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Review article

Deoxynivalenol exposure-related male reproductive toxicity in mammals: Molecular mechanisms, detoxification and future directions

Chongshan Dai [a,b,*], Zhihui Hao [a,b], Dingkuo Liu [c], Zhanhui Wang [a,b], Gea Oliveri Conti [d], Tony Velkov [e], Jianzhong Shen [a,b,*]

[a] National Key Laboratory of Veterinary Public Health and Safety, College of Veterinary Medicine, China Agricultural University, Beijing 100193, China
[b] Technology Innovation Center for Food Safety Surveillance and Detection (Hainan), Sanya Institute of China Agricultural University, Sanya 572025, China
[c] Tianjin Key Laboratory of Biological Feed Additive Enterprise, Tianjin Agricultural University, Tianjin 300392, China
[d] Environmental and Food Hygiene Laboratories (LIAA), Department of Medical, Surgical Sciences and Advanced Technologies "G.F. Ingrassia", University of Catania, Catania, Italy
[e] Department of Pharmacology, Biodiscovery Institute, Monash University, Victoria 3800, Australia

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ABSTRACT

An increasing body of evidence indicates that exposure to widespread, environmental and food contaminants such as mycotoxins may cause endocrine disorders and infertility. Deoxynivalenol (DON), which is a toxic secondary metabolite produced by *Fusarium* fungi, can lead to multiple harmful effects in humans and animals, such as hepatotoxicity, nephrotoxicity, immunotoxicity, gastrointestinal toxicity, neurotoxicity, genetic toxicity and carcinogenicity. Recently, there has been growing concern about DON-induced male infertility. Exposure to DON and its metabolites can damage the structure and function of male reproductive organs, resulting in impairment of gametogenesis and thus impaired fertility. Potential molecular mechanisms involve oxidative stress, inflammatory response, mitochondrial dysfunction, apoptosis, cell cycle arrest, pyroptosis, and ferroptosis. Moreover, several signaling pathways, including nuclear factor-kappa B, mitogen−activated protein kinase, NLR family pyrin domain containing 3, nuclear factor erythroid 2-related factor 2, AMP-activated protein kinase, mitochondrial apoptotic pathways, and microRNAs are involved in these detrimental biological processes. Research has shown that several antioxidants, small-molecule inhibitors, or proteins (such as lactoferrin) supplementation can potentially offer protective effects by targeting these signaling pathways. This review comprehensively summarizes the harmful effects of DON exposure on male reproductive function in mammals, the underlying molecular mechanisms and emphasizes the potential of several small molecules as protective therapeutics. In the further, the systematic risk assessment when DON at environmental exposure doses to human

Abbreviations: DON, DON, deoxynivalenol, deoxynivalenol; NF−κB, nuclear factor−kappa B; MAPK, mitogen−activated protein kinase; NLRP3, NLR family pyrin domain containing 3; Nrf2, nuclear factor erythroid 2−related factor 2; AMPK, AMP−activated protein kinase; WHO, The World Health Organization; OTs, ochratoxins; AFTs, aflatoxins; FMNs, fumonisins; OTA, ochratoxin A; HPG, hypothalamic−pituitary−gonadal; GnRH, gonadotropin−releasing hormone; LH, luteinizing hormone; FSH, follicle stimulating hormone; LDB, luteinizing hormone subunit beta; Erk, extracellular regulated protein kinase; SCARB1, scavenger receptor class B member 1; STAR, steroidogenic acute regulatory protein; CYP11A1, cytochrome P450 family 11 subfamily A member 1; HSD3B, hydroxy delta 5 steroid dehydrogenase, 3 beta; HSD3B1, hydroxy delta 5 steroid dehydrogenase, 3 beta 1; PI3K, phosphatidylinositide 3−kinase; AKT, protein kinase B; ROS, reactive oxygen species; H_2O_2, hydrogen peroxide; $O_2^{\bullet-}$, superoxide anion; $^1O_2$, singlet oxygen; •OH, hydroxyl radicals; SOD, superoxide dismutase; GSH, reduced glutathione; GPX, glutathione peroxidase; CAT, catalase; MDA, malondialdehyde; T-AOC, total antioxidant capacity; NAC, antioxidant *N*-acetylcysteine; PRDX4, peroxiredoxin 4; NQO-1, NAD(P)H quinone oxidoreductase-1; HO-1, heme oxygenase 1; GST, glutathione- *S*-transferase; ATP, adenosine triphosphate; ETCs, mitochondrial respiratory chain complexes; Fis1, fission 1; Drp1, dynamin-related protein 1; MFF, mitochondrial fission factor; Mfn1, mitofusins 1; MPTP, mitochondrial permeability transition pore; CytC, cytochrome *C*; Bcl-2, B-cell lymphoma-2; Bax, Bcl2-associated X; COX2, cyclooxygenase-2; IL-6, interleukin-6; TNF-α, tumor necrosis factor alpha; Tnfrsf9, tumor necrosis factor receptor superfamily, member 9; Ccl22, chemokine (C−C motif) ligand 22; Relb, reticuloendotheliosis viral (v-rel) oncogene−related B; IL6st, interleukin 6 signal transducer; GSDMD, gasdermin D; TFR1, transferrin receptor protein 1; FLH, ferritin light chain; FTH, ferritin heavy chain; FPN, ferroportin; ACSL4, acyl-CoA synthetase long-chain family member 4; LPCAT3, lysophosphatidylcholine acyltransferase 3; PCNA, proliferating cell nuclear antigen; CCNB1, cyclin B1; CDK1, cyclin-dependent kinase 1; ER, endoplasmic reticulum; CHOP, C/EBP homologous Protein 4-PBA; miRNAs, 4-phenylbutyric acid micro RNAs.

* Corresponding authors.
E-mail addresses: daichongshan@cau.edu.cn (C. Dai), sjz@cau.edu.cn (J. Shen).

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reproductive health, the in-depth and precise molecular mechanism investigation using emerging technologies, and the development of more effective intervention strategies warrant urgent investigation.

1. Introduction

Currently, there are around 48 million couples and 186 million individuals globally suffering from infertility (Rodprasert et al. 2023). The World Health Organization (WHO) has classified infertility as a major global public health issue. Of note, male related fertility issues constitute approximately 40——50 % of all infertility cases, and as many as 2 % of men globally have sub-optimal sperm parameters (Kumar and Singh 2015). Epidemiological and experimental studies have revealed correlations between diminished male fertility and exposure to diverse environmental chemical hazards, such as heavy metals, cigarette smoke, microplastics (e.g., polystyrene, polycarbonate, polypropylene, polyethylen, polyethylene terephthalate, polymethacrylate, polyvinyl chloride, and polyurethane), plasticizers (e.g., di (2-ethylhexyl) phthalate, mono (2-ethylhexyl) phthalate, and bisphenol A), persistent organic pollutants (e.g., polychlorinated biphenyls and organochlorine pesticides), and mycotoxins (Han and Huang 2021; Vessa et al. 2022; Yang et al. 2024a; Yilmaz et al. 2020; Zurub et al. 2023). Recent studies also suggested that biological factors, such as viruses or bacterial infections are emerging factors for infertility (Delli Muti et al. 2022; Wang et al. 2021).

Mycotoxins are toxic secondary metabolites generated by filamentous fungi, including *Fusarium*, *Penicillium*, and *Aspergillus*, and can cause serious diseases in humans and animals (Dai et al. 2024). To date, nearly 500 natural mycotoxins have been recognized, among which 30 mycotoxins such as ochratoxins (OTs), aflatoxins (AFTs), fumonisins (FMNs), deoxynivalenol (DON), and ochratoxin A (OTA), and patulin are posing significant risks to humans and animals due to higher occurrences in food and crops worldwide (Dai et al. 2022; Eskola et al. 2020; Li et al. 2017b). Due to global warming, the problem of mycotoxin pollution is becoming increasingly problematic, also due to the increased vehicles (such as Ready-to-Eat Food and organic dust) and the discovery of new types of mycotoxin (such as versicolorin A, beauvericin, and tenuazonic acid, and moniliformin) for human exposure (Budin et al. 2021; Carballo et al. 2018a; Carballo et al. 2018b; Křížová et al. 2021; Medina et al. 2017; Visintin et al. 2023; Ye et al. 2023a). The contamination rate of mycotoxins has increased from 25 % in the 1980 s to 60–80 % to date, or even higher in certain developing regions, but is expected to affect within 2030 the north Europe and, in general, the western countries (Eskola et al. 2020; Hao et al. 2023; Xu et al. 2022). Mycotoxins commonly enter the diet of animals and humans via the ecological food chain (Dai et al. 2024; Khan et al. 2024). Some mycotoxins can cause acute death in animals and humans, and even cause cancer through the chronic and sub-chronic exposures. For example, the T-2 toxin are extremely toxic and can induce acute death in animals (Dai et al. 2019). AFTs that occur naturally are classified as human Group 1 carcinogens and OTs and FMNs are classified as possible human Group 2B carcinogens by the International Agency for Research on Cancer, WHO (Omotayo et al. 2019). An expanding body of evidence indicates that exposure to mycotoxins is a significant risk factor contributing to male fertility (Kumar and Singh 2015; Pang et al. 2016; Yang et al. 2024a). Population cohort studies have provided demonstratable proof that environmental exposure to mycotoxins such as AFB_1, beauvericin, and citrinin are positively correlated with low semen quality in adult men (Ibeh et al. 1994; Yang et al. 2024a). So, it follows, mycotoxin contamination in food and the environment, including indoor air pollution, poses significant challenges to global public health and safety.

DON, often referred to as vomitoxin, is a noxious secondary metabolite generated by *Fusarium* fungi, particularly *F. graminearum* which infects field crops (Fig. 1). DON contamination of crops including corn, wheat, and barley is common in the North American and Asia−Pacific region (Holanda and Kim 2021; Knutsen et al. 2017; Yao and Long 2020). For instance, a global report dated January−June 2023 reported that the contamination rates of DON in samples from China, Southeast Asia, Oceania, and North America were approximately 83 %, 65 %, 65 %, and 78 %, respectively (dsm-firmenich World Mycotoxin Survey, 2023). Moreover, DON has been found in many processed grain derived products such as beer and soy sauce, as well as in primary animal products (i.e., eggs, meat, and milk) (Knutsen et al. 2017; Yao and Long 2020). Worryingly, DON has been shown to accumulate in human breast milk with a median level of 3924 ng/L (ranged from 400−14997 ng/L), which exceeds the defined risk threshold (i.e., the maximum tolerable daily intake limit is 1 μg/kg/body weight) established by the Joint Food and Agricultural Organization/World Health Organization (WHO) and the Expert Committee on Food Additives (Dinleyici et al. 2018; Gonya et al. 2024; Mishra et al. 2020). Epidemiological investigations have shown that elevated levels of mycotoxins, including DON, in breast milk are strongly associated with maternal dietary intake of mycotoxin-contaminated livestock-derived products (e.g., meat, milk, eggs) and grain-based foods (e.g., barley, sorghum, corn, wheat, and rye), as well as environmental exposure (Dinleyici et al. 2018; Güneş et al. 2023). Additionally, maternal physiological factors, such as immature

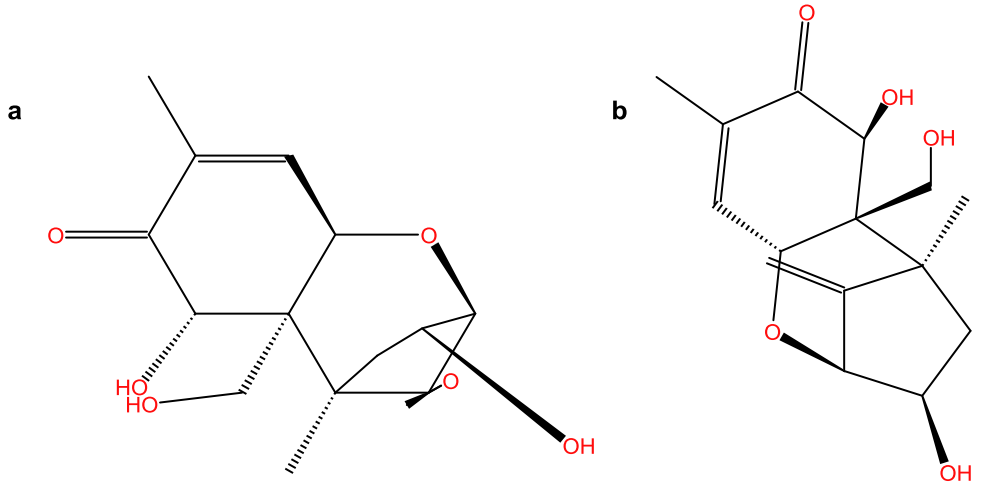

Fig. 1. The chemical structures of deoxynivalenol (i.e., 3α,7α,15-trihydroxy-12,13-epoxymonospora-9-ene-8-one) (**a**) and its metabolite deepoxy-DON (**b**).

mammary barrier function and genetic polymorphisms in detoxification enzymes (e.g., cytochrome P450 enzymes and glutathione S-transferases) governing mycotoxin metabolism, significantly contribute to interindividual variability in toxin accumulation (Bernasconi et al. 2022; Lehmann et al. 2018). For example, Sun et al. demonstrated that lactational DON exposure increased blood-milk barrier permeability by reducing the expression of ZO-1 and occludin and inducting cell apoptosis (Sun et al. 2023). It is particularly concerning because, even at relatively low concentrations, exposure to DON can still trigger the aforementioned adverse effects (Feng et al. 2024; Liu et al. 2024; Pierron et al. 2018; Pierron et al. 2016; Szabó et al. 2017; Wang et al. 2020; Yang et al. 2014; Zhang et al. 2020). Several systematic reviews and epidemiological studies suggested that DON exposure is related to numerous chronic diseases, including immunosuppressive diseases, cancer, teratogenic diseases, neurodegenerative disorders, chronic liver disease and cardiovascular disease (Claeys et al. 2020; Pestka 2010; Pestka and Smolinski 2005; Wang et al. 2014).

Recent research indicates that exposure to DON can lead to strong reproductive toxicity both *in vivo* and *in vitro* (Eze et al. 2018; Guerrero-Netro et al. 2021; Hai et al. 2023; Ruan et al. 2024b; Seyed Toutounchi et al. 2021; Song and Zhang 2021; Sprando et al. 2005; Sun et al. 2022; Sun et al. 2024; Tassis et al. 2022; Tassis et al. 2020; Urbanek et al. 2021; Yang et al. 2024b; Yang et al. 2023). For instance, in a rat model, oral DON exposure at 0.15 or 2.3 mg/kg of body weight daily for three weeks (i.e., twenty-one days), resulted in a significant decline in testicular function (Ruan et al. 2024b). Another study showed that when DON was administered orally at 0.5, 1 or 5 mg/kg of body weight daily for twenty-eight days, a marked decrease in sperm count was observed (Sprando et al. 2005). Cao *et. al.,* reported that oral treatment with DON at 1.2, 2.4, and 4.8 mg/kg of body weight for twenty-eight days caused pathological damage to the sperm ultrastructure and seminiferous tubules, which was accompanied by a marked inflammatory response (Cao et al. 2020). The mechanism through which DON and its metabolites (such as deepoxy-DON) cause male reproductive toxicity is complex and context dependent (Cao et al. 2020; Guerrero-Netro et al. 2021; Yang et al. 2019). It has been well-documented that the mechanisms of DON−induced male reproductive toxicity in mammals involves several compounding factors including oxidative stress, inflammatory responses, mitochondrial dysfunction, cell cycle arrest, apoptosis, pyroptosis, and ferroptosis (Cao et al. 2021; Cao et al. 2020; Huang et al. 2021a; Khera et al. 1984; Pestka 2010; Ruan et al. 2024b; Sprando et al. 2005; Urbanek et al. 2021; Yang et al. 2024b; Yang et al. 2019; Yang et al. 2023). In this review, we cover the most pivotal articles on the male reproductive toxicity of DON and its metabolite (i.e., deepoxy- DON; Fig. 1) from the PubMed, Web of Science databases, and Scopus published between January 1, 1980, and November 1, 2024. For the literature search, the keyword combinations used included: deoxynivalenol (or DON) or deepoxy-deoxynivalenol (or deepoxy-DON), and male reproductive toxicity (or male infertility, or endocrine disorders). We summarize the harmful effects of DON exposure on the endocrine function and reproductive organs of male mammals (both in human and animals and, through *in vivo* and *in vitro* studies), the molecular mechanisms, and potential protective agents. These findings offer crucial evidence for preventing, controlling, and treating the reproductive toxicity caused by DON exposure. This review can provide valuable evidences, perspectives and encourage further research towards developing effective strategies for preventing, controlling, and treating DON −induced reproductive toxicity in male mammalian species.

2. An overview of DON exposure-related effects on male fertility, blood-testis barrier (BBB), reproductive organs, and sperm quality

The testis is a sophisticated reproductive organ with two key functional sub-structures, the seminiferous tubules and the interstitial tissue where Leydig cells are situated (Hau et al. 2023; Zhang et al. 2024c). The seminiferous tubules are surrounded by basement membranes, and compartmentalize peritubular myoid cells, Sertoli cells, spermatogonia stem cells, and spermatogonia at various stages of maturation (Hau et al. 2023). The development of spermatozoa from spermatogonia demands a coordinated interaction among the abovementioned cells. Any disruption in these intermediate procedures or intercellular regulations can have an impact on the reproductive functions of the testis. Currently, male fertility is in decline worldwide, largely because of sub-standard sperm quality (Skakkebæk et al. 2022). It has been reported that DON exposure can induce blood-testis barrier (BBB) disruption, cause damage of reproductive organs, and decrease the sperm quality, finally resulting in the decreased reproductive ability, even infertility in males *in vitro* and *in vivo* (Cao et al. 2020; Huang et al. 2021b; Li et al. 2023; Lin et al. 2022b; Miao et al. 2023; Yang et al. 2023; Zhang et al. 2024d). Table 1 shows a summary of DON exposure-related detrimental effects on reproductive organs of male mammals and effects on cultured cell lines.

2.1. Toxic effects of DON on BBB

The BTB is a critical structure in the male reproductive system, primarily formed by Sertoli cells, which create a protected environment for the development of germ cells. It plays a vital role in maintaining the homeostasis of the seminiferous epithelium and protecting developing germ cells from xenobiotic exposure. Damage to BBB barrier would allow the toxin to further infiltrate testicular tissue, leading to abnormal histopathological changes in both testicular and epididymal tissues, eventually causing a decrease in sperm quantity and quality (Cao et al. 2020; Li et al. 2023; Miao et al. 2023; Yang et al. 2023).

Animal studies have revealed that the exposure to DON can severely damage the integrity of the blood-testis barrier (Cao et al. 2020; Li et al. 2023; Yang et al. 2023). Cao et al demonstrated that DON exposure −induced damage to the BBB is positively associated with the down-regulation of several essential tight junction proteins such as connexin 43 (Cx-43), zona occludens 1 (ZO-1), occludin, and N-cadherin using a mouse model (Cao et al. 2020). Similar findings were also reported that by Miao *et. al.* (Miao et al. 2023). Moreover, a special inhibitor of p38 signaling pathway SB203580 pretreatment can markedly block the DON-induced integrity destruction of BBB via reducing the expression of ZO-1, occludin, and claudin-11 proteins (Miao et al. 2023). Furthermore, it was demonstrated that DON-induced BTB dysfunction is partially reliant on the activation of p38/glycogen synthase kinase 3 beta (gSK-3β)/snail and p38/ATF-2/myosin light chain kinase (MLCK) signaling pathways (Miao et al. 2023). Sertoli cells, recognized as the primary supportive cells for spermatogenic development and core functional components of BBB (Yang et al. 2021), have been shown to suffer DON-induced toxicity that may contribute to BTB disruption. A study using primary Sertoli cells from *Equus asinus* demonstrated that 72 h' exposure to 10 or 30 μM DON induces dysregulation of multiple cellular pathways, including small molecule metabolism, immune responses, DNA processing, and cell cycle regulation. This exposure notably exacerbated apoptotic and inflammatory responses, as evidenced by elevated expression levels of caspase-1 (an apoptosis executor), gasdermin D (GSDMD; a pyroptosis marker), and CCL17 (a pro-inflammatory chemokine) (Song and Zhang 2021). A prior case report suggested that the exposure of mycotoxin mixture containing DON in pregnant cows might lead to Sertoli cell tumors in the neonatal calf, which may be partly due to their mutagenic effects (Vissiennon et al. 2016). Additionally, DON-mediated alterations in apical junction and immune function may also contribute to its impacts on the function of BBB (Li et al. 2023).

2.2. Toxic effects of DON on reproductive organs and sperm quality

Experimental animal studies have consistently demonstrated that DON exposure induces reproductive toxicity through structural damage to testicular and epididymal tissues, ultimately impairing

Table 1
A summary of DON exposure-related detrimental effects on reproductive organs of male mammals and effects on cultured cell lines.

Animals/cell line	Doses and times	Toxic Effects	References
Mice	DON treatment at 150 and 2300 μg/kg body weight per via the oral administration per day for 3 weeks	DON caused abscission of spermatogenic cells, disturbances in the arrangement of testicular cells, and occurrence of erythrocytes and inflammatory cells within the testicular interstitial tissue. DON treatment caused marked cellular apoptosis in the testis tissues of mice. DON exposure also significantly decreased the testosterone levels and concomitantly increased the levels of FSH and LH in serum.	(Ruan et al. 2024b)
Male Sprague–Dawley rats	Rats were treated orally with DON at the doses of 0.5, 1.0, 2.5 or 5.0 mg/kg body weight per days for 28 days	DON exposure at the dose of 5 mg/kg body weight significantly decreased the body weight, relative weight of epididymis, testicular spermatid counts, and cauda epididymal sperm counts. DON treatment significantly upregulated the levels of FHS, LH and downregulated the levels of testosterone. Histopathological damage in the testicular tissues was observed: seminiferous tubule atrophy, germ cell degeneration, failure of sperm release, abnormal germ cell development, multinucleate cell formation, fluid build-up in interstitial space, boundary layer in folded, anomalous cell types in interstitial space, and Leydig cell vacuolization.	(Sprando et al. 2005)
Mice	Mice were treated orally with DON at doses of 0.5, 1.0, and 2.0 mg/kg body weight per day for 28 days	DON treatment significantly decreased the body weight, and significantly decreased serum testosterone levels, and caused marked testicular injury. It also disturbed the blood-testis barrier, i.e., significantly decreased the levels of N-cadherin, β-catenin, ZO-1, occludin, and connexin 43 proteins in the testis tissues of mice. Additionally, DON exposure also triggered ferroptosis and oxidative damage.	(Yang et al. 2023)
Newborn rats (postnatal 21 day)	Rats were orally administrated DON (0–4 mg/kg) from postnatal days 21–28.	DON treatment significantly upregulated the serum LH level but significantly decreased the serum testosterone level. It also inhibited the development of Progenitor Leydig cell and inhibited the expression of SCARB1, STAR, CYP17A1, HSD11B1, and INSL3 mRNAs and the expression of HSD11B1 and INSL3 proteins in the testis tissues of rats.	(Yang et al. 2024b)
Mice	Mice were administered orally with DON at 1.2, 2.4, or 4.8 mg/kg body weight per day for 28 days	DON treatment induced spermatogenesis disorder, reflected by the declines of sperm concentration and quality, sperm ultrastructural damage as well as seminiferous tubular damage. Meanwhile, DON treatment also decreased the expressions of occludin, connexin 43 and N-cadherin proteins, indicating the disorders of blood-testis barrier. DON also triggered the inflammatory response and inhibited the biosynthesis of testosterone in the testis of mice.	(Cao et al. 2020)
TM3 cells	Cells were treated with DON at doses of 10–150 ng/mL for 24 h	DON treatment at doses of 10–150 ng/mL induced cytotoxicity in a dose-dependent manner. It also significantly decreased the levels of GSH and CAT activities and significantly increased the intracellular ROS and MDA levels. DON treatment at doses of 75 or 125 ng/mL significantly increased the expression of NLRP3, ASC, cleaved-caspase-1, GSDMD, IL-18, and IL-1β	(Ruan et al. 2024b)

(continued on next page)

Table 1 (*continued*)

Animals/cell line	Doses and times	Toxic Effects	References
		levels, finally resulting in cellular pyroptosis.	
Porcine primary Leydig cells	Cells were treated with DON at 0.125–8 μM for 24 h	DON alone treatment at 0.3—–4.8 μM resulted in the loss of cell viabilities in a dose-dependent manner. The co-treatment of DON (at 0.6 μM) and ZEN (at 20 μM) for 24 h significantly induced oxidative stress, mitochondrial dysfunction, cell cycle arrest, and the activation of the mitochondrial apoptotic pathway.	(Sun et al. 2022)
Porcine primary Sertoli cells	DON alone treatment at doses of 0.3–4.8 μM or combination with ZEN at 10–50 μM for 24 h	DON alone treatment at 0.3–4.8 μM resulted in the loss of cell viabilities in a dose-dependent manner. The co–treatment of DON (at 0.6 μM) and ZEN (at 20 μM) for 24 h significantly induced oxidative stress, mitochondrial dysfunction, cell cycle arrect, and the activation of mitochondrial apoptotic pathway, finally triggering cell apoptosis.	(Cao et al. 2021)
Five random straws of frozen semen from five Holstein bulls of 5 to 7 years old	60 μL aliquots (about 20 million sperm) were treated with de-epoxy-DON at doses of 10 or 100 ng/mL for 2, 4, 6, 8, and 10 h	De-epoxy-DON treatment significantly decreased the sperm motility and strength in both dose- and time-dependent manners.	(Guerrero-Netro et al. 2021)
Semen samples from active boars	Semen samples were added with DON or de-epoxy-DON at both 50.6 μM for 1–4 h	DON negatively affected several parameters, such as immotile spermatozoa and progressive motile spermatozoa, whereas those effects were absent in the case of de-epoxy-DON treatment.	(Tassis et al. 2022)
Primary Sertoli cells of *Equus asinus*	Cells were treated DON at 10 or 30 μM for 72 h	DON exposure induced apoptosis. DON-induced different genes were enriched in the small molecular metabolic process, immune system process, DNA metabolic processes, and cell cycle pathways. DON treatment also significantly promoted inflammation, which was evident by the increased expression of caspase-1 and GSDMD, and CCL17.	(Song and Zhang 2021)
MA-10 mouse Leydig tumor cells	Cells were treated with DON at 0.1, 0.25, 0.5, 1, and 2 μM for 24 h	DON induced cell death in a dose −dependent manner with the production of excessive ROS. DON treatment significantly inhibited forskolin-induced the expression of STAR and NR4A1 mRNAs and the progesterone secretion. DON treatment also significantly inhibited ZEN-induced expression of STAR.	(Savard et al. 2016)

spermatogenesis and compromising sperm quality parameters. It has been reported that various doses of DON treatment (i.e., 1.2, 2.4, and 4.8 mg/kg body weight daily for 28 days) could significantly decrease the relative weight of testicular tissues, sperm concentration, and sperm viability in mice, and the rates of abnormal sperm morphology were also significantly increased (Cao et al. 2020). In another study, it reported that DON treatment at 150 and 2300 μg/kg body weight per via the oral administration per day for 3 weeks caused markedly abscission of spermatogenic cells, disturbances in the arrangement of testicular cells, and occurrence of erythrocytes and inflammatory cells within the testicular interstitium of mice (Ruan et al. 2024b). Similarly, in a rat model, DON treatment via the oral administration at the doses of 0.5, 1.0, 2.5 or 5.0 mg/kg body weight per days for 28 days significantly decreased the body weight, relative weight of epididymis, testicular spermatid counts, and cauda epididymal sperm counts (Sprando et al. 2005). DON treatment significantly upregulated the levels of FHS, LH and downregulated the levels of testosterone with various histopathological damage of testicular tissues, such as seminiferous tubule atrophy, germ cell degeneration, failure of sperm release, abnormal germ cell development, multinucleate cell formation, fluid build-up in interstitial space, boundary layer in folded, anomalous cell types in interstitial space, and Leydig cell vacuolization (Sprando et al. 2005). Additionally, studies have also shown that DON exposure can trigger programmed cell death pathways in testicular tissues, such as pyroptosis, apoptosis, and ferroptosis (Hai et al. 2023; Ruan et al. 2024b; Yang et al. 2024b; Yang et al. 2023).

In vitro, the treatment of boar spermatids with DON at 50.6 μM *in vitro* for 1—–4 h considerably raised the sperm abnormality rate (for example, immotile spermatozoa and a reduction in progressive motile spermatozoa) and changes sperm morphology (head abnormalities) (Tassis et al. 2020). Similarly, 60 μL aliquots (about 20 million sperm) isolated from frozen semen of five 5 to 7 years old Holstein bulls were treated with de-epoxy-DON at doses of 10 or 100 ng/mL for 2, 4, 6, 8, and 10 h resulted in a significant decrease in the sperm motility and strength in both dose- and time-dependent manners (Guerrero-Netro et al. 2021). Several studies indicated that the exposure to DON and its derivative de-epoxy-DON can damage germ cells, Sertoli cells, and Leydig cells (Guerrero-Netro et al. 2021; Tassis et al. 2020). For example, in TM3 cells (a proliferating mouse Leydig cell line), DON treatment at doses of 10–150 ng/mL for 24 h induced cytotoxicity in a dose-dependent manner, significantly decreased the levels of GSH and CAT activities, significantly increased the intracellular ROS and MDA levels, significantly increased the expression of NLRP3, ASC, cleaved-caspase-1, GSDMD, IL-18, and IL-1β levels, and finally resulting in cellular pyroptosis (Ruan et al. 2024b). Similarly, in porcine primary

Leydig cells, DON alone treatment at 0.3——4.8 μM resulted in the loss of cell viabilities in a dose-dependent manner and DON (at 0.6 μM) and ZEN (at 20 μM) co-treatment markedly induced oxidative stress, mitochondrial dysfunction, cell cycle arrest, and the activation of the mitochondrial apoptotic pathway (Cao et al. 2021).

3. Effects of DON exposure on the hypothalamic-pituitary–gonadal axis

Endocrine disorders constitute one of the most compounding factors contributing to male infertility. The hormones produced via the hypothalamic−pituitary−gonadal (HPG) axis-mediated process is essential for maintaining endocrine balance. The HPG axis is regulated at multiple levels, including the brain and pituitary gland. This regulation enables either the stimulation or the suppression of gonadal sex steroid secretion and associated functions. Any imbalance of the HPG axis often results in reproductive issues (Acevedo-Rodriguez et al. 2018; Dwyer and Hayes 2019). Gonadotropin−releasing hormone (GnRH) which is secreted by the hypothalamus, mediates the secretion of pituitary gonadotropins LH and FSH. LH and FSH ultimately act on testicular Leydig cells, endocrine cells, and Sertoli cells, thereby maintaining optimal spermatogenesis (Oduwole et al. 2021). Recently, Cai *et. al.,* showed that even μM levels of DON down−regulated GnRH−induced expression of luteinizing hormone subunit beta (LDB), which is a crucial gene encoding the beta subunit of LH; and secondly, inhibited the production of LH in an immortalized gonadotrope−like cell line (i.e., LβT2 cells) (Cai et al. 2024). Furthermore, DON specifically inhibits GnRH-induced phosphorylation of extracellular regulated protein kinase (Erk) (Oduwole et al. 2021). Erk signaling is known to mediate the GnRH effects on the transcription of LH and FSH (Caunt et al. 2006). This suggests that DON can directly impede GnRH−mediated Erk activation, which in turn down-regulates the production of LH (Clarke and Ottinger 1987). However, experimental animal studies found that DON exposure significantly increased the levels of LH and FSH levels in the serum samples of male mice or rats (Ruan et al. 2024b; Sprando et al. 2005). Generally, LH regulates the production of testosterone by Leydig cells of the testis; this regulation was found to be positively associated in AFB1 treated rodents (Hassanein et al. 2024; Owumi et al. 2022; Supriya et al. 2014). Specially, unlike AFB1, it has been reported that there are opposing effects between LH (or FSH) and the levels of testosterone in the serum samples of DON-treated animals (Cao et al. 2020; Ruan et al. 2024b; Sprando et al. 2005; Yang et al. 2024b). For example, Ruan *et. al.,* found that DON exposure at 0.15 or 2.3 mg/kg body weight per day for 21 days could significantly increase the levels of FSH and LH but significantly decrease the levels of testosterone in the serum samples of mice (Ruan et al. 2024b). Similarly, Sprando *et. al.,* found that DON exposure at the dose of 5 mg/kg body weight via the oral administration for 28 days significantly increased the levels of FSH (increased from 4.07 ng/mL to 7.15 ng/mL) and LH (increased from 0.92 ng/mL to 1.71 ng/mL), but significantly downregulated the levels of testosterone (decreased from 0.82 ng/mL to 0.34 ng/mL)(Sprando et al. 2005). The decreased testicular testosterone levels resulted in incomplete spermatogenesis (Lei et al. 2004). Collectively, these studies imply that DON may directly influence intracellular testosterone synthesis and this effect is not entirely dependent on its upstream effects of LH secretion.

It is well-known that the key precursor of testosterone, cholesterol is initially transported into the cytoplasm by scavenger receptor class B member 1 (SCARB1), and then further transferred into the mitochondrial inner membrane by steroidogenic acute regulatory protein (STAR) in testicular Leydig cells (Scotto Rosato et al. 2019; Zhang et al. 2024a). The internalized cholesterol is then converted to pregnenolone by cytochrome P450 family 11 subfamily A member 1 (CYP11A1), and then into testosterone via a series of androgen synthases such as CYP17A1, hydroxy delta 5 steroid dehydrogenase, 3 beta (HSD3B), 1 (HSD3B1), and 17B1 (HSD17B1) in the smooth endoplasmic reticulum (Scotto Rosato et al. 2019; Zhang et al. 2024a). Cao *et. al.,* employed a mouse model to show that that oral administration of DON at doses of 1.2, 2.4, and 4.8 mg/kg body weight per day for twenty eight days down−regulated the expression of CYP11A1, CYP17A1, and HSD17B1 mRNAs in the testes of the treated animals in a dose−dependent manner (Cao et al. 2020). Similarly, Yang *et. al.,* found that DON exposure through oral administration at doses of 1, 2, and 4 mg/kg body weight per day for seven days significantly down−regulated the expression of SCARB1, STAR, CYP17A1, HSD11B1, and INSI3 mRNAs in the testes of rats (Yang et al. 2024b). Sun *et. al.,* reported that DON treatment at a dose of 2.5 μM (the 50 % inhibitory concentration on cell viability) for 24 h significantly down−regulated the expression of STAR and HSD3B proteins but did not change the expression of CYP11A1 protein in isolated primary porcine Leydig cells (Sun et al. 2022). Ndossi *et. al.,* showed that exposure of cultured H295R human adenocarcinoma cells to even low levels of DON (i.e., at 100 ng/mL) significantly reduced the levels of testosterone and its metabolite estradiol, but did not affect the levels of progesterone and cortisol (Ndossi et al. 2012). The authors of this study went further to show that DON treatment perturbed the mRNA expression levels of the testosterone biosynthetic and catabolism-related genes (i.e., CYP1A1 and CYP21, CYP17, HSD3B2, CYP11B2, and CYP11B1 were significantly upregulated; and the expression of hydroxymethyl-glutaryl CoA reductase, CYP19, nuclear receptor 4A1 were significantly downregulated) (Ndossi et al. 2012). In another study, it shown that DON exposure can produce differential effects on the expression of genes related to steroidogenesis in various human prostate cancer cell lines (e.g., PNT1A, PC−3, DU−145, and LNCaP cells). For example, exposure of prostatic adenocarcinoma PC-3 cells to DON at 5 μM significantly down-regulated the expression of STAR, CYP11A1, CYP17A1, and CYP19A1 mRNAs and significantly up-regulated the expression of HSD17B2 mRNA. Whereas, in prostate adenocarcinoma LNCaP cells the same treatment significantly down−regulated the expression of CYP19A1 mRNAs and sup-regulated the expression of HSD3B2 and CYP17A1 mRNA, but did not affect the expression of CYP17A1 mRNA (Urbanek et al. 2021). Consistently, Savard *et al.,* found that DON treatment at the dose of 0.1 μM could significantly inhibit forskolin (an adenylate cyclase activator) −induced expression of NR4A1 and STAR mRNAs, which in turn decreased the production of progesterone. Notably, the expression of LH receptor mRNA was upregulated in MA-10 mouse Leydig tumor cells (Savard et al. 2016). These findings indicate that DON exposure can perturb steroidogenesis via inhibition of the cAMP/NR4A1/STAR pathway.

In summary, available evidence suggests that exposure to low levels of DON can be detrimental on the HPG axis and lead to disruption of steroidogenesis and testosterone biosynthesis. Ultimately, this leads to reproductive dysfunction and male infertility (Fig. 2). Additionally, the inhibition of testosterone synthesis in Leydig following DON exposure might be directly related to the disruption of the SCARB1/STAR/CYP11A1 pathway and the inhibition of cAMP/NR4A1/STAR pathway; which appears to be independent of DONs dysregulation of LH and FSH levels in the testis tissues of male animals.

4. Molecular mechanisms of DON-induced damage on male reproductive organs

Several molecular mechanisms, such as oxidative stress, mitochondrial dysfunction, apoptosis, cell cycle arrest, ER stress, inflammatory response, pyroptosis, and ferroptosis have been implicated (Cao et al. 2020; Owumi et al. 2023; Owumi et al. 2022; Sun et al. 2022; Supriya et al. 2014). A number of signaling pathways are also involved, including nuclear factor erythroid 2−related factor 2 (Nrf2), nuclear factor−kappa B (NF−κB), p53, phosphatidylinositide 3-kinase (PI3K)/protein kinase B (AKT), mitogen−activated protein kinase (MAPK), AMP−activated protein kinase (AMPK), NLR family pyrin domain containing 3 (NLRP3), and mitochondrial apoptotic pathways (Cao et al. 2020; Owumi et al. 2023; Owumi et al. 2022; Song and Zhang 2021; Sun et al. 2022; Supriya et al. 2014). The specific molecular mechanisms

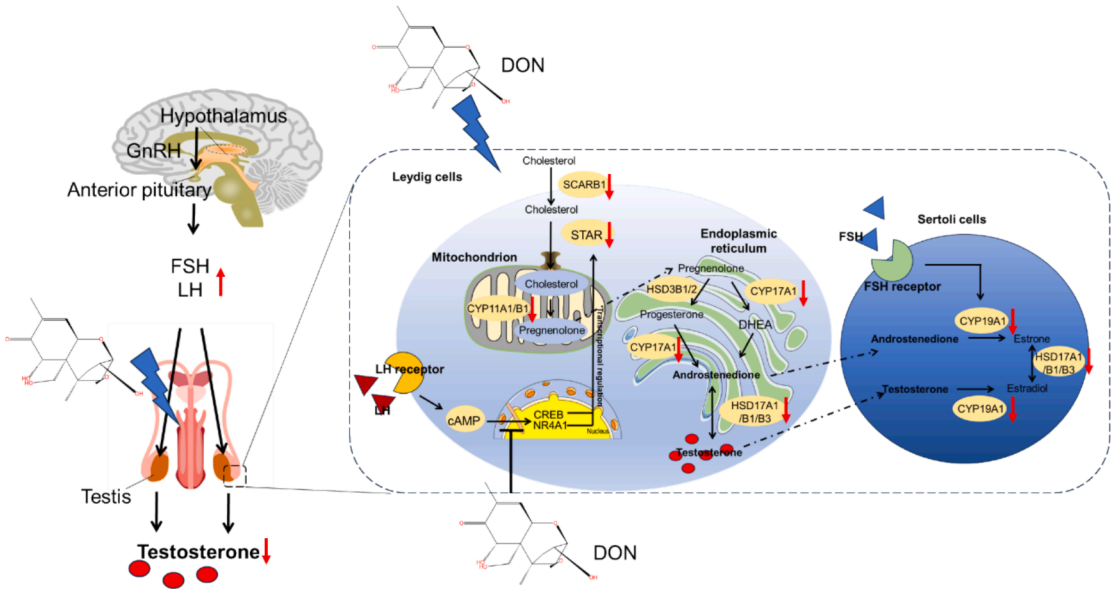

Fig. 2. Schematic diagram of DON-mediated inhibition of testosterone synthesis in male mammals. DON exposure can induce disruption of steroidogenesis and testosterone biosynthesis via disturbing HPG axis. Furthermore, DON exposure-induced the inhibition of testosterone synthesis involves the inhibition of SCARB1/STAR/CYP11A1 and cAMP/NR4A1/STAR pathways. DON, deoxynivalenol; GnRH, gonadotropin−releasing hormone; LH, luteinizing hormone; FSH, follicle−-stimulating hormone; SCARB1, scavenger receptor class B member 1; STAR, steroidogenic acute regulatory protein; CYP11A1, cytochrome P450 family 11 subfamily A member 1; CYP17A1, cytochrome P450 family 17 subfamily A member 1; CYP19A1, cytochrome P450 family 19 subfamily A member 1; HSD3B1/2, hydroxy delta 5 steroid dehydrogenase, 3 beta 1/2; HSD17B1 hydroxy delta 5 steroid dehydrogenase, 17 beta 1.

related to the damage caused by DON exposure in male reproductive organs are discussed in the forthcoming sections below.

4.1. Don-induced oxidative stress

Reactive oxygen species (ROS), comprised of various free radicals such as hydrogen peroxide (H_2O_2), superoxide anion ($O_2\bullet^-$), singlet oxygen ($^1O_2$), and hydroxyl radicals (•OH), play a critical role in cellular processes. However, an overproduction of these species can lead to significant harm to key intracellular components, including lipids, DNA, RNA, and proteins. This detrimental effect is scientifically recognized as oxidative stress damage (Chandel 2018; Takalani et al. 2023). Notably, oxidative stress has been extensively documented to impair sperm quality parameters (e.g., motility, viability, DNA integrity) and compromise reproductive function (Agarwal et al. 2012; Bisht and Dada 2017; Jing et al. 2023; Leite et al. 2022; Takalani et al. 2023; Tiwari et al. 2022; Zi et al. 2022).

Several studies reported that DON exposure resulted in excessive ROS generation and induced oxidative stress damage in the male reproductive system (Cao et al. 2021; Savard et al. 2016; Yang et al. 2019). Elevated levels of ROS can induce structural damage to cellular membranes through phospholipid peroxidation with the accumulation of malondialdehyde (MDA), a key biomarker of oxidative lipid degradation (Chandel 2018; Takalani et al. 2023). Notably, Yang *et. al.,* found that mice orally administered DON at 2.4 mg/kg body weight daily for twenty-eight days significantly increased the levels of ROS and MDA in testicular tissues (Yang et al. 2019). Li *et. al.,* reported that DON exposure via the diet at 12 mg/kg feed per day for thirty-five days significantly increased MDA levels in the testicular tissues of mice (Li et al. 2023). In another study, Ruan *et. al.,* reported DON exposure can significantly increase levels of ROS MDA in TM3 cells, and MDA levels in the testicular tissues of mice (Ruan et al. 2024b). In addition, multiple studies have reported that DON exposure can significantly upregulate MDA levels in tissues such as liver, kidney, brain, and intestinal tissues, finally inducing lipid peroxidation damage (Li et al. 2022b; Ma et al. 2022; Wang et al. 2020; Ye et al. 2023b).

Intracellular antioxidant defense systems play a crucial role in maintaining cellular homeostasis by neutralizing ROS and preventing oxidative damage. These systems are composed of both enzymatic and non-enzymatic components that work synergistically to protect cells from oxidative stress. Enzymatic antioxidants include superoxide dismutases (SOD), catalases (CAT), glutathione reductase (GR), glutathione S-transferase (GST), and glutathione peroxidases (GPx), which catalyze the conversion of ROS into less harmful molecules (Dai et al. 2019). Non-enzymatic antioxidants, such as reduced glutathione (GSH), vitamin C, and vitamin E, directly scavenge free radicals and regenerate oxidized antioxidants to their active forms (Dai et al. 2024). DON has been reported to alter the antioxidant defense system in various target tissues and cells via multiple *in vivo* and *in vitro* studies (Li et al. 2022b; Ma et al. 2022; Wang et al. 2020; Yang et al. 2019; Ye et al. 2023b). Animal experiments using mouse or rat models showed that the exposure of DON via the diet or direct gavage administration can significantly decreased the activities of activities of SOD, CAT, and total antioxidant capacity (T-AOC), and the MDA levels in the testicular tissues (Li et al. 2023; Ruan et al. 2024b; Yang et al. 2019). *In vitro* studies, the treatment of TM3 cells (a mouse testicular interstitial cell line) with DON at the dose range among 10–150 ng/mL for 24 h can induce a marked decrease of cell viability with significant reduction in CAT activities and GSH levels (Ruan et al. 2024b). At the same time, GST, and GR activities were found to be significantly decreased by DON-treated liver, kidney, and heart tissues of rats (Haus et al. 2021). These changes may also contribute to DON −induced oxidative stress damage in the testicular tissue, but the precise molecular mechanisms still need more investigation. Supplementation with *N*-acetylcysteine (NAC), an aminothiol and synthetic precursor of intracellular cysteine and GSH, significantly reduced ROS production, effectively alleviating DON−induced lipid peroxidation, oxidative damage, and cytotoxicity in TM3 cells and piglets Sertoli cells (Cao et al. 2021; Ruan et al. 2024b). Moreover, a recent investigation revealed that treatment with DON markedly reduces the expression of peroxiredoxin 4 (PRDX4) protein in primary Sertoli cells of *Equus asinus* (Song and Zhang 2021). PRDX4 stands out as the sole secreted antioxidant enzyme within the peroxidase family, capable of converting H_2O_2 into harmless O^2 to mitigate oxidative stress. It also plays a pivotal role in essential biological processes, including protein folding, DNA repair,

inflammatory regulation, and tumor development (Liang et al. 2020). At the genetic level, it has been confirmed that overexpression of PRDX4 gene can significantly ameliorate oxidative stress and cell apoptosis induced by T-2 toxin, another trichothecene mycotoxin (Lu et al. 2024). These findings suggested DON exposure-induced oxidative stress may be partly due to its inhibition of the expression of PRDX4 enzyme.

The Nrf2 signaling pathway plays an important role in reproductive function by regulating redox balance and inflammation in testis tissue (Smolková et al. 2020; Tossetta et al. 2024). In response to stress, Nrf2 transcriptional activation-mediated the expression of various downstream antioxidant genes, including NAD(P)H quinone oxidoreductase-1 (NQO-1), heme oxygenase 1 (HO-1), GPX, CAT, SOD, and GST genes (Patel et al. 2020; Smolková et al. 2020). The Nrf2 pathway is triggered by multiple mycotoxins such as AFB1, T-2, and ZEN (Dai et al. 2024; Dai et al. 2022; Jin et al. 2024; Li et al. 2024a; Zhang et al. 2018). DON exposure of mice significantly downregulated the expression of Nrf2 protein and mRNA; and the expression of mRNA of its downstream genes such as HO-1, NQO-, CAT, and SOD in the testicular tissues (Yang et al. 2023). In other studies, however; DON treatment significantly upregulated the expression of Nrf2 protein and its downstream HO-1 protein in TM3 cells, and this change is governed by ROS production (Ruan et al. 2024b). This indicates a crosstalk between the Nrf2 pathway and oxidative stress, and the precise molecular mechanisms still require further exploration.

In summary, oxidative stress related damage is an extremely important facet of male reproductive toxicity caused by DON exposure. The production of ROS can cause oxidative harm to cellular macromolecules such as lipids, proteins, and DNA, ultimately leading to different forms of regulated cell death. As shown in Fig. 3, current evidence suggests that the oxidative stress induced by DON is mainly attributable to lipid peroxidation, disruption of the body's antioxidant system, inhibition of peroxidase expression, and dysregulation of the Nrf2 pathway.

4.2. Mitochondrial dysfunction and mitochondrial apoptotic pathways

Mitochondria are organelles within mammalian cells that govern the production of adenosine triphosphate (ATP), the main energy molecule (Spinelli and Haigis 2018). Besides generating energy, mitochondria perform many other essential tasks which encompass the regulation of redox status, ROS production, signaling pathways, and diverse types of cell death (Spinelli and Haigis 2018). Additionally, mitochondria can act as both producers and targets of ROS (Spinelli and Haigis 2018). In germ cells, mitochondria are the most vital organelle for energy production. Notably, the link between mitochondrial function and sperm parameters has been highlighted in numerous studies (Barbagallo et al. 2020; Boguenet et al. 2021). Ruan *et. al.,* utilized a mouse model to demonstrate that DON exposure at 0.15 or 2.3 mg/kg body weight daily for twenty-one days severely damaged the mitochondrial ultrastructure in Leydig cells (Ruan et al. 2024b). Yang *et. al.,* discovered that there was a decline in mitochondrial membrane potential (MMP) upon exposure to DON at 2 or 4 μM for 24 h in isolated rat primary Leydig cells (Yang et al. 2024b). Similarly, Sun *et. al.,* found that treatment with DON at 2.5 μM for 24 h significantly reduced the MMP in porcine primary Leydig cells (Sun et al. 2022). It is well known that the MMP, which reflects the function and energy state of mitochondria, is related to sperm motility and viability in mammals (Bonanno et al. 2016). The MMP creates a proton gradient that is essential for ATP synthesis. Thus, any decrease in MMP can cause a reduction in ATP production in germ cells (Zorova et al. 2018). Furthermore, the activities of mitochondrial respiratory chain complexes (ETCs) I, III, and IV play critical role for the maintenance of MMP and ATP production. Previous investigations have shown that DON treatment promoted mitochondrial dysfunction with a significant drop in the ETC I, II, and III, and IV activities in the jejunum of piglets (Li et al. 2024b). These results suggest that mitochondrial dysfunction caused by DON exposure may be partially due to the inhibition of mitochondrial ETCs and MMP in testicular tissue, underlining the significance of these mechanisms regarding male reproductive

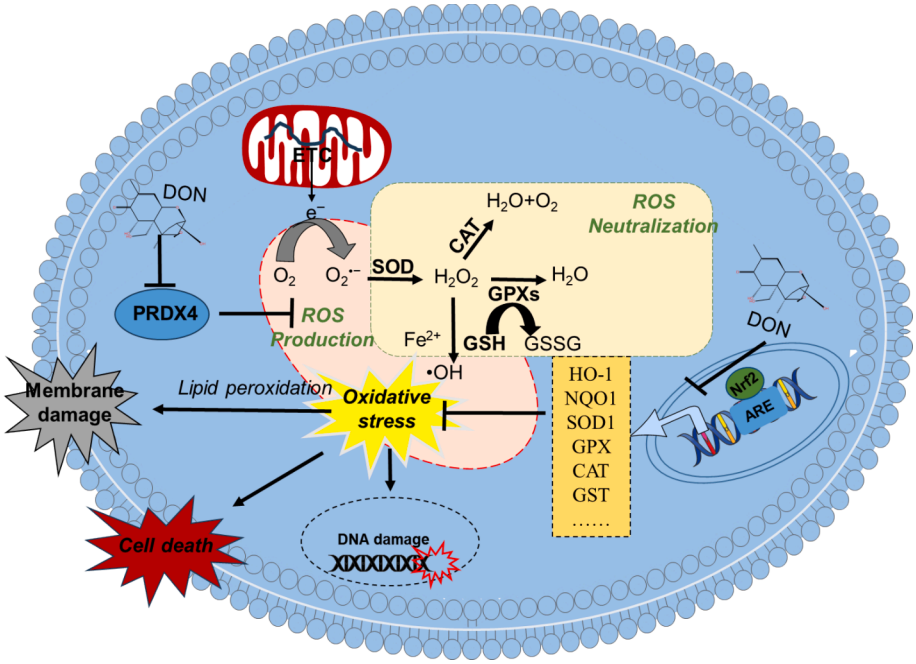

Fig. 3. A mechanism diagram of DON-caused oxidative damage in male germ cells. DON exposure can induce the production ROS and inhibit cellular antioxidant enzymes SOD, CAT, and GPXs activities or antioxidant GSH levels, following to result in lipid peroxidation and oxidative stress damage, finally inducing male reproductive toxicity. The inhibition of PRDX4 and Nrf2/ARE signaling pathways also partly contributed to DON-induced oxidative stress damage. DON, deoxynivalenol; PRDX4, peroxiredoxin 4; GSH, reduced glutathione; ROS, reactive oxygen species; GSSG, oxidized glutathione; OH-1, heme oxygenase 1; NQO1, NAD(P)H quinone oxidoreductase-1; SOD, superoxide dismutase; GPX, glutathione peroxidase; GST, glutathione S-transferase; Nrf2, nuclear factor erythroid 2-related factor 2; ARE, antioxidant response element.

toxicity.

Mitochondrial biogenesis and fission/fusion dynamics play crucial roles in maintaining mitochondrial function and cellular homeostasis, which are essential for male fertility (Scarpulla 2011; Zhang et al. 2024b). The renewal and adaptation of the mitochondrial population occurs when there is damage or a greater demand for energy production of sperm cells, which are highly reliant on ATP for motility and function. If biogenesis is hindered, mitochondrial dysfunction may become more severe (Zhu et al. 2013). The regulation of mitochondrial biogenesis involves several key factors, including peroxisome proliferators-activated receptor (PPAR) pathway, PPAR gamma coactivator 1-alpha (PGC-1α), and nuclear respiratory factor-1 (Nrf1), which coordinates the expression of genes involved in mitochondrial replication and function(van Tol Amaral Guerra et al. 2024). Previous studies have shown that DON treatment significantly decreased the expression of PGC-1α, NRF1/2, and TFAM in the cultured porcine intestinal epithelial cells (Liao et al. 2017; Xue et al. 2022). This indicated that DON exposure may decrease mitochondrial biogenesis, then promote DON induced mitochondrial damage and testicular toxicity. It was discovered that DON exposure could significantly upregulate the levels of the phosphorylated AMPK protein in isolated rat primary Leydig cells, which is a vital regulator in energy metabolism and mitochondrial biogenesis (Herzig and Shaw 2018; Yang et al. 2024b). AMPK could promote the mitochondrial biogenesis by upregulating PGC-1α-dependent activation of Nrf1, Nrf2, and PPAR pathway, which all could activate the transcriptional expression of mitochondrial transcription factor A (TFAM) (Herzig and Shaw 2018; Yang et al. 2024b). It is known that AMPK activation can protect cells against mitochondrial dysfunction and oxidative stress (Dong et al. 2014). Inhibition of AMPK markedly increased DON −induced cytotoxicity in intestinal epithelial cells (Tang et al. 2015). Overall, this information indicated that increased expression of AMPK-mediated mitochondrial biogenesis may play a protective role in protective against DON-induced mitochondrial damage and testicular toxicity. However, the precise molecular mechanisms are still unclear and more investigations are required.

Yang *et. al.,* showed that DON distinctly changed mitochondrial morphology and activated mitochondrial fission pathways in rat testis and rat primary progenitor Leydig cells (Yang et al. 2024b). This was evident from the elevated levels of fission proteins such as fission 1 (Fis1), dynamin-related protein 1 (Drp1), and mitochondrial fission factor (MFF), along with the decreased levels of fusion protein mitofusins 1 (Mfn1) (Yang et al. 2024b). The educed mitochondrial dynamics will block spermatogonial differentiation (Zhang et al. 2024b). Consistently, the deficiency in Drp1-mediated fission led to a stage-specific blockage of spermatogenesis at differentiating spermatogonia, then caused male infertility. Increased expression of Mfn1 upregulated mitochondrial respiration with the increases of intracellular ROS, which is required for spermatogonial differentiation (Zhang et al. 2024b). Moreover, research has also highlighted the role of mitochondrial dynamics in the regulation of ROS production. An imbalance in fission and fusion can lead to increased ROS levels, which can damage sperm DNA and proteins, further exacerbating infertility issues (Calkins and Reddy 2011). Therapeutic strategies aimed at modulating mitochondrial dynamics and enhancing biogenesis have shown promise in improving mitochondrial function and reducing oxidative stress, thereby potentially alleviating some forms of male infertility (Ashraf and Kumar 2022; Qin et al. 2020). Consistently, the co-supplementation of progenitor Leydig cell cultures with the mitochondrial division inhibitor MDIVI-1 effectively re-establish the balance of mitochondrial dynamics, and rescued the cells from mitochondrial damage caused by DON treatment (at 4 μM for 24 h)(Yang et al. 2024b). These pieces of information suggest that DON can regulate mitochondrial damage and testicular toxicity by interfering with mitochondrial dynamic balance.

Song *et. al.,* discovered that in the Sertoli cells of *Equus asinus*, treated with DON at a concentration of 10 or 30 μM for 72 h, markedly altered the expression of numerous genes enriched in DNA metabolic processes (i.e., DNA repair, immune system processes, and apoptotic processes) (Song and Zhang 2021). Likewise, DON treatment−induced cell apoptosis has also been detected in testis tissue *in vivo* and Leydig cells *in vitro* (Ruan et al. 2024a; Yang et al. 2019). During mitochondrial dysfunction, the formation of the mitochondrial permeability transition pore (MPTP) promotes the release of cytochrome *C* (CytC) from mitochondria into the cytoplasm, in which cascades to activating caspases −9 and −3, finally inducing apoptosis (Dai et al. 2024; Dai et al. 2022). The decreased B-cell lymphoma-2 (Bcl-2)/Bcl2-associated X (Bax) ratio also contributed to the release of CytC and the activation of caspase via promoting the formation of MPTP (Dai et al. 2022). Therefore, CytC release and the ratio of Bcl-2/Bax has been considered as two critical biomarkers of mitochondrial dysfunction. Yang et al. pointed out that DON exposure via the oral treatment at 2.4 mg/kg of body weight daily for seven days (from day 21 to day 28) could significantly boost the mRNA and protein expression of CytC, caspases-9 and-3 genes in the testis tissues of postnatal rats (Yang et al. 2019). Additionally, it has been reported that DON treatment can considerably increase the expression of caspase−8 and mitochondrial pro−apoptotic proteins Bax and Bim (Sun et al. 2024; Yang et al. 2019). These findings imply that the mitochondrial apoptotic pathway and caspase activation are involved in DON−induced apoptosis in testis tissue. Antioxidants supplementation such as *N*-acetylcysteine (NAC) could partly reduce the production of ROS, then revise DON with another mycotoxin (e.g., ZEN) combination−induced mitochondrial dysfunction and apoptosis in piglet Sertoli cells, indicating oxidative stress contributes to DON-induced the activation of mitochondrial apoptotic pathway (Cao et al. 2021). Increased expression of phosphorylated JNK and c-Jun were detected in the testis tissues of mammals in response to oxidative stress (Yang et al. 2019). This is coincident with the finding that targeted inhibition of JNK pathway by SP600125 could significantly inhibit DON-induced cell apoptosis (Lee et al. 2019), indicating oxidative stress-mediated JNK activation also contributes to DON exposure-induced apoptosis.

In summary, exposure to DON can lead to mitochondrial dysfunction in testicular tissues. Consequently, this can initiate apoptosis through the activation of mitochondrial apoptotic and JNK pathways as well as caspase activation. DON-induced mitochondrial dysfunction has been shown to involve the activation of mitochondrial fission, the inhibition of mitochondrial biogenesis, and the loss of MMP (Fig. 4). Overall, understanding the intricate relationship between mitochondrial biogenesis, fission/fusion dynamics, apoptosis, and male fertility is essential for developing targeted interventions that could improve reproductive outcomes. Further research in this area could provide valuable insights into the molecular mechanisms underlying male infertility and pave the way for novel therapeutic approaches.

4.3. Role of inflammatory responses

It is well-known that inflammation is one of the core causes of male infertility (Dutta et al. 2021). Multiple reports have shown that exposure to DON can trigger the inflammatory responses within the testicular tissues of animals (Ruan et al. 2024b; Sun et al. 2024). NF-κB is an important transcription factor that controls the expression of various pro-inflammatory genes, including cyclooxygenase-2 (COX2), interleukin-6 (IL-6), IL-, and tumor necrosis factor alpha (TNF-α) (Jobin et al. 1999; Karunaweera et al. 2015; Kumar et al. 2004). Transcriptional profiling indicated that treating mice with DON at 12 mg/kg for 35 days disrupted the expression profiles of inflammation-related genes in the testis, including tumor necrosis factor receptor superfamily, member 9 (Tnfrsf9), chemokine (C–C motif) ligand 22 (Ccl22), reticuloendotheliosis viral (v-rel) oncogene−related B (Relb), and interleukin 6 signal transducer (IL6st), which were enriched in TNFα via NFκB and TGF-β signaling pathways (Li et al. 2023). Sun *et. al.,* stated that exposure to DON at a dose of 2 mg/kg body weight per day for 21 days markedly increased the levels of IFN-γ, IL-1β, TNF-α, and IL-6 in the

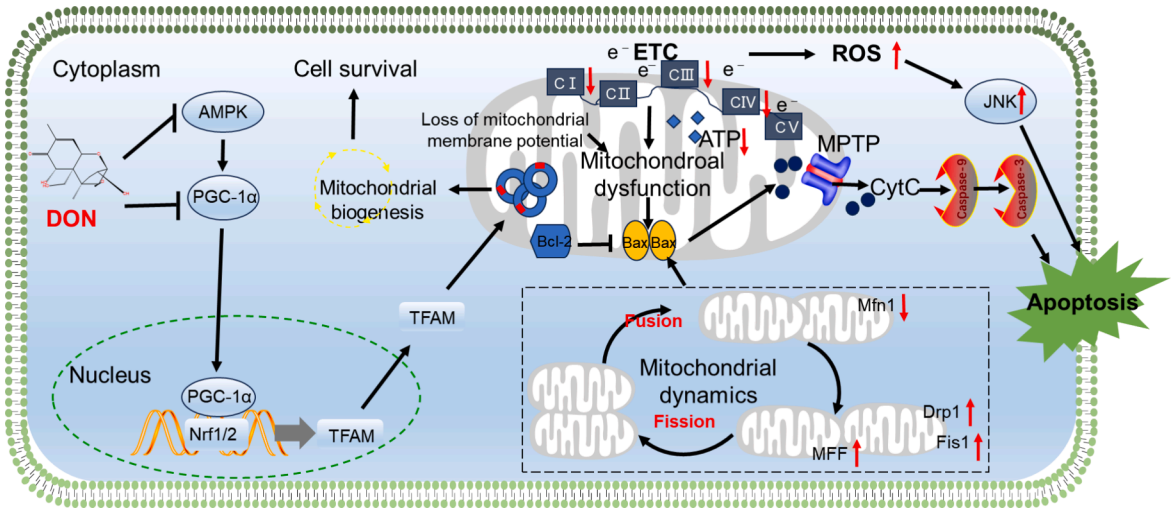

Fig. 4. A mechanistic diagram of DON-induced mitochondrial dysfunction and apoptosis in male germ cells. DON exposure can induce mitochondrial dysfunction in testicular tissues via the inhibition of mitochondrial biosynthesis, the reduction of mitochondrial membrane potential, as well as the disruption of mitochondrial energy metabolism and mitochondrial dynamic balance. Consequently, dysfunctional mitochondria can induce the production of ROS to activate JNK pathway or directly induce mitochondrial apoptotic pathway, finally causing cell apoptosis. Additionally, DON exposure can also inhibit AMPK/PGC-1α pathway, which partly contributed to its inhibitory effects on mitochondrial biosynthesis. DON, deoxynivalenol; AMPK, adenosine 5′-monophosphate (AMP)-activated protein kinase; PGC-1α, peroxisome proliferator activated receptor-γ co-activator-1α; TFAM, mitochondrial transcription factor A; Nrf1, nuclear respiratory factor 1; Nrf2, nuclear factor erythroid 2-related factor 2; MPTP, mitochondrial permeability transition pore; CytC, cytochrome *C*; Bax, Bcl2−associated X; Bcl-2, B−cell lymphoma −2; JNK, c-Jun *N*-terminal kinase; Fis1, fission proteins such as fission 1; ROS, reactive oxygen species; Drp1, dynamin−related protein 1; MFF, mitochondrial fission factor; Mfn1, mitofusins 1.

testis of offspring mice (Sun et al. 2024). The activation of the JNK pathway by DON treatment in the testis tissue might play a role in the inflammatory response (Yang et al. 2019).

NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) functions as an intracellular inflammation sensor. The NLRP3 inflammasome is a cytosolic multi−protein complex. It is composed of the innate immune receptor protein NLRP3, the adapter protein ASC, and the inflammatory protease caspase−1. This complex responds to microbial infections, endogenous danger signals, and environmental stimuli (Swanson et al. 2019; Zhang et al. 2022). The formation of the NLRP3 inflammasome can result in the activation of gasdermin D (GSDMD), i.e., GSDMD is cleaved by caspase−1 or−11 to generate GSDMD- N, a 31 kDa *N*-terminal fragment, finally triggering pyroptotic cell death (Swanson et al. 2019). It has been reported that treatment with DON can remarkably up-regulate the expressions of NLRP3, ASC, cleaved caspase-1, GSDMD, IL-18, and IL-1β proteins in the testis tissues of mice and TM3 cells (Ruan et al. 2024a). It was also discovered that when primary Sertoli cells of *E. asinus* were treated with DON at 10 or 30 μM for 24 h,

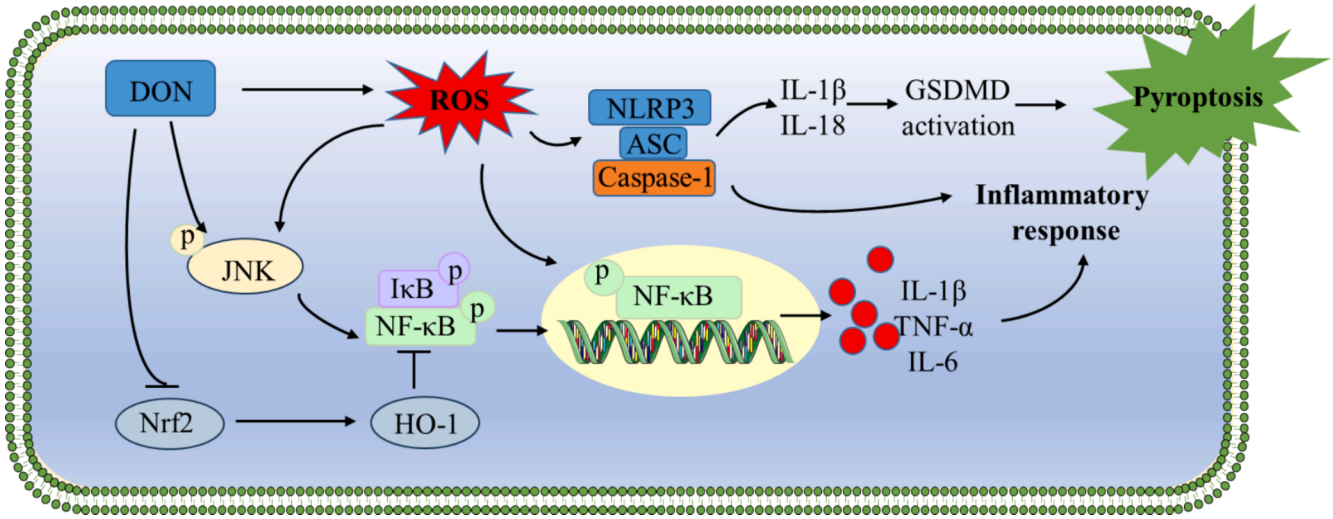

Fig. 5. A mechanistic diagram of DON-caused inflammatory response and pyroptosis in male germ cells. DON exposure can induce the production of ROS, then promote the formation of NLRP3 inflammasome, finally triggering inflammatory response. The activated NLRP3 inflammasome can also activate caspase-1 and induce the maturation of IL-1β and IL-18 as well as the processing of GSDMD, finally resulting in cell pyroptosis in male germ cells. Additionally, DON can also induce the phosphorylation of JNK, then activate the transcriptional expression of NF-κB and promote the production of pro-inflammatory factors such as IL-1β, TNF-α, and IL-6. The inhibition of Nrf2/HO-1 pathway caused by DON may also contribute to the activation of NF-κB pathway. DON, deoxynivalenol; NLRP3, NOD-, LRR- and pyrin domain−containing protein 3; JNK, c-Jun N-terminal kinase; Nrf2, nuclear factor erythroid 2-related factor 2; NF-κB, nuclear factor kappa-B; ROS, reactive oxygen species; OH-1, heme oxygenase-1; ASC, apoptosis-associated speck-like protein containing a caspase recruitment domain; GSDMD, gasdermin D; IL-6, interleukin-6; IL-18, interleukin-18; IL–1β, interleukin-1beta; TNF-α, tumor necrosis factor alpha.

the expressions of caspase-1, GSDMD-N, CCL17, IL-10RA proteins in were significantly up-regulated (Song and Zhang 2021). Moreover, inhibiting the NLRP3 pathway by MCC950 (a selective inhibitor of NLRP3) significantly decreased the expressions of ASC, cleaved-caspase-1, GSDMD, IL-18, and IL-1β proteins, thereby reducing DON-induced pyroptosis in TM3 cells (Ruan et al. 2024a). These studies emphasize that the NLRP3 inflammasome mediated inflammatory response and cell pyroptosis play a vital role in DON induced male reproductive toxicity. Additionally, a transcriptomics study in primary Sertoli cells of *E. asinus* has shown that the toxic effects induced by DON exposure involve multiple signaling pathways, such as the PI3K/AKT pathway, NOD-like receptor signaling pathway, MAPK pathway, cytokine-cytokine receptor interaction, and TNF signaling pathway(Song and Zhang 2021). The up-regulation of ROS and the inhibition of Nrf2 by DON exposure may also contribute to the activation of the inflammatory response through the upregulation of NF-κB (Morgan and Liu 2011).

In summary, current research data indicates that DON exposure could induce inflammatory responses in testicular tissue via the activation of NF-κB, NLRP3, and MAPKs pathways (Fig. 5). These findings also provide important directions for clinical targeted intervention of DON-induced testicular inflammatory damage.

4.4. Role of iron homeostasis and ferroptosis

Iron plays a crucial role in spermatogenesis and male reproductive function and testicular iron metabolism is tightly controlled (Yuan et al. 2023). Firstly, the iron set free from spermatogonia is conveyed to the developing round spermatocytes. Secondly, the subsequent outflow of iron from spermatocytes is shifted to Sertoli cells for storage through the process mediated by ferritin. This internal iron recycling is further supported by the regulated intake of external iron to keep the balance (Yuan et al. 2023). Although an overall excess of iron in the body can trigger ferroptosis in testicular cells, the testes possess distinct regulatory mechanisms to prevent local iron buildup. For instance, in hemochromatosis protein knockout mice, which serve as a model for hereditary hemochromatosis, they develop severe iron overload in the liver and heart, and the iron levels in the testes are maintained at a relatively stable level because of its unique mechanism of iron regulation (Katsarou et al. 2019; Leichtmann-Bardoogo et al. 2012).

In the testis tissues, cellular iron-transfer protein (e.g., transferrin receptor protein 1 [TFR1]), iron−storage proteins (e.g., ferritin light chain [FLH] and ferritin heavy chain [FTH]), and iron-export protein (e.g., ferroportin [FPN]) are involved in modulating iron homeostasis (Dai et al. 2020; Yuan et al. 2023). Excessive iron build-up can lead to ferroptotic cell death, which is a novel form of cell death that involves a culmination of ROS accumulation, iron-dependent lipid peroxidation and GPX4 depletion (Dai et al. 2020; Yuan et al. 2023). Early studies indicated that various mycotoxins (including DON, AFB1, T−2 toxin, and HT-2 toxin) exposure can disrupt iron homeostasis and trigger ferroptosis in mammalian cells (Fan et al. 2024a; Ma et al. 2023; Morgan and Liu 2011). Co-exposure to DON and ZEN exacerbated iron accumulation in the liver and intestinal tissues of mice, suggesting that the imbalance of iron homeostasis may play a critical role in mycotoxin toxicities (Lin et al. 2022a; Liu et al. 2023; Skiepko et al. 2020; Ye et al. 2023b). In line with these findings, Yang *et. al.,* reported that oral gavage with DON at 0.5, 1.0, and 2.0 mg/kg body weight for twenty-eight days increased the expression of TFR1 protein and reduce the expression of FLH, FTH, and FPN proteins in the testis tissues of mice (Yang et al. 2023). This implies that DON accentuates iron transport, which in turn culminates in intracellular iron overload and ferroptosis in the testis tissues.

Moreover, system Xc^- is a reverse transporter that is composed of the SLC3A2 and SLC7A11 subunits (Dai et al. 2020). System Xc^- functions to maintain the optimal uptake of cystine, which is essential for the synthesis of GSH, a cofactor of the lipid hydroperoxide enzyme GPX4 that inhibits ferroptosis (Li et al. 2022a). Yang *et. al.,* found that DON treatment of mice significantly decreased the expression of GPX4, SLC7A11, and SLC3A2, along with the depletion of system Xc^-, GPX4 and GSH and increased the cellular levels of iron in the testis (Yang et al. 2023). These findings suggest that DON exposure disrupts GSH biosynthesis through the System Xc^-/GPX4 antioxidant axis and triggers ferroptotic cell death in the testis tissues. Moreover, Nrf2 can also transcriptionally regulate the expression of SLC7A11, GPX4, FLH, FTH, and FPN, thus controlling ferroptosis (Yuan et al. 2023). Given that DON exposure significantly inhibited the expression of Nrf2, it suggests that DON-induced ferroptosis in testis tissues may involve the inhibition of Nrf2 signaling pathway. Similarly, another study highlighted the role of ferroptosis in DON-induced hepatotoxicity, where the mycotoxin was found to upregulate nicotinamide N-methyltransferase (NNMT), exacerbating ferroptosis by inhibiting the SLC7A11/GPX4 pathway (Huang et al. 2025). Correctively, these evidences indicated that DON exposure can induce ferroptosis in testicular tissues via the inhibition of Nrf2 and system Xc^- /GPX4 pathways. Additionally, it has been demonstrated that the depletion of GPX4 in spermatocytes can cause male infertility in mice (Imai et al. 2009). It also indicated that DON-trigger ferroptosis may partly contribute to male infertility.

Lipid peroxidation plays a critical "lethal factor" role in the process of ferroptosis (Jiang et al. 2021). The intracellular Fe^{2+}-driven Fenton reaction generates •OH, which in turn promotes the peroxidation of membrane polyunsaturated fatty acids (primarily arachidonic acid and phosphatidylethanolamine), finally resulting in the disruption of membrane stability and ultimately causing cell death (Yuan et al. 2023). Activation of the acyl-CoA synthetase long-chain family member 4 (ACSL4)/COX2 pathway promotes arachidonic acid metabolism during ferroptosis process (Li et al. 2022a). DON exposure was reported to increase cellular arachidonic acid levels and increase the expression of multiple enzymes of the arachidonic acid pathway, such as ACSL4, lysophosphatidylcholine acyltransferase 3 (LPCAT3), and COX2 [115]. This would suggest that DON promotes lipid peroxidation via the arachidonic acid metabolic pathway to induce ferroptosis in the testis. Similar effects were observed following DON exposure in intestinal and liver tissues (Lin et al. 2022a; Liu et al. 2023; Skiepko et al. 2020; Ye et al. 2023b).

Specially, there is an indirect risk posed by the deposition of iron in the hypothalamic-pituitary region to modulate the male reproductive function (Yuan et al. 2023). A large amount of iron accumulating in GnRH neurons or pituitary may interfere with the HPG axis. Several studies have demonstrated that DON exposure can cause increases of ferroptosis markers, such as increased lipid peroxidation, decreased intracellular GSH and GPX, and the induction of mitochondrial dysfunction in the brain tissues and neuronal cells (Kalagatur et al. 2021; Ren et al. 2016). It also found that DON exposure exhibited marked cytotoxicity to pituitary cells (Liu et al. 2020; Wan et al. 2018). This disruption may cause hypogonadotropic hypogonadism, which is marked by reduced levels of FSH, LH, and testosterone, which are essential for spermatogenesis (Kalagatur et al. 2021; Ren et al. 2016).

In summary, the exposure to DON has been shown to cause and imbalance in iron homeostasis, which in turn triggers ferroptosis in the testis. Mechanistically, DON-induced ferroptosis in testis tissues involves the excessive production of ROS, lipid peroxidation and the inactivation of Nrf2 and Xc^-/GPX4 pathways (Fig 6). Additionally, DON exposure may damage the iron metabolism of GnRH neurons, then disturb the function of HPG axis and cause an indirect effect to reproductive function. However, the precious molecular mechanisms still need more investigation.

4.5. Don-related effects on the cell cycle

Several recent studies have suggested that DON-induced male reproductive toxicity is associated with cell cycle arrest (Sun et al. 2022; Urbanek et al. 2021). In cultured porcine Leydig cells, DON exposure at 2.5 μM for 24 h considerably down-regulated the expressions of

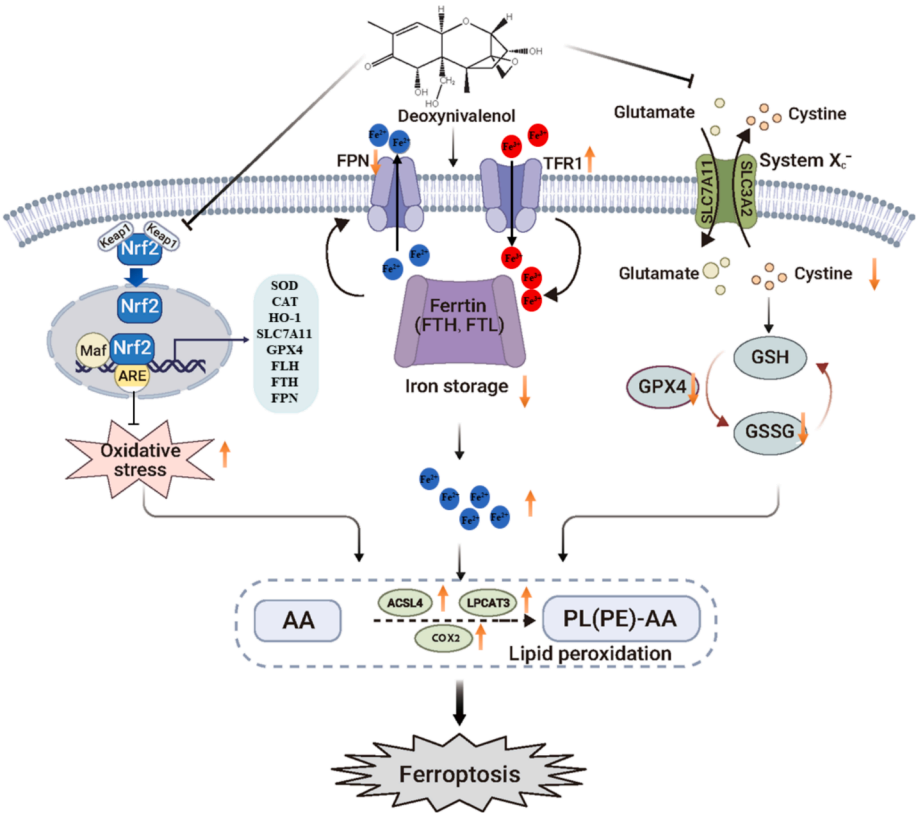

Fig. 6. A mechanistic diagram of DON-caused ferroptosis in male germ cells. The figure is referenced to Yang et. al. study (Yang et al. 2023) with minor revision. DON exposure can disrupt iron homeostasis via downregulating the express of FPN ptotein and upregulating the expression of TFR ptotein. DON can also induce the production of PL(PE)-AA via upregulating the expression of ACSL4, LPCAT3, and COX2, then inducing lipid peroxidation. Additionally, DON exposure can also inhibit Nrf2/system Xc-/GPx4 axis. These effects finally collectively induce ferroptosis in testicular tissue. DON, deoxynivalenol; GSH, reduced glutathione; GSSG, oxidized glutathione; OH-1, heme oxygenase 1; SOD, superoxide dismutase; GPX4, glutathione peroxidase 4; Nrf2, nuclear factor erythroid 2-related factor 2; ARE, antioxidant response element; CAT, catalase; SLC7A11, solute carrier family 7 member 11; SLC3A2, solute carrier family 3 member 2; ACSL4, acyl-CoA synthetase long chain family member 4; FTH, ferritin heavy chain, FLH, ferritin light chain; TFR, transferrin receptor; COX2, cyclooxygenase-2; LPCAT3, lysophosphatidylcholine acyltransferase 3.

proliferating cell nuclear antigen (PCNA) and cyclin B1 (CCNB1) proteins, thereby inducing the inhibition of cell proliferation and G1 arrest (Sun et al. 2022). DON treatment of rats at 4 mg/kg body weight daily for seven days (oral administration from day 21 to day 28) significantly decreased the number of Leydig cells in the testis tissue (Yang et al. 2024b). This evidence implies that the PCNA and CCNB1-mediated cell cycle might contribute to male reproductive toxicity caused by DON. In another study, DON treatment at 5 μM for 48 h led to a reduction in the number of cells in the G0 / G1 stage in PNT1A, PC-3 and DU-145 cells (Urbanek et al. 2021). Furthermore, DON exposure was shown to upregulated cyclin-dependent kinase 1 (CDK1) and CCNB2 proteins (Song and Zhang 2021). Cao *et. al.,* showed that combined exposure of DON and ZEN could trigger G2 phase arrest in piglet Sertoli cells which could be reversed by the antioxidant NAC (Cao et al. 2021).

4.6. Don-related effects on the endoplasmic reticulum (ER)

The endoplasmic reticulum (ER) is responsible for protein synthesis, folding, modification, calcium storage, lipid synthesis, and detoxification (Wiseman et al. 2022). ER stress can trigger cell apoptosis via caspase activation and the upregulation of JNK/C/EBP homologous protein (CHOP) pathway (Chen et al. 2023). It has been reported that exposure to DON can trigger ER stress in the mouse renal tissues, porcine alveolar macrophage cells, and porcine embryos via inositol-requiring enzyme 1/JNK/C/EBP Homologous Protein (CHOP) pathway (Kim et al. 2024; Zhang et al. 2023; Zhao et al. 2024). Not surprisingly, supplementation with the ER stress inhibitor 4-phenyl butyric acid (4-PBA) could effectively attenuate DON exposure-induced mitochondrial dysfunction, p53 activation, apoptosis in piglet Sertoli cells. This collective evidence indicates that ER stress may play a critical role in DON −induced male reproductive toxicity.

4.7. Don-related effects on miRNAs expression

MiRNAs are small (with a length of 22 nucleotides), non-coding, single-stranded RNA fragments that are evolutionarily conserved. Numerous studies have demonstrated that miRNAs take part in cytotoxicity and reproductive toxicity induced by mycotoxin exposure (Chen et al. 2022; Chen et al. 2015; Wang et al. 2019). It has been noted that certain miRNAs like miR-181a, miR-221, miR-222, miR-30c, miR-365-5p, and miR-769-3p are involved in the damage to intestinal epithelial cells caused by DON (Hou et al. 2021; Xie et al. 2020). Yu et al. discovered that miR-34a participates in DON−induced apoptosis in HepG2 cells (Yu et al. 2023). Recently, a genome−wide transcriptional profiling and functional analysis showed that exposure to DON can change the expression of about 110 differentially expressed miRNAs in porcine intestinal epithelial cells and further verified that the miR−330−MAPK15 axis plays a crucial role in DON−induced cell apoptosis (Wang et al. 2022). Prior studies have reported that a variety of miRNAs are involved in the regulation of steroidogenesis in testis tissues. For instance, miR-376b, miR-330, miR-150, and miR-138 can regulate the expression of STAR, and miR-134 can regulate the expression of CYP11A1 (Hu et al. 2013; Urbanek et al. 2018). Consequently, this information suggests that miRNAs may be involved in the regulation

of male reproductive toxicity induced by DON. However, the exact molecular mechanisms are not yet fully comprehended, and further research is still needed.

5. Chemo-protective agents against DON −induced male reproductive toxicity

The persistent prevalence of DON contamination throughout agri-food systems from field crops to commercial food matrices necessitates both the implementation of advanced biomonitoring programs to quantify cross-species exposure thresholds and the development of precision interventions targeting molecular toxicity mechanisms in mammalian systems. Accumulating evidence demonstrates that specific antioxidants, natural products, and small-molecule inhibitors can effectively mitigate DON-mediated reproductive toxicity by simultaneously addressing oxidative stress, inflammatory cascades, and programmed cell death pathways. Table 2 systematically summarizes these neuroprotective agents with clinical potential. Furthermore, we explore natural dietary compounds, particularly polyphenols and flavonoids, that show functionality in modulating the aforementioned pathogenic pathway.

5.1. Specific antioxidants

GSH, a critical tripeptide orchestrating cellular detoxification, antioxidant defense, thiol homeostasis, and proliferation regulation, undergoes tightly controlled biosynthesis in the cytosol. Experimental studies have consistently demonstrated that DON exposure induces significant depletion of testicular GSH reserves at both tissue and cellular levels (Cao et al. 2021; Ruan et al. 2024b). The limited membrane permeability of exogenous GSH renders oral supplementation biologically ineffective for direct intracellular delivery. NAC, a precursor in GSH synthesis, serves as a potent therapeutic alternative by enhancing endogenous GSH production (Jenkins et al. 2016). Consistently, Ruan *et. al.* reproted that NAC supplementation can significantly increase the levels of intracellular GSH and CAT, then markedly attenuate DON exposure-induced oxidative stress and lipid peroxidation damage (Ruan et al. 2024b). Additionally, NAC supplementation also markedly alleviated DON exposure-induced cell pyroptosis via the inhibition of NLRP3 pathways (Ruan et al. 2024b). This process may be dependent on its radical scavenging activities. Importantly, several clicial trials have indicated that NAC supplmentaon can maredly improve semen parameters and oxidative/antioxidant status in males (Ciftci et al. 2009; Safarinejad and Safarinejad 2009).

Vitamin E, or alpha-tocopherol, is a fat-soluble vitamin that acts as a powerful antioxidant to protect cells from free radical damage and is involved in immune function. It was reported that vitamin E supplementation can significantly inhibite DON exposure-induced the production of ROS, but it had no significant effect on the viability of DON-exposed cells (Savard et al. 2016). Notaly, vitamin E supplementation can not revise DON-induced decreases in the production of the secretion of progesterone in MA-10 mouse Leydig tumor cell line *in vitro*.

In addition, some antioxidants such as melatonin, vitamin C, silymarin L-carnitineor coenzyme Q10 (CoQ10) have been reported to have potent radical scavenging activities against various environmental toxic substances (such as mycotoxins, heavy metals, plasticizers)-caused male reproductive toxicity using *in vitro* and *in vivo* studies(Eid et al. 2023; Gao et al. 2018; Gupta et al. 2023; Iftikhar et al. 2022; Khedr and Werida 2022; Ogunlade et al. 2022). Clinical trials also confirmed that these potential antioxidants supplementation can effectively improve sperm parameters (Etemadi et al. 2022; Ma and Sun 2022). Therefore, it is worth further exploring whether these antioxidants can effectively improve DON induced reproductive organ damage and sperm quality reduction, and more clinical trial studies are needed.

Table 2
A tabulated summary of reported protective agents targeting DON-induced male reproductive toxicity.

Natural products/ Bioactive substances	Models	Treatments	The protective effects	Reference
NAC	Mouse Leydig (TM3) cells	Cells were treated with NAC at 10 mM or cotreated with DON at 125 ng/mL for 24 h.	NAC supplementation significantly improved DON exposure-induced increases of MDA and ROS levels via upregulating the activities of antioxidant enzymes. NAC supplementation also alleviated the pyroptosis caused by DON via inhibiting the expression of NLRP3, ASC, Cleaved-Caspase-1, and GSDMD proteins.	(Ruan et al. 2024b)
Vitamin E	MA-10 mouse Leydig tumor cell line	Cells were treated with DON at doses of 0.25 μM or co-treated with vitamin E at 10, 25 or 50 μM for 24 h.	Vitamin E supplementation significantly inhibited DON exposure-induced the production of ROS but had no significant effect on the viability of DON-exposed cells.	(Savard et al. 2016)
Sesamin	MA-10 mouse Leydig tumor cell line	Cells were treated with DON at doses of 0.25 μM or co-treated with sesamin at 10, 25 or 50 μM for 24 h.	Sesamin supplementation significantly attenuated DON-induced the decrease of cell viability via the marked decreases of ROS production.	(Savard et al. 2016)
4-PBA	Primary Piglet Sertoli cells	Cells were pre-treated with 4-PBA at the doses of 0.1–2.5 μM for 2 h, then co-treated with ZEN + DON (30 μM + 1.2 μM) for additional 24 h.	4-PBA supplementation markedly attenuated the combination exposure of ZEN and DON −induced cytotoxicity. In addition, 4-PBA supplementation attenuated the combination exposure of ZEN and DON −induced −induced mitochondrial dysfunction and apoptosis via inhibiting p53 and mitochondrial apoptotic pathways and re-balancing mitochondrial dynamics.	(Hai et al. 2023)

(*continued on next page*)

Table 2 (*continued*)

Natural products/ Bioactive substances	Models	Treatments	The protective effects	Reference
Lactoferrin	Mice	Mice were orally administration with lactoferrin at 10 mg per day or co-treated with DON at 12 mg/kg body weight per day via the diet. All mice were treated for thirty-five days.	LF supplementation markedly eliminated the DON-induced adverse on spermatogenesis and cell connections between Sertoli cells and spermatids via inhibiting oxidative stress and modifying the inflammatory response and cell adhesion genes.	(Li et al. 2023)
MCC950	Mouse Leydig (TM3) cells	Cells were per-treated with MCC950 at 10 μM for 30 min, then cotreated with DON at 125 ng/mL for 24 h.	MCC950 supplementation significantly improved DON exposure-induced cell pyroptosis via the targeted inhibition of NLRP3 pathway.	(Ruan et al. 2024b)
Mdivi-1	Primaryrat progenitor Leydig cells (PLCs)	The isolated PLCs were treated with DON at 4 μM or co-treated with mdivi-1 at 10 μM for 24 h.	The treatment of mdivi-1 reversed the inhibitory effect of DON on testosterone production in PLCs by targeting to mitochondrial fission.	(Yang et al. 2024b)
SB203580	Mouse TM4 Sertoli cells	Cells were pretreated with SB203580, then cotreated with DON at 0.8 μM for additional 24 h.	Pretreatment with SB203580 markedly decreased the DON-induced phosphorylation of p38 and its downstream GSK-3β, p-GSK-3β, snail, ATF-2, p-ATF-2, MLCK, and p-MLC-2 expression Moreover, SB203580 pretreatment also also reversed the reduction in ZO-1, occludin, and claudin-11 mRNA expression.	(Miao et al. 2023)

5.2. Small-molecule inhibitors

Several small-molecule inhibitors such as 4-PBA, MCC950, Mdivi-1, SB203580 supplementation can target to ER stress, NLRP3 pathway, Drp1-mediated mitochondrial fission, and p38 pathway, respectively, finally inhibiting DON exposure-caused cell apoptosis, inflammatory response, mitochondrial dysfunction, and dysfunction of the BBB (Hai et al. 2023; Ruan et al. 2024b; Yang et al. 2024b). For example, 4-PBA supplementation can markedly attenuate the co-treatment of ZEN and DON −induced cytotoxicity as well as the reduction of mitochondrial dysfunction and apoptosis by inhibiting p53 and mitochondrial apoptotic pathways and re-balancing mitochondrial dynamics (Hai et al. 2023). Pretreatment with SB203580 markedly decreased the DON-induced the activation of p38 and downstream pathways, then effectively reduced DON exposure-caused BBB dysfunction (Miao et al. 2023). The treatment of mdivi-1, a DRP1 inhibitor, can markedly reverse the inhibitory effect of DON on testosterone production in PLCs by targeting to mitochondrial fission (Yang et al. 2024b). These findings provide important evidence for improving DON exposure-related male reproductive toxicity and infertility in animals and humans. Several clinical trials have showed that 4-PBA and SB203580 supplementation displayed potential therapeutic effects on inflammatory or neurological disorder-related diseases (Cornelissen et al. 2006; Paganoni et al. 2021; Paganoni et al. 2020). However, there is still a lack of relevant clinical research on the reproductive system. Therefore, more animal and clinical experiments are still needed.

5.3. Bioactive phytochemicals

It has been reported that some natural products such as lycopene, curcumin, and caffeic acid have strong antioxidant, anti-inflammatory, and immune regulatory activities, exhibiting potential the protective effects against mycotoxins and anticancer agents-caused the reproductive toxicity. It has raised concern in the field of toxicology and public health (Kang et al. 2023; Rahimi et al. 2022). Consistently, Savard et. al. found that sesamin, a major lignin isolated from sesame (Sesamum indicum) seeds and sesame oil, can markedly inhibit the DON exposures −induced the decreases of cell viability and ROS production in MA-10 mouse Leydig tumor cells (Savard et al. 2016). However, they found that sesamin supplementation cannot revise DON exposure-induced decreases of progesterone (Savard et al. 2016). This is a critical limitation for its application in treating DON-induced male reproductive toxicity.

Recent studies have demonstrated that various flavonoids and polyphenols from natural sources, such as curcumin, resveratrol, chrysin, quercetin, ellagic acid, epigallocatechin gallate, gallic acid, and caffeic acid, can effectively target Nrf2, NF-κB, NLRP3, and MAPKs to mitigate oxidative stress, inflammatory response, and programmed cell death (e.g., apoptosis, pyroptosis, and ferroptosis) (Dai et al. 2024; Dai et al. 2022; Fang et al. 2024; Galati and O'Brien 2004; Li et al. 2017a). These compounds have shown potential in alleviating reproductive toxicity induced by factors such as drugs (e.g., cyclophosphamide), environmental hazards (e.g., arsenic, copper, cadmium, lead, and di-(2-ethylhexyl) phthalate), and infections in both animal models and clinical trials (Alizadeh et al. 2018; Dai et al. 2022; Fan et al. 2024b; Hong et al. 2021; Ileriturk et al. 2021; Owumi et al. 2022; Sarawi et al. 2022). For instance, quercetin supplementation at 50 mg/kg per day can markedly attenuate DON exposure-induced intestinal oxidative stress, inflammatory response and ferroptosis via inhibiting the TLR4/NF-κB signaling pathway, enhancing antioxidant enzymes' activities, and activating the SLC7A11/GPX4/GSH pathway (Ye et al. 2023b). Sarawiet *et. al.* found that both curcumin and nano-curcumin supplementation have been shown to counteract copper (sulfate) exposure-induced NF-κB activation, thereby reducing inflammatory responses in rat testicular tissues (Sarawi et al. 2022). A clinical trial further confirmed that curcumin nanomicelle supplementation significantly enhances semen quality while reducing inflammatory biomarkers (Alizadeh et al. 2018). These findings underscore the therapeutic potential of these compounds in addressing oxidative stress- and inflammation-associated reproductive toxicities, offering promising avenues for future research and clinical applications for diminish DON-induced reproductive toxicity or male reproductive disorders.

5.4. Others

Lactoferrin, an evolutionarily conserved iron-binding glycoprotein abundantly present in human colostrum and bovine milk, demonstrates multifaceted cytoprotective properties. Current research reveals its

therapeutic efficacy in counteracting oxidative stress and inflammation-induced pathologies through reducing Fenton reaction-driven ROS generation, modulating iron metabolism, enhancing endogenous antioxidant defenses, and mitigating NLRP3 and NF-κB signaling pathways (Habib et al. 2023). Clinical evidence positions lactoferrin as a promising nutraceutical for preventive management of chronic inflammatory disorders, including atherosclerosis and neurodegenerative conditions (Rascón-Cruz et al. 2024). Li *et. al.* found that lactoferrin supplementation markedly improved testis weight and sperm production and eliminated the DON-induced adverse on spermatogenesis and cell connections between Sertoli cells and spermatids via inhibiting oxidative stress and modifying the inflammatory response and cell adhesion genes (Li et al. 2023). In another study, it was found that lactoferrin supplementation can markedly alleviate spermatogenesis dysfunction caused by bisphenol A and cadmium via ameliorating disordered autophagy, apoptosis and oxidative stress through modulating AMPK, MAPK, and mitochondrial apoptotic pathways in mice(He et al. 2022). A human clinical trial showed that lactoferrin administration with other natural antioxidant agents such as vitamin C and vitamin E improved semen quality in asthenoteratospermic men with leukocytospermia (Piomboni et al. 2008). This information indicated that Lactoferrin may be a promising protective agent against DON exposure-induced male reproductive toxicity and infertility in animals and humans. More animal model evaluations and clinical studies are still needed.

6. Conclusion and future perspectives

Reproductive toxicity is a highly significant adverse effect resulting from exposure to environmental mycotoxin contaminants, particularly DON. Animal experiments have revealed that continuous exposure to DON allows the toxin to penetrate the blood-testis barrier and damage testicular tissues. Such penetration leads to irreversible pathological damage which manifests as a decline in testicular function. DON-induced reproductive toxicity is related to multiple detrimental mechanisms, including oxidative stress, cell cycle arrest, inflammatory response, apoptosis, pyroptosis, ER stress, and ferroptosis. Additionally, numerous signaling pathways, such as Nrf2, MAPK, NLRP3, STAR, NF-κB, AMPK, and mitochondrial apoptotic pathways, are involved in these untoward biological processes. It is worth noting that the male reproductive toxicity induced following DON exposure may be related to its direct inhibition of testosterone synthesis through the destruction of the SCARB1/STAR/CYP11A1 pathway. Several antioxidants (e.g. NAC and vitamin E), small-molecule inhibitors (e.g., 4 −PBA, SB203580, mdivi-1, and MCC950), or proteins (e.g., lactoferrin) supplementation have been demonstrated to protect against and reverse the effects of DON-induced reproductive toxicity through their targeted effects along these signaling pathways. Notably, human clinical trials have suggested that supplementation with lactoferrin and NAC can both improve sperm quality. It indicated that lactoferrin and NAC may be considered as the promising candidate therapeutic drugs for DON exposure-induced male reproductive toxicity and infertility in animals and humans, but more animal model evaluations and clinical studies are still needed.

To develop effective policy and regulatory implications for reducing human exposure to DON, several directions for future research were suggested:

(i) It is crucial to investigate the relationships between DON at the environmental exposure dose and male infertility in humans as well as the underlying molecular mechanisms. Currently, it still lacks the systematic evaluation on DON exposure to humans, especially the reproductive system. It is necessary for establishing dose-dependent correlations between chronic low-level DON exposure via diet and clinically relevant spermatogenic impairments (such as oligospermia and teratozoospermia). Additionally, the knowledge regarding the underlying molecular mechanisms of DON-induced male reproductive organ damage remains unclear and more in−depth studies are urgently required. For example, miRNAs have been proven to play critical roles in testicular function and hormone homeostasis, but its role in DON-induced reproductive toxicity was rarely studied. In addition, in animal models, DON treatment results in an opposing trend between gonadotropins (e.g., FSH and LH) and testosterone, which contrasts the reported effects observed with other mycotoxins. Theses emerging technologies (such as single-cell sequencing, and CRISPR-Cas9, and multi-omics) may help elucidate new mechanisms.

(ii) It has been reported that DON can be metabolized into different metabolites, such as de-epoxy-DON, DON-15S, DON-15GlcA, DON-15G, DON-10S, DON-8G, DON-7GlcA, DON-3G, DON-3GlcA, and DON-3S. these metabolites may also have potential reproductive toxicity. For example, de-epoxy-DON exposure can markedly reduce motility of bull spermatozoa *in vitro* (Guerrero-Netro et al. 2021). Therefore, it is necessary to evaluate the potential reproductive toxicity of these various metabolites and determine whether they can generate synergistic toxic effects through interactions.

(iii) The precise molecular mechanisms by which the above-mentioned dietary supplements such as lactoferrin and NAC protect against DON-induced reproductive toxicity requires further exploration. Human clinical trials and animal experiments are required to fully substantiate the reproductive protection offered by these agents. Additionally, some bioactive phytochemicals, particularly dietary flavonoids (such as quercetin) and polyphenolic compounds (such curcumin and resveratrol) can be considered when screening and developing new protective agents. Because previous studies have demonstrated that these bioactive phytochemicals can protect against oxidative stress and inflammatory response through modulating Nrf2, MAPK, NLRP3, STAR, NF-κB, and AMPK pathways, which are play critical role in DON exposure-induced male reproductive toxicity and infertility.

Correctively, a synergistic policy framework combining preventive agriculture, technological innovation, global standardization, and consumer empowerment is critical to curb DON exposure. Success hinges on balancing public health priorities with socioeconomic realities, ensuring equitable access to safe food systems worldwide. Policymakers must prioritize adaptive regulations that evolve with emerging science and climate challenges.

CRediT authorship contribution statement

Chongshan Dai: Writing – review & editing, Writing – original draft, Supervision, Project administration, Funding acquisition. **Zhihui Hao:** Funding acquisition, Formal analysis. **Dingkuo Liu:** Formal analysis. **Zhanhui Wang:** Formal analysis, Data curation. **Gea Oliveri Conti:** Writing – review & editing, Methodology. **Tony Velkov:** Writing – review & editing, Writing – original draft, Formal analysis. **Jianzhong Shen:** Writing – review & editing, Validation, Supervision, Project administration.

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Declaration of competing interest

The authors declare the following financial interests/personal

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Data availability

Data will be made available on request.

References:

dsm-firmenich World Mycotoxin Survey. 2023.

Acevedo-Rodriguez, A., Kauffman, A.S., Cherrington, B.D., Borges, C.S., Roepke, T.A., Laconi, M., 2018. Emerging insights into hypothalamic-pituitary-gonadal axis regulation and interaction with stress signalling. J. Neuroendocrinol. 30, e12590.

Agarwal, A., Aponte-Mellado, A., Premkumar, B.J., Shaman, A., Gupta, S., 2012. The effects of oxidative stress on female reproduction: a review. Reproductive Biology and Endocrinology : RB&E 10, 49.

Alizadeh, F., Javadi, M., Karami, A.A., Gholaminejad, F., Kavianpour, M., Haghighian, H. K., 2018. Curcumin nanomicelle improves semen parameters, oxidative stress, inflammatory biomarkers, and reproductive hormones in infertile men: a randomized clinical trial. Phytotherapy Research : PTR 32, 514–521.

Ashraf, R., Kumar, S., 2022. Mfn2-mediated mitochondrial fusion promotes autophagy and suppresses ovarian cancer progression by reducing ROS through AMPK/mTOR/ERK signaling. Cell. Mol. Life Sci. 79, 573.

Barbagallo, F., La Vignera, S., Cannarella, R., Aversa, A., Calogero, A.E., Condorelli, R.A., 2020. Evaluation of sperm mitochondrial function: a key organelle for sperm motility. J. Clin. Med. 9.

Bernasconi, S., Street, M.E., Iughetti, L., Predieri, B., 2022. Chemical contaminants in breast milk: a brief critical overview. Global Pediatrics 2, 100017.

Bisht, S., Dada, R., 2017. Oxidative stress: major executioner in disease pathology, role in sperm DNA damage and preventive strategies. Front. Biosci. (Schol. Ed.) 9, 420–447.

Boguenet, M., Bouet, P.E., Spiers, A., Reynier, P., May-Panloup, P., 2021. Mitochondria: their role in spermatozoa and in male infertility. Hum. Reprod. Update 27, 697–719.

Bonanno, O., Romeo, G., Asero, P., Pezzino, F.M., Castiglione, R., Burrello, N., Sidoti, G., Frajese, G.V., Vicari, E., D'Agata, R., 2016. Sperm of patients with severe asthenozoospermia show biochemical, molecular and genomic alterations. Reproduction (cambridge, England) 152, 695–704.

Budin, C., Man, H.Y., Al-Ayoubi, C., Puel, S., van Vugt-Lussenburg, B.M.A., Brouwer, A., Oswald, I.P., van der Burg, B., Soler, L., 2021. Versicolorin A enhances the genotoxicity of aflatoxin B1 in human liver cells by inducing the transactivation of the Ah-receptor. Food Chem Toxicol 153, 112258.

Cai, G.; Yang, L.; Marien-Bourgeois, F.; Boerboom, D.; Zamberlam, G.; Alassane-Kpembi, I. Low concentrations of the food contaminant Deoxynivalenol trigger apoptosis and impair GnRH-induced LH secretion in pituitary gonadotrope-like cells. bioRxiv : the preprint server for biology 2024.

Calkins, M.J., Reddy, P.H., 2011. Assessment of newly synthesized mitochondrial DNA using BrdU labeling in primary neurons from Alzheimer's disease mice: implications for impaired mitochondrial biogenesis and synaptic damage. Biochim Biophys Acta 1812, 1182–1189.

Cao, L., Zhao, J., Xu, J., Zhu, L., Rahman, S.U., Feng, S., Li, Y., Wu, J., Wang, X., 2021. N-acetylcysteine ameliorate cytotoxic injury in piglets sertoli cells induced by zearalenone and deoxynivalenol. Environ Sci Pollut Res Int 28, 60276–60289.

Cao, Z., Huang, W., Sun, Y., Li, Y., 2020. Deoxynivalenol induced spermatogenesis disorder byblood-testis barrier disruption associated with testosterone deficiency and infammation inmice. Environ Pollut 264, 114748.

Carballo, D.; Font, G.; Ferrer, E.; Berrada, H. Evaluation of Mycotoxin Residues on Ready-to-Eat Food by Chromatographic Methods Coupled to Mass Spectrometry in Tandem. Toxins 2018a;10.

Carballo, D., Moltó, J.C., Berrada, H., Ferrer, E., 2018. Presence of mycotoxins in ready-to-eat food and subsequent risk assessment. Food Chem Toxicol 121, 558–565.

Caunt, C.J., Finch, A.R., Sedgley, K.R., McArdle, C.A., 2006. GnRH receptor signalling to ERK: kinetics and compartmentalization. Trends Endocrinol Metab 17, 308–313.

Chandel, N.S., 2018. Mitochondria: back to the future. Nat Rev Mol Cell Biol 19, 76.

Chen, J., Yang, S., Li, P., Wu, A., Nepovimova, E., Long, M., Wu, W., Kuca, K., 2022. MicroRNA regulates the toxicological mechanism of four mycotoxins in vivo and in vitro. J. Anim. Sci. Biotechnol. 13, 37.

Chen, R., Deng, L., Yu, X., Wang, X., Zhu, L., Yu, T., Zhang, Y., Zhou, B., Xu, W., Chen, L., Luo, H., 2015. MiR-122 partly mediates the ochratoxin A-induced GC-2 cell apoptosis. Toxicology in Vitro : an International Journal Published in Association with BIBRA 30, 264–273.

Chen, X., Shi, C., He, M., Xiong, S., Xia, X., 2023. Endoplasmic reticulum stress: molecular mechanism and therapeutic targets. Signal Transduct Target Ther 8, 352.

Ciftci, H., Verit, A., Savas, M., Yeni, E., Erel, O., 2009. Effects of N-acetylcysteine on semen parameters and oxidative/antioxidant status. Urology 74, 73–76.

Claeys, L., Romano, C., De Ruyck, K., Wilson, H., Fervers, B., Korenjak, M., Zavadil, J., Gunter, M.J., De Saeger, S., De Boevre, M., Huybrechts, I., 2020. Mycotoxin exposure and human cancer risk: a systematic review of epidemiological studies. Compr. Rev. Food Sci. Food Saf. 19, 1449–1464.

Clarke, R.N., Ottinger, M.A., 1987. The response of the anterior pituitary and testes to synthetic luteinizing hormone-releasing hormone (LHRH) and the effect of castration on pituitary responsiveness in the maturing chicken fed aflatoxin. Biol. Reprod. 37, 556–563.

Cornelissen, J., Kirtland, S., Lim, E., Goddard, M., Bellm, S., Sheridan, K., Large, S., Vuylsteke, A., 2006. Biological efficacy of low against medium dose aspirin regimen after coronary surgery: analysis of platelet function. Thromb. Haemost. 95, 476–482.

Dai, C., Chen, X., Li, J., Comish, P., Kang, R., Tang, D., 2020. Transcription factors in ferroptotic cell death. Cancer Gene Ther. 27, 645–656.

Dai, C., Sharma, G., Liu, G., Shen, J., Shao, B., Hao, Z., 2024. Therapeutic detoxification ofquercetin for aflatoxin Bl-related toxicity: roles of oxidative stress, inflammation, andmetabolic enzymes. Environmen Pollut 345, 123474.

Dai, C., Tian, E., Hao, Z., Tang, S., Wang, Z., Sharma, G., Jiang, H., Shen, J., 2022. Aflatoxin B1 toxicity and protective effects of curcumin: molecular mechanisms and clinical implications. Antioxidants (basel) 11.

Dai, C., Xiao, X., Sun, F., Zhang, Y., Hoyer, D., Shen, J., Tang, S., Velkov, T., 2019. T-2 toxin neurotoxicity: role of oxidative stress and mitochondrial dysfunction. Arch Toxicol 93, 3041–3056.

Delli Muti, N., Finocchi, F., Tossetta, G., Salvio, G., Cutini, M., Marzioni, D., Balercia, G., 2022. Could SARS-CoV-2 infection affect male fertility and sexuality? APMIS : Acta Pathologica, Microbiologica, et Immunologica Scandinavica 130, 243–252.

Dinleyici, M., Aydemir, O., Yildirim, G.K., Kaya, T.B., Carman, K.B., 2018. Human mature milk zearalenone and deoxynivalenol levels in Turkey. Neuro Endocrinol. Lett. 39, 325–330.

Dong, G.Z., Lee, J.H., Ki, S.H., Yang, J.H., Cho, I.J., Kang, S.H., Zhao, R.J., Kim, S.C., Kim, Y.W., 2014. AMPK activation by isorhamnetin protects hepatocytes against oxidative stress and mitochondrial dysfunction. Eur J Pharmacol 740, 634–640.

Dutta, S., Sengupta, P., Slama, P., Roychoudhury, S., 2021. Oxidative stress, testicular inflammatory pathways, and male reproduction. Int J Mol Sci 22.

Dwyer, A.A., Hayes, F.J., 2019. Evaluation of endocrine disorders of the Hypothalamic-Pituitary-Gonadal (HPG) axis. In: Llahana, S., Follin, C., Yedinak, C., Grossman, A. (Eds.), Advanced Practice in Endocrinology Nursing. Springer International Publishing, Cham.

Eid, R.A., Abadi, A.M., El-Kott, A.F., Zaki, M.S.A., Abd-Ella, E.M., 2023. The antioxidant effects of coenzyme Q10 on albino rat testicular toxicity and apoptosis triggered by bisphenol A. Environ Sci Pollut Res Int 30, 42339–42350.

Eskola, M., Kos, G., Elliott, C.T., Hajšlová, J., Mayar, S., Krska, R., 2020. Worldwide contamination of food-crops with mycotoxins: Validity of the widely cited 'FAO estimate' of 25. Crit Rev Food Sci Nutr 60, 2773–2789.

Etemadi, T., Momeni, H.R., Darbandi, N., Abnosi, M.H., 2022. Silymarin modulates cadmium-induced oxidative stress in human spermatozoa. Andrologia 54.

Eze, U.A., Huntriss, J., Routledge, M.N., Gong, Y.Y., 2018. Toxicological effects of regulated mycotoxins and persistent organochloride pesticides: In vitro cytotoxic assessment of single and defined mixtures on MA-10 murine Leydig cell line. Toxicology in Vitro : an International Journal Published in Association with BIBRA 48, 93–103.

Fan, S., Lin, L., Li, P., Tian, H., Shen, J., Zhou, L., Zhao, Q., Zhang, J., Qin, Y., Tang, C., 2024a. Selenomethionine protects the liver from dietary deoxynivalenol exposure via Nrf2/PPARγ-GPX4-ferroptosis pathway in mice. Toxicology 501, 153689.

Fan, Y., Jiang, X., Xiao, Y., Li, H., Chen, J., Bai, W., 2024b. Natural antioxidants mitigate heavy metal induced reproductive toxicity: prospective mechanisms and biomarkers. Crit Rev Food Sci Nutr 64, 11530–11542.

Fang, C., Li, Y., He, G., Gan, R.Y., Luo, F., Lei, L., Hou, X., Ye, Y., 2024. Silk fibroin microneedles loaded with epigallocatechin gallate mitigate atrazine-induced testicular toxicity. J. Hazard. Mater. 480, 136252.

Feng, Y., Shen, J., Lin, Z., Chen, Z., Zhou, M., Ma, X., 2024. PXR activation relieves deoxynivalenol-induced liver oxidative stress via malat1 LncRNA m(6)A demethylation. Adv Sci (weinh) 11, e2308742.

Güneş, B., Yalçın, S., Yalçın, S.S., 2023. Longitudinal follow-up of zearalenone and deoxynivalenol mycotoxins in breast milk in the first five months of life. BMC Pharmacol Toxicol 24, 37.

Galati, G., O'Brien, P.J., 2004. Potential toxicity of flavonoids and other dietary phenolics: significance for their chemopreventive and anticancer properties. Free Radic. Biol. Med. 37, 287–303.

Gao, X., Xiao, Z.H., Liu, M., Zhang, N.Y., Khalil, M.M., Gu, C.Q., Qi, D.S., Sun, L.H., 2018. Dietary silymarin supplementation alleviates zearalenone-induced hepatotoxicity and reproductive toxicity in rats. J Nutr 148, 1209–1216.

Gonya, S.; Kallmerten, P.; Dinapoli, P. Are Infants and Children at Risk of Adverse Health Effects from Dietary Deoxynivalenol Exposure? An Integrative Review, International Journal of Environmental Research and Public Health. (2024) 21.

Guerrero-Netro, H.M., Barreta, M.H., Costa, E., Goetten, A., Dupras, R., Mills, L., Koch, J., Portela, V.M., Price, C.A., Chorfi, Y., 2021. Effects of the mycotoxin metabolite de-epoxy-deoxynivalenol (DOM-1) on embryo development and sperm motility in cattle. J. Appl. Toxicol. 41, 1180–1187.

Gupta, R., Gupta, T., Kaushik, D., 2023. Ameliorative effect of ellagic acid and Vitamin C against malathion-induced toxicity in testis of adult Wistar rats. J. Biochem. Mol. Toxicol. 37, e23314.

Habib, C.N., Ali, A.E., Anber, N.H., George, M.Y., 2023. Lactoferrin ameliorates carfilzomib-induced renal and pulmonary deficits: Insights to the inflammasome NLRP3/NF-κB and PI3K/Akt/GSK-3β/MAPK axes. Life Sci. 335, 122245.

Hai, S., Chen, J., Ma, L., Wang, C., Chen, C., Rahman, S.U., Zhao, C., Feng, S., Wu, J., Wang, X., 2023. Combination of zearalenone and deoxynivalenol induces apoptosis by mitochondrial pathway in piglet sertoli cells: role of endoplasmic reticulum stress. Toxins 15.

Han, X., Huang, Q., 2021. Environmental pollutants exposure and male reproductive toxicity: the role of epigenetic modifications. Toxicology 456, 152780.

Hao, W., Guan, S., Li, A., Wang, J., An, G., Hofstetter, U., Schatzmayr, G., 2023. Mycotoxin occurrence in feeds and raw materials in china: a five-year investigation. Toxins 15.
Hassanein, E.M., Szelényi, Z., Szenci, O., 2024. Gonadotropin-Releasing Hormone (GnRH) and its agonists in bovine reproduction i: structure, biosynthesis, physiological effects, and its role in estrous synchronization. Animals : an Open Access Journal from MDPI 14.
Hau, R.K., Wright, S.H., Cherrington, N.J., 2023. Drug transporters at the human blood-testis barrier. Drug Metab. Dispos. 51, 560–571.
Haus, M., Žatko, D., Vašková, J., Vaško, L., 2021. The effect of humic acid in chronic deoxynivalenol intoxication. Environ Sci Pollut Res Int 28, 1612–1618.
He, H., Chen, X., Li, X., Yang, K., Li, J., Shi, H., 2022. Lactoferrin alleviates spermatogenesis dysfunction caused by bisphenol A and cadmium via ameliorating disordered autophagy, apoptosis and oxidative stress. Int. J. Biol. Macromol. 222, 1048–1062.
Herzig, S., Shaw, R.J., 2018. AMPK: guardian of metabolism and mitochondrial homeostasis. Nat. Rev. Mol. Cell Biol. 19, 121–135.
Holanda, D.M., Kim, S.W., 2021. Mycotoxin occurrence, toxicity, and detoxifying agents in pig production with an emphasis on deoxynivalenol. Toxins 13.
Hong, Y., Zhou, Y., Shen, L., Wei, Y., Long, C., Fu, Y., Wu, H., Wang, J., Wu, Y., Wu, S., Wei, G., 2021. Exposure to DEHP induces testis toxicity and injury through the ROS/mTOR/NLRP3 signaling pathway in immature rats. Ecotoxicol. Environ. Saf. 227, 112889.
Hou, L., Tong, X., Lin, S., Yu, M., Ye, W.C., Xie, M., 2021. MiR-221/222 ameliorates deoxynivalenol-induced apoptosis and proliferation inhibition in intestinal epithelial cells by targeting PTEN. Front. Cell Dev. Biol. 9, 652939.
Hu, Z., Shen, W.J., Cortez, Y., Tang, X., Liu, L.F., Kraemer, F.B., Azhar, S., 2013. Hormonal regulation of microRNA expression in steroid producing cells of the ovary, testis and adrenal gland. PLoS One 8, e78040.
Huang, M.C., Furr, J.R., Robinson, V.G., Betz, L., Shockley, K., Cunny, H., Witt, K., Waidyanatha, S., Germolec, D., 2021a. Oral deoxynivalenol toxicity in Harlan Sprague Dawley (Hsd:Sprague Dawley® SD®) rat dams and their offspring. Food Chem Toxicol 148, 111963.
Huang, W., Liu, M., Xiao, B., Zhang, J., Song, M., Li, Y., Cao, Z., 2021b. Aflatoxin B(1) disrupts blood-testis barrier integrity by reducing junction protein and promoting apoptosis in mice testes. Food Chem Toxicol 148, 111972.
Huang, W., Song, C., Hua, Y., Liu, A., 2025. NNMT is involved in deoxynivalenol-induced hepatocyte toxicity via promoting ferroptosis. Toxicology 513, 154084.
Ibeh, I.N., Uraih, N., Ogonar, J.I., 1994. Dietary exposure to aflatoxin in human male infertility in Benin City, Nigeria. Int. J. Fertil. Menopausal Stud. 39, 208–214.
Iftikhar, A., Akhtar, M.F., Saleem, A., Riaz, A., Zehravi, M., Rahman, M.H., Md Ashraf, G., 2022. Comparative potential of zinc sulfate, L-carnitine, lycopene, and coenzyme Q10 on cadmium-induced male infertility. Int. J. Endocrinol. 2022, 6266613.
Ileriturk, M., Benzer, F., Aksu, E.H., Yildirim, S., Kandemir, F.M., Dogan, T., Dortbudak, M.B., Genc, A., 2021. Chrysin protects against testicular toxicity caused by lead acetate in rats with its antioxidant, anti-inflammatory, and antiapoptotic properties. J. Food Biochem. 45, e13593.
Imai, H., Hakkaku, N., Iwamoto, R., Suzuki, J., Suzuki, T., Tajima, Y., Konishi, K., Minami, S., Ichinose, S., Ishizaka, K., Shioda, S., Arata, S., Nishimura, M., Naito, S., Nakagawa, Y., 2009. Depletion of selenoprotein GPx4 in spermatocytes causes male infertility in mice*. J. Biol. Chem. 284, 32522–32532.
Jenkins, D.D., Wiest, D.B., Mulvihill, D.M., Hlavacek, A.M., Majstoravich, S.J., Brown, T. R., Taylor, J.J., Buckley, J.R., Turner, R.P., Rollins, L.G., Bentzley, J.P., Hope, K.E., Barbour, A.B., Lowe, D.W., Martin, R.H., Chang, E.Y., 2016. Fetal and neonatal effects of N-acetylcysteine when used for neuroprotection in maternal chorioamnionitis. J. Pediatr. 168, 67–76.e66.
Jiang, X., Stockwell, B.R., Conrad, M., 2021. Ferroptosis: mechanisms, biology and role in disease. Nat. Rev. Mol. Cell Biol. 22, 266–282.
Jin, H., He, J., Wu, M., Wang, X., Jia, L., Zhang, L., Guo, J., 2024. Resveratrol alleviated T-2 toxin-induced liver injury via preservation of Nrf2 pathway and GSH synthesis. Environ. Toxicol.
Jing, J., Peng, Y., Fan, W., Han, S., Peng, Q., Xue, C., Qin, X., Liu, Y., Ding, Z., 2023. Obesity-induced oxidative stress and mitochondrial dysfunction negatively affect sperm quality. FEBS Open Bio 13, 763–778.
Jobin, C., Bradham, C.A., Russo, M.P., Juma, B., Narula, A.S., Brenner, D.A., Sartor, R.B., 1999. Curcumin blocks cytokine-mediated NF-kappa B activation and proinflammatory gene expression by inhibiting inhibitory factor I-kappa B kinase activity. J Immunol 163, 3474–3483.
Kalagatur, N.K., Abd Allah, E.F., Poda, S., Kadirvelu, K., Hashem, A., Mudili, V., Siddaiah, C., 2021. Quercetin mitigates the deoxynivalenol mycotoxin induced apoptosis in SH-SY5Y cells by modulating the oxidative stress mediators. Saudi Journal of Biological Sciences 28, 465–477.
Kang, J., Li, Y., Ma, Z., Wang, Y., Zhu, W., Jiang, G., 2023. Protective effects of lycopene against zearalenone-induced reproductive toxicity in early pregnancy through anti-inflammatory, antioxidant and anti-apoptotic effects. Food Chem Toxicol 179, 113936.
Karunaweera, N., Raju, R., Gyengesi, E., Munch, G., 2015. Plant polyphenols as inhibitors of NF-kappa B induced cytokine production a potential anti-inflammatory treatment for Alzheimer's disease? Front Mol Neurosci 8.
Katsarou, M.S., Papasavva, M., Latsi, R., Drakoulis, N., 2019. Hemochromatosis: hereditary hemochromatosis and HFE gene. Vitam. Horm. 110, 201–222.
Khan, R., Anwar, F., Ghazali, F.M., 2024. A comprehensive review of mycotoxins: toxicology, detection, and effective mitigation approaches. Heliyon 10.
Khedr, N.F., Werida, R.H., 2022. l-carnitine modulates autophagy, oxidative stress and inflammation in trazodone induced testicular toxicity. Life Sci. 290, 120025.
Khera, K.S., Arnold, D.L., Whalen, C., Angers, G., Scott, P.M., 1984. Vomitoxin (4-deoxynivalenol): effects on reproduction of mice and rats. Toxicol. Appl. Pharmacol. 74, 345–356.
Kim, Y.W., Yang, S.G., Seo, B.B., Koo, D.B., Park, H.J., 2024. Deoxynivalenol leads to endoplasmic reticulum stress-mediated apoptosis via the IRE1/JNK/CHOP pathways in porcine embryos. Food Chem Toxicol 188, 114633.
Knutsen, H.K., Alexander, J., Barregård, L., Bignami, M., Brüschweiler, B., Ceccatelli, S., Cottrill, B., Dinovi, M., Grasl-Kraupp, B., Hogstrand, C., Hoogenboom, L.R., Nebbia, C.S., Oswald, I.P., Petersen, A., Rose, M., Roudot, A.C., Schwerdtle, T., Vleminckx, C., Vollmer, G., Wallace, H., De Saeger, S., Eriksen, G.S., Farmer, P., Fremy, J.M., Gong, Y.Y., Meyer, K., Naegeli, H., Parent-Massin, D., Rietjens, I., van Egmond, H., Altieri, A., Eskola, M., Gergelova, P., Ramos Bordajandi, L., Benkova, B., Dörr, B., Gkrillas, A., Gustavsson, N., van Manen, M., Edler, L., 2017. Risks to human and animal health related to the presence of deoxynivalenol and its acetylated and modified forms in food and feed. EFSA Journal European Food Safety Authority 15, e04718.
Křížová, L., Dadáková, K., Dvořáčková, M., Kašparovský, T., 2021. Feedborne mycotoxins beauvericin and enniatins and livestock animals. Toxins 13.
Kumar, A., Takada, Y., Boriek, A.M., Aggarwal, B.B., 2004. Nuclear factor-kappaB: its role in health and disease. J Mol Med (berl) 82, 434–448.
Kumar, N., Singh, A.K., 2015. Trends of male factor infertility, an important cause of infertility: a review of literature. Journal of Human Reproductive Sciences 8, 191–196.
Lee, J.Y., Lim, W., Park, S., Kim, J., You, S., Song, G., 2019. Deoxynivalenol inducesapoptosis and disrupts cellular homeostasis through MAPK signaling pathways in bovinemammary epithelial cells. Environmental Pollution. 252, 879–887.
Lehmann, G.M., LaKind, J.S., Davis, M.H., Hines, E.P., Marchitti, S.A., Alcala, C., Lorber, M., 2018. Environmental chemicals in breast milk and formula: exposure and risk assessment implications. Environ. Health Perspect. 126, 96001.
Lei, Z.M., Mishra, S., Ponnuru, P., Li, X., Yang, Z.W., Rao Ch, V., 2004. Testicular phenotype in luteinizing hormone receptor knockout animals and the effect of testosterone replacement therapy. Biol. Reprod. 71, 1605–1613.
Leichtmann-Bardoogo, Y., Cohen, L.A., Weiss, A., Marohn, B., Schubert, S., Meinhardt, A., Meyron-Holtz, E.G., 2012. Compartmentalization and regulation of iron metabolism proteins protect male germ cells from iron overload. Am. J. Phys. Endocrinol. Metab. 302, E1519–E1530.
Leite, R.F., Losano, J.D.A., Kawai, G.K.V., Rui, B.R., Nagai, K.K., Castiglioni, V.C., Siqueira, A.F.P., D'Avila Assumpção, M.E.O., Baruselli, P.S., Nichi, M., 2022. Sperm function and oxidative status: effect on fertility in Bos taurus and Bos indicus bulls when semen is used for fixed-time artificial insemination. Anim. Reprod. Sci. 237, 106922.
Li, F.J., Long, H.Z., Zhou, Z.W., Luo, H.Y., Xu, S.G., Gao, L.C., 2022a. System X(c) (-)/GSH/GPX4 axis: an important antioxidant system for the ferroptosis in drug-resistant solid tumor therapy. Front. Pharmacol. 13, 910292.
Li, J., Bai, Y., Ma, K., Ren, Z., Li, J., Zhang, J., Shan, A., 2022b. Dihydroartemisinin alleviates deoxynivalenol induced liver apoptosis and inflammation in piglets. Ecotoxicol. Environ. Saf. 241, 113811.
Li, M.; Tang, S.; Peng, X.; Sharma, G.; Yin, S.; Hao, Z.; Li, J.; Shen, J.; Dai, C. Lycopene as a Therapeutic Agent against Aflatoxin B1-Related Toxicity: Mechanistic Insights and Future Directions, Antioxidants (Basel). (2024a) 13.
Li, X., Gou, F., Zhu, J., Lin, Q., Yu, M., Tu, X., Hong, Q., Hu, C., 2024b. Deoxynivalenol induced intestinal barrier injury, mitochondrial dysfunction and calcium overload by inositol 1,4,5-triphosphate receptors (IP3Rs)-mitochondrial calcium uniporter (MCU) calcium axis. Sci. Total Environ. 913, 169729.
Li, X., Jiang, X., Sun, J., Zhu, C., Li, X., Tian, L., Liu, L., Bai, W., 2017a. Cytoprotective effects of dietary flavonoids against cadmium-induced toxicity. Ann. N. Y. Acad. Sci. 1398, 5–19.
Li, X., Li, H., Li, X., Zhang, Q., 2017b. Determination of trace patulin in apple-based food matrices. Food Chem. 233, 290–301.
Li, Z., Zhao, Y., Zong, Q., Hu, P., Bao, W., Liu, H.Y., Cai, D., 2023. Lactoferrin restores the deoxynivalenol-impaired spermatogenesis and blood-testis barrier integrity via improving the antioxidant capacity and modifying the cell adhesion and inflammatory response. Antioxidants (basel) 12.
Liang, X., Yan, Z., Ma, W., Qian, Y., Zou, X., Cui, Y., Liu, J., Meng, Y., 2020. Peroxiredoxin 4 protects against ovarian ageing by ameliorating D-galactose-induced oxidative damage in mice. Cell Death Dis 11, 1053.
Liao, P., Liao, M., Li, L., Tan, B., Yin, Y., 2017. Effect of deoxynivalenol on apoptosis, barrier function, and expression levels of genes involved in nutrient transport, mitochondrial biogenesis and function in IPEC-J2 cells. Toxicol. Res. 6, 866–877.
Lin, J., Huang, F., Liang, T., Qin, Q., Xu, Q., Huang, X., Zhang, J., Xiao, K., Zhu, H., Zhao, J., Liu, Y., 2022a. EPA and DHA confer protection against deoxynivalenol-induced endoplasmic reticulum stress and iron imbalance in IPEC-1 cells. Br. J. Nutr. 128, 161–171.
Lin, L.X., Cao, Q.Q., Zhang, C.D., Xu, T.T., Yue, K., Li, Q., Liu, F., Wang, X., Dong, H.J., Huang, S.C., Jian, F.C., 2022b. Aflatoxin B1 causes oxidative stress and apoptosis in sheep testes associated with disrupting rumen microbiota. Ecotoxicol. Environ. Saf. 232, 113225.
Liu, A., Hu, S., Wu, Q., Ares, I., Martínez, M., Martínez-Larrañaga, M.R., Anadón, A., Wang, X., Martínez, M.A., 2020. Epigenetic upregulation of galanin-like peptide mediates deoxynivalenol induced-growth inhibition in pituitary cells. Toxicol. Appl. Pharmacol. 403, 115166.
Liu, M., Zhang, L., Mo, Y., Li, J., Yang, J., Wang, J., Karrow, N.A., Wu, H., Sun, L., 2023. Ferroptosis is involved in deoxynivalenol-induced intestinal damage in pigs. J. Anim. Sci. Biotechnol. 14, 29.

Liu, X., Peng, Y., Chen, R., Zhou, Y., Xia, M., Wu, X., Yu, M., 2024. Nomilin reversed cardiotoxicity caused by co-exposure to zearalenone and deoxynivalenol via the Keap1/Nrf2 signaling pathway in zebrafish. Plant Foods for Human Nutrition (dordrecht, Netherlands).
Lu, Q., Zhu, Y., Wang, L., Mei, M., Qiu, Y., Liu, Y., Fu, S., Xiong, J., Guo, P., Wu, Z., Wang, X., 2024. Peroxiredoxin 4 ameliorates T-2 toxin-induced growth retardation in GH3 cells by inhibiting oxidative stress and apoptosis. Molecules (basel, Switzerland) 29.
Ma, J., Han, Y., Yang, H., Liu, L., Wei, Z., Wang, F., Wan, Y., 2023. Melatonin protects Leydig cells from HT-2 toxin-induced ferroptosis and apoptosis via glucose-6-phosphate dehydrogenase/glutathione -dependent pathway. Int. J. Biochem. Cell Biol. 159, 106410.
Ma, K., Bai, Y., Li, J., Ren, Z., Li, J., Zhang, J., Shan, A., 2022. Lactobacillus rhamnosus GG ameliorates deoxynivalenol-induced kidney oxidative damage and mitochondrial injury in weaned piglets. Food Funct. 13, 3905–3916.
Ma, L.; Sun, Y. Comparison of L-Carnitine vs. Coq10 and Vitamin E for idiopathic male infertility: a randomized controlled trial, European review for medical and pharmacological sciences. (2022) 26 pp4698-4704.
Medina, Á., González-Jartín, J.M., Sainz, M.J., 2017. Impact of global warming on mycotoxins. Curr. Opin. Food Sci. 18, 76–81.
Miao, C., Wang, Z., Wang, X., Huang, W., Gao, X., Cao, Z., 2023. Deoxynivalenol induces blood-testis barrier dysfunction through disrupting p38 signaling pathway-mediated tight junction protein expression and distribution in mice. J Agric Food Chem 71, 12829–12838.
Mishra, S., Srivastava, S., Dewangan, J., Divakar, A., Kumar Rath, S., 2020. Global occurrence of deoxynivalenol in food commodities and exposure risk assessment in humans in the last decade: a survey. Crit Rev Food Sci Nutr 60, 1346–1374.
Morgan, M.J., Liu, Z.G., 2011. Crosstalk of reactive oxygen species and NF-κB signaling. Cell Res. 21, 103–115.
Ndossi, D.G., Frizzell, C., Tremoen, N.H., Fæste, C.K., Verhaegen, S., Dahl, E., Eriksen, G. S., Sørlie, M., Connolly, L., Ropstad, E., 2012. An in vitro investigation of endocrine disrupting effects of trichothecenes deoxynivalenol (DON), T-2 and HT-2 toxins. Toxicol. Lett. 214, 268–278.
Oduwole, O.O., Huhtaniemi, I.T., Misrahi, M., 2021. The roles of luteinizing hormone, follicle-stimulating hormone and testosterone in spermatogenesis and folliculogenesis revisited. Int J Mol Sci 22.
Ogunlade, B., Gbotolorun, S.C., Adedotun, O.A., Iteire, K., Adejayi, J., 2022. Vanillic acid and vitamin C attenuated di-2-ethylhexyl phthalate-induced testicular toxicity in adult male rats. Reproduction & Fertility 3, 220–230.
Omotayo, O.P., Omotayo, A.O., Mwanza, M., Babalola, O.O., 2019. Prevalence of mycotoxins and their consequences on human health. Toxicological Research 35, 1–7.
Owumi, S.E., Akinwunmi, A.O., Nwozo, S.O., Arunsi, U.O., Oyelere, A.K., 2023. Aflatoxin B1-induced dysfunction in male rats' reproductive indices were abated by Sorghum bicolor (L.Moench) hydrophobic fraction. Reproductive toxicology (Elmsford. NY) 120, 108425.
Owumi, S.E., Irozuru, C.E., Arunsi, U.O., Faleke, H.O., Oyelere, A.K., 2022. Caffeic acid mitigates aflatoxin B1-mediated toxicity in the male rat reproductive system by modulating inflammatory and apoptotic responses, testicular function, and the redox-regulatory systems. J. Food Biochem. 46, e14090.
Paganoni, S., Hendrix, S., Dickson, S.P., Knowlton, N., Macklin, E.A., Berry, J.D., Elliott, M.A., Maiser, S., Karam, C., Caress, J.B., Owegi, M.A., Quick, A., Wymer, J., Goutman, S.A., Heitzman, D., Heiman-Patterson, T.D., Jackson, C.E., Quinn, C., Rothstein, J.D., Kasarskis, E.J., Katz, J., Jenkins, L., Ladha, S., Miller, T.M., Scelsa, S. N., Vu, T.H., Fournier, C.N., Glass, J.D., Johnson, K.M., Swenson, A., Goyal, N.A., Pattee, G.L., Andres, P.L., Babu, S., Chase, M., Dagostino, D., Hall, M., Kittle, G., Eydinov, M., McGovern, M., Ostrow, J., Pothier, L., Randall, R., Shefner, J.M., Sherman, A.V., St Pierre, M.E., Tustison, E., Vigneswaran, P., Walker, J., Yu, H., Chan, J., Wittes, J., Yu, Z.F., Cohen, J., Klee, J., Leslie, K., Tanzi, R.E., Gilbert, W., Yeramian, P.D., Schoenfeld, D., Cudkowicz, M.E., 2021. Long-term survival of participants in the CENTAUR trial of sodium phenylbutyrate-taurursodiol in amyotrophic lateral sclerosis. Muscle Nerve 63, 31–39.
Paganoni, S., Macklin, E.A., Hendrix, S., Berry, J.D., Elliott, M.A., Maiser, S., Karam, C., Caress, J.B., Owegi, M.A., Quick, A., Wymer, J., Goutman, S.A., Heitzman, D., Heiman-Patterson, T., Jackson, C.E., Quinn, C., Rothstein, J.D., Kasarskis, E.J., Katz, J., Jenkins, L., Ladha, S., Miller, T.M., Scelsa, S.N., Vu, T.H., Fournier, C.N., Glass, J.D., Johnson, K.M., Swenson, A., Goyal, N.A., Pattee, G.L., Andres, P.L., Babu, S., Chase, M., Dagostino, D., Dickson, S.P., Ellison, N., Hall, M., Hendrix, K., Kittle, G., McGovern, M., Ostrow, J., Pothier, L., Randall, R., Shefner, J.M., Sherman, A.V., Tustison, E., Vigneswaran, P., Walker, J., Yu, H., Chan, J., Wittes, J., Cohen, J., Klee, J., Leslie, K., Tanzi, R.E., Gilbert, W., Yeramian, P.D., Schoenfeld, D., Cudkowicz, M.E., 2020. Trial of sodium phenylbutyrate-taurursodiol for amyotrophic lateral sclerosis. N. Engl. J. Med. 383, 919–930.
Pang, J., Cao, Q.F., Sun, Z.Y., 2016. [Impact of zearalenone on male fertility: An update]. Zhonghua nan ke xue =. Natl. J. Androl. 22, 1034–1037.
Patel, S.S., Acharya, A., Ray, R.S., Agrawal, R., Raghuwanshi, R., Jain, P., 2020. Cellular and molecular mechanisms of curcumin in prevention and treatment of disease. Crit Rev Food Sci Nutr 60, 887–939.
Pestka, J.J., 2010. Deoxynivalenol: mechanisms of action, human exposure, and toxicological relevance. Arch Toxicol 84, 663–679.
Pestka, J.J., Smolinski, A.T., 2005. Deoxynivalenol: toxicology and potential effects on humans. J. Toxicol. Environ. Health B Crit. Rev. 8, 39–69.
Pierron, A., Bracarense, A., Cossalter, A.M., Laffitte, J., Schwartz-Zimmermann, H.E., Schatzmayr, G., Pinton, P., Moll, W.D., Oswald, I.P., 2018. Deepoxy-deoxynivalenol retains some immune-modulatory properties of the parent molecule deoxynivalenol in piglets. Arch Toxicol 92, 3381–3389.
Pierron, A., Mimoun, S., Murate, L.S., Loiseau, N., Lippi, Y., Bracarense, A.P., Liaubet, L., Schatzmayr, G., Berthiller, F., Moll, W.D., Oswald, I.P., 2016. Intestinal toxicity of the masked mycotoxin deoxynivalenol-3-β-D-glucoside. Arch Toxicol 90, 2037–2046.
Piomboni, P., Gambera, L., Serafini, F., Campanella, G., Morgante, G., De Leo, V., 2008. Sperm quality improvement after natural anti-oxidant treatment of asthenoteratospermic men with leukocytospermia. Asian J. Androl. 10, 201–206.
Qin, Y., Li, A., Liu, B., Jiang, W., Gao, M., Tian, X., Gong, G., 2020. Mitochondrial fusion mediated by fusion promotion and fission inhibition directs adult mouse heart function toward a different direction. Faseb j 34, 663–675.
Rahimi, A., Asadi, F., Rezghi, M., Kazemi, S., Soorani, F., Memariani, Z., 2022. Natural products against cisplatin-induced male reproductive toxicity: a comprehensive review. J. Biochem. Mol. Toxicol. 36, e22970.
Rascón-Cruz, Q., Siqueiros-Cendón, T.S., Siañez-Estrada, L.I., Villaseñor-Rivera, C.M., Ángel-Lerma, L.E., Olivas-Espino, J.A., León-Flores, D.B., Espinoza-Sánchez, E.A., Arévalo-Gallegos, S., Iglesias-Figueroa, B.F., 2024. Antioxidant potential of lactoferrin and its protective effect on health: an overview. Int J Mol Sci 26.
Ren, Z.H., Deng, H.D., Deng, Y.T., Deng, J.L., Zuo, Z.C., Yu, S.M., Shen, L.H., Cui, H.M., Xu, Z.W., Hu, Y.C., 2016. Effect of the Fusarium toxins, zearalenone and deoxynivalenol, on the mouse brain. Environ. Toxicol. Pharmacol. 46, 62–70.
Rodprasert, W., Toppari, J., Virtanen, H.E., 2023. Environmental toxicants and male fertility. Best Pract. Res. Clin. Obstet. Gynaecol. 86, 102298.
Ruan, Y.-B., Liu, X.-H., Jiang, J.-Z., Nie, T., Ma, J., 2024. Leydig cells pyroptosis in testis mediates deoxynivalenol-induced male reproductive toxicity in mice. Sci. Total Environ. 954, 176432.
Safarinejad, M.R., Safarinejad, S., 2009. Efficacy of selenium and/or N-acetyl-cysteine for improving semen parameters in infertile men: a double-blind, placebo controlled, randomized study. J. Urol. 181, 741–751.
Sarawi, W.S., Alhusaini, A.M., Fadda, L.M., Alomar, H.A., Albaker, A.B., Alghibiwi, H.K., Aljrboa, A.S., Alotaibi, A.M., Hasan, I.H., Mahmoud, A.M., 2022. Nano-curcumin prevents copper reproductive toxicity by attenuating oxidative stress and inflammation and improving Nrf2/HO-1 signaling and pituitary-gonadal axis in male rats. Toxics 10.
Savard, C., Nogues, P., Boyer, A., Chorfi, Y., 2016. Prevention of deoxynivalenol- and zearalenone-associated oxidative stress does not restore MA-10 Leydig cell functions. Toxicology 341–343, 17–27.
Scarpulla, R.C., 2011. Metabolic control of mitochondrial biogenesis through the PGC-1 family regulatory network. Biochim Biophys Acta 1813, 1269–1278.
Scotto Rosato, A., Montefusco, S., Soldati, C., Di Paola, S., Capuozzo, A., Monfregola, J., Polishchuk, E., Amabile, A., Grimm, C., Lombardo, A., De Matteis, M.A., Ballabio, A., Medina, D.L., 2019. TRPML1 links lysosomal calcium to autophagosome biogenesis through the activation of the CaMKKβ/VPS34 pathway. Nat Commun 10, 5630.
Seyed Toutounchi, N., Braber, S., Van't Land, B., Thijssen, S., Garssen, J., Kraneveld, A. D., Folkerts, G., Hogenkamp, A., 2021. Exposure to deoxynivalenol during pregnancy and lactation enhances food allergy and reduces vaccine responsiveness in the offspring in a mouse model. Front Immunol 12, 797152.
Skakkebæk, N.E., Lindahl-Jacobsen, R., Levine, H., Andersson, A.M., Jørgensen, N., Main, K.M., Lidegaard, Ø., Priskorn, L., Holmboe, S.A., Bräuner, E.V., Almstrup, K., Franca, L.R., Znaor, A., Kortenkamp, A., Hart, R.J., Juul, A., 2022. Environmental factors in declining human fertility. Nat. Rev. Endocrinol. 18, 139–157.
Skiepko, N., Przybylska-Gornowicz, B., Gajęcka, M., Gajęcki, M., Lewczuk, B., 2020. Effects of deoxynivalenol and zearalenone on the histology and ultrastructure of pig liver. Toxins 12.
Smolková, K., Mikó, E., Kovács, T., Leguina-Ruzzi, A., Sipos, A., Bai, P., 2020. Nuclear factor erythroid 2-related factor 2 in regulating cancer metabolism. Antioxid. Redox Signal. 33, 966–997.
Song, J.L., Zhang, G.L., 2021. Deoxynivalenol and zearalenone: different mycotoxins with different toxic effects in the sertoli cells of equus asinus. Cells 10.
Spinelli, J.B., Haigis, M.C., 2018. The multifaceted contributions of mitochondria to cellular metabolism. Nat Cell Biol 20, 745–754.
Sprando, R.L., Collins, T.F., Black, T.N., Olejnik, N., Rorie, J.I., Eppley, R.M., Ruggles, D. I., 2005. Characterization of the effect of deoxynivalenol on selected male reproductive endpoints. Food Chem Toxicol 43, 623–635.
Sun, L., Dai, J., Xu, J., Yang, J., Zhang, D., 2022. Comparative cytotoxic effects and possible mechanisms of deoxynivalenol, zearalenone and T-2 toxin exposure to porcine leydig cells in vitro. Toxins 14.
Sun, P., Liu, M., Zhou, S., Yang, L., Xie, S., Riaz, H., Huo, L., Liang, A., 2024. Maternal exposure to DON during lactation induces testicular toxicity in pubertal and adult offspring mice. Ecotoxicol. Environ. Saf. 279, 116468.
Sun, P., Zhao, X., Liu, M., Wu, H., Lv, C., Zhou, S., Ding, Z., Huo, L., Yang, L., Liang, A., 2023. Lactational exposure to Deoxynivalenol causes mammary gland injury via inducing inflammatory response and impairing blood-milk barrier integrity in mice. Ecotoxicol. Environ. Saf. 255, 114773.
Supriya, C., Girish, B.P., Reddy, P.S., 2014. Aflatoxin B1-induced reproductive toxicity in male rats: possible mechanism of action. Int. J. Toxicol. 33, 155–161.
Swanson, K.V., Deng, M., Ting, J.P., 2019. The NLRP3 inflammasome: molecular activation and regulation to therapeutics. Nat. Rev. Immunol. 19, 477–489.
Szabó, A., Szabó-Fodor, J., Fébel, H., Mézes, M., Balogh, K., Bázár, G., Kocsó, D., Ali, O., Kovács, M., 2017. Individual and combined effects of fumonisin B_1, deoxynivalenol and zearalenone on the hepatic and renal membrane lipid integrity of rats. Toxins 10.
Takalani, N.B., Monageng, E.M., Mohlala, K., Monsees, T.K., Henkel, R., Opuwari, C.S., 2023. Role of oxidative stress in male infertility. Reproduction & Fertility 4.
Tang, Y., Li, J., Li, F., Hu, C.A., Liao, P., Tan, K., Tan, B., Xiong, X., Liu, G., Li, T., Yin, Y., 2015. Autophagy protects intestinal epithelial cells against deoxynivalenol toxicity

by alleviating oxidative stress via IKK signaling pathway. Free Radic. Biol. Med. 89, 944–951.
Tassis, P.D., Reisinger, N., Nagl, V., Tzika, E., Schatzmayr, D., Mittas, N., Basioura, A., Michos, I., Tsakmakidis, I.A., 2022. Comparative effects of deoxynivalenol, zearalenone and its modified forms de-epoxy-deoxynivalenol and hydrolyzed zearalenone on boar semen in vitro. Toxins 14.
Tassis, P.D., Tsakmakidis, I.A., Nagl, V., Reisinger, N., Tzika, E., Gruber-Dorninger, C., Michos, I., Mittas, N., Basioura, A., Schatzmayr, D., 2020. Individual and combined in vitro effects of deoxynivalenol and zearalenone on boar semen. Toxins 12.
Tiwari, S., Dewry, R.K., Srivastava, R., Nath, S., Mohanty, T.K., 2022. Targeted antioxidant delivery modulates mitochondrial functions, ameliorates oxidative stress and preserve sperm quality during cryopreservation. Theriogenology 179, 22–31.
Tossetta, G., Fantone, S., Togni, L., Santarelli, A., Olivieri, F., Marzioni, D., Rippo, M.R., 2024. Modulation of NRF2/KEAP1 signaling by phytotherapeutics in periodontitis. Antioxidants (basel) 13.
Urbanek, K.A., Habrowska-Górczyńska, D.E., Kowalska, K., Stańczyk, A., Domińska, K., Piastowska-Ciesielska, A.W., 2018. Deoxynivalenol as potential modulator of human steroidogenesis. J. Appl. Toxicol. 38, 1450–1459.
Urbanek, K.A., Kowalska, K., Habrowska-Górczyńska, D.E., Domińska, K., Sakowicz, A., Piastowska-Ciesielska, A.W., 2021. In Vitro analysis of deoxynivalenol influence on steroidogenesis in prostate. Toxins 13.
van Tol Amaral Guerra, S.M.; Cordeiro Koppe de França, L.; Neto da Silva, K.; Scolari Grotto, F.; Glaser, V. Copper dyshomeostasis and its relationship to AMPK activation, mitochondrial dynamics, and biogenesis of mitochondria: A systematic review of in vivo studies, Journal of trace elements in medicine and biology : organ of the Society for Minerals and Trace Elements (GMS). (2024) 86 pp127549.
Vessa, B., Perlman, B., McGovern, P.G., Morelli, S.S., 2022. Endocrine disruptors and female fertility: a review of pesticide and plasticizer effects. F&S Reports 3, 86–90.
Visintin, L., García Nicolás, M., Vangeenderhuysen, P., Goessens, T., Alladio, E., Pomian, B., Vanhaecke, L., De Saeger, S., De Boevre, M., 2023. Unraveling biomarkers of exposure for tenuazonic acid through urinary metabolomics. Food Chem Toxicol 182, 114183.
Vissiennon, T., Freick, M., Kilic, E., Schmidt, T., Dänicke, S., Schmicke, M., Schneider, E., 2016. Sertoli cell tumour in a neonate calf: an unusual congenital tumour. a case report. Tierarztliche Praxis Ausgabe g, Grosstiere/nutztiere 44, 371–378.
Wan, D., Wu, Q., Qu, W., Liu, G., Wang, X., 2018. Pyrrolidine dithiocarbamate (PDTC) inhibits DON-induced mitochondrial dysfunction and apoptosis via the NF-κB/iNOS pathway. Oxid. Med. Cell. Longev. 2018, 1324173.
Wang, H., Zhou, Y., Xu, C., Cao, Y., Xiao, Y., Cai, D., Uemoto, Y., Wu, S., Bao, W., 2022. Genome-wide transcriptional profiling and functional analysis reveal miR-330-MAPK15 axis involving in cellular responses to deoxynivalenol exposure. Chemosphere 298, 134199.
Wang, M., Wu, W., Li, L., He, J., Huang, S., Chen, S., Chen, J., Long, M., Yang, S., Li, P., 2019. Analysis of the miRNA Expression Profiles in the Zearalenone-Exposed TM3 Leydig Cell Line. Int J Mol Sci 20.
Wang, S., Zhang, K., Yao, Y., Li, J., Deng, S., 2021. Bacterial infections affect male fertility: a focus on the oxidative stress-autophagy axis. Front. Cell Dev. Biol. 9, 727812.
Wang, X., Chen, X., Cao, L., Zhu, L., Zhang, Y., Chu, X., Zhu, D., Rahman, S.U., Peng, C., Feng, S., Li, Y., Wu, J., 2020. Mechanism of deoxynivalenol-induced neurotoxicity in weaned piglets is linked to lipid peroxidation, dampened neurotransmitter levels, and interference with calcium signaling. Ecotoxicol. Environ. Saf. 194, 110382.
Wang, Z., Wu, Q., Kuča, K., Dohnal, V., Tian, Z., 2014. Deoxynivalenol: signaling pathways and human exposure risk assessment–an update. Arch Toxicol 88, 1915–1928.
Wiseman, R.L., Mesgarzadeh, J.S., Hendershot, L.M., 2022. Reshaping endoplasmic reticulum quality control through the unfolded protein response. Mol. Cell 82, 1477–1491.
Xie, M.Y., Chen, T., Xi, Q.Y., Hou, L.J., Luo, J.Y., Zeng, B., Li, M., Sun, J.J., Zhang, Y.L., 2020. Porcine milk exosome miRNAs protect intestinal epithelial cells against deoxynivalenol-induced damage. Biochem Pharmacol 175, 113898.
Xu, H., Wang, L., Sun, J., Wang, L., Guo, H., Ye, Y., Sun, X., 2022. Microbial detoxification of mycotoxins in food and feed. Crit Rev Food Sci Nutr 62, 4951–4969.
Xue, D., Yang, P., Yang, Y., Wang, Y., Wu, K., Qi, D., Wang, S., 2022. Deoxynivalenol triggers porcine intestinal tight junction disorder through hijacking SLC5A1 and PGC1α-mediated mitochondrial function. Food Chem Toxicol 163, 112921.
Yang, C., Ning, X., Wang, B., Tian, T., Chen, Y., Ma, L., Wang, L., 2024a. Association between spectrum of mycotoxins and semen quality: a cross-sectional study in Beijing. China. Journal of Hazardous Materials 476, 135124.
Yang, J., Ye, L., Cui, R., Zheng, K., Qiao, X., Wang, M., Su, M., Li, X., Ge, R.S., Wang, Y., 2024b. Deoxynivalenol inhibits progenitor leydig cell development by stimulating mitochondrial fission in rats. J Agric Food Chem 72, 10616–10626.
Yang, J.H., Wang, J.H., Guo, W.B., Ling, A.R., Luo, A.Q., Liu, D., Yang, X.L., Zhao, Z.H., 2019. Toxic Effects and Possible Mechanisms of Deoxynivalenol Exposure on Sperm and Testicular Damage in BALB/c Mice. J Agric Food Chem 67, 2289–2295.
Yang, W., Yu, M., Fu, J., Bao, W., Wang, D., Hao, L., Yao, P., Nüssler, A.K., Yan, H., Liu, L., 2014. Deoxynivalenol induced oxidative stress and genotoxicity in human peripheral blood lymphocytes. Food Chem Toxicol 64, 383–396.
Yang, X., Huang, T., Chen, Y., Chen, F., Liu, Y., Wang, Y., Song, W., Zhang, J., Jiang, Y., Wang, F., Zhang, C., 2023. Deoxynivalenol induces testicular ferroptosis by regulating the Nrf2/System Xc(-)/GPX4 axis. Food Chem Toxicol 175, 113730.
Yang, X., Liu, P., Zhang, X., Zhang, J., Cui, Y., Song, M., Li, Y., 2021. T-2 toxin causes dysfunction of Sertoli cells by inducing oxidative stress. Ecotoxicol. Environ. Saf. 225, 112702.
Yao, Y., Long, M., 2020. The biological detoxification of deoxynivalenol: A review. Food Chem Toxicol 145, 111649.
Ye, G., Jiao, Y., Deng, L., Cheng, M., Wang, S., Zhang, J., Ouyang, J., Li, Y., He, Y., Tu, Z., Wang, Z., Song, X., Wang, C., Qi, Q., Zhang, D., Wang, L., Huang, M., Ye, W., Chen, M., 2023a. Beauvericin suppresses the proliferation and pulmonary metastasis of osteosarcoma by selectively inhibiting TGFBR2 pathway. Int. J. Biol. Sci. 19, 4376–4392.
Ye, Y., Jiang, M., Hong, X., Fu, Y., Chen, Y., Wu, H., Sun, Y., Wang, X., Zhou, E., Wang, J., Yang, Z., 2023b. Quercetin Alleviates Deoxynivalenol-Induced Intestinal Damage by Suppressing Inflammation and Ferroptosis in Mice. J Agric Food Chem 71, 10761–10772.
Yilmaz, B., Terekeci, H., Sandal, S., Kelestimur, F., 2020. Endocrine disrupting chemicals: exposure, effects on human health, mechanism of action, models for testing and strategies for prevention. Rev. Endocr. Metab. Disord. 21, 127–147.
Yu, W., Kang, L., Lin, X., Duan, N., Ying, D., Wang, Z., Wu, S., 2023. Deoxynivalenol (DON)-Triggered Dual-Color Composite Probe Based on Gold Nanoclusters for Simultaneous Imaging of DON and miR-34a in Living Cells. Anal. Chem. 95, 18611–18618.
Yuan, W., Sun, Z., Ji, G., Hu, H., 2023. Emerging roles of ferroptosis in male reproductive diseases. Cell Death Discovery 9, 358.
Zhang, F.L., Ma, H.H., Dong, P.Y., Yan, Y.C., Chen, Y., Yang, G.M., Shen, W., Zhang, X.F., 2024a. Bacillus licheniformis ameliorates Aflatoxin B1-induced testicular damage by improving the gut-metabolism-testis axis. J. Hazard. Mater. 468, 133836.
Zhang, J., Su, D., Liu, Q., Yuan, Q., Ouyang, Z., Wei, Y., Xiao, C., Li, L., Yang, C., Jiang, W., Guo, L., Zhou, T., 2022. Gasdermin D-mediated microglial pyroptosis exacerbates neurotoxicity of aflatoxins B1 and M1 in mouse primary microglia and neuronal cultures. Neurotoxicology 91, 305–320.
Zhang, J., You, L., Wu, W., Wang, X., Chrienova, Z., Nepovimova, E., Wu, Q., Kuca, K., 2020. The neurotoxicity of trichothecenes T-2 toxin and deoxynivalenol (DON): Current status and future perspectives. Food Chem Toxicol 145, 111676.
Zhang, J., Zhao, Q., Xue, Z., Zhang, S., Ren, Z., Chen, S., Zhou, A., Chen, H., Liu, Y., 2023. Deoxynivalenol induces endoplasmic reticulum stress-associated apoptosis via the IRE1/JNK/CHOP pathway in porcine alveolar macrophage 3D4/21 cells. Food Chem Toxicol 180, 114033.
Zhang, X., Wang, Y., Velkov, T., Tang, S., Dai, C., 2018. T-2 toxin-induced toxicity in neuroblastoma-2a cells involves the generation of reactive oxygen, mitochondrial dysfunction and inhibition of Nrf2/HO-1 pathway. Food Chem Toxicol 114, 88–97.
Zhang, Z., Miao, J., Wang, H., Ali, I., Nguyen, D., Chen, W., Wang, Y., 2024b. Accelerated mitochondrial dynamics promote spermatogonial differentiation. Stem Cell Rep. 19, 1548–1563.
Zhang, Z., Wang, Q., Gao, X., Tang, X., Xu, H., Wang, W., Lei, X., 2024c. Reproductive toxicity of cadmium stress in male animals. Toxicology 504, 153787.
Zhang, Z., Zhang, Z., Liu, S., Wei, S., Wei, L., Zhu, X., Ding, K., Liu, Y., 2024d. Protective effect of selenomethionine on rabbit testicular injury induced by Aflatoxin B1. Sci Total Environ 927, 171973.
Zhao, Q., Zhang, S., Feng, W., Zhou, A., Shi, L., Zhang, J., 2024. Deoxynivalenol-mediated kidney injury via endoplasmic reticulum stress in mice. Ecotoxicol. Environ. Saf. 286, 117243.
Zhu, J., Wang, K.Z., Chu, C.T., 2013. After the banquet: mitochondrial biogenesis, mitophagy, and cell survival. Autophagy 9, 1663–1676.
Zi, T., Liu, Y., Zhang, Y., Wang, Z., Wang, Z., Zhan, S., Peng, Z., Li, N., Liu, X., Liu, F., 2022. Protective effect of melatonin on alleviating early oxidative stress induced by DOX in mice spermatogenesis and sperm quality maintaining. Reproductive Biology and Endocrinology : RB&E 20, 105.
Zorova, L.D., Popkov, V.A., Plotnikov, E.Y., Silachev, D.N., Pevzner, I.B., Jankauskas, S. S., Babenko, V.A., Zorov, S.D., Balakireva, A.V., Juhaszova, M., Sollott, S.J., Zorov, D.B., 2018. Mitochondrial membrane potential. Anal Biochem 552, 50–59.
Zurub, R.E., Cariaco, Y., Wade, M.G., Bainbridge, S.A., 2023. Microplastics exposure: implications for human fertility, pregnancy and child health. Front. Endocrinol. 14, 1330396.