Zearalenone Mycotoxicosis: Pathophysiology and Immunotoxicity

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Review Article

ABSTRACT

Mycotoxicosis refers to the deleterious pathological effects of different types of toxins produced by some worldwide distributing fungi. Mycotoxins, as secondary metabolites are affecting different organs and systems both in animals and human beings. Zearalenone (ZEA), the well-known estrogenic mycotoxins, is an immunotoxic agent. This macrocyclic beta-resorcyclic acid lactone is mycotoxin procreated as a secondary metabolic byproduct by several types of *Fusarium*, encompassing *Fusarium roseum*, *Fusarium culmorum*, *Fusarium graminearum*, and different other types. Attributing to its potent estrogenic activity, ZEA has been incriminated as one of the major causes of female reproductive disorders. Thus, the purpose of the present review article is to appraise the pathophysiological consequences and subsequent explore the progress in the research field of zearalenone immunotoxicities.

Keywords; **Zearalenone, Pathophysiology, Immunotoxicity**

General Introduction

Mycotoxins are toxic secondary metabolites that are naturally created by fungi that make a toxic response when introduced in low concentrations to vertebrates and other animals (1). Mycotoxin as a term had been initially utilized within 1960s to describe the contaminated peanuts with toxin in animal feed that cause a loss of turkeys in England. Many factors participate in the presence of these mycotoxins in food, such as poor harvest, storage habits, climatic situations, and pest infestation. Mycotoxins exposure, which happened generally through intake of contaminated food. Ultimately, mycotoxicosis and mycosis will be established which in turn, may lead to death (2). Obviously, the production of mycotoxins is mostly done by different species of *Aspergillus, Penicillium, Claviceps, Alternaria and Fusarium* (3).

Mycotoxicosis is a disease caused by these mycotoxins which affect animals and humans consuming feedstuffs and mycotoxins contaminated foods. These toxins can produce harmful lesions in different organs and systems. Kidneys and livers may be damaged by mycotoxins and lead to a chronic illness and death. These toxins can also damage the reproductive, nervous, immune, cardiovascular and endocrine systems. They can cause immune system abnormality, tremors, hemorrhage, reproductive defects, convulsions, abortion, skin lesions and appendages gangrene. Additionally, mycotoxins cause tremendous economic losses from unthriftiness, growth rate reduction, poor feeding, agalactia and lameness (4).

Types of Mycotoxins

Mycotoxins are produced by molds that classified as field and storage molds

1. Field type mold: grow in grains before harvest and humidity requirements are above 70% and typically grain moisture above 22%.
2. Storage type molds: grow in grains after harvest and during storage of these grains. Seemingly, these molds do not need high humidity and grow efficiently in 12-18% moisture.

1. Aflatoxin

Aflatoxins represent the highly potent poisonous mycotoxins produced by molds of *Aspergillus*

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species before harvest and in storage periods. Type B1 aflatoxin being the most abundant type of aflatoxins is aflatoxin B_1 and is often produced by *Aspergillus flavus*. Liver, kidney, and immune system are the main affected organs in this type of mycotoxicity. Aflatoxins affect hepatic functions and acute aflatoxicosis causes severe lesions and signs as a consequence of liver dysfunction, such as hemorrhages, jaundice, immune suppression and sudden death (5). Aflatoxin at lower doses is of cumulative effects. Thus, chronic aflatoxicosis is more common, as a sequel of intake of little quantum of aflatoxin for a long duration (6). Consequently, the appearance of secondary diseases can arise as well as response to vaccination can decrease because of immune suppression (7).

2. Vomitoxin

Vomitoxin is the synonym term for deoxynivalenol (DON), a mycotoxin that usually manufactured by *Fusarium graminearum* before harvesting. Vomitoxin can disturbing the protein synthesis, modulating immunity, and retarding neurotransmitters activity in the brain. Obviously, the main affected organs belong to the central nervous system, the alimentary tract epithelium, liver, and some organs of the immune system (8). Chronic vomitoxin toxicity is more common and of practical importance. In most cases, a sharp decrease in feed intake is obvious and, consequently, reduction in growth rate was noticed in a time and dose dependant process (9)**.**

3. Fumonisin

Fumonisin as a potent mycotoxin that can cause immune suppression (10). Furthermore, acute fumonisin toxicity mostly leads to a pulmonary edema, which is characteristic of its intoxication and ultimately causes heart failure (11). Obliviously, the ingestion of smaller amounts of fumonisin for a long term may causing chronic course toxicity. The main target organs and systems of this toxin are lungs, heart, central nervous system, liver and immune system (12).

4. Ochratoxin

Ochratoxin is produced by different species of *Aspergillus* and *Penicillium* such as *Aspergillus ochraceus, and Penicillium viridicatum*. Primarily, ochratoxin A is nephrotoxic and hepatotoxic mycotoxin (13). Occasionally, the only effect of ochratoxin A toxicity is the presence of pale, solid, and edematous kidneys (14, 15). Seemingly, Ochratoxin A contamination is also a critical issue for human health because of pork consumption in the western countries that may cause carcinogenic potentials (16, 17). Ostensibly, the most affected systems are urinary, gastrointestinal (liver), and immune system.

5. T-2 Mycotoxin

T_2-toxin which belongs to non-macrocyclic type-A trichothecenes. It is a potent cytotoxic mycotoxin yielded by multiple species of the genus Fusarium (*F. poae*, *F. sporotichioides*, *F. equiseti, and F. acuminatum*). T-2 toxin represents a prime toxic trichothecene of human consideration and animal concern. The human clinical condition of its toxicity is termed alimentary toxic aleukia. T2 mycotoxicity may come through consuming of moldy grains. Though, T-2 can permeate through human skin, no significant systemic impacts are expected after dermal exposure, but local skin lesions cannot be eliminated (18).

6. Zearalenone

Zearalenone (ZEN) which further declared as RAL/F-2 toxin, is strong estrogenic metabolite yielded mostly by *Fusarium graminearum* and other wide variety types. Zearalenone is an estrogen analog that can mimic the effects of the hormone estrogen. In bred sows, false pregnancy and early embryo loss may occur. Furthermore, zearalenone has the ability to pass through milk during lactation and promote vulvar enlargement and redness in recently born nurslings and lactating gilts (19).

Zearalenone Structure

As a macrolide, zearalenone consists of 14-membered lactone linked to 1,3-dihydroxybenzene; a formidable estrogenic metabolite toxin. In animals, the biotransformation of this estrogenic mycotoxin results in the formation of α- and β-zearalenol metabolites. All these structures are of estrogenic property, with the alpha-zearalenol being the most potent one (19, 20). Multiple studies have proposed that the enterohepatic pathway cycle was responsible for the extension of this mycotoxin and its metabolic derivatives retentivity in the body, suppressing its

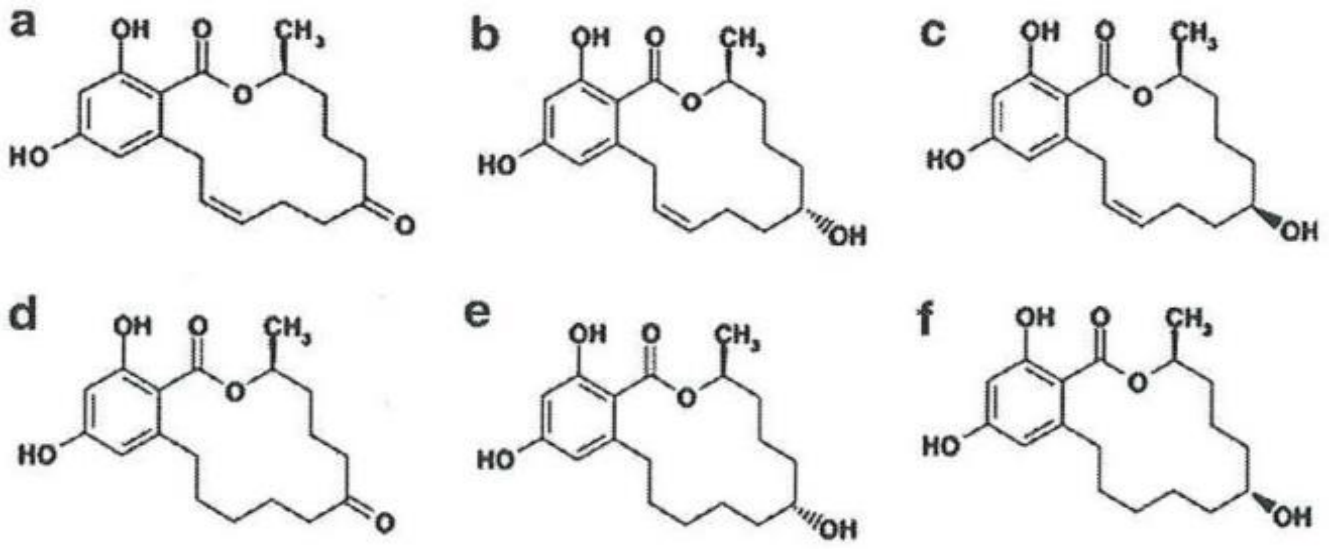

Figure 1. Chemical structures of zearalenone and its derivatives: a) zearalenone (ZEA), b) α-zearalenol (α-ZOL), c) β-zearalenol (β-ZOL), d) zearalanone (ZAN), e) α-zearalanol (α-ZAL), f) β-zearalanol (β-ZAL) (19)

excretion and prolonging the adverse actions of them (21).

Zearalenone Toxicity in Animals

Zearalenone has a deleterious effect on the fertilization capability of spermatozoa because of their negative impact on activity, motility, and acrosomal development in a dose and time-dependent pathway. Farm animals are exposed to this mycotoxin by means of feed ingestion because of the global distribution of this mycotoxin Studies on the kinetic routes and patterns of zearalenone ingestion revealed and interpret the causation of the broad differences in its pathogenicity.

a. Effect of Zearalenone in Poultry

There is a broad variation regarding the sensitivity between different types of avian species especially the laying hens and broiler chickens regarding zeralenone toxicities due to differences in disposition and/or biotransformation approach. Osselaere (22) reported a fast excretion of zearalenone after intravenous administration of 0.3 mg zeralenone/kg b.w to broiler chickens, meanwhile, no zeralenone could be noticed in plasma after oral conduction of this dose. Furthermore, alimentation laying hens a pellet contaminated with ZEN more than 800 mg/kg did not influence the activities belong to their reproductive system (23). Concurrently, providing 100 mg ZEN/kg to adult female turkeys, led to retardation in the egg production by 20% (24). Furthermore, the administration of 800 mg ZEN/kilogram body weight to turkey for 2 weeks can initiated swagger behavior and an increase in size and change in color of dewlap, that never observed in chickens fed zeralenone free chow (25).

b. Effects of Zearalenone in Bovine

Consequences of bovine zearalenone mycointoxication are compromised both, hyperoestrogenism and infertility. Apparently, when heifers were fed zearalenone contaminated feed over three estrous cycles, the conception means were significantly decreased (26).

c. Effects of Zearalenone in Ovine

The negative impact of zearalenone on ovine reproductive system is characterized by pronounced suppression in fertility and in the percentages of ovulation (27).

d. Effect of Zearalenone in Horses

In horses, zearalenone contaminated diet can clinically established (Mare Reproductive Loss Syndrome) outbreak. This rising outbreak attributed to zeralenone contaminated corn was announced through multiple mare abortions, stillbirths and by increasing neonatal foal mortality (28).

Human Mycotoxicosis

Acute and chronic human mycotoxicoses can occurred. The lesions of acute mycotoxicoses comprise kidney and liver, central nervous system and coetaneous structural changes. hormonal effects, miscarriage, hemorrhage, vomiting, diarrhea and further many clinical signs. Meanwhile, chronic mycotoxicoses enrolled: Reye syndrome, Kwashiorkor, and cancers (29-31). blamed the estrogenic structure of zeralenone to elicit (hyper estrogenic syndromes in humans), in a pathogenesis which was depended on the time and amount of the dose. Additionally, multiple clinical cases of mycotoxicosis were observed.

1. Holy Fire: due to convulsive type and gangrenous type (*Claviceps purpurea*) ergotism (32).
2. "Yellow Rice Disease" was recorded in soma Asian countries due to consumption of contaminated rice (33).
3. "Acute Cardiac Beriberi" which was caused by a mycotoxin called citreoviridin (neuro-cardiotoxic toxin) produced by some *Penicillium* species (34).
4. Increased incidence of cancer (especially the esophageal tumor) in humans had been noticed due to several mycotoxins (35).

Furthermore, the influence of mycotoxins on human health can be related to age, sex, weight, diet, exposure to infectious agents, amount of toxins exposed, the presence of other mycotoxins (synergistic effects) and pharmacologically active substances (36). Seemingly, in humans, the rate of exposure to mycotoxins, appeared to affect young persons or infants in a higher percentage than an adult (37). Besides, the amount of exposure is a major determinantal factor regarding the degree of toxicity. However, several other factors such as vitamin deficiency, low-calorie intake, alcohol abuse, or the presence of an infectious disease can fortify the severity of these toxins. European Food Safety Authority (EFSA) has recently been reviewed the toxicity of zearalenone with a tolerable daily intake (TDI) of 0.25µg/kg body weight was established (38, 39).

Toxicokinetic and Pathophysiology of Zearalenone in Animals

Two essential biotransformation pathways for ZEA in animals have been suggested. First route is occurred via hydroxylation of this mycotoxin by glucuronic acid. Secondly, by conjugation and subsequently, formation of alpha- and Beta-zearalenol (40,41), a process that catalyzed by both (hydroxysteroid dehydrogenase) (HSDs) and (uridine diphosphate glucuronyl transferase) (UDPGT) (42).

After its intake, zearalenone is localized in reproductive tissues (ovaries, uterus in female reproductive system) and (leydig cells in the interstitial connective tissue of testis in male reproductive system) (43, 44). In the liver, all absorbed zearalenone together with its α-zearalenol will be undergo glucuronidation type conjugation. In ruminants, the estrogenic zearalenone can expose to ruminal metabolism characterized primarily by reduction to alpha-zearalenol majorly and minimally to beta-zearalenol (45).

Obviously, an active enterohepatic circulation and potent bile excretion of zearalenone was established in most species. The major excretion pathway of zeralenone was occurred via feces, meanwhile, in rabbits, it is primarily excreted via urine (46).

Several studies had been reported that zeralenone has a minimal transmission through milk in certain circumstances only after being exposed to high concentrations of it (47-50).

Several studies have shown that this mycotoxin can inhibit cell metabolism and subsequently lead to suicidal cell death (apoptosis) or homicidal cell death (necrosis) (51-53). Moreover, zearalenone can be addressed the regulatory type proteins which are participating in expressions of cell cycle activities including the cell cycle tabulation and distribution especially cells that bear factors like (Cyclin-B1, Cyclin-D1, CDK-2, and CDK-4). Ultimately, it will lead to suppression of target cell long activity and viability (54).

Obviously, ZEA produces frank apoptosis in the uterus stromal cells, interstitial Leydig cells, seminiferous Sertoli cells, macrophages, and porcine granulosa cells (55).

Hyperestrogenism due to prolong zearalenone feeding has been reported in ovine and swine nursing dams (56-58). Concurrently, not all animal species have the same sensitive reactivity toward the estrogenic effects of this mycotoxin (59). Another pathophysiological effect of Zearalenone, mycotoxicosis was compromised the obvious decline in serum testosterone, a state that induces feminization and suppresses libido (60).

Immunotoxicity of Zearalenone

Zearalenone (ZEN) is genotoxic and responsible for potent reproductive toxicity in humans and animals. Zearalenone is an immunotoxic and effective reproductive mycotoxin in animals and humans' beings. It has the ability to be a rapidly absorbable toxin in the intestinal tract. Liver and intestine are the central sites for its metabolism. It is primarily metabolized in liver by oxidase and cytosolic enzymes into numeral metabolites. Alpha and beta zeralenol are the most representative metabolites of zearalenone which exert diverse biological activities (61).

The estrogenic action of zearalenone and its secondary metabolites is mediated by their powerful attachment tendency to the cellular estrogen receptors. However, unlike the phytoestrogens, which bind favorably to beta-estrogen receptor, ZEA and its reductive metabolites have an equal tropism to attach both alpha and beta receptors of this compound. Organs of reproductive system (especially, uterus and ovary) in laboratory and domestic animals are the main target organs for its deleterious toxic effects. Obviously, in most mammalian species, this mycotoxin can induce strong uterotrophic activity (62).

Moreover, in spite of some researchers' efforts to describe the ZEA impact on the immune system of different animal species, few of them try to evaluate the aftermath of this mycotoxin on the innate and acquired immune responses**.** It is likely that hormones and cytokines have a very important function in the transmission of information between the two systems: the immune and the reproductive one (63-65). This coherent co-operation supposes that the influence of the environmental estrogens on the tissues in the reproductive system can affect also the immune system (66).

Feeding mice with zearalenone alone in a dose of (40mg/kg) for fourteen days revealed lymphopenia, significant decreases in some immunoglobulin (IgG and IgM) levels, thymocyte sub-types ($CD3^+$, $CD4^+$ and $CD8^+$), NK-cells and pro-inflammatory cytokines suppression (67,68).

Zearalenone is a mycotoxin with a potent estrogenic activity, exerts immune modulatory effects on cell-mediated responses (Cellular immunity) and antibody dependant immunity (Humoral immunity) (69,70) As in pregnancy, period of high estrogen levels, affects the maternal immunity to permit normal fetal development, cell-mediated immunity to be negatively modulated and to increase immunoglobulin secretion (71-73). Estrogen stimulates the humoral immune responses. Another study done on rats fed 5.0 mg zearalenone/kg for 36 days revealed that ZEA alone can decrease the production of immunoglobulins (74). Also, an *in vitro* study with peripheral blood mononuclear cells of piglets treated with zearalenone showed a pronounced reduction in immunoglobulin levels (75). Thus, the contradictory effects of estrogen and ZEA on humoral immune response could be linked to specific receptor effects (76).

Therefore, estrogens can also affect the B cell production pathway in the bone marrow by a number of mechanisms, including inhibitory effect and apoptosis induction (77). The reduction in the mature spleen B cell population could be the direct effect of ZEA on these cells after leaving the bone marrow. A study conducted by Salah-Abbès *et al*. (78) was also found that ZEA can reduce the number of circulating bone marrow dependant lymphocytes in the blood of mice.

As expected, the estrogen-responsive tissues, such as the uterus, mammary gland, brain, and other organs, contain both types of estrogen receptors, the expression of which is tissue-specific. In addition to these tissues, however, cells in the immune system also have the same receptors; for example, alpha-estrogen receptor is expressed in T cells, natural killer cells, and some macrophages, Contrary, beta receptors are expressed mainly in B cells and monocytes. Seemingly, the immune-modulatory effects of estrogen on cell-mediated actions and antibody production had addressed much attention due to its role in pathogenesis of autoimmune diseases (79). Furthermore, different, *in vivo* studies, showed that high zearalenone administration led to an immunological suppression of (mitogen stimulated lymphocyte proliferation factor) together with elevation of interleukin-2 and interleukin-5 synthesis (80).

Summing up, it is possible that zeralenone can negatively affects both types of immunity (humoral and cellular), induce thymus atrophy, and evoke depletion of immunological cells in its architectural histology. Obviously, zearalenone and its related metabolites may hinder B cells development pathway in bone marrow through different types of mechanisms, like suppression and induction of the programmed cell death (apoptosis). Furthermore, it

is critical issue to determine the upper acceptable limits for different mycotoxins in milk and other sources that can alter the state of normal immune homeostasis (81).

In conclusion, globally, mycotoxins are fungal originated contaminants. They are significantly harmful to human and animal health if absorbed through the skin, inhaled, or ingested by mouth. Zearalenone, deoxynivalenol, ochratoxins, fumonisins, aflatoxins, T-2 toxins, and patulin are some potent mycotoxins produced by different species of *Penicillium, Aspergillus, and Fusarium* mycotic agents. Aflatoxins, fumonisins, T-2 toxins, and ochratoxins have the most serious threats to human and animal health universally. Attributing to its tropism to join the cellular estrogenic receptors, zearalenone has been considered as the most serious estrogenic mycotoxin. In male, this mycotoxin has the ability to induce considerable suppression in the testicular spermatogenesis, testosterone level, and significantly reduce libido beside its immunosuppressive effect. Furthermore, it may cause loss in body weight not just related to the reduction of food consumption but due to its capabilities to modulate some fundamental immune responses and subsequently to initiate damaging in the primary or in secondary lymphatic organs too. Moreover; ZEA also can initiate some phenotypic changes of lymphocytes in the spleen and thymus as a marker of its immunotoxicity. This review is summarizing the scientifically proven research data related to the pathophysiological consequences of zearalenone mycotoxicity in general and its immunotoxic effects on the immune system which eventually causing a lot of diseases and even death in human and animal beings.

Conflict of Interest

The authors declare that there is no conflict of interest.

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التسمم بالسم الفطري الزيرالنون : إستعراض فسلجي-إمراضي وتسمم مناعي

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الخلاصة

يشير مصطلح التسمم الفطري الى مجموعة التاثيرات المرضية الموءذيه للعديد من السموم التي التي تنتجها انواع عده من الفطريات في ارجاء العالم المختلفه. تصيب السموم الفطرية وهي مؤيضات ثانوية عدة اعضاء واجهزه في الانسان والحيوان.

يعتبر الزيرالينون وهو احد انواع السموم الفطرية المعروفة بتاثيراتها المشابهة للاستروجين سما مناعيا. هذا المركب الدائري الكبير ذو حلقة بيتا الحامضيه تنتجه انواع عده من الفطريات التابعه لجنس الفيوزيريوم مثل الروسيوم والكولموريوم والكراميزيريوم وانواع اخرى ووفقا لنشاطه الاستروجيني الفعالفقد تم تسبيبه للعديد من الاضطرابات التناسليه عند الاناث.

وهكذا فان الهدف من مقال المراجعه هذا هو هو لتقييم المالات الفسلجية المرضية وتبعاتها وفقا لتطور البحوث عليه في حقل التسممات المناعية الناشئة جراءه.

الكلمات المفتاحية: التسمم الفطري , الزيرالنون ,تسمم مناعي