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MYCOTOXINS AND IMMUNITY: THEORETICAL CONSIDERATION AND PRACTICAL APPLICATIONS

Review article

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ABSTRACT. - "Silent killers", "invisible thieves", "unavoidable contaminants", and "natural toxicants" - all these names have been given to the fungal secondary metabolites, mycotoxins. In general mycotoxins are considered to be unavoidable contaminants in foods and feeds and are a major problem all over the world. More than 300 mycotoxins have been shown to induce signs of toxicity in mammalian and avian species and this number is increasing. It has been estimated that 25% of the world's crop production is contaminated with mycotoxins. The most significant mycotoxins in naturally-contaminated foods and feeds are aflatoxins (AF), ochratoxins (OTA), zearalenone (ZEA), T-2 toxin, deoxynivalenol (DON) and fumonisins (FB). In many cases these mycotoxins can be found in combination in contaminated feed. Data presented in the review clearly show that immunosuppression is one of the most important consequences of mycotoxin contamination of the feed. It seems likely that mycotoxins impose oxidative stress, stimulate apoptosis and involved in gene expression regulation. These changes are responsible for immunosuppressive action of mycotoxins. In particular, damages to receptors on the surface of macrophages, neutrophils and lymphocytes could cause miscommunication between the cells leading to immunosuppression. It seems likely that adding to the feed such adsorbents as modified glucans could be an important solution for mycotoxin problems in animal industry.

Key words: mycotoxins, immunity, antioxidants, oxidative stress, adsorbents

INTRODUCTION

"Silent killers", "invisible thieves", "unavoidable contaminants", and "natural toxicants" - all these names have been given to the fungal secondary metabolites, mycotoxins. In general mycotoxins are considered to be unavoidable contaminants in foods and feeds and are a major problem all over the world (Wood, 1992). Interest in these naturally occurring chemical compounds is intense due to their detrimental, sometimes carcinogenic, effect on human

health, animal production and reproductive traits. More than 300 mycotoxins have been shown to induce signs of toxicity in mammalian and avian species (Fink-Gremmels, 1999; Leeson *et al.,* 1995) and this number is increasing. It has been estimated that 25% of the world's crop production is contaminated with mycotoxins (Fink-Gremmels, 1999). The most significant mycotoxins in naturally-contaminated foods and feeds are aflatoxins (AF), ochratoxins (OTA), zearalenone (ZEA), T-2 toxin, deoxynivalenol (DON) and fumonisins (FB) (Devegowda *et al.,* 1998). In many cases these mycotoxins can be found in combination in contaminated feed.

Mycotoxins appear at different stages of grain production. For example, *Fusarium* species are known to invade grains during the growth of the plant and they produce so-called "field mycotoxins", i.e. toxins present on developing grain. *Aspergillus* and *Penicillium* species generally develop after harvesting and so are referred to as "storage mycotoxins" (Table 1).

This simple classification tends to over-simplify the situation. However, two facts are clear: mycotoxin contamination depends on moisture con-

Table 1

COMMON MYCOTOXINS, THEIR MODE OF ACTION AND CONSEQUENCES IN POULTRY PRODUCTION
(Yaroshenko *et al.*, 2003; Devegowda and Murthy, 2005; Surai, 2005)

Mycotoxin	Producing fungi	Mode of action	Physiological consequences
Aflatoxin B1	*Aspergillus flavus* *A. parasiticus* *A. nomius*	Covalent binding of activated AFB1 to cellular proteins DNA and RNA	Protein adduct formation leads to cytotoxicity
		Stimulation of lipid peroxidation	DNA-adduct formation leads to mutation & cancer
		Apoptosis	Ilipid peroxidation, apoptosis and gene expression changes
Ochratoxin A	*Aspergillus Ochraceus* *Penicillium aurantiogriseum* *P. verrucosum* *P. viridicatum* *P. cyclopium*	Inhibition of protein synthesis	ATP depletion
		Decreased mitochondrial respiration	Decreased gluconeogenesis
		Stimulation of lipid peroxidation	Ilipid peroxidation, apoptosis and gene expression changes
		Apoptosis	
Fumonisin B1	*Fusarium monilforme* *F. proliferatum* *F. verticillioide*	Inhibition of sphinganine N-acyl-transferase	Disruption of sphingolipid metabolism
		Stimulation of lipid peroxidation	Ilipid peroxidation, apoptosis and gene expression changes
		Apoptosis	
T-2 toxin, DON	*Fusarium poae* *F. acuminatum* *F. sporotrichioides* *F. graminearum*	Inhibition of protein synthesis	Inhibition of cell proliferation
		Stimulation of lipid peroxidation	Inhibition of protein synthesis
		Apoptosis	Ilipid peroxidation, apoptosis and gene expression changes
Zearalenone	*Fusarium culmurum* *F. sporotrichioides* *F. graminearum*	Oestrogen-like properties	Competition for oestrogen receptors
			Imitation of oestrogen effects
			Ilipid peroxidation, apoptosis and gene expression changes

Tablica 1

NAJČEŠĆI MIKOTOKSINI, NJIHOV NAČIN DJELOVANJA I POSLJEDICE U PROIZVODNJI PERADI
(Yaroshenko i sur., 2003; Devegowda i Murthy, 2005; Surai, 2005)

Mikotoksin	Gljivice koje ga proizvode	Način djelovanja	Fiziološke posljedice
Aflatoksin B1	*Aspergillus flavus* *A. parasiticus* *A. nomius*	Kovalentno vezivanje aktiviranog AFB1 na stanične proteine DNA i RNA	Citotoksičnost Mutacije i karcinomi
		Poticanje peroksidacije lipida	Peroksidacija lipida, apoptoza i promjene ekspresije gena
		Apoptoza	
Okratoksin A	*Aspergillus Ochraceus* *Penicillium aurantiogriseum* *P. verrucosum* *P. viridicatum* *P. cyclopium*	Inhibicija sinteze proteina	Deplecija ATP
		Smanjena mitohondrijska respiracija	Smanjena glukoneogeneza
		Poticanje peroksidacije lipida	Peroksidacija lipida, apoptoza i promjene ekspresije gena
		Apoptoza	
Fumonizin B1	*Fusarium monilforme* *F. proliferatum* *F. verticillioide*	Inhibicija sfinganin N-acil-transferaze	Prekid sfingolipidnog metabolizma
		Poticanje peroksidacije lipida	Peroksidacija lipida, apoptoza i promjene ekspresije gena
		Apoptoza	
T-2 toksin, DON	*Fusarium poae* *F. acuminatum* *F. sporotrichioides* *F. graminearum*	Inhibicija sinteze proteina	Inhibicija proliferacije stanica
		Poticanje peroksidacije lipida	Inhibicija sinteze proteina
		Apoptoza	Peroksidacija lipida, apoptoza i promjene ekspresije gena
Zearalenon	*Fusarium culmurum* *F. sporotrichioides* *F. graminearum*	Svojstva slična estrogenu	Natjecanje za receptore estrogena
			Imitacija učinaka estrogena
			Peroksidacija lipida, apoptoza i promjene ekspresije gena

tent of grain, which should be less than 15%. Drought stress can increase opportunities for fungal, and in the case ot toxicogenic strains mycotoxin, contamination of grain. In practice, a range of mycotoxins can be found in contaminated feeds, the type and level depending on climatic and storage conditions. Temperate climates with high moisture conditions, e.g. Canada, USA and Europe, encourage the growth of *Fusarium* and *Penicillium* species, as well as DON, ZEA, OTA and T-2 toxin that are of concern for human health. On the other hand, warm and humid climatic conditions, e.g. Latin America, Asian countries and some parts of Australia, are ideal for the growth of *Aspergillus* and the production of carcinogenic aflatoxin. The winter season in these countries favours the development of ZEA, DON, T-2 toxin and OTA. Worldwide trade in feed raw materials has lead to wide distribution of mycotoxins not necessarily indigenous to the country where they are fed.

Among all mycotoxins, those from *Fusarium* species are considered to be key contaminants of poultry feed. Trichothecenes, zearalenone, fumonisins, moniliformin and fusaric acid are the major *Fusarium* mycotoxins occurring on a

worldwide basis in cereal grains, animal feeds and forages (D'Mello *et al.,* 1999). Furthermore, the trichothecene mycotoxins themselves comprise a vast group of over 100 fungal compounds with the same basic structure (Leeson *et al.,* 1995). Acute mycotoxicosis outbreaks are rare events in modern animal production, however, low mycotoxin doses (often below detection level) are responsible for reduced efficiency of production and increased susceptibility to infectious disease. Detrimental consequences of mycotoxin feed contamination vary substantially for various species and are summarised in Table 2.

Biochemical changes in mycotoxicosis vary greatly and lipid peroxidation and membrane disruption, apoptosis (programmed cell death) and compromised synthesis of DNA/protein are regarded as the most important consequences of mycotoxicosis (Surai, 2002). Three main mechanisms of mycotoxin toxicity include stimulation of lipid peroxidation, apoptosis and inhibition of DNA, RNA and protein synthesis (Sheme 1). In this reagard, immunotoxicity is considered to be the most common consequence of major mycotoxicosis (Bondy and Pestka, 2000).

Experimental data show that membrane-active properties of various mycotoxins can determine their toxicity as incorporation of mycotoxins into membrane structures causes detrimental changes such as alteration of fatty acid composition of the membrane structures and with peroxidati-

Table 2

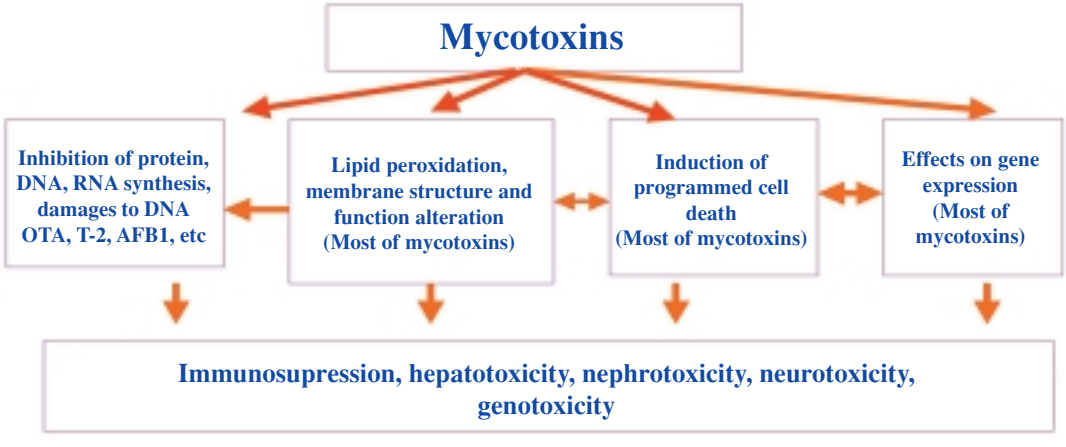
EFFECTS OF COMMON MYCOTOXINS ON POULTRY (Yaroshenko *et al.*, 2003; Devegowda and Murthy, 2005; Surai, 2005)

Mycotoxin	Effects on poultry
Aflatoxin B1	Decreased performance Reduced egg production and hatchability Decreased serum proteins Increased liver and kidney weight Liver and kidney lesions Decreased semen volume and testes weights Disruption of germinal epithelium Decreased hatchability Enlarged, fatty livers and enlarged spleens Immunosupression
Ochratoxin A	Reduced weight gain and feed consumption Impaired feed efficiency Reduced egg production Reduced egg quality Induced immunosuppression Kidney lesions
Fumonisin B1	Rickets like deformities in chickens with leg weakness Hepatocellular hyperplasia Increased kidney and proventriculus weights Liver lesions Immunotoxicity
T-2 toxin, DON	Reductions in feed consumption and weight gain Severe oral lesions Abnormal behaviour Altered feathering Decreased resistance to pathogens Decreased egg production Immunosuppresion
Zearalenone	Impaired shell quality Decreased egg production

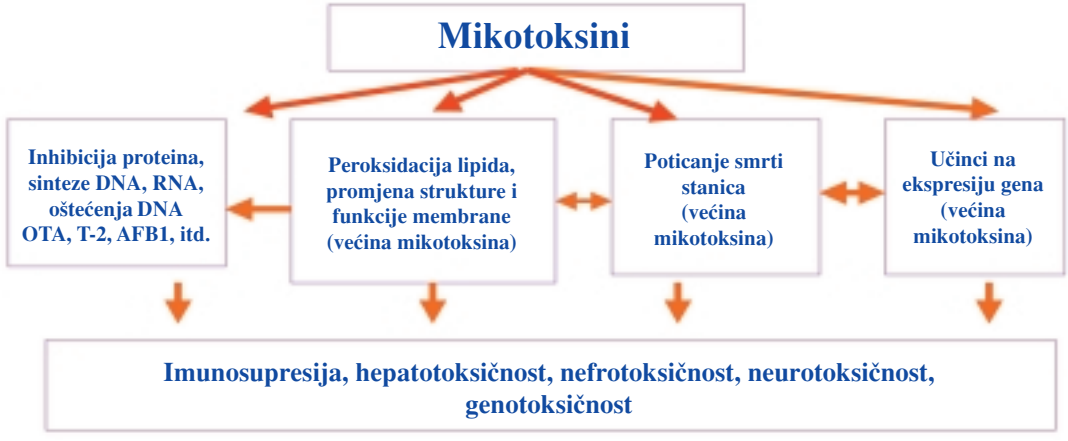
Tablica 2

UČINCI POJEDINIH MIKOTOKSINA NA PERAD
(Yaroshenko i sur., 2003; Devegowda i Murthy, 2005; Surai, 2005)

Mikotoksin	Učinci na perad
Aflatoksin B1	Smanjena proizvodnost Smanjena proizvodnja jaja i valivost Smanjenje serumskih proteina Povećana težina jetre i bubrega Lezije jetre i bubrega Smanjena količina sperme i težine testisa Prekid razvoja zametnog epitela Smanjena valivost Povećane, masne jetre i povećane slezene Imunosupresija
Ohratoksin A	Smanjeni prirast i potrošnja hrane Slabija iskoristivost hrane Smanjena proizvodnja jaja Slabija kvaliteta jaja Inducirana imunosupresija Lezije bubrega
Fumonizin B1	Deformacije slične rahitisu u pilića sa slabosti nogu Hepatocelularna hiperplazija Povećane težine bubrega i proventrikulusa Lezije jetre Imunotoksičnost
T-2 toksin, DON	Smanjenje potrošnje hrane i prirasta Teške lezije u sluznici usta Abnormalno ponašanje Promijenjeno opernjavanje Smanjena otpornost na mikrobne infekcije Smanjena proizvodnja jaja Imunosupresija
Zearalenon	Slabija kvaliteta ljuske jaja Smanjena proizvodnja jaja



Sheme 1
Major mechanisms of mycotoxin toxicity (Adapted from Surai, 2005)



Shema 1
Glavni mehanizmi toksičnosti mikotoksina (prema Surai, 2005)

on of long chain PUFAs inside membranes. This ultimately damages membrane receptors, causing alterations in second messenger systems and inactivation of membrane-binding enzymes responsible for regulation of key pathways. The resulting alterations in membrane permeability and fluidity cause changes in biochemical pathways and physiological functions including growth, development and reproduction. The protective effects imparted by the use of natural antioxidant supplementation confirm the importance of lipid peroxidation in all these processes.

MYCOTOXINS AND HUMAN HEALTH

The chance of getting traces of mycotoxins in our diet appears to be high. For example, the results of survey of 313 UK retail foods and 153 UK cereal samples showed that OTA was detected in 25% samples with 27 samples containing ochratoxin-A (OA) at concentrations above 4 ng/g (Atkins and Norman, 1998). OA was found in a number of samples of feed and food from various countries with its detection in human blood (Peraica and Domijan, 2001). In fact, OA can be detected at levels greater than 0.1 ppb in more than 90% of human and swine blood samples in central European countries (Petzinger and Weidenbach, 2002). Indeed, OA has been found in human blood samples in number of countries in cool temperate areas of the Northern Hemisphere (Creppy, 2002). When blood analyses were performed in Scandinavian blood donors the mean plasma levels of OA were 0.18 mg/L in Oslo and 0.21 mg/L in Visby (Thuvander *et al.,* 2001). In particular in Croatia OA consumption was estimated to be 0.4 ng/kg body weight (Peraica and Domijan, 2001). In the UK composite duplicate diet samples from 50 individuals and corresponding plasma and urine samples were obtained over 30 days. Average intake of OA varied in a range of 0.24-3.54 µg/kg body weight/day and OA was detected in all plasma samples and in 92% of urine samples (Gilbert *et al.,* 2001). In Germany the absolute OA intake was approximately 28.7-290.8 ng/day in 1996-1999 and the calculated total daily intake of OA varied between 0.9 ng/kg body weight in Germany and 4.6 ng/kg body weight in Italy (Petzinger and Weidenbach, 2002). It is necessary to mention that OA altered both barrier and absorption function of the intestinal epithelium causing intestinal injuries, including inflammation and diarrhoea (Maresca *et al.,* 2001). Ochratoxin in combination with aflatoxin showed a synergistic toxicity (Campbell *et al.,* 1983). For ochratoxin the elimination half-life in human was calculated to be 840 hours (Creppy, 2002).
Consumption of mouldy sorghum or maize containing high levels of fumonisin B1 has been linked to an outbreak a human disease in India involving gastrointestinal symptoms (Creppy, 2002). Estimated intake of fumonisin in Europe, Far East, Latin America, Middle East and Africa comprises 0.2, 0.7, 1.0, 1.1 and 2.4 µg/kg body

weight respectively (Creppy, 2002). Many outbreaks of acute human disease involving gastrointestinal problems and diarrhoea in Asia have been attributed to consumption of *Fusarium*-contaminated grain (Creppy, 2002). DON has been detected in various foods including bread, breakfast cereals, beer, baby and infant foods, in both Europe and Northern America (Creppy, 2002). When 88 commercially available samples of wheat-based breakfast cereals were randomly collected from different supermarkets in Lisbon, 72.8% samples contained levels of DON between 103 and 6040 µg/kg with mean level of 754 µg/kg (Martins and Martins, 2001).

It is interesting that inhibition of protein synthesis and induction of apoptosis is the main mechanisms of DON toxicity in intestinal cells (Maresca *et al.,* 2002). Patulin, a common contaminant of apples and apple products, affects the barrier function of the gut wall by inducing epithelial cell degeneration, inflammation, ulceration and hemorrhages (Mahfoud *et al*., 2002). The intake of aflatoxin M1 from milk was calculated to vary from 0.1 ng/person/day in Africa up to 12 ng/person/day in Far Eastern countries (Creppy, 2002). In a study where milk and dairy products sourced from Egyptian markets and breast milk from lactating mothers were analysed, 20% of the cow's milk samples were positive for AFM1 (mean 6.3 µg/kg), 20% hard cheese samples contained AFM1 and one sample in ten contained AFB1 and AFG1. For breast milk, 20% were positive for AFM1 (mean 2.75 µg/kg), while 30% of samples were positive for OA (Ei-Sayed *et al.,* 2000). In Turkey, the incidence of AFM1 in cheese was 89.5% with the highest concentration at 810 ng/kg (Huseyin and Sonal, 2001). From fifty four samples of fresh full cream and skimmed milk, powdered milk, yoghurt and infant formula collected in Kuwait, 28% were contaminated with AFM1 with 6% being above the maximum permissible limit of 0.2 µg/L (Srivastava *et al.,* 2001).

MYCOTOXINS AND THE IMMUNE SYSTEM

All animals protect themselves from invasion of micro-organisms, parasites, fungi, viruses and any foreign molecules. This protective capacity is based on the establishment of an effective immune system, which is considered to be an important determinant of animal health and well being. The remarkable ability of the immune system to distinguish between self and non-self is a great achievement of animal evolution. Commercial animal production is based on balanced feed, providing requirements in major nutrients, and optimised environmental conditions. However, it is very difficult to avoid nutritional or environmental stresses, which are responsible for immunosuppression and increased susceptibility to disease, which consequently decrease productive and reproductive performance. Mycotoxins are among major immuno-suppressive agents in poultry/animal diet.

The effect and role of the immune system in modern animal production is difficult to overestimate. Banning feed grade antibiotics in Europe has made immuno-competence a major factor determining the efficiency of meat, milk and eggs production. Molecular immunology is developing very quickly and mechanisms of chicken immuno-competence recently have received substantial attention (McCorkle, 1998; Saif and Swayne, 1998) Nutritional modulation of resistance to infectious diseases in poultry (Klasing, 1998) is at the front line of future research. It is necessary to underline that cellular integrity is very important for receiving, and responding to the messages needed to co-ordinate an immune response (Latshaw, 1991). Therefore, the antioxidant/pro-oxidant balance of the host is a critical consideration in the optimal functioning of the immune system.

The clinical symptoms of mycotoxin ingestion have been well characterized in domestic animals, poultry and laboratory animals and range from mortality to mild performance reduction. Consumption of some mycotoxins, at levels that do not cause overt clinical signs, suppresses immune functions and may decrease resistance to infectious disease (Corrier, 1991). The effects of several mycotoxins on the immune responses have been mainly confined to laboratory animal studies. A smaller pool of data exists where farm animals and cells derived from livestock species have been employed to evaluate the immuno-toxicity of mycotoxins (Sharma, 1993; Bondy and Pestka, 2000).

The immuno-suppressive potency of various mycotoxins differs substantially. Effects of DON, 3-acetyldeoxynivalenol, fusarenon-X, T-2 toxin, ZEA, alpha-zearalenol, beta-zearalenol and nivalenol on T and B cells in a proliferation assay, antibody-dependent cellular cytotoxicity NK cell activity on human peripheral blood mononuclear cells have been studied (Berek *et al*., 2001). Mycotoxin concentrations used were comparable with those found in normal human peripheral blood system (0.2-1800 ng/ml). Among the mycotoxins tested, T-2 toxin, fusarenon X, nivalenol and DON showed the highest immuno-suppressing effect *in vitro*, and mycotoxins-induced immuno-suppression was related to depressed T or B lymphocyte activity. Furthermore, they also inhibited NK cell activity (Berek *et al*., 2001).
Immunosuppression caused by AFB1 has been demonstrated in chickens, turkeys, pigs and lambs, mice and rats and in various *in vitro* systems. Aflatoxin is an immuno-modulating agent that acts primarily on cell-mediated immunity and phagocytic cell function, and mainly decreases lymphocyte functions and macrophages that assist lymphocyte functions (Surai, 2005). AFB1 can be transferred from chicken to the egg and into the developing embryo. Therefore, the progeny from hens consuming an AFB1-contaminated diet may be increasingly susceptible to disease owing to suppression of humoral and cellular immunity. Published data shows that anti-*Brucella abortus* antibody production can be compromised and macrophage ROS production decreased in AFB1 progeny (Qureshi *et al*., 1998). Long-term immune depression of macrophage-mediated functions can occur following embryonic exposure to AFB1 (Neldon-Ortiz and Qureshi, 1992). Mixtures of aflatoxin with other mycotoxins can result in greatly augmented biological responses in terms of rate of gain, mortality, and immune reactivity (Pier, 1992).
The immuno-modulatory effects of ochratoxins have also been determined (Surai, 2005), and OTA has been shown to affect humoral immunity (antibody synthesis) in chickens, rats and mice. The number and phagocytic activity of macrophages are also decreased in growing gilts receiving OTA for 35 days (Harvey *et al*., 1992), and interleukin (IL) production compromised. It has been demonstrated that exposure of purified human lymphocytes to OTA will reduce the cells' ability to respond to activating stimuli *in vitro* (Lea *et al*., 1989). Thus, both IL-2 production and IL-2 receptor expression of activated T lymphocytes may be impaired. The results strongly suggest that the toxin caused its immunosuppression through interference with essential processes in cell metabolism (Lea *et al*., 1989). In particular, OTA appears to suppress NK cell activity by inhibiting production of basal interferon. (Luster *et al*., 1987).
Fumonisin toxicity has been characterized relatively recently in comparison to aflatoxin and ochratoxin and fumonisin-induced immuno-toxicity is an area of active research (Bondy and Pestka, 2000). In fact, FB1 has diverse effects on the immune system, causing both stimulation and suppression of the response to foreign antigens, and apparently inducing an antigenic response to FB1. For example, in chickens FB1 causes a decrease in total immuno-globulins, in IgG and macrophage phagocytic activity also decreased (Qureshi *et al*., 1995). However, in turkey poults a combination of FB1 and AFB1 was responsible for the increase of primary immune response to SRBC (Weibking *et al*., 1994). In weaned pigs, FB1 (up to 100 mg/animal/day) did not affect immunity (Tornyos *et al*., 2003). The effects of FB1 on immuno-competence of laboratory animals also varies substantially. Immuno-modulatory properties of FB1 appear to depend on its effect on lipid metabolism, antioxidant-prooxidant balance and interactions with other factors. For example, FB1 decreased the receptor CD3 expression on the surface of thymus cells *in vitro* and *in vivo*, which is consistent with the sharp decrease of the ceramide content in this organ (Martynova *et al*., 1995).
In a similar manner to FB1, the trichothecenes can both suppress and stimulate immune function. Most of research on T-2 toxin effects on immunity was performed with laboratory animals and only a few publications address the immuno-modulating properties of T-2 toxin in farm animals. The molecular basis of immune function modulation by mycotoxins remains unknown (Bondy and Pestka, 2000). It seems likely that trichothecenes are potent immunosuppressive agents that directly affect immune cells and modify immune responses because of tissue dama-

ge elsewhere. For example, sheep and calves treated with T-2 toxin show decreased functioning of peripheral lymphocytes (Sharma, 1993). In fact, exposure of experimental animals and humans to T-2 toxin has been shown to cause a variety of immunosuppressive effects, including changes in humoral-mediated immunity. It is well established that T-2 toxin is cytotoxic *in vitro* to lymphocytic cells, however, limited information is presently available regarding the contribution of such a mechanism to immunosuppression *in vivo*, or to potential immune cell targets. It seems likely, that lymphocyte progenitors, in contrast to thymocytes, are sensitive targets of T-2 toxin exposure, responsible for thymic atrophy (Holladay *et al*., 1993). Poor resistance to pathogenic micro-organisms occurs after exposure to the trichothecenes T-2 toxin and DON. This may predispose food animals to infectious disease and could result in decreased productivity as well as increased animal-to-human transmission of pathogens such as *Salmonella* and *Listeria*. It seems likely that there are species-specific features in sensitivity to trichothecenes. For example, recently it has been shown that up to 1 ppm T-2 toxin in turkey poult diets did not affect antibody (AB) production to a variety of antigens (Sklan *et al*., 2003).

Immuno-modulating properties of DON have been studied mainly with rodents. The evidence is quickly accumulating showing that DON can be immunosuppressive or immuno-stimulatory, depending upon the dose and duration of exposure. While immunosuppression is probably related to the inhibition of translation, immuno-stimulation can be a result of interference with various cellular regulatory mechanisms (Rotter *et al.,* 1996). Therefore, DON can up-regulate or down-regulate critical functions of macrophages. Males appeared more susceptible than female mice to DON-induced IgA dysregulation and IgA nephropathy in terms of latency, threshold dose, and severity (Greene *et al*., 1994).

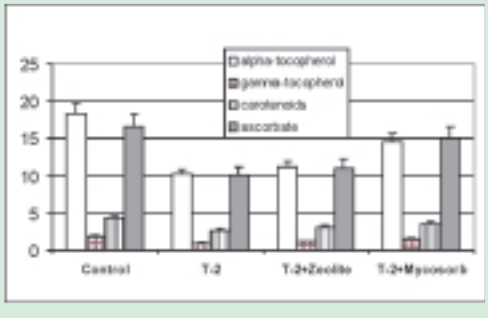
Mycotoxin-induced immunosuppression is related to both natural and adaptive immunity (Table 3):

- Depressed T or B lymphocyte activity;
- Depressed NK cell activity;
- Suppressed immuno-globulin and antibody production;
- Reduced complement or interferon activity;
- Impaired macrophage functions.

The sensitivity of the immune system to mycotoxin-induced immunosuppression arises from the vulnerability of continually proliferating and differentiating cells that participate in immuno-mediated activities and regulate the complex communication network between cellular and humoral components (Corrier, 1991). In fact, high levels of polyunsaturated fatty acids in the immune cells and presence of sensitive receptors on their surface make them an important, and susceptible, target for free radical attack (Surai, 2002). Although the molecular basis for many of the specific immunosuppressive effects of mycotoxins is presently unclear, inhibition of DNA, RNA and protein synthesis appears to

Graph 1

EFFECT OF T-2 TOXIN ON ANTIOXIDANT CONCENTRATIONS IN QUAIL LIVER, µg/g TISSUE (Adapted from Dvorska and Surai, 2001)



Grafikon 1

UČINAK T-2 TOKSINA NA KONCENTRACIJE ANTIOKSIDANTA U JETRI PREPELICA (µg/g tkiva) (Dvorska i Surai, 2001)

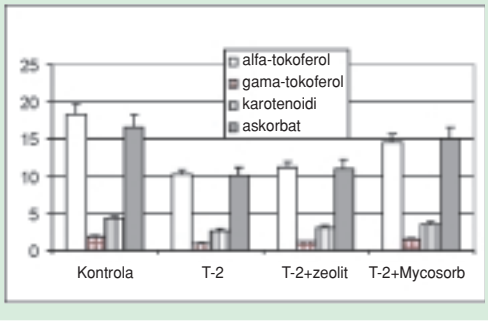


Table 3

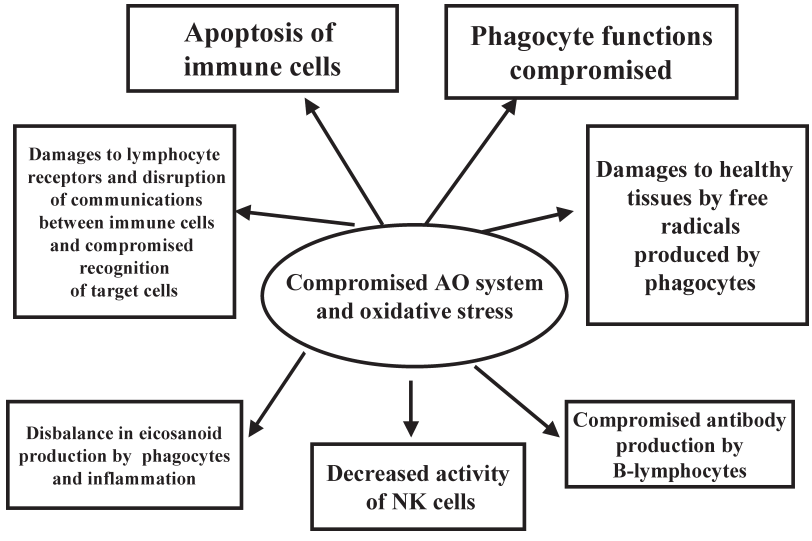
SUMMARY OF EFFECTS OF SELECTED MYCOTOXINS ON THE IMMUNE SYSTEM
(adapted from Yaroshenko *et al.,* 2003; Surai and Dvorska, 2005)

Mycotoxin	Effect on immune system
Aflatoxin B1	Immune system is compromised; detrimental effects on cell-mediated immunity and phagocytic cell functions including decreased peripheral T-lymphocyte counts Decreased antibody response to injected sheep red blood cells and decreased weight of the Bursa of Fabricius and thymus Aflatoxin carry-over via the egg to the embryo compromises immune system of the progeny, including cell-mediated, humoral immunity and phagocytic functions. Progeny are more susceptible to various pathogens
Ochratoxin A	Inhibition of humoral, cellular and innate immune responses Cellular depletion of lymphoid organs Depressed delayed hypersensitivity responses Depressed blood monocyte phagocytic activity Increased susceptibility to infectious agents
Fumonisins	Depressed antibody responses to various mitogens and decreased serum globulins Diffuse thymic cortical thinning, mild bursal follicular atrophy and mild splenic lymphocyte depletion Decreased peritoneal macrophage numbers and compromised phagocytic functional activity Reduced white blood cell counts
T-2 toxin	Increased susceptibility to a range of pathogens Inhibition of lymphocyte proliferation and NK cell activity Alteration in interleukin metabolism
DON	Inhibition of lymphocyte proliferation Alteration in interleukin metabolism Inhibition of NK cell activity

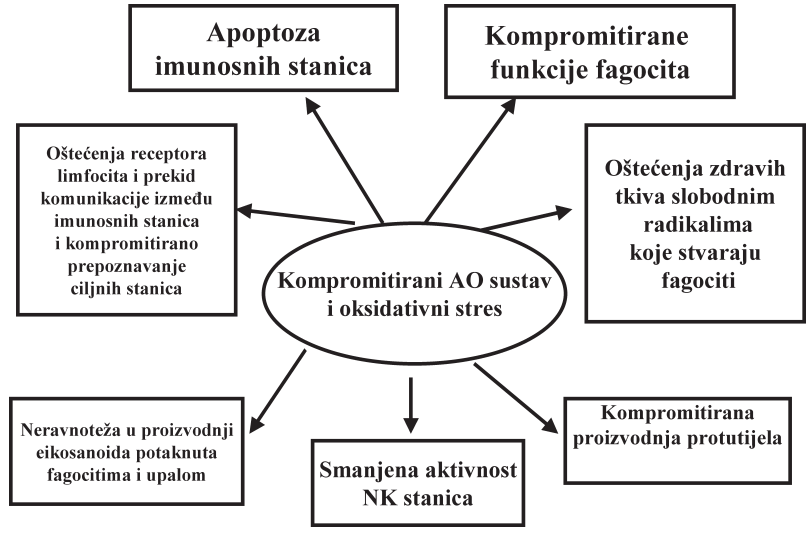
Tablica 3

SAŽETI PREGLED UČINAKA POJEDINIH MIKOTOKSINA NA IMUNOSNI SUSTAV
(prema Yaroshenko i sur., 2003; Surai i Dvorska, 2005)

Mikotoksin	Učinak na imunosni sustav
Aflatoksin B1	Imunosni sustav je kompromitiran; štetni učinci na staničnu imunost i funkcije fagocitnih stanica uključivši smanjeni broj perifernih T-limfocita Smanjeni odgovor protutijela na ubrizgane eritrocite ovce i manja težina Fabricijeve burze i timusa Prijenos aflatoksina preko jaja na embrio kompromitira imunosni sustav podmlatka, uključivši stanično-posredovani, humoralne i funkcije fagocita. Veća primljivost podmlatka na infekcije, imunost
Ohratoksin A	Inhibicija humoralnih, celularnih i urođenih imunosnih odgovora Celularna deplecija limfnih organa Oslabljeni mehanizmi kasne preosjetljivosti Oslabljena fagocitna aktivnost monocita u krvi Povećana primljivost na infekcije
Fumonizini	Oslabljeni odgovori tijela na razne mitogene i niža razina globulina u krvnom serumu Difuzno kortikalno stanjivanje timusa, blaga folikularna atrofija burze i blaga deplecija limfocita slezene Smanjeni broj peritonejskih makrofaga i kompromitirana funkcionalna aktivnost fagocita Smanjeni broj eritrocita
T-2 toksin	Povećana prijemljivost na infekcije Kočenje proliferacije limfocita i aktivnosti NK stanica Promjena u metabolizmu interleukina
DON	Kočenje proliferacije limfocita Promjena u metabolizmu interleukina Inhibicija aktivnosti NK stanica



Sheme 2
Oxidative stress and the immune system (Adapted from Surai, 2002)



Shema 2
Oksidativni stres i imunosni sustav (Surai, 2002)

be directly or indirectly responsible for the immunosuppressive action of many mycotoxins (Corrier, 1991). Detrimental effects on antioxidant defences, lipid peroxidation, apoptosis and damage to immune cell receptors seem to be involved in immuno-modulation properties of mycotoxins. Consequences of oxidative stress for the immunocompetence are shown in Sheme 2.

PRACTICAL STRATEGIES FOR MYCOTOXICOSIS PREVENTION

The wide range of mycotoxins that can contaminate poultry feed and their different chemical compositions make protection against mycotoxin-related toxicity a difficult task. There are several problems that complicate mycotoxin prevention issues:

- In many cases, the low levels of mycotoxins remain undetected in feed ingredients and their effects may also go unseen. For example, a decrease in hatchability by 0.5% would be difficult to notice. Detrimental effects on the immune system would be even more difficult to assess. However, the immunosuppressive activities of the mycotoxins become of particular concern in EU countries after a ban on feed-grade antibiotics.
- Very often, a combination of various mycotoxins is present in the feed because the various fungal species can produce several toxins. A combination of several mycotoxins in low doses can have a bigger detrimental effect than a single mycotoxin at a higher dose.
- Mycotoxins can contaminate practically all feed ingredients. For example, *Fusarium* species have been found in wheat, maize, barley, oats and rye. On the other hand, aflatoxins can also contaminate oilseeds and other feed ingredients.
- There are no safe doses of mycotoxins. A dose that does not affect animal at short exposure could be toxic at longer consumption. Doses that may be safe under laboratory conditions can have detrimental effects on growth and reproduction under conditions of commercial poultry production.
- International trade of feed ingredients, e.g. maize and soybeans, especially long shipments from Latin America to European and Asian countries, is another important risk factor.
- Most of mycotoxins are stable compounds that do not degrade during storage, milling or high-temperature feed manufacturing processes.

CONTROLLING MYCOTOXINS AND THEIR EFFECTS

There are various approaches to control or combat mycotoxin problems. The simplest strategy is based on the prevention of the formation of mycotoxins in feeds by special management programmes including storage at low moisture levels and prevention of grain damage during processing. However, modern agronomic technology - such as using resistant genotypes, pesticides etc. - is unable to prevent pre-harvest infection of susceptible crops by field fungi and so this strategy can only be partially effective. In countries with warm and humid conditions, it could also be quite costly and may cause environmental hazard.

Other strategies, which rely on microbial or thermal inactivation of toxins, physical separation of contaminated feedstuffs, irradiation, ammoniation and ozone degradation, have not been developed to the industrial level because they are either time-consuming or comparatively expensive.

In recent years, nutritional adjustments have been used to improve the animal's self-defence against mycotoxins or to decrease the detrimental consequences of mycotoxin consumption. Since lipid peroxidation plays an important role in mycotoxin toxicity, a protective effect of antioxidants would be expected and indeed, in several experiments with various animal species, protective effects of antioxidants against toxic effects of mycotoxins have been observed.

PROTECTIVE EFFECT OF ANTIOXIDANTS AGAINST MYCOTOXICOSES

As lipid peroxidation plays an important role in mycotoxin toxicity, a protective effect of antioxidants is expected (Galvano *et al*., 2001). Indeed, in several experiments with various animal species, protective effects of antioxidants against toxic effects of mycotoxins were observed. For example, vitamin E ameliorates the pro-oxidative effects of OTA in the chicken and mice. Protective effects of vitamin E were also obvious in aflatoxicosis, DON or T-2 toxic sis in rats; T-2 toxic sis in mice *in vivo* or *in vitro* systems using cell lines (Surai, 2005). Vitamin E was also effective in protection against fumonisin B1 or ZEA and decreased cytotoxic effect of T-2 toxin in cell culture.

Other antioxidant compounds also have protective effects against various mycotoxins. Burguera *et al*. (1983) indicated that selenium (Se) has a protective effect against AFB1 toxicity in turkey poults. The results provided clear evidence of Se-induced enhancement of aflatoxin detoxification (Gregory and Edds, 1984), although the protective action of Se was not mediated by an increase in glutathione availability for aflatoxin

conjugation or by effects on the activities of these enzymes as measured *in vitro*. Dietary supplements such as Se are considered effective in the reduction of aflatoxicosis in poultry (Dalvi, 1986) and the protective antioxidant effect of organic Se in combination with vitamin E has recently been shown in chicks exposed to cold stress and aflatoxin-contaminated feed (Stanley, 1998).

Similar protective effects of Se against aflatoxicosis have been shown with mammalian species. Pigs fed a diet containing 2.5 mg Se/kg of feed were protected from toxic effects of AFB1 (Davila *et al*., 1983). Effects of a single intramuscular injection of Se-vitamin E (5 mg of Se + 68 IU of α-tocopherol/60 kg of body weight) as a pretreatment 14 days before an oral dose of AFB1 (1.0 mg/kg) were studied in 24 dairy calves. Although aflatoxin exposure caused a significant decrease in body weight and feed intake, Se was demonstrated to interact significantly with AFB1 to improve feed intake (Brucato *et al*., 1986).

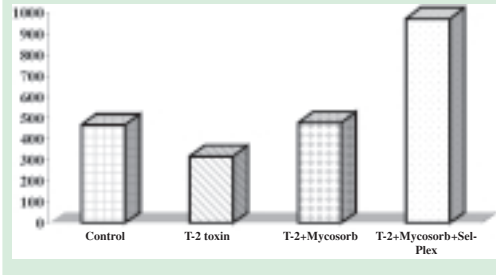
It has been demonstrated that Se can inhibit the formation of hyperplastic foci and enzyme-altered foci in DNA as well as hepato-carcinogenesis induced by AFB1, but Se can neither prevent the enlargement nor accelerate the regression of the foci already developed after administration of carcinogens (Wang, 1990). Therefore Lei *et al*. (1990) concluded that Se had an inhibitory effect on the initiation and promotion stages of AFB1-induced DNA damage.

A protective effect of Se is not restricted to aflatoxins, but is obvious with T-2 toxin as well. For example when rats were fed diets supplemented with either 0.5 or 2.5 mg/kg Se for 6 weeks, T-2 toxicity and mortality was between 2 and 5 times lower compared to the unsupplemented group (Kravchenko *et al*., 1990; Tutelyan *et al*., 1990). The acute lethal toxicity of T-2 toxin has also been shown to be reduced by dietary Se supplementation (Yazdanpanah *et al*., 1997).

In summary, Se has a protective effect against T-2 toxicity, decreases damage caused by AFB1 and prevents DON toxicosis (Surai and Dvorska, 2005). In trials a synthetic seleno-organic compound (Ebselen) showed potent protection against AFB1-induced cytotoxicity (Yang *et al.,* 2000). Protective effects against lipid peroxidation caused by mycotoxins have been attributed to various antioxidant compounds including vitamins A and E, ascorbic acid, co-enzyme Q10, selenium, antioxidant enzymes as well as synthetic antioxidants and various plant extracts (Surai, 2002). Indeed, T-2 toxin in the chicken diet decreased Se concentration in the liver (Graph 2) whilst binding the toxin in feed using a commercial yeast cell wall preparation, Mycosorb™ restored Se level in the liver to normal levels. A combination of Mycosorb™ and Sel-Plex™ has been demonstrated to be most effective in preventing lipid peroxidation in the chicken liver caused by T-2 toxin consumption (Graph 3).

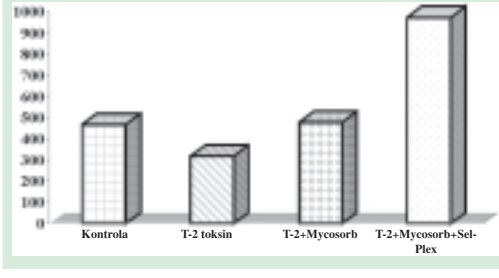
Graph 2

EFFECT T-2 TOXIN, MYCOSORB AND SEL-PLEX ON SE LEVEL IN CHICKEN LIVER, ng/g
(Dvorska *et al.*, 2003)



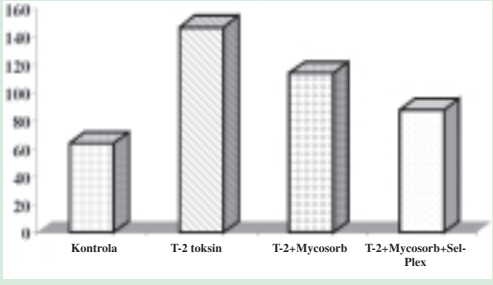
Grafikon 2

UČINAK T-2 TOKSINA, MYCOSORBA I SEL-PLEX-A NA KONCENTRACIJU SELENA U JETRI PILIĆA (ng/g)
(Dvorska i sur., 2003)



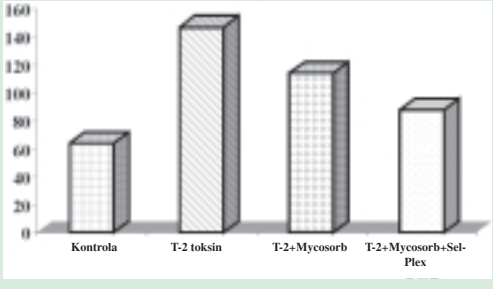
Graph 3

EFFECT T-2 TOXIN, MYCOSORB AND SEL-PLEX ON LIPID PEROXIDATION IN CHICKEN LIVER (MDA, mg/g) (Dvorska *et al.*, 2003)



Grafikon 3

UČINAK T-2 TOKSINA, MYCOSORBA I SEL-PLEX-A NA PEROKSIDACIJU LIPIDA U JETRI PILIĆA (MDA, mg/g) (Dvorska i sur., 2003)



USING ADSORBENTS

In spite of positive effects of natural antioxidants on animals fed mycotoxin contaminated diets, the most promising and practical approach has been the addition of adsorbents to contaminated feed (Ledoux and Rottinghaus, 2000). Therefore, mycotoxins can be bound to the adsorbent and pass harmlessly through the digestive tract. An ideal adsorbent for mycotoxin-binding should be characterized by (Surai, 2005):

1. **ability to bind a range of mycotoxins**. Indeed in the contaminated feed a range of mycotoxins can be found.
2. **low effective inclusion rate**. High doses of inclusion could interfere with the diet energy density and decrease feed efficiency.
3. **rapid and uniform dispersion in the feed during mixing**. A uniform dispersion in the feed is an important point for commercial feed producers.
4. **heat stability during pelleting, extrusion, and during storage**. Indeed, commercial feed treatments should not affect adsorbent efficiency.
5. **no affinity for vitamins, minerals or other nutrients**. The main task is to bind harmful mycotoxins without affecting other nutrients in the feed.
6. **strong mycotoxin binding at different pH**. If the binding is not strong there is a possibility that mycotoxins can be released from the adsorbent in the lower digestive tract.
7. **fast binding during first 30 minutes**. If mycotoxins are not bound to the adsorbent during first 30 minutes the chances that they will be absorbed are very high.
8. **high binding ability**. Ideally a low dose of adsorbent should be able to bind a range of mycotoxins even if they present at high doses
9. **high affinity for low doses of mycotoxins**. An adsorbent should be able to bound even low doses mycotoxins if they are present in the feed
10. **safety for animals and humans**. The product should not possess any harmful effects per ser
11. **biodegradability after excretion**. Ideally the adsorbent should be degraded in natural conditions as a results of environmental actions.
12. **palatability**. The adsorbent should not affect feed palatability.

Many compounds have been tested for adsorbent effects, however comparatively few have proven successful and still fewer (mainly bentonites, zeolites, alumosilicates and Mycosorb) are used commercially (Devegowda *et al*., 1998). The extent to which various compounds bind specific toxins varies considerably. Many products only bind aflatoxin, leaving such mycotoxins as T-2 in the intestinal tract without alteration. In acontrast to the various clays and zeolites binding mainly aflatoxin, a yeast cell wall-derived glucomannan (Mycosorb) has been shown to be effective against a wide range of mycotoxins (Devegowda *et al*., 1998). Indeed, Mycosorb is shown to be

well related to all those 12 requirements for an ideal mycotoxin adsorbent mentioned above.

It is interesting that mycotoxin binders can substantially improve antioxidant systems of the animals. This effect depends on the mycotoxin-binding activity of adsorbents. For example, inclusion of zeolite in the quail diet at 3% had a minor protective effect on the antioxidants in the quail liver, however changes were not statistically significant (Dvorska and Surai, 2001). Only the concentration of retinyl-linoleate in the liver of quail exposed to T-2 toxin simultaneously with zeolite was significantly higher compared with birds fed the diet containing T-2 toxin alone. These data indicate that zeolites alone were not effective in prevention of toxic effects of T-2 toxin. These data are in agreement with observations of Kubena *et al*. (1990; 1998) indicating absence of protective effects of aluminosilicate sorbents against T-2 toxicosis. Superactivated charcoal (Edrington *et al*., 1997) and organic sorbents (Bailey *et al*., 1998) were also ineffective against T-2 toxicosis. Therefore, zeolite probably was not able to bind a substantial amount of T-2 toxin in the digestive tract; and as a result did not interfere with pro-oxidant properties of this mycotoxin.

In marked contrast, inclusion of yeast glucomannans (Mycosorb) in T-2 toxin-containing diets fed quail significantly slowed the depletion of natural antioxidants and vitamin A in the liver (Dvorska and Surai, 2001). This protective effect can be attributed to the high adsorbent capability that esterified glucomannans have for T-2 (Dawson, 2001). It could well be that mycotoxin binding by Mycosorb also prevents T-2 toxin participation in development of oxidative stress in the intestine. As a result, damage to the enterocytes is prevented thereby maintaining effective antioxidant absorption, assimilation and delivery to the target tissues.

Due to antioxidant depletion in the liver, susceptibility to lipid peroxidation increased more than 2-fold. Inclusion of zeolites in the diet did not prevent antioxidant depletion; and therefore susceptibility to lipid peroxidation in the liver was increased, showing no significant difference from the group fed the T-2 toxin treatment without an adsorbent additive. On the other hand, inclusion of Mycosorb in the T-2 contaminated diet significantly decreased tissue susceptibility to lipid peroxidation in comparison to diets containing toxin only, although the inclusion of the Mycosorb adsorbent material was unable to completely mitigate the powerful stimulating effect of T-2 toxin on lipid peroxidation. Therefore, MDA accumulation in the livers of the quail in the Mycosorb group was still significantly higher than MDA levels in controls.

However, despite positive effects on the birds, inclusion of Mycosorb in the quail diet was unable to completely prevent the adverse effects of T-2 toxin on the antioxidant systems of the liver of the growing quail; indicating that not all T-2 toxin was bound and released from the intestine. Therefore a combination of mycotoxin binders with natural antioxidants, in particular with Se and vitamin E, could be the next step in preventing damaging effects of mycotoxins on animals including poultry.

CONCLUSIONS

Considering data reviewed, we can suggest a hypothetical scheme of mycotoxin-immune system interactions:

- Mycotoxins promote free radical formation (O_2^- and OH^*) in the intestine, which cause antioxidant depletion, oxidative stress, and enterocyte apoptosis and contribute to the development of malabsorption and decreased antioxidant absorption and accumulation.
- Apoptosis of enterocytes and malabsorption are responsible for impaired absorption and deceased concentrations of vitamin E, C, and carotenoids in tissues.
- Mycotoxins and their active metabolites are absorbed from the intestine and accumulated in target tissues.
- Mycotoxin in tissues can generate free radicals, decreasing further antioxidant protection, causing lipid peroxidation and damage to other biological molecules including lipids, proteins and DNA. This could lead to anti-oxidant/pro-oxidant imbalance causing oxidative stress, which further leads to apoptosis, gene down-regulation and other cytotoxic effects of mycotoxins.
- Immuno-suppressive action of mycotoxins could be associated with down-regulation of

communications between various cells due to damages to receptors as well as down-regulation of communicating molecule (cytokines, eicosanoids, etc.) production by macrophages. Furthermore, apoptosis of immune cells also contributes to immunosuppression caused by mycotoxins.

- Increased antioxidant supplementation decreases toxic actions of mycotoxins by interfering with one or several steps described above, including gastrointestinal tract, plasma and tissue membranes.
- A combination of natural antioxidants with mycotoxin binders, such as Mycosorb, could be a next step in combating mycotoxicoses in poultry and animal production production.

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MIKOTOKSINI I IMUNOST: TEORIJSKO RAZMATRANJE I PRAKTIČNA PRIMJENA U PRAKSI

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IZVADAK. - "Tihe ubojice", "nevidljivi lopovi", "neizbježni onečišćivaći" i "prirodni otrovi" - sve su to nazivi za sekundarne metabolite plijesni, odnosno mikotoksine. Mikotoksini se uglavnom smatraju neizbježnim onečišćivaćima hrane za ljude i životinje i oni predstavljaju velik problem u cijelom svijetu. Ustanovljeno je da više od 300 mikotoksina uzrokuje znakove toksičnosti u sisavaca i peradi, a taj broj stalno raste. Procjenjuje se da je 25% svjetske proizvodnje usjeva kontaminirano mikotoksinima. Najznačajniji mikotoksini u prirodno kontaminiranoj hrani za ljude i životinje su aflatoksini (AF), okratoksini (OTA), zearalenon (ZEA), T-2 toksin, deoksinivalenol (DON) i fumonizini (FB). U brojnim se slučajevima ovi mikotoksini mogu naći u kombinaciji u onečišćenoj stočnoj hrani. Podaci izneseni u ovom pregledu jasno pokazuju da je imunosupresija jedna od najznačajnijih posljedica kontaminacije stočne hrane mikotoksinima. Čini se vjerojatnim da mikotoksini utječu na pojavu oksidativnog stresa, potiču apoptozu, te da se uključuju u poremećaje regulacije ekspresije gena. Ove su promjene odgovorne za imunosupresijsko djelovanje mikotoksina. Osobito oštećenja receptora na površini makrofaga, neutrofila i limfocita mogu uzrokovati lošu komunikaciju među stanicama što dovodi do imunosupresije. Izgleda da bi se problemi s mikotoksinima i mikotoksikozama u industrijskom proizvodnji životinja mogli na zadovoljavajući način riješiti dodavanjem stočnoj hrani sredstava za adsorpciju kao što su modificirani glukani.

Ključne riječi: mikotoksini, imunost, antioksidanti, oksidativni stres, adsorbensi