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Reproductive Toxicity Caused by Zearalenone on Animals and Its Possible Interventions

Qingyan Wang[1], Wei Sun[2], Wenjie Chen[1], Ruiping Li[1], Hongxi Xu[1], Samuel Kumi Okyere[3], Jun Jiang[1]

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ABSTRACT

Zearalenone (ZEN) is a mycotoxin that is usually found in moldy grains. ZEN causes reproductive toxicity to domestic animals by interfering with follicular and embryonic development, reducing sperm vitality and destroying the homeostasis of endogenous hormones, leading to reproductive system diseases such as abortion, ovarian dysfunction and stillbirth. The reproductive damage caused by zearalenone is mainly attributed to the factors as follows: (1) interaction with estrogen receptor; (2) induction of oxidative stress; (3) induction of apoptosis, necrosis, autophagy and iron prolapse and (4) interference with cell replication cycle. Natural compounds and micro-nutrients have the potential to alleviate the oxidative stress caused by ZEN. In addition, some microorganisms and enzymes have also shown good detoxification effects. Therefore, in this review, we focus on the damage caused by ZEN on animal gamete development and embryonic development, its molecular mechanisms and suggested some potential mitigation measures for the prevention of ZEN-induced toxicity to provide information for preventing toxicity associated with ZEN as well as serve as a foundation for further development of drug candidates for the treatment of ZEN induced damage.

Key words: Microorganisms, Molecular mechanism, Prevention, Reproductive toxicity, Zearalenone.

Zearalenone (ZEN) is a non-steroidal estrogen mycotoxin, mainly produced by Fusarium fungi such as *F. graminearum, F. culmorum, F. cerealis, F. equiseti, F. crookwellense* and *F. semitectum*. It is widely found in cereals and their by-products (Rai *et al*., 2020). ZEN is a resorcinol lactone with molecular formula C18H22O5 and chemical name, 6-[10-hydroxy-6-oxy-trans-1-undecenyl]-B-resorcinol lactone (Fig 1A). ZEN and its metabolites are similar to nature estrogens in molecular structure, such as 17β-estradiol (Fig 1B), which can bind to estrogen receptors, causing severe damage to the reproductive system by triggering estrogen-like effects (Cai *et al.,* 2019). Furthermore, due to the thermal stability of ZEN, it could be transported from farmland to the aquatic system through rainwater (Döll *et al.,* 2011).

Once ingested into the body, ZEN will be transformed, absorbed and metabolized by gut microbiota or mucosal cells. ZEN will be converted into two main metabolites in the intestines, *i.e*, α-zearalenol (α-ZOL) and β-zearalenol (β-ZOL), which are formed by the ZEN reduction reaction. These metabolites, including α- zearamycin and β- Zearaziol, penetrate different tissues and organs (Buranatragool *et al.,* 2015). These α and β metabolites increase and decrease estrogen activity respectively compared to ZEN (Ali *et al.,* 2018). ZEN and its derivatives conjugate *in vivo* with glucuronic acid to form glucuronic acid polymer, which has been reported to weaken estrogen activity (Caroline *et al.,* 2015). ZEN has stability, leading to slow degradation during storage. ZEN can target multiple organs thus, causes cytotoxicity, genotoxicity, hepatotoxicity, immunotoxicity and reproductive toxicity (Ropejko *et al.,* 2021).

Owing to its extensive toxicity, the detoxification of ZEN has always been a hot topic for researchers, largely focusing on physical, chemical and biological methods. Studies have shown that ZEN causes many reproductive dysfunction in sows, such as infertility, abortion, ovarian dysfunction, ovulation inhibition, vulvovaginitis, embryonic toxicity of wig, pathological changes, ovarian changes, abnormal birth and stillbirth (Shi *et al.,* 2018). In this review, we focus on the reproductive damage caused by ZEN, its potential mechanisms and the available mitigation measures for prevention or treatment of ZEN-induced toxicity.

[1]Wenzhou Vocational College of Science and Technology, Wenzhou 325 006, Zhejiang, China.
[2]Tongren Polytechnic College, Bijiang District, Tongren, Guizhou, 554 300, China.
[3]Department of Pharmaceutical Sciences, School of Medicine, Wayne State University, Detroit, USA.

Corresponding Author: Jun Jiang, Wenzhou Vocational College of Science and Technology, Wenzhou 325 006, Zhejiang, China. Email: genzzj@163.com

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ZEN-induced reproductive toxicity in animals

ZEN toxicity on sperm vitality

ZEN causes damage to the male animal's reproduction by reducing semen quality and hindering spermatogenesis Pang *et al.* (2017) reported that the spermatogenic cells in the convoluted seminiferous tubules of male mice fed ZEN at the dose of 20 or 40 µg/kg were significantly decreased after 14 days of treatment. In the same study, after 28 or 42 days of ZEN treatment, the authors observed an increase in DNA breaks in spermatogenic cells at a ZEN dose-dependent mode. Furthermore, by comparing with that in the control group, the concentration, vitality and hyperactivity rate of sperm in the ZEN-treated groups decreased in a dose and time-dependent manner, whereas the sperm malformation rate and mortality rate in the ZEN groups increased significantly.

Another study also reported a reduction of the weight of testes and epididymis of male Kunming mice that were intraperitoneal injected with doses of 25, 50 and 75 mg/kg for one week (Long *et al.,* 2017). ZEN was also reported to reduce the quantity of mouse sperm cells, destroy the intercellular connection as well as reduce the pregnancy rate (Zhou *et al.,* 2020) ZEN affects the reproductive function of male offspring through the cytotoxicity of transgenic mouse spermatogonia, resulting in a significant decrease in semen quality and sperm quantity, an increase in malformation rate and a decrease in the testosterone level of male in F1 offspring (Zhou *et al*., 2020). Further more, after 30 µg/kg ZEN treated male mice for 5 weeks, the vitality and concentration of mouse sperm were reduced, the structure of testicular convoluted tubules was destroyed and the antioxidant system was damaged (Li *et al*., 2022). *In vitro* tests showed that 0.1 mM ZEN could not induce acrosome reaction in horse sperm, but led to an abnormal sperm activity (Filannino *et al.,* 2011). ZEN is the main factor leading to the decline of boar sperm vitality and viability. It has shown stronger toxicity compared to other mycotoxins in many parameters of boar semen, including vitality, morphology, vitality, low osmotic swelling and DNA integrity damage (Tassis *et al.,* 2022). ZEN can have an inflammatory effect on bovine oviductal epithelial cells (BOEC) by stimulating the expression of pro-inflammatory cytokines and affects bovine sperm survival by disrupting normal sperm-BOEC interactions at the level of cytokine expression and PGE2 production (Mohamed *et al.,* 2017).

ZEN toxicity on follicular and embryonic development

As an estrogen-like molecular, ZEN poses a harmful to the female reproductive system, especially in the egg production and follicle formation. Fenglei *et al.* (2015) discovered that long-term exposure to ZEN in female mice during late pregnancy severely damages the formation of primordial ovarian follicles in newborn mice. Sequence analysis demonstrated that ZEN changed the expression of genes associated with the development of the oocytes. In addition, even 1 µmol/L ZEN could damage the morphology of primitive and primary follicles in sheep (Brito *et al*., 2022). The toxic effect of ZEN on the function of organelles during meiotic maturation of porcine oocytes is primarily through distortion of protein synthesis, transport and degradation (Wang *et al*., 2022). A study by Wang *et al.* (2022) showed that exposure to ZEN interferes with the expansion of granulosa cumulus cells and the compression of oocyte polar bodies. In addition, the distribution of mitochondria and mitochondrial membrane potential was abnormal during the maturation of porcine oocytes treated with ZEN.

Mycotoxins may be transferred into milk through maternal blood, thus affecting offspring. The results from Kong *et al.* (2021) study showed that the assembly process of primordial follicles was inhibited after maternal ZEN exposureand the number of primordial follicles in the ovaries of lactating offspring was reduced as well as the degree of DNA damage was increased. These results indicated that the mother's exposure to ZEN will affect the ovarian development of her offspring through breast milk, which may damage her reproductive capacity in adulthood.

The proper embryo implantation directly affects their pregnancy as well as postpartum development. Even minor damage caused by ZEN to the reproductive system of sows, may affect embryo implantation time, leading to implantation failure. The influence of ZEN on embryo implantation is

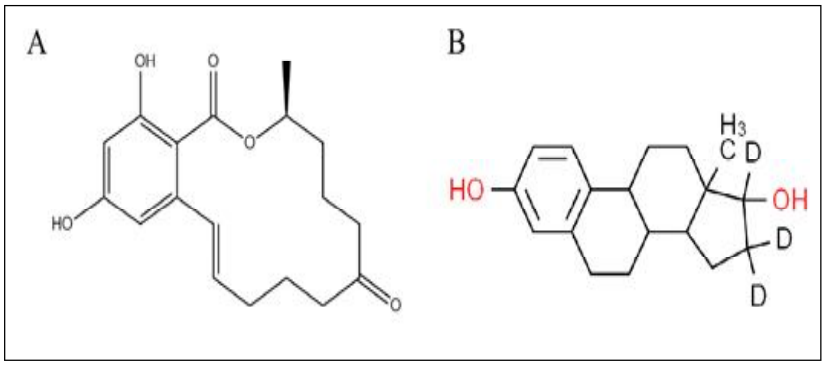

Fig 1: The chemical structure of zearalenone (A) and 17β-estradiol (B)

reflected not only manifested in the state of the embryo, but also destroy the stability of the internal environment of the uterus, affect the transformation of nutrients and energy, as well as the immune factors between the mother and the embryo, resulting in delayed embryonic development (Wu *et al.,* 2020).

The results from Mitsuhiro *et al.* (2008) study showed that the maturation rate of bovine oocytes after fertilisation was correlated with the dose of Zen. The maturation of 62 (50%) of 124 oocytes in the 1000 µg/L group stalled at stage I, but did not affect the fertilisation rate. There was no significant difference in the rate of blastocyst formation between the groups. High concentrations of Zen may adversely affect meiotic competence.

ZEN activity on the homeostasis of endogenous hormones

Estrogen secreted by the ovaries and placenta can promote animal growth and sexual organ maturation. It is reported that ZEN can disrupt hormones in the reproductive organs and cause toxin accumulation, which may be related to the abnormal expression of estrogen receptors (Adibnia *et al.,* 2016). Studies have shown that the reproductive toxicity induced by ZEN correspondence with the changes in estrogen in the body. ZEN has a special binding force with estradiol and may interfere with the hormone level of the body's endocrine system. ZEN inhibits the synthesis and release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) by binding to specific receptors on pituitary gonadotropes (Wan *et al.,* 2021).

Hypothalamus pituitary gonad (HPG) axis has a pivotal role in reproductive endocrine function. Studies have shown that ZEN interferes with the HPG axis and has and adverse effect function on the reproductive system in pre-pubertal animals (Grenier *et al*., 2013). The excessive intake of ZEN may inhibit the synthesis and secretion of follicle-stimulating hormones through negative feedback (Pompili *et al*., 2020). The excessive intake of ZEN in the body might inhibit the synthesis and release of FSH in a negative feedback regulation manner. Feeding sows with very low concentrations of ZEN in the feed will accumulate in the reproductive system, hypothalamus and pituitary gland (Gajêcka *et al.,* 2022). ZEN destroys biological functions, including FSH levels, in the process of controlling the release of neurotrans mitters in physiological homeostasis (Zhao *et al.,* 2021), which lead to overexcitation of gilts. ZEN-induces reproductive toxicity in animals are shown in Fig 2.

The molecular mechanism of ZEN on reproductive toxicity

Interaction with estrogen receptor (ER)

ZEN has estrogenic activity, which is similar to endogenous steroid hormone 17β-estradiol. ZEN competes for ER binding sites with endogenous hormones in sows, leading to severe hyperestrogenism. As a result, exposure to ZEN typically leads to precocious puberty and reproductive system disorder (Zinedine *et al.,* 2007). ERα and ERβ, two components of ER, their expression and distribution *in vivo* are different. Studies have shown that the down-regulation of ERα leads to apoptosis and even necrosis in testicular tissue. On the contrary, excessive expression of ERβ in testicular tissue could induce apoptosis of spermatocytes (Adibnia *et al.,* 2016). ZEN down-regulates the mRNA and protein levels. ERα signaling pathway plays an important role in the regulation of histone methylation during spermatogenesis. H3K27, a histone methylation marker in mice testes, increased after exposure to low-dose ZEN, while the expression of DNA methylation markers was decreased, including 5 mC and 5 hmC. This indicated that the epigenetic pathway and its interaction with the estrogen signal may be involved in the process of ZEN damage to sperm development (Gao *et al.,* 2019). The relative expression levels of ERα and ERβ in mRNA and protein of the ovaries in weaned sows showed a linear increasing trend with the dose of ZEN in the diet. The expression levels of ERβ in the ovaries of weaning piglets that were treated with ZEN were stronger than that of ERα (Yang *et al.,* 2018). In summary, the damage of ZEN to the structure and function of germ cells and follicles is

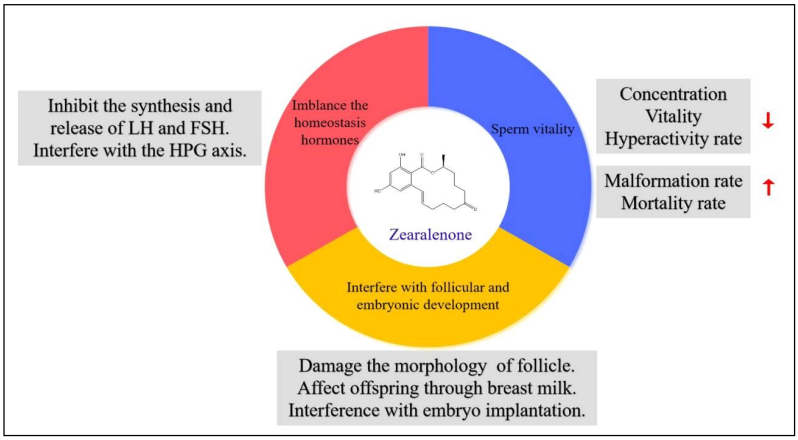

Fig 2: ZEN-induces reproductive toxicity in animals.

closely related to the changes in ER expression at both mRNA and translation levels.

Inducing oxidative stress

Total oxidative stress (OS) is an out-of-balance between oxidation and antioxidant activities *in vivo*, leading to an elevation in reactive oxygen species (ROS) levels. Generally, ROS is the major by-product of cell metabolism, mainly composed of active molecules derived from O^{2-} or H_2O_2 (Steinbrenner *et al.,* 2009). A Low ROS level has a regulatory effect on cell activity, while a high ROS level induces oxidative damage *in vivo*. Intracellular ROS can directly reflect OS leveland MDA is a commonly used OS marker (Cserháti *et al.,* 2013). The intracellular ROS can directly reflect the body's OS stage to a certain extent. MDA is a common marker of OS. The balance of ROS between production and elimination is related to the stability and degree of damage of gametocytes.

It is generally believed that OS damages spermatogenic cells through the internal apoptosis of mitochondria, which leads to abnormal function and metabolism of male Germ cells. ZEN could induce OS in testicular tissue, mainly through mitochondrial pathways leading to mitochondrial dysfunction and germ cell apoptosis (Qin *et al.,* 2015). A few studies have shown that ZEN at a low dose could enhance the cell's antioxidant capacity, which is beneficial for eliminating ROS in the body. However, ZEN, with a high concentration, may directly disrupt the activity of antioxidant enzymes *in vivo*, leading to ROS accumulation and ultimately inducing OS (Mahato *et al.,* 2021; Mavrommatis *et al.,* 2021). Mitochondria is the main source of intracellular ROS. However, some studies show that ZEN can affect mitochondrial quantity, structure, distribution and function (Yao *et al.,* 2019). ZEN-induced mitochondrial damage may be a key pathway for the promotion of ROS. ZEN exposure also increased the levels of phosphorylated JNK and p38 MAPK, triggering mitochondrial stress and ROS. Furthermore, ZEN also decreases mitochondrial membrane potential (MMP) and enhances the production of ROS through the p53 signal pathway (Yu *et al.,* 2011). Excessive ROS in mitochondria may activate the autophagy pathway, thereby reducing ROS generation (Gao *et al.,* 2013).

Endogenous antioxidants serve as the first line in defending against OS and their level can indirectly to some extent reflect the degree of OS. In addition, the decrease of endogenous antioxidants will aggravate OS and the increase in their levels is helpful to eliminate oxidative damage. ZEN induces germ cells to produce ROS and MDA. Numerous studies have shown that ZEN inhibits ROS clearance by interfering with the activity of antioxidant enzymes, such as glutathione (GSH), catalase (CAT), superoxide dismutase (SOD) and reduced glutathione peroxidase (GPx) (Kaarniranta *et al.,* 2019); Xu *et al.* (2022). found that ZEN induced TM4 cells to produce OS, characterized by an increase of ROS and MDA and a decrease in GSH and CAT. After 28 days of administration of 40 mg/kg ZEN (B.M.) to mice, MDA content increased whereas SOD and reduced GPx activity decreased (Kaarniranta *et al.,* 2019). Furthermore, ZEN could reduce the expression of Nrf2, a gene encoding transcription factor that can be neutralized with ROS and reduce the activities of CAT, GPX, SOD and other antioxidant enzymes (Wang *et al.,* 2019).

Inducing cells death

ZEN is considered an estrogen mycotoxin that competitively binds with ER to affect the synthesis and secretion of steroidal reproductive hormones and sperm quality by inducing apoptosis and necrosis (Rai *et al*., 2020). It is reported that ZEN can increase endoplasmic reticulum (ER) stressand then induce cell apoptosis (Rai *et al.,* 2020) ER is the main organelle responsible for the storage and release of Ca^{2+} in cells (Celli *et al.,* 2016). However, ZEN induces bovine aortic endothelial cells (BAECs) apoptosis through a mechanism independent of ER and ROS, but closely related to the cytoplasmic Ca^{2+} pathway. Interestingly, ZEN has also been reported to increase cytosolic Ca^{2+} levels by causing ER stress in prepubertal female ovary cells.

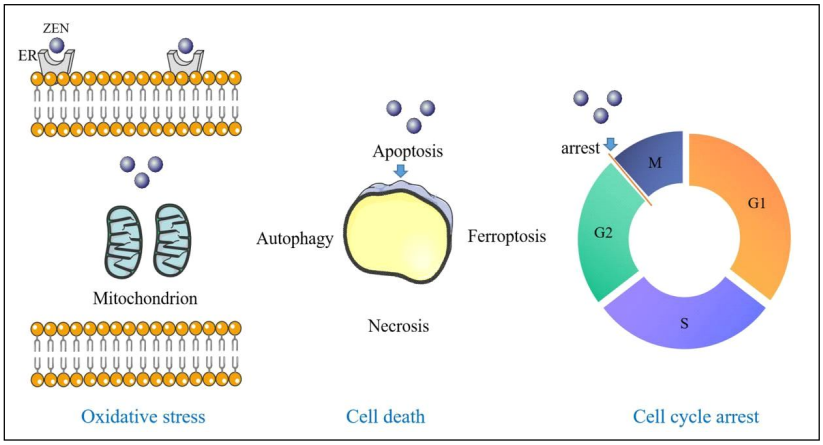

Fig 3: The mechanism of ZEN on animal reproductive toxicity.

ERK1/2 is a member of the MAPK family, more familiar is that it is a signaling molecule that promotes cell proliferation (Cagnol *et al.,* 2010). A study showed that ZEN destroyed vascular function by causing endothelial cell apoptosis and death, mainly through ERK1/2/pp53/caspase3 signaling pathway (Lee *et al.,* 2021).

Necrosis is a programmed cell death form, that was mediated by receptor-interacting protein kinase1 (RIPK1), RIPK3 and mixed lineage kinase region-like kinase (MLKL) (Bertheloot *et al.,* 2021); (Yi *et al.,* 2022) using the LDH release assay and staining of dead/living cells, reported that the LDH level and the proportion of PI-positive cells in goat endometrial stromal cells (gESCs) treated with ZEN were significantly increased, indicating that ZEN induced gESCs necrosis. ROS production and mitochondrial damage have the effect of triggering or mediating cell necrosis. Zhang *et al.* (2017) found that mitochondrial ROS would lead to autophosphorylation of RIPK1 and induce further recruitment of RIPK3 to form microsomes and cell necrosis (Zhang *et al*., 2017). MLKL inhibitor significantly reduced the excess production of ROS and alleviated the ZEN-induced reduction of gESCs mitochondrial membrane potential and ATP. The result indicated that mitochondrial dysfunction and ROS production are both essential in the process of ZEN-induced MLKL-driven necrosis (Yi *et al.,* 2022).

Exposure to ZEN during embryo implantation activates autophagy and blocks the autophagic flow, leading to endometritis and a large accumulation of autophagy. Electron microscope observation showed that ZEN increased the percentage of autophagy and lysosomes in PE cells, indicating that autophagy occurred. The relative expression of LC3 and P62, two autophagy markers, increased, further confirming the occurrence of endometrial cell autophagy. The expression of LC3 protein increased with an increase in ZEN concentration indicating that ZEN caused autophagic damage to endometrial tissue during embryo implantation.

ZEN could induce lipid peroxidation in mice (Hassen *et al.,* 2007). However, it is surprising that, compared with the control group, the relative contents of Fe^{3+} and Fe^{2+} increased in testicular tissue after ZEN intake, which indicates that ZEN can induce lipid peroxidation and iron accumulation, suggesting that ferroptosis might be caused by ZEN (Rai *et al.,* 2020). Ferroptosis is a newly discovered type of programmed cell death, which depends on iron accumulation and lipids (Dixon *et al*., 2012). Ferroptosis is a newly discovered type of programmed cell death, which is characterized by iron accumulation and lipid peroxidation. The occurrence of ferroptosis is regulated by various cellular metabolic pathways including redox homeostasis. GPX4 plays a role in enzyme reactions and reduces lipid hydrogen peroxide to lipid alcohols, a non-toxic substance. When GPX4 activity is inhibited, it induces ferroptosis (Xu *et al.,* 2021). The deletion of the GPX4 gene in mouse spermatocytes leads to a significant decrease in sperm concentration and motility (Atala, 2010).

Inhibition of cell cycle

The cell replication cycle is the basic process of cell life activities, which is the process of cell division and reproduction in a certain order under the regulation of internal and external factors (Bordhan *et al.,* 2022). A high dose of ZEN interferes with cell differentiation and induces germ cell death to some extent (Zheng *et al.,* 2018). The quantity of Sertoli cells (SCs) largely determines the size of testes and spermatogenesis in adult male animals (Griswold *et al*., 1998). ZEN significantly inhibited the proliferation of SCs at a certain concentration and led to cell cycle arrest at the G2/M stage (Wang *et al.,* 2018). In addition, CHK1 and CHK2, two DNA damage checkpoint proteinsand G2/M cell cycle checkpoint protein Wee1 jointly caused cell cycle arrest (Vera *et al*., 2015). Over-expression of CHK1 and down-regulation of CHK2 lead to degradation of CDC25C, thus preventing G2/M in SCs (Liu *et al*., 2020). ZEN affects the expression of cyclin B1, cyclin D1, CDK2 and CDK4 in a dose-dependent mannerand affects the distribution of the cell cycle, which may lead to the decline of cell viability through the signaling pathway of ROS-ER stress-AMPK in mouse SCs (Wang-long *et al*., 2018). In summary, high dose ZEN (100 µM) causes DNA damage by the CHK1/CK2 and the Wee1 responsible for oocyte meiosis resumption. Suspension of the cell cycle process will lead to stagnation of DNA replication, thus inhibiting cell proliferation (Abid-Essefi *et al.,* 2004). The mechanism of ZEN on animal reproductive toxicity are shown in Fig 3.

Potential therapeutic interventions against ZEN's toxicity

ZEN causes toxic damage to the reproductive system of animals, especially in pigs. Therefore, it is particularly important to explore effective methods that can reduce ZEN damage (Xue-lian *et al.,* 2018). Although traditional methods such as grinding, fermentation, or extrusion are helpful for the elimination of ZEN in food and feed, but cannot be eradicated (Han *et al.,* 2022). In recent years, many compounds from nature and dietary supplements that could alleviate the systemic toxicity caused by ZEN, have received extensive attention.

Anti-Oxidant therapeutic candidates for ZEN toxicity

Most effective compound's antioxidant activity will help alleviate the endocrine-disrupting effect and toxic effect of oxidative stress induced by ZEN. Plant polyphenol extracted from grape seeds has antioxidant activity, which can reduce the production of ROS by ZEN (Althali *et al.,* 2019). In addition, radish extraction also reverses the decrease of sperm count induced by ZEN through the changes in the testosterone level and antioxidant enzyme activity, even the DNA banding pattern in mice (Ben Salah-Abbès *et al.,* 2009). Baicalin is a natural compound from Erigeron *breviscapus, Scutellaria barbata, Scutellaria baicalensis* and other plants (Jing *et al.,* 2022). It has been reported that baicalin down-regulated the expression of MAPK/JNK

signal pathway, there by reducing the injury caused by ZEN (Hu *et al*., 2021). Further more, it was also reported that baicalin disrupts cell cycle distribution and apoptosis and targets mouse ovarian granulosa cells, leading to reduce ZEN-induced reproductive toxicity in female Kunming mice (Yi *et al.,* 2021).

Studies have also shown that glucose has a crucial role in the development embryonic at the early stage of pregnant animals (Kim *et al*., 2013). Glucosamine (GlcN) is a kind of amino monosaccharide synthesized by glucose and glutamine under the action of fructose-6-phosphate acyltransferase (Dissanayake *et al.,* 2021). GlcN supplementation in the diet of Wistar rats increased the GSH level, which indicated that GlcN has an antioxidant effect (Roy *et al.,* 2022). It was found that GlcN reverses ZEN-mediated phenotype by the activation of PI3K and inhibition of the MAPK pathway. This indicated that GlcN has an effective protective effect on ZEN-induced placental dysfunction and reproductive toxicity in pregnant mice (Bai *et al.,* 2022). GlcN may be a potential additive to reduce the toxicity induced by ZEN in pregnant mice.

Lycopene is a high antioxidant fat-soluble carotenoid widely distributed in red tomatoes, fruitsand vegetables. Studies have shown that lycopene effectively reduced the damage of ZEN to mouse testes by reducing antioxidant enzyme activity and limiting inflammatory reactions (Boeira *et al.,* 2015). In addition, after pre-treatment with lycopene, the mRNA levels of Nrf2, HO-1and GPX1 in the cell nucleus increased and antioxidant enzyme activity increased as well as MDA and ROS reduced, thereby improving the survival rate of piglet SC induced by ZEN (Cao *et al*., 2021).

In addition to the natural molecules derived from plants, trace nutrients such as vitamins and minerals can also effectively prevent damage caused by ZEN. *In vitro*, a mixture of ZEN and vitamin E was added to cellsand it was found that vitamin E reduced DNA breakage and apoptotic bodies caused by ZEN and alleviated G2/M phase cell cycle arrest. Further more, vitamin C alleviates ZEN-induced female weanling piglet injury through nuclear receptor signal transduction. Piglets treated with vitamin C and ZEN mixture showed that vitamin C can effectively clear ZEN, reduce MDA and increase SOD/T-AOC and GSH-Px levels in the body (Shi *et al.,* 2017). Selenium (Se) is an element in the micronutrient group, which involves cell protection from excessive ROS and regulation of the immune and reproductive systems (Dufrasne *et al*., 2016). Se improves the decrease of the epididymal index and testicular index caused by ZEN by reducing the content of MDA and increasing the activities of antioxidant enzymes, such as SOD and GPx in testicular tissue (Dufrasne *et al.,* 2016). Zinc, as an essential metal element, has a strong antioxidant effectand is a co-factor for various enzymes and transcription factors (Jeong *et al.,* 2013). Zinc significantly reduced the rise of ROS and MDA by regulating the transcription of Mtf1 and Mt2 in murine ovarian granular KK^{-1} cells caused by ZEN (Miao *et al.,* 2016).

Degrading microbes and enzyme therapeutic candidates for ZEN toxicity

It has been confirmed that various microorganisms can convert mycotoxins through biochemical reaction processes such as acetylation, glucose, ring cleavage, hydrolysis, deamination and decarboxylation, as well as biological transformation (Qu *et al.,* 2022). ATP binding cassette (ABC) transporters are widely present in various tissues and complete the transport of various substrates such as endogenous molecules, nutrients, mycotoxins, *etc*. through the consumption of ATP. ZEN increased the mRNA expression of the ABC transporter in piglets, indicating that piglets can use the increased ABC transporter to remove ZEN deposited in organs and tissues. Similar results were also obtained in rat experiments. The mRNA expression of ABCB1 and ABCG2 in the uterus of pregnant rats fed with ZEN (dose of 100 mg/kg ZEN and 1 mg/kg) was increased (Koraichi *et al.,* 2012; Yuanyuan *et al.,* 2013).

Biodegradation of ZEN by microorganisms is more beneficial to nature and ecologically friendly. Microbial-based technologies include mycotoxin decomposition and bio-transformation. Mucor Barnelli and Thalamia elegans can transform ZEN into non-estrogen components (ZEN-4-O-β Glucoside). In addition, *Cunninghamella bainieri* and *Streptomyces marginalis* modify ZEN and converts it into 8-hydroxy ZEN and 2,4-dimethoxy-ZENm respectively. *Gliocladium roseum* causes a spontaneous decarboxylation reaction by destroying the ZEN lactone ring (Zinedine *et al.,* 2007). It was reported that the fungus *Sphaerodes mycoparasitica* also can degrade ZEN. The mixture of *Geo-bacillus* and *Tepidi-microbium* reduces ZEN pollution by 88.50%, which has great application prospects (Wang *et al.,* 2018). In addition, according to the investigation, the degradation rates of ZEN by *R. erythopolis*, *R. ruber* and *R. pyridinovorans* all exceeded 50%, with R. pyridinovorans reaching up to 70% (Cserháti *et al.,* 2013).

Various beneficial microorganisms and their combinations with different mycotoxin-degrading enzymes were studied. It showed that the degradation rate of *Bacillus* subtilis for ZEN was 42.17%. The recombinant fusion enzyme produced by ZEN hydrolase and carboxypeptidase, two single genes degrades, degraded ZEN into non-toxic products within 2 h at 35°C and pH 7 (Azam *et al.,* 2019). The results of the *Lactobacillus* plantarum test indicated that the increase in esterase activity was related to cell growth and the ability of isolated strains to remove ZEN was related to the concentration of bacteria. ZEN degradation test and fat decomposition ability showed that the removal of ZEN by culture supernatant depended on esterase activity (Chen *et al*., 2018).

CONCLUSION

ZEN is a common fungal toxin with a chemical structure of dihydroxybenzoic acid lactone. ZEN is widely distributed in

food and feed around the world, which poses a threat to livestock security and causes serious economic losses by inducing irreversible toxic damage to the embryonic development and biological reproductive system. Broadly, low-dose ZEN can play an estrogen-like role, while long-term high-dose ZEN can cause OS, DNA damage, mitochondrial deficiency, cell cycle arrest, ferroptosis and apoptosis. However, due to the limitations of the literature, there are few reports on the accumulation of ZEN residues in food in the human body and damage to the human reproductive system, which needs to be further researched.

Studies show that the uptake of ZEN can be degraded through detoxification. ZEN's detoxification *in vivo* is mainly achieved by using natural products, probiotics, enzymesand others, to reduce or counteract its toxic effects through anti-oxidation and bio-degradation.

In summary, ZEN pollution is hazardous to reproductive systems in animals, which may hurt the animal husbandry industry as well as threaten human health. Clarifying the poisoning mechanism and comprehensively using biological, physicaland chemical methods to find the detoxification measures of ZEN are some possible solutions to prevent ZEN from causing harm to animals.

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Conflict of interest

The authors declare that there is no conflict of interests in this research.

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