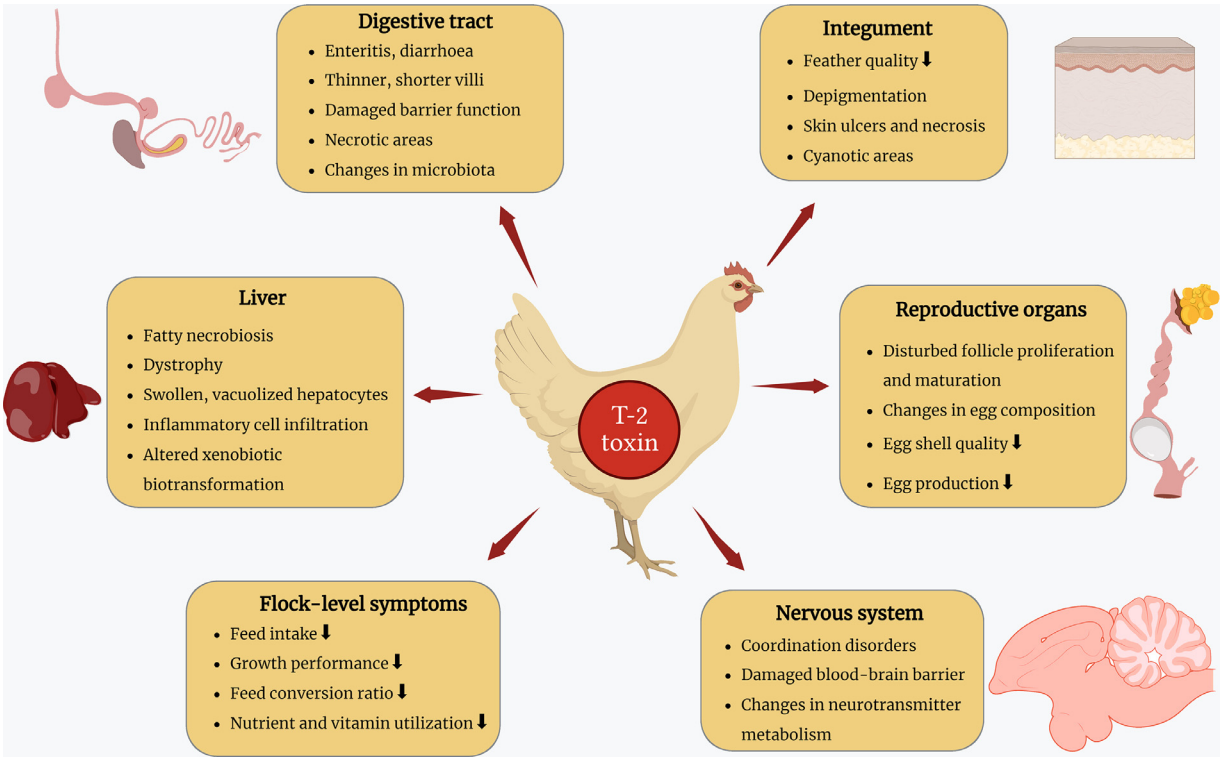

Figure 2. Detailed summary of the major pathological findings in poultry resulting from exposure to T-2 toxin. The figure was fully prepared by the authors.

According to currently available results, the median lethal dose 50 (**LD50**) for broiler chickens was described at 4.97 mg per kilogram of body weight (mg/[kg·bw]), while for laying hens, the LD50 was determined to be 6.27 mg/(kg·bw) (Liu et al., 2019; Gu et al., 2023). In bobwhite quails, on the other hand, LD50 was registered remarkably higher, as 14.7 mg/kg bw (Grizzle et al., 2004). The degree of damage caused by T-2 toxin depends on various parameters, such as the mode and frequency of intake, duration of exposure, dose of the toxin, the age, sex and health status of the animal, as well as the presence of other mycotoxins. The latter is particularly important because co-existing mycotoxins may have additive or even synergistic effects on the organism (Palumbo et al., 2020; Kulcsár et al., 2023). Similar synergism has been found in instances where aflatoxin, ochratoxin-A and cyclopiazonic acid co-occurred together with T-2 toxin in chickens (Huff et al., 1988; Pál et al., 2009; Manafi et al., 2012; Stefanović et al., 2023). In 2011, a comprehensive meta-analysis of over 100 previous publications described several sometimes contradictory results, including cases of antagonistic effects between different mycotoxins (Grenier and Oswald, 2011).

Previous research and observations indicate that the toxin significantly affects other fungal species, plants, insects and all domestic animal species including avians (Haque et al., 2020; Berenbaum et al., 2021). The symptoms of T-2 toxicosis closely resemble to those seen in mammals, differing mainly in frequency and severity. In poultry, initial signs of toxicosis may manifest as a decline in body weight gain, weight loss, skin and feather abnormalities, diarrhea, and coordination problems (Yang et al., 2017a; Salah et al., 2021). Figure 2 presents a detailed summary of major pathological findings in poultry.

Necrotizing dermatitis and other localized external lesions, such as depigmentation of the legs or skin cyanosis have been observed in birds, albeit less frequently and at significantly higher toxin doses compared to mammals (Sokolovic et al., 2008). Animals may also develop feathering disorders leading to a shaggy appearance. The lesions are primarily observed on the wings (Raju and Devegowda, 2000; Gu et al., 2023). Increased susceptibility to the dermatotoxic effects of T-2 toxin has also been observed in Muscovy ducks (Rafai et al., 2000).

The toxin was found to induce musculoskeletal abnormalities in poultry. Additionally, in White Roman geese, both the incidence and severity score of angel wing syndrome were reported to increase due to the effect of T-2 toxin-containing diet (Lin et al., 2018). On the other hand, no significant histological findings were observed in the heart muscle (Grizzle et al., 2004).

In the digestive tract, even small doses of the toxin, can irritate and damage the mucosa, leading to reduced absorption of nutrients and decreased feed efficiency. The toxin exposure causes necrotic areas not only around the beak, oral cavity, and pharyngeal mucosa but also in the gizzard or other regions of the gastrointestinal tract, along with potential effects on the liver (Chi and Mirocha, 1978; Kubena et al., 1995; Richard, 2007). Alterations in the histology of the gastrointestinal tract are frequently observed, including shorter and thinner villi, reduced migration rate and damaged barrier function (Sklan et al., 2003). In the glandular

stomach of chicks, T-2 induces mucosal edema, increases inflammatory cell counts together with epithelial desquamation and necrosis (Luo et al., 2019). Toxin contamination of the feed has significant negative impact on the utilization of vitamins, such as vitamin E in broiler chickens (Weber et al., 2007). Due to enterohepatic circulation, increased damage to the intestinal tract and liver is often observed (Yuan et al., 2013). In mild cases of exposure, mucosal irritation occurs, while in more severe cases, acute enteritis with watery diarrhea may develop (Wei et al., 2019). Changes in the microbiota were also reported following T-2 exposure. The toxin significantly decreased *Firmicutes*, and increased *Bacteroidetes* and *Proteobacteria* abundance on the phylum level. On genus level, there were increased abundances of *Brachybacterium, Blautia, Dorea, Ruminococcus, Bradyrhizobium,* and *Sphingomonas* following treatment, which indicating an impairment of intestinal health (Liu et al., 2023b).

Under in vivo conditions, the main target of the toxin is the liver, where a significant proportion of protein synthesis occurs. Exposure may result in fatty necrobiosis, hepatic dystrophy and other regressive disorders (Krishnamoorthy et al., 2007). Regarding histologic findings, hepatocytes exhibit swelling and tend to show balloon-like deformation. In most cases, the cytoplasm is vacuolated, and the nucleus appears to be located either in the center of the vacuole or squeezed on the side of the cell. Furthermore, exposure to the T-2 toxin in chickens and bobwhite quails resulted in stenosis of hepatic sinuses, deposits of red blood cells, focal inflammatory cell infiltration and intense interlobular bile duct epithelial cell proliferation (Grizzle et al., 2004; Yin et al., 2020a). It is also presumed that the toxin affects wound healing, angiogenesis and blood vessel remodeling, contributing to its widespread negative effects in poultry (Luo et al., 2019).

Furthermore, reduced egg production, changes in egg weight, shell structure and pigmentation can also be results of T-2 toxin uptake (Dazuk et al., 2020). Other signs include alterations in egg composition such as lower vitamin, protein and mineral content, reduced hatchability, slower follicle maturation, follicle proliferation and rupture and consequent peritonitis (Ványi et al., 1994; Yang et al., 2020; Dazuk et al., 2020). Interestingly, no egg production and quality-related negative effects were observed in bobwhite quails following prepuberal exposure. Conversely, the investigated parameters were significantly affected if the toxin was in presence already in the egg yolk (Grizzle et al., 2005).

In some cases, T-2 toxin may also have neurotoxic effects, which may occur partly due to the damage of the blood-brain barrier and to changes in serotonin levels in the central nervous system (Wang et al., 1998; Wan et al., 2016; Salah et al., 2021). It has also been described that dopamine and norepinephrine concentrations in the brain can be modified by the effects of the toxin (Smith, 1992). Clinical changes in neurotransmitter levels, such as food refusal, unsteady movements, and incoordination typically manifest at the herd level (Zhang et al., 2020).

Regarding general hematologic parameters, the toxin induces anemia as indicated by significant decrease in total erythrocyte counts, hemoglobin levels, and cell volume values in chickens. Additionally, exposed birds often exhibit leucopenia, lymphocytopenia, heterophilia, and thrombocytopenia (Yohannes et al., 2013). Hypoproteinemia along with hypoalbuminemia and hyperglobulinemia were also observed concurrently. Moreover, the toxin increased alkaline phosphatase (**ALP**) enzyme activity (Yohannes et al., 2013). Observations revealed that serum uric acid, cholesterol and hemoglobin concentrations as well as aspartate transaminase (**AST**) and alanine transaminase (**ALT**) activities and heterophil/lymphocyte ratio values were significantly higher in T-2 treated chickens compared to those of the control groups (Singh et al., 2020; Jiang et al., 2023).

Highly significant differences were also observed in total protein, albumin, globulin, cholesterol and glucose concentrations along with AST, ALT, ALP and gamma glutamyl transferase (**GGT**) activities in Japanese quails (Madheswaran et al., 2004). On the contrary, T-2 toxin treatment only resulted in alterations regarding ALP activity in White Roman geese and did not cause any detrimental metabolic disturbances in broiler ducks even following 7 wk of treatment (Kutasi et al., 2012). In ducklings, T-2 toxin induced hypocalcemia and hypomagnesemia, and decreased activities of creatine phosphokinase (**CPK**) and ALP, while in correlation with the aforementioned findings in chickens, it increased blood urea nitrogen concentration and AST activity (Tso et al., 2021).

In addition, a metabolomic study revealed changes in several plasma, liver, kidney and spleen metabolites after intravenous T-2 toxin injection. These changes are involved in energy, amino acid, and nucleotide metabolism as well as oxidative stress. Notably, tryptophan levels were increased during this experiment, potentially explaining the neurotoxic effect of the toxin (Wan et al., 2016).

Immunomodulatory Effects

Once trichothecenes penetrate the intestinal epithelium, their subsequent target is the immune system (Maresca, 2013). These agents can cause damage to various organs by upregulating pro-inflammatory factors and triggering immunotoxicity (Minervini et al., 2005). T-2 toxin has been found to exert an immunosuppressive effect on the animal organism in several cases. However, some studies have reported an apparently opposite immunostimulatory effect (Pestka et al., 2004). The observed differences depend on the route of administration, the quantity of toxin and the duration of exposure. According to certain studies, immunosuppression occurs in almost all cases when the organism is exposed to higher levels of T-2 toxin. Degeneration, atrophy of bone marrow, lymph nodes, as well as lymphocyte depletion and hemorrhages in the spleen were also observed in

connection with the immunomodulatory effects in chickens (Kamalavenkatesh et al., 2005; Venkatesh et al., 2005; Xue et al., 2010; Yohannes et al., 2012). Increased numbers of necrotic cells and spleen peripheral lymphocytes may also indicate the extensive necrosis of B and T cells, which can affect the spleen's ability to function properly as a key organ in the immune response of the body (Chen et al., 2019a). Similarly, marked lymphocyte necrosis as well as depletion throughout the thymus, bursa of Fabricius, spleen, and gut-associated lymphoid tissue (**GALT**) were observed in bobwhite quails due to exposure to 50% lethal dose (LD50) of T-2 toxin. On the other hand no negative histological finding was observed in bone marrow samples (Grizzle et al., 2004).

T-2 toxin in combination with ochratoxin-A (**OTA**) decreased the weight of the spleen, thymus and bursa of *Fabricius* (Wang et al., 2009). In the same study, flow cytometry results showed that this toxin combination treatment significantly decreased CD4+ cell count along with CD4+/CD3+ and CD4+/CD8+ ratios, while increased CD8+/CD3+ ratio (Wang et al., 2009). Similar observations were described following T-2 toxin treatment alone and also in combination with cyclopiazonic acid, where both CD4+ and CD8+ lymphocyte counts were decreased in the thymus and spleen of chickens (Kamalavenkatesh et al., 2005; Wang et al., 2009; Chen et al., 2019a). This finding has been further supported by a recent study where T-2 toxin induced the decrement in CD4+ and CD8+ lymphocyte counts, although it did not cause any consequences regarding these parameters applied in smaller concentrations (Chen et al., 2019b). CD4+ and CD8+ T cells are key components of the acquired immune system and are of pivotal importance for successful vaccination. In general, CD4+ T lymphocytes correspond to the helper T cell population, while CD8+ T lymphocytes are antigen-specific cytotoxic T lymphocytes responsible for the recognition and elimination of cells infected by intracellular pathogens. Under physiological circumstances, the ratio of CD4+/ CD8+ T cells is about 2:1 (Muller et al., 2015). Deviations from this ratio can significantly reduce immune function and the normal immune response (Obar and Lefrançois, 2010; McBride and Striker, 2017; Sekelova et al., 2017; Lee et al., 2018). Increased jejunal levels of $CD3^{+}$ and Goblet cells were also described along with alterations in circulating macrophage and suppressor macrophage, B-lymphocyte and T-lymphocyte numbers. Virgin cytotoxic T-lymphocyte and terminally activated cytotoxic T-lymphocyte counts have been also increased simultaneously (Koppenol et al., 2019). In broiler ducks, T-2 toxin depressed the blastogenic response of lymphocytes by nonspecific mitogens (Kutasi et al., 2012). There are contradictory results available about the effects of T-2 on the vaccination of poultry. According to some results, T-2 toxin lowered antibody titers post-vaccination against Newcastle disease (**ND**) and infectious bursal disease (**IBD**) (Girish and Devegowda, 2006; Xue et al., 2010), while on the contrary, another study showed that antibody formation against ND was not suppressed by the short-term sublethal toxin load (Weber et al., 2008).

T-2 toxin affected the defensive function of chicken HD-11 macrophages against *Aspergillus fumigatus* infection in vitro. The toxin impaired antifungal activity against conidial infection and promoted a pro-inflammatory response in infected macrophages, which might compensate for the caused macrophage-related functional damage (Li et al., 2013). In response to *A. fumigatus* infection, the expression of pro-inflammatory cytokines, including chemokine (C-X-C motif) ligand 1 and 2 (**CXCLi1, CXCLi2**; respectively), interleukin (**IL**)-1β, IL-6, IL-12β and IL-18 and chemokine ligand 2 (**CCLi2**) was upregulated and transforming growth factor (**TGF**)-β4, IL-2 and interferon-γ (**IFN-γ**) was downregulated in T-2 toxin-exposed HD-11 macrophages compared with the non-T-2 toxin-exposed macrophages (Li et al., 2013). Accordingly, experimental inoculation of chickens with *A. fumigatus in vivo* revealed that exposure to the toxin significantly exacerbated aspergillosis in chickens exposed to dietary T-2 toxin (Li et al., 2015). Regarding IL-6 and IL-8 concentrations, similar findings were described using chicken in vitro hepatocyte and hepatocyte—non-parenchymal cell (mostly macrophage Kupffer cells) models (Mackei et al., 2020).

A major cause of the harmful effects on immune cells and the reduction of CD4+/CD8+ T cell ratio is supposed to be the increased oxidative stress induced by the toxin (Chen et al., 2019b). Furthermore, type A trichothecenes, such as T-2 toxin, were found to be even more genotoxic to chicken spleen leukocytes than the type B trichothecene deoxynivalenol (**DON**) (Frankic et al., 2006). As a consequence, susceptibility to pathogens such as infectious bronchitis virus (**IBV**) or *Salmonella* Typhimurium is increased, resulting in further damage, possibly death, and significant production losses (Kubena et al., 2001; Yohannes et al., 2012, 2013). It is also highly relevant that the presence of T-2 toxin may also affect the efficacy of vaccination. In such cases, reduced antibody titers may be observed in diseases of high economic importance such as avian influenza or Marek's disease (Kamalavenkatesh et al., 2005; Kufuor-Mensah et al., 2015). Other studies also suggest that exposure to sublethal doses of T-2 toxin may influence the development of turkey herpesvirus viremia and Marek's disease-related lesions and mortality, but only in unvaccinated chickens (Kufuor-Mensah et al., 2015).

In contrast to the results of high concentration T-2 toxin exposure, other researchers have reported that prolonged effects of lower toxin concentrations may have an immunostimulatory effect. In this case, serum immunoglobulin (**Ig**)A and IgE concentrations increase significantly, which may be explained by a transient activation of gene sequences involved in the inflammatory response and in the function of certain immune processes (Pestka et al., 2004). It is important to note; however, that most of the research on this topic has been carried out so far mainly in laboratory experimental animals, so that the precise mechanisms by which

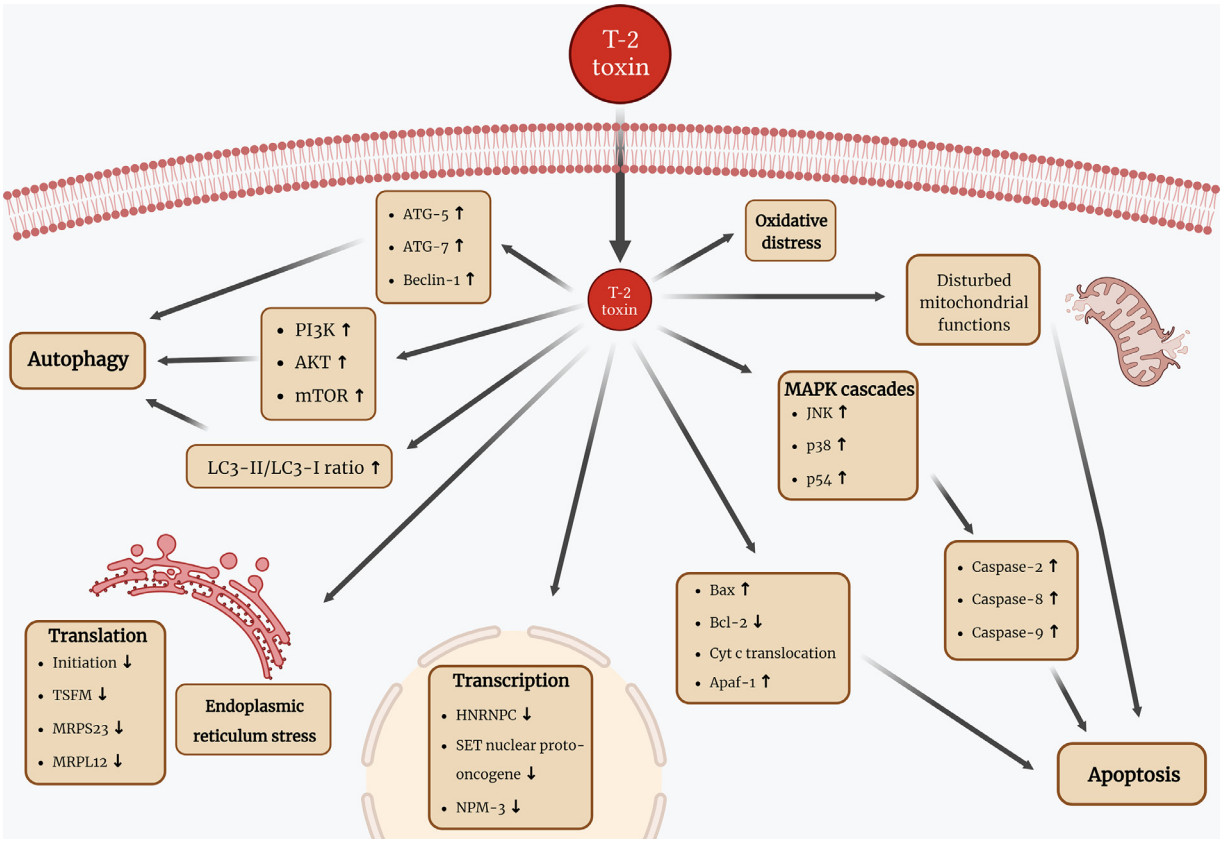

Figure 3. Schematic summary of T-2 toxin exposure-related cellular effects in poultry focusing on apoptosis, autophagy, as well as translation and transcription. Abbreviations used in the figure are all explained and can be found in the main text. The figure was fully prepared by the authors.

T-2 toxin exerts its immunomodulatory effects in poultry, either by impairing or by promoting the mechanisms of action, are not completely understood.

Detailed Mechanism of Action

In both poultry and mammalian species, wide variety of detrimental effects were described connected to T-2 toxin exposure. The genotoxic effects were described also in broiler chicken red blood cells and leukocytes (Rezar et al., 2007; Szabó et al., 2019), while general cytotoxicity was detected in rat and human, as well as in several farm animal species such as rabbit, chicken and pig (Wu et al., 2014). Furthermore, teratogenic effects and developmental toxicity were detected in studies using zebrafish embryos, but according to our knowledge, no further study is available in poultry (Yuan et al., 2014). The toxin disrupts DNA, RNA and protein synthesis, acting mainly at the ribosomal level. Trichothecenes inhibit protein synthesis by binding to the peptidyl transferase enzyme. In contrast to DON and trichodermin—2 other trichothecene mycotoxins that has an effect on the termination and chain formation of the protein synthesis—T-2 toxin inhibits the initiation step (Shifrin and Anderson, 1999; Li and Pestka, 2008). Proteomic analysis also revealed that other translational proteins are also affected by the toxin, such as the Ts translation elongation factor, mitochondrial (**TSFM**), the mitochondrial ribosomal protein S23 (**MRPS23**) and the mitochondrial ribosomal protein L12 (**MRPL12**). Furthermore, transcription proteins, including SET nuclear proto-oncogene, heterogeneous nuclear ribonucleoprotein C (**HNRNPC**) and nucleoplasmin-3 (**NPM3**) are also affected, resulting in the inhibition of RNA synthesis (Mu et al., 2013). It also impairs mitochondrial electron transport and affects the cell cycle, inducing apoptosis both in vivo and in vitro (Figure 3) (Fang et al., 2012; Liu et al., 2017; Dai et al., 2019).

Actively dividing cells such as those found in the digestive tract, spleen, liver, bone marrow or bursa of Fabricius are more sensitive to the presence of T-2 toxin (Konjević et al., 2004; Krishnamoorthy et al., 2007; Xue et al., 2010). Some mitogen-activated protein kinase (**MAPK**) cascades, such as the c-Jun N-terminal kinase (**JNK**), p38 and p54 protein kinase pathways, participate in the induction of cell death in different species. However, the exact background of this process remains incompletely understood, especially in case of poultry species (Kong et al., 2021; Liu et al., 2023b; Lee and Park, 2023). It is also noteworthy that the expression levels of certain genes are significantly affected by the toxin through these MAPK and JNK signaling pathways (El Golli et al., 2006; Wu et al., 2011; Fang et al., 2012). Further results in U937 cells of human origin revealed, that the caspase-2 pathway plays a key role in T-2 toxin-induced apoptosis, and that the process is not

solely regulated by the mitochondrial pathway but also by the caspase-8 and caspase-3 mediated cascades (Huang et al., 2007). Recent studies in poultry emphasize the caspase-related apoptotic effects of T-2 toxin, demonstrating that the exposure leads to decreased concentrations of pro-caspase-3 and pro-caspase-9, coupled with increased levels of caspase-3 and caspase-9 in a dose-dependent manner (Figure 3) (Yin et al., 2020b). The proteomic analysis mentioned previously also found T-2 toxin interference with several proteins involved in the cellular redox homeostasis, regulation of transcription and translation, lipid and carbohydrate metabolism, transport processes and protein degradation in chickens (Mu et al., 2013). Recent findings indicate that the toxin disrupts physiological nucleotide, phospholipid and energy metabolism in chicken intestinal and hepatic samples (Mackei et al., 2020; Liu et al., 2023b).

OXIDATIVE STRESS

The oxidative stress-inducing effects of T-2 toxin have also been described in a number of tissues and cell types. It is often hypothesized to be the major underlying cause of T-2 toxin induced cytotoxicity and apoptosis (Yang et al., 2016). T-2 toxin can increase the formation of ROS causing oxidative stress leading to DNA damage, increased lipid peroxidation and subsequently compromising membrane integrity (Sokolovic et al., 2007; Awuchi et al., 2022; Liu et al., 2023b). In chickens, akin to mammalian species, T-2 exposure significantly increases malondialdehyde (**MDA**) concentrations, a specific marker indicating the terminal phase of lipid peroxidation. It also elevates glutathione peroxidase (**GPx**), superoxide dismutase (**SOD**) and catalase (**CAT**) activities, 3 enzymes crucial for maintaining the oxidative homeostasis. Concurrently, T-2 toxin decreased the levels of reduced glutathione (**GSH**), α-tocopherol, carotenoids, and ascorbic acid. These findings were predominantly described in hepatocytes in both *in vivo* and *in vitro* studies (Leal et al., 1998; Dvorska et al., 2007; Mu et al., 2013; Balogh et al., 2015; Yang et al., 2016, 2019; Nakade et al., 2018; Yin et al., 2020b; Liu et al., 2023b; Jiang et al., 2023). Similar results were found in the intestines of chicks, where besides the abovementioned parameters, T-2 toxin also reduced antioxidant capacity and increased protein carbonyl content (Liu et al., 2023b). Other research groups also pointed out an age-dependent manner regarding the effects of the toxin on glutathione system (Pelyhe et al., 2018). These detrimental effects on the redox homeostasis were also described in quails, resulting in lower levels in antioxidants such as tocopherols, ascorbic acid, retinol and retinyl esters (Dvorska and Surai, 2001). On the other hand, further studies found that acute exposure did not result in elevated ROS production, though, metabolic activity was intensely decreased and interleukin production such as IL-6 and IL-8 were increased in hepatic cell culture models of chicken origin (Mackei et al., 2020).

In chicken splenocytes, the elevation of ROS, SOD, CAT and GPx along with a decrease in MDA concentration was observed similarly to the liver (Chen et al., 2019a). Studies involving chicken leukocytes described that T-2 toxin causes DNA fragmentation together with lipid peroxidation (Frankic et al., 2006; Rezar et al., 2007). It was also shown that in chicken chondrocytes, T-2 toxin increased ROS and MDA levels in a dose-dependent manner (He et al., 2012). In addition, T-2 toxin induced the formation of heterophil extracellular traps (**HETs**) composed of DNA, elastase and citrullinated H3 (citH3). The same experiment also demonstrated a potential link between their formation and toxin-stimulated ROS production (Liu et al., 2021).

Regarding species-specific characteristics, it is also important to highlight, that according to some results, the most sensitive species to oxidative stress were geese, followed by ducks and chickens (Mezes et al., 1999). Pheasants, compared to other poultry species appeared to exhibit higher tolerance to T-2 toxin, possibly correlated with the slightly different function of the glutathione redox system against oxidative damage (Fernye et al., 2018).

ROS accumulation can also lead to an increased mitochondrial mass indicating potential oxidative stress (Chen et al., 2019a; Yin et al., 2020b). The mitochondrial apoptotic pathway plays a pivotal role in the initiation of apoptosis due to toxic effects. Its activation requires the translocation of cytochrome c (**cyt c**) into the cytoplasm via the Bcl-2 associated X protein (**Bax**)/ B-cell lymphoma 2 (**Bcl-2**) pathway (Figure 3). The relative levels of the pro-apoptotic Bax and anti-apoptotic Bcl-2 proteins determine the activation of the caspase system, as they form heterodimers influencing the cell-death-inducing effects of Bax (Yang et al., 2017b; Yin et al., 2020b). In vivo observations indicated that T-2 toxin downregulated Bcl-2 while upregulated Bax levels, consequently increasing the Bax/Bcl-2 ratio. In addition, cyt c was also translocated into the cytoplasm, resulting in an apoptosome with the apoptotic protease activating factor 1 (**Apaf-1**) and the caspase-9 apoptotic proteases (Yin et al., 2020b). Similar results were observed in chicken splenocytes, where the concentration of the cytosolic cyt c increased, while the mitochondrial cyt c level decreased (Chen et al., 2019a).

Furthermore, it has also been described in chickens *in vivo*, that T-2 toxin can induce autophagy via the phosphoinositide 3-kinase (**PI3K**)/ Protein kinase B (**AKT**)/ Mechanistic target of rapamycin (**mTOR**) pathway (Figure 3). Autophagy plays a crucial role in maintaining the cell homeostasis and is associated with apoptosis by inducing caspase-dependent cell death and enhancing cell survival, thus providing protection against the adverse effects of the toxin. In correlation with this hypothesis, T-2 toxin was found to induce the expression levels of Autophagy related 5 and 7 (**ATG5, ATG7** respectively) and Beclin-1 genes. Further, ratio of LC3-II/LC3-I increased depending on the T-2 toxin dosage, while the concentration of p62 protein decreased significantly (Yin et al., 2020b). Endoplasmic reticulum

(**ER**) stress is also frequently associated with oxidative stress (Yao et al., 2015; Burban et al., 2018). Newly synthesized proteins undergo folding and modification in the ER facilitated by various chaperones and folding enzymes, including members of the heat shock protein 70 (**HSP70**) family as well as further heat shock proteins. Correspondingly, levels of HSP70 were also found to increase upon exposure to T-2 toxin in chicken hepatic cell culture models (Mackei et al., 2020).

ACKNOWLEDGMENTS

The work was supported by the Hungarian National Research, Development and Innovation Office (grant number OTKA FK 134940). Project no. RRF-2.3.1-21-2022-00001 has been implemented with the support provided by the Recovery and Resilience Facility (RRF), financed under the National Recovery Fund budget estimate, RRF-2.3.1−21 funding scheme.

DISCLOSURES

The authors of the following manuscript declare no conflict of interest.

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