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Zearalenone toxins produced by some species of *Fusarium*

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A B S T R A C T

Mycotoxins or fungal toxins are secondary metabolism comounds of filamentous fungi that are released at the end of the growth phase of particular species of *Fusarium spp., Aspergillus spp., Penicillium spp.* They are generated in hot and humid conditions. These toxins are included the most usual groups of food pollutants. Of the 400 kinds of mycotoxins identified, about 20 of them are considered a global threat to human being and animal health. Because these toxins can modify the food chain in different stages of planting, collecting, packing and processing. Zearalenone is a kind of mycotoxin created by the fungi Fusarium genus. They are found more in grains for instance corn, barley, wheat, oats and sorghum and have estrogenic effects on different organisms. Zeralenone is quickly absorbed and by binding to estrogen receptors, it disrupts the quantity of reproductive hormones. In this article, we review information on zearalenone generated by certain Fusarium species.

Introduction

Different species of the *Fusarim* fungi are considered as important pathogens in different plants. According to the Food and Agriculture Organization of the United Nations (FAO), every year millions of tons of food are lost due to contamination with mycotoxins generated by storage fungi. As a result of a study carried out on grain-based food products such as corn, bread, baby food and similar products, the presence of mycotoxins in excess of the permissible limit has been reported [1].

Most of the fungi in the world are mycotoxin-producing fungi, which they are found in different amounts in agricultural products. These filamentous fungi multiply mostly on edible plants, thus contaminating foods with mycotoxins in toxicologically relevant concentrations [2]. Their existence depends on weather conditions and it is difficult to control them and sometimes even impossible. So they can create significant risks for human and animal health. In addition, they cause economic losses and negative effects on business [3, 4]. [6]. Estrogenic mycotoxin Zearalenone (ZEN) is generated by genus Fusarium [7], *F. graminearum, F. culmorum, F. cerealis, F. equiseti, F. crookwellense, F. semitectum [8], F. verticillioides, F. sporotrichioides, F. oxysporum [9] and F. acuminatum [10]*. Among the mentioned fungi, *F. graminearum* manufacters this toxin the most, like other toxins, they multiply in warm and temperate climates [11]. Zeralenone has the chemical formula (C18H22O5) and was obtained for the first time as (F-2) in corn inoculated with Fumonisins, trichothecenes, and zearalenone are among the highly significant and toxic Fusarium toxins that are economically important. These toxins are also associated with acute and chronic human and animal diseases, which have carcinogenic, mutagenic, teratogenic, estrogenic, hemorrhagic, neurotoxic, hepatotoxic and immunosuppressive effects [5]. Also, these toxins, in addition to significant risks to health, are among the main food pollutants that have a transitory effect on global food security, especially in developing countriesFusarium (Figure 1) [12].

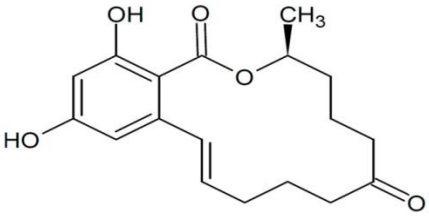

Figure 1. Structural formula of ziralenone

Zearalenone is a white crystal with a melting point of 161-163℃ and has a weak polarity [13]. Also, this poison is soluble in fats and alkaline aqueous solution and insoluble in carbon tetrachloride water [14]. Because the construction of Zearalenone is identical to estrogen, it can disrupt the endocrine system and lead to the propagation of estrogen receptor-positive cell lines. Furthermore, Zearalenone can initiate oxidative harm, stress in endoplasmic reticulum, apoptosis, and additional risks, leading to general toxic results, involving hepatotoxicity, reproductive toxicity, and immunotoxicity [15]. Humidity above 20% and temperature between 20 and 25℃ and humidity are favorable conditions for the growth and production of zearalenone by fungi [9].

Zearalenone is found in different forms, α-zearalenone (α-ZEL) (the synthetic form of zearalenone) and β-zearalenol (β-ZEL) are the two main metabolites of zearalenone that are metabolized in the liver. Zearalenone alpha-zeralanone (α-ZAL) and beta-zeralanol (β-ZAL) are other forms of zearalenone (Figure 2).

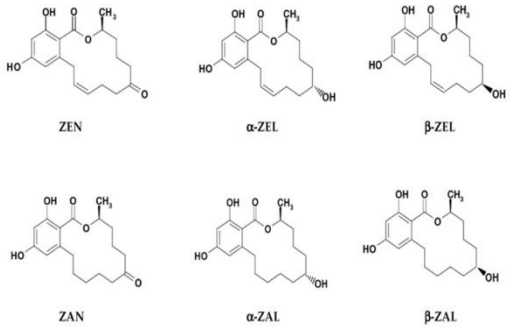

Figure 2. Chemical formula of zearalenone (ZEN/ZEA/ZON)[16]

2- Production of mycotoxin and its toxins by Fusarium

Fusarium is amoung the most vital and well-known genera of pathogenic fungi in plants, which due to the high disease losses in several crops has made *Fusarium* among the greatest important plant pathogenic groups in the world. *Fusarium species* are pathogens that cause crown rot diseases in cereal grains and cause infection in humans and animals [17]. These fungi are commonly found in soil, underground and aerial parts of plants, plant residue and other organic substrates [18]. They are also present in water as part of biofilms of water structure (19). Further than 50 species of *Fusarium* which are mostly animal and plant pathogenic organisms, have been identified. Trichothecenes, fumonisins, and zearalenones are three groups of mycotoxins manufactured by *Fusarium species* [21, 20].

2-1- Trichocenes

Trichocenes are the highly significant class of mycotoxins in terms of diversity and extent, so that more than 150 types of them have been identified. Trichothecenes are secondary metabolism compound formed via many genera of fungi such as *Fusarium, Myrotecium, , Trichoderma,* and *Trichothecium* [23, 22]. Structurally, they have a common nucleus, an olefinic group, an epoxide group and a different number of hydroxyl and acetyl groups (Figure 3).

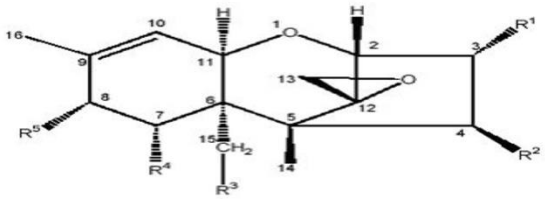

Figure 3. The structure of trichocenes and their related structures.

Also, they are a family of sesquiterpenoids with natural four rings and part of a terpene class consisting of three units of isoprene [25, 24].

Based on their performance, they are classified into four groups A to D. In fact, trichocenes are either classified as macrocyclic (characterized by the presence of a stereo-ether bridge between carbon numbers 4 and 15) or as non-macrocyclic (characterized by the lack of a stereo-ether bridge). Non-macrocyclic trichocenes are constructed via the genus *Fusarium* They are divided into trichocenes A (T-2 toxin, HT-2 toxin, T-2 triol, T-2 tetraol, scirpentriol, and disethoxyskirpanol) and B (DON, nivalenol, acetylated DON, and fusarnone X) [27, 26].(Figure 4).

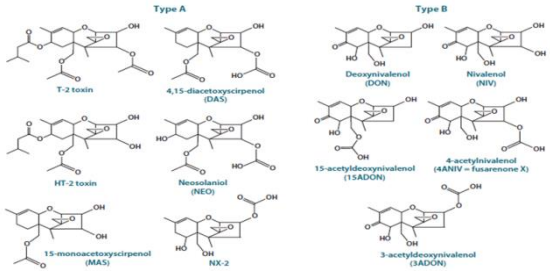

Figure 4. Chemical structures of selected A and B trichocene analogs created via Fusarium species.

These two groups are more toxic and are of particular importance in food [25]. As a result, trichocenes are generally a global concern because they are present in cereals for example corn, barley, oats, and wheat that are commonly consumed by livestock and humans [28, 29]. By preventing the synthesis of proteins in eukaryotes, this toxin can result in suppression or stimulation of the immune system and disrupt growth [30]. Consumption of this poison by livestock causes a reduction in nutrition and disruption of the immune system and changes in the nervous, endocrine, hepatic and digestive systems (31). Also, its consumption by humans leads to nausea, vomiting, abortion, weight loss, skin inflammation, internal organ bleeding, blood disorders, immune system suppression, and nervous system disorders [32].

2-2- Fumonisins

Fumonisins are cytotoxic and carcinogenic mycotoxins that were first discovered in 1988 [33]. Fumonisins are manufactured by various *Fusarium* species by condensing the amino acid alanine into an acetate-derived precursor. More than 28 different forms of fumonisins are known, which are grouped into A, B, C and P series (Figure 5).

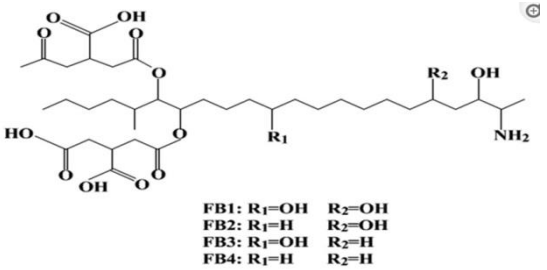

Figure 5. Chemical structure of fumonisin B

Fumonisin B (and especially fumonisin B1) is considered the extremely toxic type of fumonisin in the field of feed contamination. Fumonisin B1 is the major cause of one of the famouse corn plant diseases. Hot and dry periods followed by wet conditions and insect damage are the main predisposing factors for Fumonisin secretion by Fusarium species [34]. Fumonisin B1 causes cell destruction and death through preventing the biosynthesis of sphingolipid complexes, because it is structurally similar to sphingolipid bases [35, 36].

2-3- Zearalenones

Zearalenone is an estrogenic metabolite manufactured via numerous *Fusarium* species for instance *F. graminearum*, *F. roseum*, *F. culmorum* and *Fusarium crookwellense*. Zeralenone and its metabolites, which are called mycoestrogens, are natural estrogenic compounds and the main representative of this group of non-steroidal mycoestrogens.

Zearalenone is a 6-(10-hydroxy-6-oxo-trans-1-undesenyl)-β-resorcylic acid lactone that is biosynthesized from the polyketide pathway. α-zeralenol and β-zeralenol are the main metabolites of Zearalenone, which are mainly metabolized in the liver [37] (Figure 6).

Fusarium graminearum occurs certainly within corn along with great wetness content and has also been observed in moldy dry forage and pelleted feed. Zeralenone, as well identified as F-2, ordinarily infects corn, while can too happen in further crops around the world. Very humid conditions with alternating low (11 to 14 °C) and moderate (27 °C) temperatures are suitable for its production [39, 38].

2-3-1- Zearalenones toxicokinetic

The toxicokinetic of ZEA is mostly related to the speed of entering the body, circulation, absorption, metabolism and final elimination. ZEA enters the animal bulk through contaminated feed, it may undergo structural changes by intestinal microflora or liver metabolic enzymes during absorption and metabolism, and eventually produce numerous ZEN metabolites [40].

2-3-2- Absorption and distribution of Zearalenones

Feeds containing zearalenones are rapidly absorbed by the intestinal walls of monogastric animals and human digestive system. Although it seems difficult to check the amount of absorption of this poison due to the high secretion of bile acid [41]. There are many studies that have shown that Zearalenones are broadly allocated in animal tissues and are slowly eliminated [44, 43, 42]. Although the main site of Zearalenones deposition is the liver, it can be distributed to other body tissues such as kidney, intestine, adipose tissue and reproductive organs (uterus, testes and ovaries) [45].

3-2-3- Metabolism and excretion of zearalenone

Liver and intestine are the greatest significant organs that play an essential role in the biological transformation of zearalenone. Of course, estrogen target organs, for instance the ovary, can convert zearalenone, which is known as steroid metabolism. At this stage, the toxin and its metabolic compounds are conjugated via uridine diphosphate glucuronyl transferase. Thus, it forms modified or masked metabolites like derivatives conjugated with glucose, sulfate, or glucuronide [46]. This intraovarian reaction is catalyzed by hydrogenase enzymes such as 3α- or 3β-hydroxysteroid dehydrogenase (HSD), leading to the production of α- and β-ZEL metabolites. Its α form is more toxic than ZEA due to its high affinity for estrogen receptors, but the β form has a lower affinity for these receptors and is practically less toxic. This pathway is the first stage in the biological transformation of ZEA. The highest amount of α-ZEL is produced by pig liver microsomes, while chicken microsomes produce the most β-ZEL [9]. In fact, as a minimum four ZEA metabolic compounds such as α-ZOL, β-ZOL, α-ZEL, or β-ZEL are produced at this stage. These metabolic compounds suggest the reducing metabolic compounds of ZEA in the stage I metabolism procedure [43]. The second step of biotransformation relies on the uridine-5-diphospho-glucuronosyltransferase (UDPGT) enhanced conjugation of ZEN in addition to its metabolites with glucuronic acid. At this stage, the toxin and its metabolic compounds are conjugated via uridine diphosphate glucuronyl transferase. Therefore, it forms modified metabolites such as derivatives conjugated with glucose, sulfate or glucuronide [47]. In humans, biotransformations of ZEN occur in the liver, lungs, kidneys, and intestines, but in other living organisms, it mostly happens within liver [48, 49, 50]. Parts of ZEA and its metabolic compounds that are produced in the second stage will be excreted through the urine or feces. For example, in a study conducted on young female mice, it was shown that consuming 1 or 10 mg/kg body weight of ZEA as feed, about 55% of the poison was excreted through feces and another 15-20% through urine [51]. In many mammals, biliary secretion and hepatic circulation (EHC) are the very significant processes involved in the excretion and absorption of ZEA [52]. So that ZEA-glucuronide derivatives are repeatedly collected and reabsorbed in bile, which are finally metabolized via the cells of intestinal mucosa. So again, toxins go into the portal vein, liver, and systemic circulation, where ZOL with extreme estrogenic action may form. The reabsorption process affects the metabolized and endocrine balance, extends the shelf life of ZEA, prolongs the duration of toxic effects, and delays its elimination [53].

2-3-4- The entry of Zearalenone into food

Due to the toxicity of zearalenone, their introduction into feed has led to concerns in this field, which had been broadly studied. The presence of zeralenone has been confirmed in various plant grains for instance wheat, barley, corn, sorghum, rye [8, 11], rice [8], corn silage [9], sesame seeds, alfalfa [54], flour and malt. Also, this toxin may be added to cereal products for human consumption, baked goods, breakfast cereals [55] and bread [46]. On the other hand, it may reach the individual food chain indirectly through the consumption of milk, meat and eggs of animals that have consumed feed contaminated with zearalenone [57, 56]. According to the studies conducted in this field, the highest level of zearalenone was found in samples of corn, corn seeds, fiber feed, mixed feed for fattening pigs and fish feed. As a result, it can be seen that cereals and food items are the greatest exposed to the presence of Zearalenon [58, 59, 61, 60].

2-3-5- The effects of zearalenone on living organisms

Zearalenone mycotoxin has immunotoxic [62], hepatotoxic [62] and xenobiotic [63] effects on living organisms. Its activity depends on the immune status and generative approach of living organisms [64]. According to Rai et al. [65], the liver is the core position for the distribution of zearalenone. The presence of zearalenone in the liver leads to histopathological changes and liver cancer [66]. Transaminases and serum bilirubin levels increase in rodents when the liver is damaged by zearalenone [46]. Also, the liver damage of mice [67] and fish [68] caused by zaralenone leads to weight loss in these organisms. Intravenous zeralenone has hematotoxic effects on blood coagulation and blood parameter modification [8,65]. In the study, it was shown that the amount of ALT (alanine aminotransferase), ALP (alkaline phosphatase) and AST (aspartate aminotransferase) increased in the serum of mice treated with Zeralenone, but total protein and serum albumin decreased [65]. In the studies conducted, rise in hematocrit and MCV index (mean body volume) was observed in mice treated with Zearalenone, but the number of platelets decreased significantly and the quantity of white blood cells increased [69].

The mycotoxin zearalenone also has strong estrogenic [71, 70] and anabolic [71, 70] effects. As α-ZAL is a metabolite of ZEN, it is used as a growth stimulant due to its anabolic activity [72].

Zeralenone in humans can disrupt the functioning of the endocrine system by binding to alpha and beta estrogen receptors [73]. Among the living organisms, pigs [65] and ruminants [49] are in the middle of the greatest sensitive and birds such as poultry [74] are the most resistant to the properties of zearalenone. With the most significant estrogenic effects of zearalnones, we can mention fertility disorders (infertility or reduced fertility), uterine enlargement, increased incidence false pregnancy, stillbirth and small babies [9].

In the study, redness and swelling of the vulva, uterus enlargement, cyst formation in the ovaries, and mammary glands enlargement occurred in female pigs treated with zearalenone, but testicular atrophy and a decrease in sperm concentration were observed in the treated male pigs [75]. Due to their structure, Zearalenone inhibits steroid hormones secretion and interferes in the pre-ovulatory stage, thereby inhibiting follicle maturation in mammals [76]. The first symptoms caused by the consumption of Zearalenone in cows can be mentioned swelling of the vulva, disturbance in the estrous cycle, infertility, inflammation of the uterus and mammary glands, abortion, placental retention and vaginitis [77]. Zearalnones additionally show an important function in hyperestrogenic syndrome [76, 78].

Also, zearalenone used by human cause premature puberty [79], abortion and weight loss of the fetus, in addition to a decrease in milk production in women. It is hypothesized that zearalenone can change the morphology of uterine tissue and cause a decrease in LH and progesterone levels [8]. Zearalenone also reduces the number of sperm and their viability in men [80]. Gil-Serna et al [8], reported that zearalenone is genotoxic and can form DNA adducts in vitro. Zearalenone is also involved in DNA fragmentation, micronucleus formation, chromosomal aberration, cell proliferation and cell apoptosis [65]. Research has shown that zearalenone and its metabolite β-ZEL can mimic the capability of 17-β-estradiol to stimulate estrogen receptor transcriptional activity [81]. In a study on male rats treated with zearalenone, cytotoxicity and apoptosis were observed [82].

2-3-6- Zeralanone detoxification

Today, most of the research is focused on the detoxification of mycotoxins such as zearalenone using non-pathogenic microorganisms, promising to find a new way to achieve Mycotoxin detoxification in practical situations. Biological detoxification mainly involves the absorption of mycotoxins on the walls of microbial cells or the destruction of mycotoxins caused by microbial secretions. In the cell wall of some probiotics, there are special structures that allow them to absorb the zaralenone toxin. For example, cell walls contain carbohydrates (peptidoglycan, mannose, Glucan), proteins, and lipids that may represent different adsorption sites. Therefore, the development and use of probiotics as mycotoxin absorbing agents in production was investigated [83]. Yeasts also absorb mycotoxins, these compounds are relatively stable in the body. In a study, adding 0.2% of yeast cell wall extract to food effectively prevented reproductive toxicity caused by 0.4 mg/L of zearalenone in piglets [55, 56]. The capability of Saccharomyces cerevisiae to absorb mycotoxins into its cell wall was investigated by Swamy et al. [84]. The usage of S. cerevisiae as an additive that inhibits the toxicity of zearalenone added to feed is actually known as a detoxification agent. In one study, colonization of S. cerevisiae in the gastrointestinal tract was shown not only to improve animal productivity and health, but also to minimize the bioavailability of zearalenone in the tract [86, 85]. The usage of Lactobacillus strains as zearalenone detoxification was investigated as Murphy et al. [87] showed that when zearalenone (0.2 μg/ml) was incubated with each strain of L. rhamnosus, a significant proportion (38% to 46%) of zearalenone toxin was absorbed through bacteria. It was also shown that L. plantarum has a high potential in absorbing mycotoxin zearalenone [88].

Conclusion

Zearalenone is one of the main mycotoxins manufactured by *Fusarium*, which can directly and indirectly have negative effects on many species. It causes various changes and disorders related to the reproductive system and significant economic losses. Due to the toxicity of zearalenone and its metabolites, it has endangered the health of humans and living organisms and has caused concerns in the consumption of feeds, especially corn and its products. By using detoxification additives such as probiotics and other agents, this concern can be reduced to some extent. Considering the ubiquitous occurrence of these compounds, it is suggested that, in addition to the use of detoxification, anti-pollution methods and preventing the production of zearalenone should be investigated.

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Competing Interests

There are no competing interests.

References

[1] Kumar, R., Mishra, A. K., Dubey, N. K., & Tripathi, Y. B. (2007). Evaluation of Chenopodium ambrosioides oil as a potential source of antifungal, antiaflatoxigenic and antioxidant activity.

International journal of food microbiology, 115(2), 159-164.

[2] Bennett, J. W. (2003). Klich. M. Mycotoxins. Clinical Microbiology Reviews, 16(3), 497-516.

[3] Wild, C. P., & Gong, Y. Y. (2010). Mycotoxins and human disease: a largely ignored global health issue. Carcinogenesis, 31(1), 71-82.

[4] Smith, J. E., Solomons, G., Lewis, C., & Anderson, J. G. (1995). Role of mycotoxins in human and animal nutrition and health. Natural toxins, 3(4), 187-192.

[5] Yazar, S., & Omurtag, G. Z. (2008). Fumonisins, trichothecenes and zearalenone in cereals. International Journal of Molecular Sciences, 9(11), 2062-2090.

[6] Smith, J. E., Solomons, G. L., Lewis, C. W., & Anderson, J. G. (1994). Mycotoxins in human nutrition and health. European Commision, Directorate-General XII, Science. Research and Development. EUY16048EN, Brussels, Belgium.

[7] SCOOP (European Commission, Directorate-General Health and Consumer Protection- Scientific Co-Operation on Questions relating to Food) SCOOP, Task 3.2.10. Collection of Occurrence Data of Fusarium Toxins in Food and Assessment of Dietary Intake by the Populstion of EU Member States. European Commission, Directorate-General Health and Consumer Protection, Reports on Tasks Forscientific Co-Operation. European Commission, Directorate-General Health and Consumer Protection; Brussel, Belgium: 2003.

[8] Batt, C. A., & Tortorello, M. L. (2014). Encyclopedia of food microbiology. (No Title).

[9] Gupta, R. C. (Ed.). (2012). Veterinary toxicology: basic and clinical principles. Academic press.

[10] Mizutani, K., Nagatomi, Y., & Mochizuki, N. (2011). Metabolism of zearalenone in the course of beer fermentation. Toxins, 3(2), 134-141.

[11] Mally, A., Solfrizzo, M., & Degen, G. H. (2016). Biomonitoring of the mycotoxin Zearalenone: Current state-of-the art and application to human exposure assessment. Archives of toxicology, 90, 1281-1292.

[12] Urry, W. H., Wehrmeister, H. L., Hodge, E. B., & Hidy, P. H. (1966). The structure of zearalenone. Tetrahedron Letters, 7(27), 3109-3114.

[13] EFSA Panel on Contaminants in the Food Chain. (2011). Scientific Opinion on the risks for public health related to the presence of zearalenone in food. EFSA Journal, 9(6), 2197.

[14] Alshannaq, A., & Yu, J. H. (2017). Occurrence, toxicity, and analysis of major mycotoxins in food. International journal of environmental research and public health, 14(6), 632.

[15] Takemura, H., Shim, J. Y., Sayama, K., Tsubura, A., Zhu, B. T., & Shimoi, K. (2007). Characterization of the estrogenic activities of zearalenone and zeranol in vivo and in vitro. The Journal of steroid biochemistry and molecular biology, 103(2), 170-177.

[16] Urraca, J. L., Marazuela, M. D., & Moreno-Bondi, M. C. (2004). Analysis for zearalenone and α-zearalenol in cereals and swine feed using accelerated solvent extraction and liquid chromatography with fluorescence detection. Analytica Chimica Acta, 524(1-2), 175-183.

[17] Evans, J., Levesque, D., De Lahunta, A., & Jensen, H. E. (2004). Intracranial fusariosis: a novel cause of fungal meningoencephalitis in a dog. Veterinary pathology, 41(5), 510-514.

[18] Nelson, P. E., Dignani, M. C., & Anaissie, E. J. (1994). Taxonomy, biology, and clinical aspects of Fusarium species. Clinical microbiology reviews, 7(4), 479-504.

[19] Elvers, K. T., Leeming, K., Moore, C. P., & Lappin-Scott, H. M. (1998). Bacterial-fungal biofilms in flowing water photo-processing tanks. Journal of Applied Microbiology, 84(4), 607-618.

[20] Ekwomadu, T. I., & Mwanza, M. (2015). ADECADE OF MYCOTOXINS RESEARCH IN AFRICA: AREVIEW. OCCURRENCE, TOXICOLOGY AND MANAGEMENT STRATEGIES, 169.

[21] Zhou, T., He, J., & Gong, J. (2008). Microbial transformation of trichothecene mycotoxins. World Mycotoxin Journal, 1(1), 23-30.

[22] Foroud, N. A., Baines, D., Gagkaeva, T. Y., Thakor, N., Badea, A., Steiner, B., ... & Bürstmayr, H. (2019). Trichothecenes in cereal grains–an update. Toxins, 11(11), 634.

[23] Wu, Q., Huang, L., Liu, Z., Yao, M., Wang, Y., Dai, M., & Yuan, Z. (2011). A comparison of hepatic in vitro metabolism of T-2 toxin in rats, pigs, chickens, and carp. Xenobiotica, 41(10), 863-873.

[24] Shank, R. A., Foroud, N. A., Hazendonk, P., Eudes, F., & Blackwell, B. A. (2011). Current and future experimental strategies for structural analysis of trichothecene mycotoxins—A prospectus. Toxins, 3(12), 1518-1553.

[25] Desjardins, A. E. (2006). Fusarium mycotoxins: chemistry, genetics, and biology. American Phytopathological Society (APS Press).

[26] Thrane, U., Adler, A., Clasen, P. E., Galvano, F., Langseth, W., Lew, H., ... & Ritieni, A. (2004). Diversity in metabolite production by Fusarium langsethiae, Fusarium poae, and Fusarium sporotrichioides. International Journal of Food Microbiology, 95(3), 257-266.

[27] Rocha, O., Ansari, K., & Doohan, F. M. (2005). Effects of trichothecene mycotoxins on eukaryotic cells: a review. Food additives and contaminants, 22(4), 369-378.

[28] Eriksen, G. S., & Pettersson, H. (2004). Toxicological evaluation of trichothecenes in animal feed. Animal feed science and technology, 114(1-4), 205-239.

[29] Wu, Q., Kuča, K., Humpf, H. U., Klímová, B., & Cramer, B. (2017). Fate of deoxynivalenol and deoxynivalenol-3-glucoside during cereal-based

thermal food processing: a review study. Mycotoxin Research, 33, 79-91.

[30] Council for Agricultural Science. (2003). Mycotoxins: risks in plant, animal, and human systems (No. 139). Council for Agricultural.

[31] Sampietro, D. A., Díaz, C. G., González, V., Vattuone, M. A., Ploper, L. D., Catalán, C. A. N., & Ward, T. J. (2011). Species diversity and toxigenic potential of Fusarium graminearum complex isolates from maize fields in northwest Argentina. International Journal of Food Microbiology, 145(1), 359-364.

[32] Logrieco, A., Bottalico, A., Mulé, G., Moretti, A., & Perrone, G. (2003). Epidemiology of toxigenic fungi and their associated mycotoxins for some Mediterranean crops. Epidemiology of Mycotoxin Producing Fungi: Under the aegis of COST Action 835 'Agriculturally Important Toxigenic Fungi 1998–2003', EU project (QLK 1-CT-1998–01380), 645-667.

[33] Gelderblom, W. C., Jaskiewicz, K., Marasas, W. F., Thiel, P. G., Horak, R. M., Vleggaar, R., & Kriek, N. (1988). Fumonisins--novel mycotoxins with cancer-promoting activity produced by Fusarium moniliforme. Applied and environmental microbiology, 54(7), 1806-1811.

[34] Marasas, W. F. (1996). Fumonisins: history, world-wide occurrence and impact. Fumonisins in food, 1-17.

[35] Richard, J. L. (2000). Mycotoxins-an overview. Romer Labs' guide to mycotoxins, 1, 1-48.

[36] Rodrigues, I., Handl, J., & Binder, E. M. (2011). Mycotoxin occurrence in commodities, feeds and feed ingredients sourced in the Middle East and Africa. Food Additives and Contaminants: Part B, 4(3), 168-179.

[37] Zinedine, A., Soriano, J. M., Juan, C., Mojemmi, B., Molto, J. C., Bouklouze, A., ... & Manes, J. (2007). Incidence of ochratoxin A in rice and dried fruits from Rabat and Salé area, Morocco. Food Additives and Contaminants, 24(3), 285-291.

[38] EFSA Panel on Contaminants in the Food Chain. (2011). Scientific Opinion on the risks for public health related to the presence of zearalenone in food. EFSA Journal, 9(6), 2197.

[39] Richard, J. L. (2000). Mycotoxins-an overview. Romer Labs' guide to mycotoxins, 1, 1-48.

[40] Rai, A., Das, M., & Tripathi, A. (2020). Occurrence and toxicity of a fusarium mycotoxin, zearalenone. Critical Reviews in Food Science and Nutrition, 60(16), 2710-2729.

[41] Kuiper-Goodman, T., Scott, P., & Watanabe, H. (1987). Risk assessment of the mycotoxin zearalenone. Regulatory toxicology and pharmacology, 7(3), 253-306.

[42] Biehl, M. L., Prelusky, D. B., Koritz, G. D., Hartin, K. E., Buck, W. B., & Trenholm, H. L. (1993). Biliary excretion and enterohepatic cycling of zearalenone in immature pigs. Toxicology and applied pharmacology, 121(1), 152-159.

[43] Dänicke, S., Swiech, E., Buraczewska, L., & Ueberschär, K. H. (2005). Kinetics and metabolism of zearalenone in young female pigs. Journal of animal physiology and animal nutrition, 89(7-8), 268-276.

[44] Devreese, M., Antonissen, G., Broekaert, N., De Baere, S., Vanhaecke, L., De Backer, P., & Croubels, S. (2015). Comparative toxicokinetics, absolute oral bioavailability, and biotransformation of zearalenone in different poultry species. Journal of agricultural and food chemistry, 63(20), 5092-5098.

[45] Liang, Z., Ren, Z., Gao, S., Chen, Y., Yang, Y., Yang, D., ... & Shen, L. (2015). Individual and combined effects of deoxynivalenol and zearalenone on mouse kidney. Environmental toxicology and pharmacology, 40(3), 686-691.

[46] Fink-Gremmels, J., & Malekinejad, H. J. A. F. (2007). Clinical effects and biochemical mechanisms associated with exposure to the mycoestrogen zearalenone. Animal Feed Science and Technology, 137(3-4), 326-341.

[47] Dong, M., He, X. J., Tulayakul, P., Li, J. Y., Dong, K. S., Manabe, N., ... & Kumagai, S. (2010). The toxic effects and fate of intravenously administered zearalenone in goats. Toxicon, 55(2-3), 523-530.

[48] Zinedine, A., Soriano, J. M., Moltó, J. C., & Manes, J. (2007). Review on the toxicity, occurrence, metabolism, detoxification, regulations and intake of zearalenone: an oestrogenic mycotoxin. Food and chemical toxicology, 45(1), 1-18.

[49] Minervini, F., Giannoccaro, A., Fornelli, F., Dell'Aquila, M. E., Minoia, P., & Visconti, A. (2006). Influence of mycotoxin zearalenone and its derivatives (alpha and beta zearalenol) on apoptosis and proliferation of cultured granulosa cells from equine ovaries. Reproductive Biology and Endocrinology, 4, 1-9.

[50] Kwaśniewska, K., Gadzała-Kopciuch, R., & Cendrowski, K. (2015). Analytical procedure for the determination of zearalenone in environmental and biological samples. Critical Reviews in Analytical Chemistry, 45(2), 119-130.

[51] Fitzpatrick, D. W., Arbuckle, L. D., & Hassen, A. M. (1988). Zearalenone metabolism and excretion in the rat: effect of different doses. Journal of Environmental Science & Health Part B, 23(4), 343-354.

[52] Biehl, M. L., Prelusky, D. B., Koritz, G. D., Hartin, K. E., Buck, W. B., & Trenholm, H. L. (1993). Biliary excretion and enterohepatic cycling of zearalenone in immature pigs. Toxicology and applied pharmacology, 121(1), 152-159.

[53] Shin, B. S., Hong, S. H., Bulitta, J. B., Lee, J. B., Hwang, S. W., Kim, H. J., ... & Yoo, S. D. (2009). Physiologically based pharmacokinetics of zearalenone. Journal of Toxicology and Environmental Health, Part A, 72(21-22), 1395-1405.

[54] Gromadzka, K., Waskiewicz, A., Chelkowski, J., & Golinski, P. (2008). Zearalenone and its

metabolites: occurrence, detection, toxicity and guidelines. World Mycotoxin Journal, 1(2), 209-220.

[55] da Rocha, M. E. B., Freire, F. D. C. O., Maia, F. E. F., Guedes, M. I. F., & Rondina, D. (2014). Mycotoxins and their effects on human and animal health. Food control, 36(1), 159-165.

[56] Prelusky, D. B., Scott, P. M., Trenholm, H. L., & Lawrence, G. A. (1990). Minimal transmission of zearalenone to milk of dairy cows. Journal of Environmental Science & Health Part B, 25(1), 87-103.

[57] Coffey, R., Cummins, E., & Ward, S. (2009). Exposure assessment of mycotoxins in dairy milk. Food control, 20(3), 239-249.

[58] Domijan, A., Peraica, M., Cvjetkovic, B. O. G. D. A. N., Turcin, S., Jurjevic, Z. E. L. J. K. O., & Ivic, D. A. R. I. O. (2005). Mould contamination and co-occurrence of mycotoxins in maize grain in Croatia. ACTA PHARMACEUTICA-ZAGREB-, 55(4), 349.

[59] Scudamore, K. A., & Patel, S. (2009). Occurrence of Fusarium mycotoxins in maize imported into the UK, 2004–2007. Food Additives & Contaminants: Part A, 26(3), 363-371.

[60] Manova, R., & Mladenova, R. (2009). Incidence of zearalenone and fumonisins in Bulgarian cereal production. Food control, 20(4), 362-365.

[61] Zinedine, A., Brera, C., Elakhdari, S., Catano, C., Debegnach, F., Angelini, S., ... & Miraglia, M. (2006). Natural occurrence of mycotoxins in cereals and spices commercialized in Morocco. Food control, 17(11), 868-874.

[62] Zinedine, A., Soriano, J. M., Moltó, J. C., & Manes, J. (2007). Review on the toxicity, occurrence, metabolism, detoxification, regulations and intake of zearalenone: an oestrogenic mycotoxin. Food and chemical toxicology, 45(1), 1-18.

[63] Buszewska-Forajta, M. (2020). Mycotoxins, invisible danger of feedstuff with toxic effect on animals. Toxicon, 182, 34-53.

[64] Gajecka, M., & Gajecki, M. (2014). Is mycotoxins can be used as inhibitors in milk. Innow. MLecz, 2, 22-29.

[65] Rai, A., Das, M., & Tripathi, A. (2020). Occurrence and toxicity of a fusarium mycotoxin, zearalenone. Critical Reviews in Food Science and Nutrition, 60(16), 2710-2729.

[66] Marin, D. E., Pistol, G. C., Bulgaru, C. V., & Taranu, I. (2019). Cytotoxic and inflammatory effects of individual and combined exposure of HepG2 cells to zearalenone and its metabolites. Naunyn-Schmiedeberg's archives of pharmacology, 392(8), 937-947.

[67] Hueza, I. M., Raspantini, P. C. F., Raspantini, L. E. R., Latorre, A. O., & Górniak, S. L. (2014). Zearalenone, an estrogenic mycotoxin, is an immunotoxic compound. Toxins, 6(3), 1080-1095.

[68] Pietsch, C., Kersten, S., Valenta, H., Dänicke, S., Schulz, C., Burkhardt-Holm, P., & Junge, R. (2015). Effects of dietary exposure to zearalenone (ZEN) on carp (Cyprinus carpio L.). Toxins, 7(9), 3465-3480.

[69] Maaroufi, K., Chekir, L., Creppy, E. E., Ellouz, F., & Bacha, H. (1996). Zearalenone induces modifications of haematological and biochemical parameters in rats. Toxicon, 34(5), 535-540.

[70] Jodlbauer, J., Zöllner, P., & Lindner, W. (2000). Determination of zearalenone and its metabolites in urine and tissue samples of cow and pig by LC-MS/MS. Mycotoxin Research, 16, 174-178.

[71] Takagi, M., Uno, S., Kokushi, E., Shiga, S., Mukai, S., Kuriyagawa, T., ... & Fink-Gremmels, J. (2011). Measurement of urinary zearalenone concentrations for monitoring natural feed contamination in cattle herds: On-farm trials1. Journal of animal science, 89(1), 287-296.

[72] Songsermsakul, P., Sontag, G., Cichna-Markl, M., Zentek, J., & Razzazi-Fazeli, E. (2006). Determination of zearalenone and its metabolites in urine, plasma and faeces of horses by HPLC–APCI–MS. Journal of Chromatography B, 843(2), 252-261.

[73] Kovalsky Paris, M. P., Schweiger, W., Hametner, C., Stückler, R., Muehlbauer, G. J., Varga, E., ... & Adam, G. (2014). Zearalenone-16-O-glucoside: a new masked mycotoxin. Journal of agricultural and food chemistry, 62(5), 1181-1189.

[74] Zain, M. E. (2011). Impact of mycotoxins on humans and animals. Journal of Saudi chemical society, 15(2), 129-144.

[75] Binder, S. B., Schwartz-Zimmermann, H. E., Varga, E., Bichl, G., Michlmayr, H., Adam, G., & Berthiller, F. (2017). Metabolism of zearalenone and its major modified forms in pigs. Toxins, 9(2), 56.

[76] Zhang, G. L., Feng, Y. L., Song, J. L., & Zhou, X. S. (2018). Zearalenone: A mycotoxin with different toxic effect in domestic and laboratory animals' granulosa cells. Frontiers in genetics, 9, 667.

[77] Gliński, Z., Kostro, K., & Gajęcki, M. (2011). Mikozy i mikotoksykozy zwierząt. Wyd. UP w Lublinie.

[78] El-Sharkaway, S. H., Selim, M. I., Afifi, M. S., & Halaweish, F. T. (1991). Microbial transformation of zearalenone to a zearalenone sulfate. Applied and Environmental Microbiology, 57(2), 549-552.

[79] de Rodriguez, C. A. S., Bongiovanni, A. M., & de Borrego, L. C. (1985). An epidemic of precocious development in Puerto Rican children. The Journal of pediatrics, 107(3), 393-396.

[80] Kwaśniewska, K., Gadzała-Kopciuch, R., & Cendrowski, K. (2015). Analytical procedure for the determination of zearalenone in environmental and biological samples. Critical Reviews in Analytical Chemistry, 45(2), 119-130.

[81] Miksicek, R. J. (1994). Interaction of naturally occurring nonsteroidal estrogens with expressed recombinant human estrogen receptor. The Journal

of steroid biochemistry and molecular biology, 49(2-3), 153-160.

[82] Kim, I. H., Son, H. Y., Cho, S. W., Ha, C. S., & Kang, B. H. (2003). Zearalenone induces male germ cell apoptosis in rats. Toxicology letters, 138(3), 185-192.

[83] Wang, N., Wu, W., Pan, J., & Long, M. (2019). Detoxification strategies for zearalenone using microorganisms: A review. Microorganisms, 7(7), 208.

[84] Swamy, H. V. L. N., Smith, T. K., MacDonald, E. J., Boermans, H. J., & Squires, E. J. (2002). Effects of feeding a blend of grains naturally contaminated with Fusarium mycotoxins on swine performance, brain regional neurochemistry, and serum chemistry and the efficacy of a polymeric glucomannan mycotoxin adsorbent. Journal of Animal Science, 80(12), 3257-3267.

[85] Ghosh, T. K., Haldar, S., Bedford, M. R., Muthusami, N., & Samanta, I. (2012). Assessment of yeast cell wall as replacements for antibiotic growth promoters in broiler diets: effects on performance, intestinal histo-morphology and humoral immune responses. Journal of Animal Physiology and Animal Nutrition, 96(2), 275-284.

[86] Liu, N., Wang, J., Liu, Z., Wang, Y., & Wang, J. (2018). Effect of supplemental yeast cell walls on growth performance, gut mucosal glutathione pathway, proteolytic enzymes and transporters in growing broiler chickens. Journal of Animal Science, 96(4), 1330-1337.

[87] Wan, M. L., Turner, P. C., Allen, K. J., & El-Nezami, H. (2016). Lactobacillus rhamnosus GG modulates intestinal mucosal barrier and inflammation in mice following combined dietary exposure to deoxynivalenol and zearalenone. Journal of Functional Foods, 22, 34-43.

[88] Vega, M. F., Dieguez, S. N., Riccio, B., Aranguren, S., Giordano, A., Denzoin, L., ... & González, S. N. (2017). Zearalenone adsorption capacity of lactic acid bacteria isolated from pigs. brazilian journal of microbiology, 48, 715-723.