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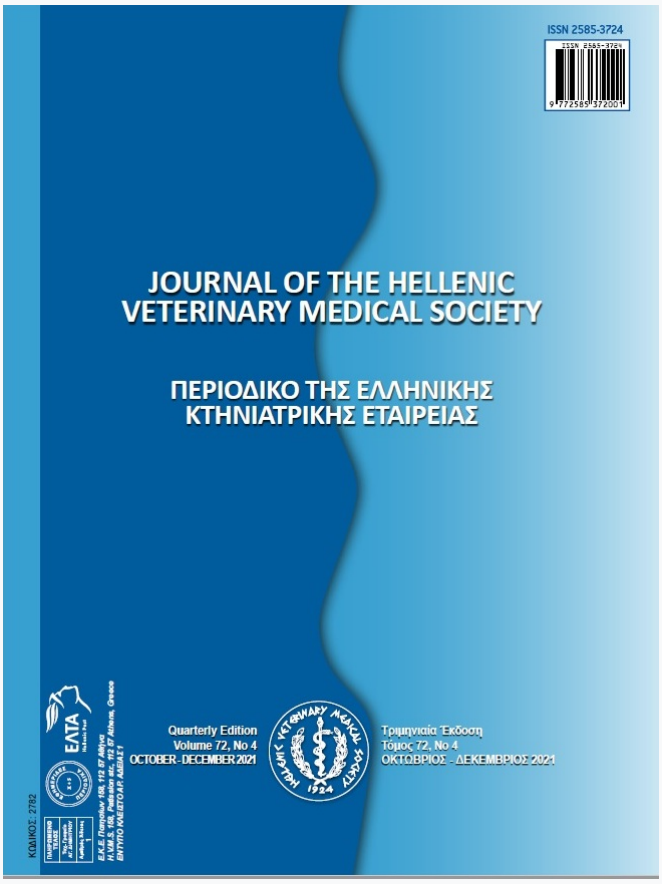

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Review article
Ανασκόπηση

Ochratoxin A occurrence, its pathological effects on poultry health and decontamination approaches

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ABSTRACT: Mycotoxins are filamentous fungi which can be seen microscopically and they impart adverse effects on poultry health. The occurrence of mycotoxins in poultry feed imparts adverse effects not only to the birds' health but also causes huge economic losses by affecting feed conversion ratio, production of meat and eggs,and also responsible for histopathological changes in lymphoid organs of chicken. More than 300 different species of mycotoxins have been reported from which the ochratoxin and aflatoxins are the most harmful for poultry industry. Among ochratoxins, especially the Ochratoxin A (OTA) is produced from *Aspergillus Ochraceus* and and *Penicillium verrucosum* species as storage fungi inside stored drains and feed ingredients. The ochratoxicity is a dose-dependent factor and hits the immune system of birds besides decreased feed intake and decreased body weight. Higher doses of OTA toxicity resulted in deterioration of egg shell quality and hatchability in layers and breeders. Histopathological profile of ochratoxicity affected birds showed severe to moderate changes in the kidney, bursa of Fabricius, liver, thymus, spleen, heart, and lungs depending on dosage. In this review article, an attempt has been made to concise the OTA associated alterations in growth pattern, production index, biochemical changes and histopathological profile of the poultry. The current approaches and agents (Vitamin-E, Silymarin), which are being used to reduce the effects of OTA toxicity in birds, have also been discussed.

***Keywords*:** Ochratoxins, Poultry, Immunity, Biochemical changes

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INTRODUCTION

The poultry sector is an important and vibrant segment of agriculture which plays important role in national economy of many countries (Zhang *et al.,* 2020; Khater *et al.,* 2020; Yasim *et al.,* 2020). However, its progress is affected by various diseases including mycotoxins (Baran *et al.,* 2020; Elmossalamy *et al.,* 2020; Shoaib *et al.,* 2020; Sugiharto *et al.,* 2020). Mycotoxins occurrence is global issue with strong economically negative impact on health of livestock, poultry and humans (Ali *et al.,* 2020; Moussa *et al.,* 2020; Lin *et al.,* 2020). Among mycotoxins, ochratoxin is a well-known toxin that survives in the agriculture and livestock sector damaging the cereal grains, poultry and livestock by-products (Ghonaim*et al.,* 2020; Imran *et al.,* 2020; Khaskheli *et al.,* 2020). Several fungi species like *Aspergillus ochraceus, Aspergillus carbonarius, Aspergillus niger* and *Penicillium verrucosum* are responsible for ochratoxin production due to un-hygienic and improper storage of products under optimal temperature and humid conditions (Kembo *et al*.,2020). Ochratoxin (OTA) is a chemically stable compound and its toxicity cannot be averted by adopting normal food storage procedures. OTA is found as a deleterious and carcinogenic substance in contrast to other live species. In animals, the kidneys is the chief target organ for OTA (Joint *et al.*, 2002; Duarte *et al.*, 2011; Kembo *et al*.,2020). Immunosuppression and immune toxic effects are also reported due to OTA (Bondy and Pestka, 2000). Other deleterious effects of OTA includes the increased lipid peroxidation, mitochondrial damage and reduced macromolecules formation (Tinelli *et al.*,2019).

During the last decade, several scientific studies have been conducted on mycotoxins to check their presence in the agriculture fields (Jarvis and Miller, 2005). Wang *et al.* (2006) confirmed different studies regarding the airborne presence of *Aspergillus* and *Fusarium* species in poultry sheds ranging from 361.3 and 74.6 CFU/m3 and taken as toxicogenic.

Toxico-pathological mechanism of *Alternaria* toxins (plants such as oilseeds and cereals) includes genotoxicity, cytotoxicity, teratogenicity and fetotoxicity which were hazardous to animal health (Kembo *et al*., 2020). Mycotoxin contaminated poultry houses were reported by researchers due to unhygienic environmental conditions taking both the birds and workers at risk by inhaling the toxic air. The adverse effects of mycotoxins have made scientists to ponder in order to abate the escalating OTA in food chain supplies to overcome the economic crises globally (Wang *et al.,* 2006). Similarly, in poultry sector the major devastating mycotoxins includes the aflatoxins (AF), ochratoxin A (OTA), fumonisins (FUM), deoxynivalenol (DON) and T2 toxin (Ghor *et al.,* 2020). Mycotoxin type-2 is considered 10 to 20 times more toxic when absorbed by the digestive system instead of inhaled, similarly 20 to 40times more toxic if absorbed through the skin (Schleibinger *et al.*, 2004). Regarding the economic losses caused by OTA in the poultry include the stunted growth, poor FCR and enhanced mortality ratio. Peanuts and cereal grains are most commonly affected by mycotoxins globally and their 100% removal is still not possible. (Vieira *et al.,* 2004; El Miniawy *et al.,* 2014; Khatoon *et al.,* 2016). The different studies through toxicity testing approved the oral median lethal dose (LD 50) of OTA as 2-4mg/kg in chicken, 5.9 in turkeys and in quails& ducks 16.5 (Elaroussi *et al.,* 2006, 2008; Santin *et al.,* 2002).

Initially the OTA was discovered at Balkan region, but currently it is present around the globe due to its favorable growth rate in storage components under optimum conditions (Bui-Klimke *et al.,* 2014; Khatoon *et al.,* 2017; Sharif *et al.,* 2018). The OTA elimination is still a major issue in poultry sector due to is capability to survive the higher temperature. However, several different approaches are now approved for reduced OTA contamination at all levels. This review article summarizes the OTA associated alterations in growth pattern, production index, biochemical changes and histopathological profile of poultry. The current approaches and agents (Vitamin-E, Silymarin), which are being used to reduce the effects of OTA toxicity in birds, have also been discussed in the following sections.

Table 1 shows International standards and codes of practice to limit exposure to mycotoxins from certain foods established by the Codex Alimentarius Commission based on JECFA assessments.

These tolerable daily intakes are used by governments and international risk managers, such as the Codex Alimentarius Commission, to establish maximum levels for mycotoxins in food. The maximum levels for mycotoxins in food are very low due to their severe toxicity. For example, the maximum levels for aflatoxins set by the Codex in various nuts, grains, dried figs and milk are in the range of 0.5 to 15 μg/kg (a μg is one billionth of a kilogram). The Codex maximum limit for patulin in apple juice is 50 μg/L.

Table 1: Approved Level of OTA Species in Poultry Feed (JECFA, 2001)

OTA- Spp.	Optimal Temp.Range (Min-Max) °C	Water Activity	Affected Food Products
Ochraceus	24-31 (8-37)	0.95-0.99	chickpeas, rapeseed, pepper, and sesame seeds, nuts, oats rice, grain, maize, wheat, flour, and grain, espresso beans.
Ochraceus carbonarius	32-25	0.82	Grapes and grape items, including table grapes, wines, and dried vine organic products.
Ochraceus niger	35-37 (6-47)	0.77	Nuts, apples, pears, peaches, citrus, grapes, figs, strawberries, mangoes, tomatoes, melons, onions, garlic, and yams.
Ochraceus verrucosum	20 (0-30)	0.80	Oat crops; cheddar, meat items.

Chemistry of Ochratoxins

Ochratoxins are toxic metabolites consisting of dihydro-isocoumarin moiety linked with a phenylalanine through an amide bond. The chemical and physical properties involve the molecular weight of 403.8, being a white, odorless and heat stable crystalline substance having a melting point of 168-173°Cresisting the 3 hours of sterilization process at 121°C (Ko″szegi *et al.,* 2013). Its partial degradation is noted at 250°C (Trivedi *et al.,*1992). The OTA exhibits a strong fluorescence due to its specific structure property and existed in non-ionic, monoanionic and dianionic forms depending upon the microenvironment (Poór *et al.,*2013; Kembo *et al*., 2020).

Pathophysiology of Ochratoxins

Ochratoxins (OTA) is the causing agent of nephropathy and increases the incidence of renal carcinomas and adenomas in rats. Pathophysiological studies revealed that OTA acts on different sites along the nephron. Acute OTA exposure leads to an impairment of postproximal nephron function, predominantly of the collecting duct, resulting in altered electrolyte and titratable acid excretion (Pozo *et al.,* 2013). After activity of poison it assimilates into alimentary canal, wherever it ties with egg whites which supplies OTA an extended half-life from few days to month, depending on plasma grouping (Roth *et al.,* 1988; Berger *et al.,* 2003; Lino *et al.,* 2008). In rabbits, OTA is extremely cytotoxic and may cause hemolysis in red blood cells (Jan *et al*., 2017). Low doses of OTA cause influence energy metabolism (amino acid, cofactors, vitamins and carbohydrates) while in high doses of OTA, different body systems are influenced like excretory, digestive, endocrine and circulatory system (Anzai *et al.,* 2010; Tinelli *et al.,* 2019).

In rodents, OTA caused effect on lymphoid organs such as enlarged kidneys and liver (Schwerdt *et al.,* 1999; Zlender *et al.,* 2009).Discharge of poison is finished by cylindrical emission and re-retention is guilty of intra amassing of poison (Leier *et al.,* 2000; Jung *et al.,* 2001). Poison may be reabsorbed (from nephron) by dynamic vehicle and distant dispersion in pH.

Clinical Signs of Ochratoxins Toxicity in Poultry

The severity of clinical signs and symptoms of OTA toxicity depends upon the dose rate and the duration of exposure. The major signs exhibited by birds include general weakness, low FCR, stunted growth, poor egg and feathering quality, increased mortality, elevated weight of visceral organs like liver, spleen, pancreas, proventiculus, gizzard and testes in male birds (Resanovic, 2009).The kidney impairment leads to a decrease in urine concentration, glomerular filtration rate, impaired proximal tubule and degenerated ultrastructural changes in renal integrity (Elaroussi *et al.,* 2008).Day-old chicks when exposed to low dose of OTA, caused marked reduction in circulating lymphocytes in contrast to the enhanced ratio of monocytes and heterophils reported. This change in inflammatory cells profile in newly hatched day old chicks is ultimately related to their inflammation response against a variety of ecological pathogens and certainly disturbs their capability to react against vaccines (Moura *et al.*, 2004).

OTA along with nephrotoxicity also affects the liver and compromises the immune response, causing histopathological lesions in vital organs (Sharif *et al.*, 2018).OTA at 20mg/kg induces severe lesions in the glomerulus and convoluted tubules of the kidney. Interstitium incorporated with elevated levels of collagen fibers ultimately increases the membrane thickness. OTA also tempts abnormal mitochondria peroxisomes, lipid droplets inside the cytoplasm and nucleus, while the epithelium of convoluted tubules can be infiltrated with round electron-dense bodies, enhanced SER, intra-cytoplasmic and intra-nuclear myelin like projections (Sugiharto *et al.*, 2020).400 and 800 µg level of OTA in poultry feed caused enlargement in renal and hepatic size along with ele-

vated levels of serum creatinine, uric acid, glutamic oxaloacetic transaminase, and glutamic pyruvic transaminase (Elaroussi *et al.*, 2008).In rabbits, teratogenic effects were found as skeleton abnormalities like incomplete ossification of ribs and skull bones, and soft tissues abnormalities due to OTA (Tinelli *et al.,*2019).

Effect of Ochratoxinson Biochemical &Histopathological Profile

Element of OTA remains beneath discussion and reported to be cancer-causing agent, toxic, immunotoxin and teratologic agent in poultry (Koszegi *et al.,* 2016). Elevated levels of ochratoxins ultimately causes adverse histopathological and biochemical changes along with reduced performance (Hassan *et al.*, 2010; Mohamed *et al*., 2019).A high level of OTA showed a significant reduction ($p<0.05$) in the antibody titers of anti-NDV by 10.4% and a non-significant reduction in mRNA cytokine IL-2 and IFR-gamma level upon induction of lipopolysaccharides. However, serum levels of these two parameters (IL-2 and interferon-gamma) significantly drop ($p<0.05$) in the OTA toxin group. Anomalies in bursa, thymus, spleen, and liver with OTA+T-2 toxin and the use of commercially available mycofix Plus as treatment, encounter its toxic effects significantly (Xue *et al.*, 2010).

Moura *et al*. (2004) worked on different combination of OTA and PBS(Phosphate-buffered saline) to check effects of OTA on broilers leucocytes and reported that exposure of day old chicks to low doses of OTA resulted in a significant decline in proportion of circulating lymphocytes with a marked increase in proportion of monocytes and heterophils.

Indresh *et al*. (2013) observed the impacts of OTA upon the general performance, immunological and biochemical profile of broilers chicks. Both toxins caused dejecting effects on serum biochemical, hematological and immunological specifications, also affected health status of birds. Bharathi *et al*. (2014) assessed the changes in biochemical and liver antioxidant profile of birds by feeding of OTA at the rate of 100 ppb for 4 weeks. Results showed a prominent reduction in globulin level and IgA to IgG ratio in OTA fed birds. Moreover, hypo-glycaemia, hypo-amylasaemia, reduced high density lipids and elevated levels of ALT, ALP, and blood urea nitrogen, triglycerides were recorded. Thus, conclusively it was considered that 100 ppb OTA in feed results in severe damage to liver and kidneys along with causing adulterations in their normal biochemical and antioxidant profile.

Hassan *et al*. (2018) studied to investigate the prevalence of OTA in animal feed by using glutathione an antioxidant in rats. Using glutathione, an increase in urea, ALT, AST and decrease in serum total protein, albumin and globulin level was recorded in OTA treated rats. Results indicated the economic importance of glutathione by addition in healthy animal feed to overcome the deleterious effects of ochratoxins.

The suppression of the immune system and impairment of the normal physiology of several constituents of the immune system is also caused by OTA toxicity (Hassan *et al.*, 2012). A study affirmed the enhanced effects of bentonite clay in broiler chicks fed with aflatoxin and Ochratoxin treated feed by evaluating the pathological changes besides alterations in the immune system of treated birds. A depressed immune reaction in combination with pathological lesions in the immune system, reduced antibody (Ab) titer against sheep red blood cells, low response to PHA-P and impaired phagocytic activity was reported. The addition of bentonite clay in the aflatoxin group treated with 0.1 and 0.2mg/kg dose rate exhibited an enriched response against immune-toxicity whereas no such prompt results were recorded in 0.6mg/kg dose rate group. The OTA treated group showed only mild ameliorative effects upon bentonite clay addition in contrast to the aflatoxin group (Bhatti *et al.*, 2017). Histopathologic findings included vacuolation of hepatocytes, megalocytosis along with hyperplastic binary epithelial cell layer and increased liver weights. In kidneys, hypertrophied proximal tubule epithelial cell layer can be found beside a solidifying glomerulus basal membrane (Santin *et al.*, 2002). Pathological alterations induced by OTA are dependent on the duration of exposure and dose rate (Hameed *et al.*, 2013).The maximum acceptable level of OTA 0.1 mg OTA/kg was established by the European Commission considered as safe and no traces can be examined on breast and thigh muscles at this level. At 0.1 mg OTA/kg level no clinical sign and symptoms were examined because the dose level is less while mild histopathological lesions can be examined in such cases (Pozzo *et al.*, 2013).Liver and kidneys involvement in body's detoxification mechanism leads to hepato-renal enlargement, swollen and tan with white urate crystals in mild and complete failure with dehydration, hyper-uricemia in advanced OTA toxicity cases (Biró *et al.,* 2002).

Activity of Silymarin, Vitamin E and Absorbents against Ochratoxins

Different types of absorbents like Bentonite clay,

activated charchol, distillarysludge, vitamin E, silymarin are used to control the activity of mycotoxins depending upon their mode of action. The use of vitamin E and selenium are beneficial to cope with the immunosuppressive effects of OTA. A study showed 11% gain in body weight caused by OTA but with less severe lesions in selenium and vitamin E treated birds (Ahmad *et al.*, 2012). 2% level of yeast sludge is more profitable in contrast to 1% and has safer zone against mycotoxins (Mujahid *et al.*, 2012). The effects of Ochratoxin A and its amelioration with silymarin and vitamin E in separate groups of white leghorn cockerels were tested. Hematological and serum biochemical parameters when evaluated in OTA treated birds showed diminish levels of PCV (packed cell volume), Hb. (hemoglobin), erythrocytic count, albumin, serum while increased levels of creatinine and urea as compared to vitamin E and silymarin treated groups (Ahmad *et al.*, 2012). Mycotoxin deactivator reduces the accumulation of ochratoxin in the organs while fecal excretion can be increased in such cases (Joo *et al.*, 2013).

Comparatively investigation of the 3 different adsorbents against Ochratoxin toxicity in birds show that the three different adsorbents effects on mycotoxin feed (a) esterified glucomannans, organic in nature, (b) modified zeolite of inorganic nature, and (c) combination of both glucomannan and zeolite. OTA treated groups and a combination of adsorbents show enhanced FCR and advanced histopathological changes in the kidney and liver. Organic and inorganic nature show high body weight and minimized histopathological changes (Nedeljković-Trailović *et al.*, 2015).Unique sugar (STOC) termed as sucrose thermal oligosaccharide caramel on hematology, particular biochemical components, and hormones, fibro-nectin and cecal gram-negative bacterial levels affect the physiology. The addition of STOC in feed leads to improve the physiology of several parameters in exposure to OTA (Khaskheli *et al.,*2020).

Abidin *et al*. (2013) focused on hematological and serum biochemical parameters in white Leghorn cockerels feeding OTA contaminated feed to study ameliorative effects of L-carnitine and vitamin E (α-tocopherol).Vitamin-E and L-carnitine alone or combination with OTA (1.0 mg/kg) can mitigate toxin produced hematological and serum biochemical specifications.

CONCLUSIONS

Conclusively, the presence of ochratoxins in poultry feed produces adverse effects on the poultry health and performance parameters. They also have immunosuppressive effects on birds. Ochratoxins also induce mild to moderate changes in the biochemical and histopathological profile. Wherever, the use of some absorbents like bentonite, silymarin, and vitamin E proved to be effective against the adverse effects caused by OTA in birds and also improve performance parameters of birds.

CONFLICT OF INTEREST

None declared by the authors.

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