DOI: 10.1002/vms3.814

REVIEW

WILEY

# Beneficial and toxicological aspects of zinc oxide nanoparticles in animals

**Heshu Sulaiman Rahman**[1,2] | **Hemn Hassan Othman**[3] | **Rasedee Abdullah**[4] | **Hareth Yahya Ahmed Shujaa Edin**[5] | **Nagi A. AL-Haj**[6]

[1]Department of Physiology, College of Medicine, University of Sulaimani, Sulaimaniyah, Republic of Iraq

[2]Department of Medical Laboratory Sciences, Komar University of Science and Technology, Sulaimaniyah, Republic of Iraq

[3]Department of Pharmacology and Toxicology, College of Pharmacy, University of Sulaimani, Sulaimaniyah, Republic of Iraq

[4]Department of Veterinary Laboratory Diagnosis, Faculty of Veterinary Medicine, Universiti Putra Malaysia, Serdang, Malaysia

[5]Institute of Bioscience, Universiti Putra Malaysia, Serdang, Malaysia

[6]Faculty of Medicine and Health Sciences, Sana'a University, Sana'a, Yemen

**Correspondence**
Heshu Sulaiman Rahman, Department of Physiology, College of Medicine, University of Sulaimani, Sulaimaniyah, Republic of Iraq.
Email: heshu.rhaman@univsul.edu.iq

## Abstract

Nanotechnology is a far-reaching technology with tremendous applications in various aspects, including general medicine, veterinary medicine, agriculture, aquaculture, and food production. Nanomaterials have exceptional physicochemical characteristics, including increased intestinal absorption, biodistribution, bioavailability, and improved antimicrobial and catalytic properties. Although nanotechnology is gaining ground in animal management, husbandry, and production, its wide use is still hampered by occasional toxicity and side effects. Zinc oxide nanoparticles (ZnO-NPs) have long been utilized in animal production, aquaculture, and pet animal medicine. However, the use ZnO-NPs in animals has been associated with reports of toxicity and side effects. ZnO-NPs may have shown numerous beneficial effects in animals; its use must be regulated with care to avoid unwanted consequences. Thus, this review emphasizes the usage of ZnO-NPs in animal production and laboratory animals and the potential side effects associated with the use of nanoparticles as a feed supplement and therapeutic compound.

**KEYWORDS**
advantage, nanomaterials, toxicity, veterinary medicine, zinc oxide nanoparticle

## 1 | INTRODUCTION

Zinc (Zn) is a trace mineral that can enhance growth, repair injuries, modulate immune responses, improve fertility and metabolism, and scavenge free radicals (Kujur et al., 2016). Zn from organic sources is in the form of zinc lactate, zinc amino acid, and zinc chelate, while those from inorganic are zinc sulphate and zinc oxide. Regarding the bioavailability of Zn, the organic one is better than that of inorganic Zn. Zn insufficiency is primarily due to dietary deficiency. Zn is used as a food additive to improve animal health and production (Saptarshi et al., 2015). In livestock, Zn insufficiency reduces appetite, skin disorders, and poor growth. In addition, excess Zn in animal feed will be excreted in faeces and wasted (Hill & Li, 2017). Therefore, there is a need to balance dietary requirements and faecal elimination to avoid environmental Zn contamination.

Advances in nanotechnology over the last decades have facilitated the use of nanomaterials not only in humans but also in veterinary medicine (El-Sayed & Kamel, 2020; Youssef et al., 2019). In animal medicine and production, nanomaterials are used to improve disease diagnosis and treatment, improve feed digestibility and feeding, and promote health (Banumathi et al., 2017; Bogdan et al., 2017). These nanomaterials are metal oxides, particularly zinc oxide nanoparticles

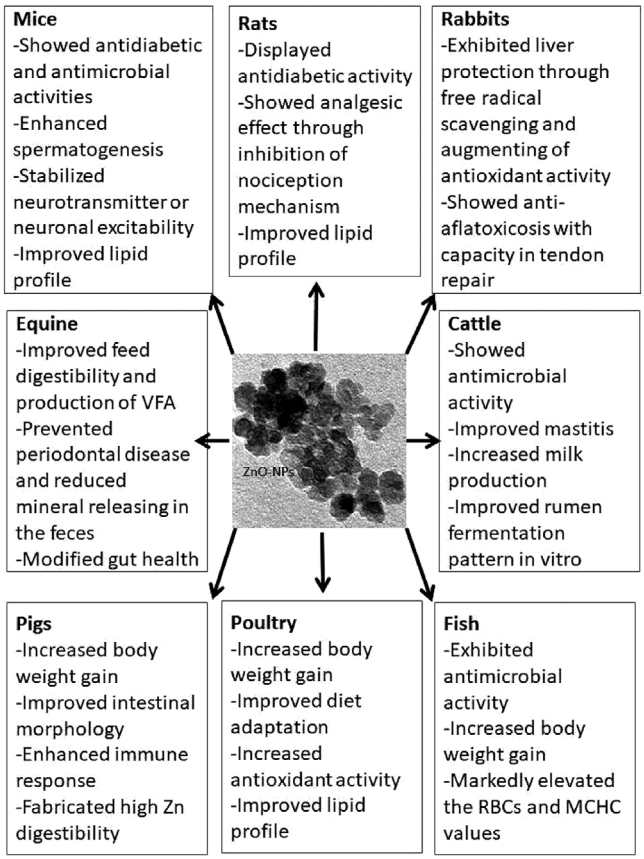


**FIGURE 1** Various advantages of zinc oxide nanoparticles (ZnO-NPs) in different animal species

(ZnO-NPs). The estimated total yearly manufacture of ZnO-NP is about 550–33400 tons globally (Czyzowska & Barbasz, 2020; Faizan et al., 2020). It is the third most frequently used metal nanoparticle in various industrial products, including rubber, paint, coating, and cosmetics.

The ZnO-NP is a more potent compound than ZnO. In addition, it has high permeability and is easily absorbed in the gastrointestinal tract (GIT), which enhances its utility as a potential therapeutic compound (Baltić et al., 2013). However, ZnO-NP is vulnerable to oxidative reactions with different organic materials. High exposure to ZnO-NP (4.0 or 8.0 $\mu$g/ml for 24 and 48 h) results in loss of DNA methylation as found in treated human MRC5 lung fibroblast cells. Additionally, ZnO-NPs treatment at a 50 $\mu$g/ml concentration results in a considerable expression of 5-hmeC in DNA that is accompanied by a drastic expression of the TET1 and TET2 genes (Pogribna & Hammons, 2021).

## 2 | BENEFICIAL EFFECTS OF ZnO-NPs IN DIFFERENT ANIMAL SPECIES

ZnO-NPs are considered one of the most prevalent metal oxide nanoparticles in several animal species (Figure 1) for various biological, medical, and industrial claims due to their exceptional biocompatibility, economic, and less toxicity.

### 2.1 | Poultry

ZnO-NPs were revealed to increase body weight gain in broilers. At low ZnO-NP treatment doses (20 and 60 mg/kg body weight), the body weights of the chicken markedly increased after 14 days. However, high doses of the nanoparticles (100 mg/kg body weight) caused decreases in body weight gain after 28 days. The serum and liver tissue malondialdehyde (MDA) levels were also significantly ($p < 0.05$) reduced with ZnO-NP treatment (20, 60, and 100 mg/kg body weight) (Zhao et al., 2014). ZnO-NPs supplemented to broiler diets (50 mg/kg of diet) significantly ($p < 0.05$) increased copper and iron levels in the liver tissues and Zn in the tibia, while the levels of serum total cholesterol (TC), triglycerides (TG), and very-low-density lipoprotein (LDL) were significantly ($p < 0.05$) reduced. The activity of MDA was significantly ($p < 0.05$) decreased, while the superoxide dismutase (SOD) level was significantly ($p < 0.05$) increased.

Also, in broilers, dietary ZnO-NPs potentially enhanced mRNA expression of insulin-like growth factor 1 (IGF-1) and growth hormone genes (Ibrahim et al., 2017). ZnO-NPs also increased feed consumption and weight gain and improved antioxidant capacity in broilers when given as a feed supplement (20 mg/kg body weight). In these birds, the ZnO-NPs significantly ($p < 0.05$) increased serum concentrations of SOD and alkaline phosphatase (ALP) activities as well as high-density lipoprotein (HDL) and cholesterol levels (Fathi et al., 2016) (Table 1).

Similarly, significant ($p < 0.05$) improvements in the health status of broilers decreased in the levels of cholesterol, and increased alanine aminotransferase (ALT) with elevated bird immunity was found after ZnO-NPs addition (0.6 mg/kg diet) (Sahoo et al., 2014). Furthermore, adding ZnO-NPs at 30 and 40 ppm to the diet reduces chances of footpad dermatitis (FPD) from *Staphylococcus aureus* in broilers (Mahmoud et al., 2021). More recently, the in ovo injection of ZnO-NPs (50, 75, and 100 ppm) into fertile eggs; enhanced the embryonic development and significantly ($p < 0.05$) improved the hatchability of the eggs; however, it increased the early embryonic mortality rate (Biria et al., 2021) (Table 1).

Additionally, in layer chicken, ZnO-NPs addition at 1/500th level of basal diet significantly ($p < 0.05$) improved growth rate, as well as increased serum glucose and ALP and diminished ALT (Mishra et al., 2014). Moreover, ZnO-NPs (0.2 g/kg diet) show a progressive outcome on Japanese quails' growth and physiological performance through enhancement in body weight, food consumption, and food adaptation ratio. Also, ZnO-NPs improve SOD, glutathione peroxidase (GPX), MDA, ALT, AST, lactate dehydrogenase (LDH), TC, HDL, LDL, immunoglobulin G (IgG), and IgM contents (Table 1) (Reda et al., 2021).

### 2.2 | Ruminants

In dairy cattle with sub-clinical mastitis, feed supplementation with ZnO-NPs reduced the somatic cell count (SCC), improved the condition, and increased milk production (Hozyen et al., 2019). ZnO-NPs also showed antibacterial activities towards *Staphylococcus aureus* and

**TABLE 1** Advantages of zinc oxide nanoparticles (ZnO-NPs) application in different animal species

| Animal species | ZnO-NPs dose | Effect | References |
|---|---|---|---|
| Poultry | 20 and 60 mg/kg body weight | -Increased body weight gains in broilers | Zhao et al. (2014) |
| | 50 mg/kg diet | -Increased mineral contents (iron, copper, and Zn) in hepatic tissues and tibia in broilers with improved antioxidant activities and lipid profile | Ibrahim et al. (2017) |
| | 20 mg/kg body weight | -Improved feed consumption, growth performance, and antioxidant status in broilers | Fathi et al. (2016) |
| | 0.6 mg/kg diet | -Improved the health status of broilers, decreased cholesterol, and increased alanine aminotransferase with elevated immunity | Sahoo et al. (2014) |
| | 30 and 40 ppm | -Reduced *Staphylococcus aureus*-induced negative effects of footpad dermatitis in broilers | Mahmoud et al. (2021) |
| | 50, 75, and 100 ppm | -Enhanced the embryonic development and significantly and increased the hatchability of the eggs | Biria et al. (2021) |
| | 1/500th level of basal dose of diet | -Improved growth rate in layer chicken and increased the levels of serum glucose and alkaline phosphatase and decreased alanine aminotransferase | Mishra et al. (2014) |
| | 0.2 g/kg diet | -Potentially affected the performance and physiological status of growing Japanese quails and improved oxidative stress with lipid profile | Reda et al. (2021) |
| Ruminant | 40 mg/ml | -Inhibited the growth of bacteria, moulds, and yeasts in buffaloes | Hassan et al. (2014) |
| | 1.0–50 mg/ml | -Showed antibacterial effects in cows with clinical mastitis | Hozyen et al. (2019) |
| | 1.0 and 2.0 mg/ml | -Improved mastitis in cows and increased milk production | Bai et al. (2018) and Hassan et al. (2014) |
| | 100 and 200 mg/kg | -Improved the in vitro growth of ruminal microorganisms, increased ruminal microbial protein synthesis, and raised the energy utilization efficiency | Chen et al. (2011) |
| Equine | 30 ppm | -Improved feed digestibility, gas production, and production of volatile fatty acid | Adegbeye et al. (2019) |
| | 40 ppm | -Prevented periodontal disease | Adegbeye et al. (2019) |
| | 1200 mg/kg diet | -Reduced mineral releasing in the faeces, and modified gut health | Adegbeye et al. (2019) |
| | 30 and 60 mg/kg diet | -Showed antioxidant and anti-inflammatory activities and enhanced wound healing | Adegbeye et al. (2019) |
| Pig | 1200 mg/kg diet | -Increased body weight gain and improved intestinal morphology | Wang et al. (2017) |
| | 120 mg/kg | -Enhanced immune response and fabricated high Zn digestibility | Li et al. (2016) |
| | 500–800 ppm | -Efficiently controlled post-weaning diarrhoea that exacerbated by *E. coli* F4 (K88) infections | Bonetti et al. (2021) |
| Fish | 15.75 and 31.5 $\mu$g/ml | -Antimicrobial activity | Shaalan et al. (2017) |
| | 30 mg/kg diet | -Increased body weight gain, markedly elevated the erythrocyte count, and improved intestinal absorption and Zn bioavailability | Faiz et al. (2015) |
| | 10 mg/kg body weight | -Improved growth performance, blood health, oxidative stress parameters, and intestinal histo-morphology | Ghazi et al. (2021) |

*Escherichia coli* isolated from the diseased udder of cows (Bai et al., 2018). ZnO-NPs (40 mg/ml) also inhibited the growth of bacteria, molds, and yeasts isolated from superficial or deep infections (nasal swabs/pharyngeal swabs of buffaloes with respiratory disease, faecal swabs of diarrheic buffaloes, and milk samples of mastitic buffaloes), suggesting that the nanoparticles have potential as a bactericidal and fungicidal compound (Hassan et al., 2014).

At a 1.0 and 2.0 mg/ml concentration, ZnO-NPs prevented the propagation of the mastitis causative bacteria such as *Streptococcus epidermis*, *Streptococcus agalactiae*, *Klebsiella pneumoniae*, and *E. coli*

(Chen et al., 2011). Hence, the bactericidal activities of ZnO-NPs are suggested to be related to the nanoparticle's small size that could be 250 times lesser than a bacterium size. Thus, nanoparticles can easily stick to the bacterial surface, destroy it and result in bacterial death. Moreover, it was found that nanoparticles' small size provides great surface reactivity and can be simply adopted by cells, discharging Zn that could be lethal to the bacteria's biomolecules (Hozyen et al., 2019).

Based on freeing methane, total antioxidant capacity (TAC), and microbial biomass formation, the inclusion of 100 and 200 mg/kg ZnO-NPs was sufficient to advance the ruminal fermentation in vitro. In this regard, supplementation of ZnO-NPs improved the in vitro development of ruminal microorganisms, improved microbial protein production of the rumen, and raised the energy use capacity in the initial stage. In addition, the volatile fatty acid (VFA) with microbial essential protein concentrations and organic matter fermentation increased. At the same time, the ammonia nitrogen and the acetate to propionate ratio decreased with ZnO-NPs supplementation (Chen et al., 2011) (Table 1).

### 2.3 | Equine

It was found that ZnO-NPs (30 ppm) improved feed digestibility, gas production, releasing of VFA as well as prevented periodontal disease (40 ppm), reduced mineral releasing in the faeces, and modified gut health (1200 mg/kg diet) in equine species. Additionally, ZnO-NPs at 30 and 60 mg/kg diet shows antioxidant and anti-inflammatory activities and enhanced wound healing (Adegbeye et al., 2019) (Table 1).

### 2.4 | Pigs

ZnO-NPs can be replaced in weaned piglets with colistin sulphate (CS) or ZnO. ZnO-NPs supplementation (1200 mg/kg) significantly ($p < 0.05$) impacted body weight gain, improved the length of duodenal and ileal villi, depth of crypts, and the surface of villi (Wang et al., 2017). The nanoparticles (120 mg/kg diet) also enhanced Zn digestion, growth hormone amounts, carbonic anhydrase activities, and the immune status of weaned piglets (Li et al., 2016). Moreover, ZnO-NPs (500–800 ppm) supplementation is considered practical to efficient control of post-weaning diarrhoea (PWD) that is worsened by *E. coli* F4 (K88) infection in piglets (Bonetti et al., 2021) (Table 1).

### 2.5 | Fish

Recently, ZnO-NPs (15.75 $\mu$g/ml) were shown to exhibit antimicrobial activities against fish pathogens, *Aeromonas salmonicida* subsp. *Salmonicida* and *A. hydrophila*, while it reserved *Yersinia ruckeri* growth at a concentration of 31.5 $\mu$g/ml (Shaalan et al., 2017). Additionally, diet ZnO-NPs supplementation (30 mg/kg) had profound effects on growth performance and red blood cell (RBC) count of juvenile grass carp fish (*Ctenopharyngodon idella*). It was also suggested that the ZnO-NPs improved intestinal absorption and bioavailability of Zn in fish (Faiz et al., 2015). Moreover, in Nile tilapia fish, ZnO-NPs (10 mg/kg diet) improved growth performance (including increased body weight, weight gain rate, and growth rate), lowered food conversion ratio, and enhanced haemogram parameters such as haemoglobin (Hb), RBC, and globulin, increased oxidative stress parameters such as SOD and catalase while decreased MDA activity and intestinal histo-morphology (including villi length and goblet cell number increments) (Ghazi et al., 2022) (Table 1).

### 2.6 | Miscellaneous

Green ZnO-NPs (4.76 mg/L) are found to be effective, safe, and eco-friendly candidature against *Hyalomma* ticks, the most critical ticks of tropical and sub-tropical areas with potential public health issues as Crimean-Congo haemorrhagic fever vector (Zaheer et al., 2021).

## 3 | BENEFICIAL EFFECTS OF ZnO-NPs IN LABORATORY ANIMALS

### 3.1 | Mice

The effect of ZnO-NPs was determined in the lipopolysaccharide (LPS)-induced depression mice model. Then, the injected LPS mice showed disrupted spatial memory. However, these mice's behavioural and electrophysiological patterns improved after treatment with ZnO-NPs (5.6 mg/kg body weight) (Xie et al., 2012). Also, ZnO-NPs appeared to have beneficial effects in female BALB/c mice with skin infections that were shown by the intradermal injection of ZnO-NPs that markedly improved healing from diseases. In these mice, ZnO-NP treatment (1.0 g/kg body weight) diminished the bacterial load and inflammation and improved the architecture of infected skin (Pati et al., 2014). Furthermore, ZnO-NPs (0.12 g for 4 days) improved skin absorption of Zn in hairless mice. This was evident when the visceral organs of mice exposed to topical sunscreen with ZnO-NPs showed higher concentrations of Zn than those treated with sunscreen with ZnO (Osmond-McLeod et al., 2014) (Table 2).

The antidiabetic properties of ZnO-NPs were determined in mice induced to develop diabetes mellitus with intra-peritoneal (IP) alloxan injections. ZnO-NPs (0.1 mg/kg IP) augmented the mean islet area volume of the pancreas while decreasing serum TG, LDL, TC and blood glucose. The study showed that ZnO-NPs have potent antidiabetic activities (Amiri et al., 2018). Moreover, ZnO-NPs (0.1 and 0.5 mg/kg by oropharyngeal aspiration) caused significant ($p < 0.05$) neutrophilia and eosinophilia in mice within the first 7 days of exposure, especially the high dose. Furthermore, the expression levels of the T-helper 2 (Th2) cytokine interleukin 4 (IL-4), IL-5, and IL-13 peaked significantly ($p < 0.05$) after 24 h and gradually decreased thereon. Thus, it was concluded that ZnO-NPs could, in the absence of allergens, cause eosinophilic airway inflammation (Huang et al., 2015). Recently, the healing of mice wounds was investigated through ZnO-NP (30 ppm) dressings, and the result demonstrated that the nanoparticles reduced

**TABLE 2** Beneficial effects of zinc oxide nanoparticles (ZnO-NPs) in laboratory animals

| Animal species | ZnO-NPs dose/kg body weight | Effect | References |
|---|---|---|---|
| Mice | 5.6 mg | -Improved depression, behavioural and electrophysiological patterns | Xie et al. (2012) |
| | 1.0 g | -Decreased the bacterial load and inflammation and improved the architecture of infected skin | Pati et al., 2014) |
| | 0.12 mg | -Improved skin absorption of Zn | Osmond-McLeod et al. (2014) |
| | 0.1 mg | -Showed antidiabetic activity and improved lipid profile | Amiri et al. (2018) |
| | 0.1 and 0.5 mg | -Induced eosinophilic airway inflammation in the absence of allergens | Huang et al. (2015) |
| | 30 ppm | -Reduced wound area significantly and enhanced the skin repairing | Batool et al. (2021) |
| Rats | 3.0 mg | -Ameliorated testicular toxicity and genotoxicity | El-Maddawy and El Naby (2019) |
| | 10 mg | -Showed antidiabetic activity and improved lipid profile | Alkaladi et al. (2014), Umrani and Paknikar (2014) |
| | 0.5 mg | -Reduced acute somatic pain and analgesic effect through inhibition of nociception mechanism | Kesmati et al. (2014) |
| Rabbits | 25 $\mu$g | -Liver protection through free radical scavenging and augmenting of antioxidant activity, as well as, showed anti-aflatoxicosis with capacity in tendon repair | Atef et al. (2016) |
| | 100 mg | -Improve digestibility, male fertility, and liver, and kidney functions | Abdel-Wareth et al. (2020) |

wound area significantly ($p < 0.05$) and enhanced skin-repairing (Batool et al., 2021) (Table 2).

### 3.2 | Rats

The healing effects of ZnO-NPs (3.0 mg/kg body weight) on testicular wounds induced by doxorubicin was investigated in male adult rats. ZnO-NPs significantly ($p < 0.05$) reduced doxorubicin-induced changes in sperm parameters. ZnO-NPs exposure also potentiated the activities of reproduction factors. It markedly elevated testosterone levels in studied rats, indicating that the nanoparticles can ameliorate testicular toxicity and genotoxicity via its antioxidant and androgenic activities (El-Maddawy & El Naby, 2019). The efficacy of ZnO-NPs was also investigated in streptozotocin (STZ)-induced diabetic rats. In these rats, oral ZnO-NPs (10 mg/kg body weight) improved glucose tolerance and insulin release while decreasing non-esterified fatty acids, TG, and blood glucose concentrations.

Furthermore, rats administered with ZnO-NPs expressed glucokinase genes, insulin receptors and GLUT-2, deposited Zn in the adipose and hepatic tissues and pancreas, and enhanced Zn absorption in the intestinal tract (Umrani & Paknikar, 2014). Additionally, ZnO-NPs (0.5 mg/kg body weight) have an anti-nociception effect in female Wistar rats. The nanoparticles also improved the anti-nociception effect of morphine and naloxone (Kesmati et al., 2014) (Table 2).

### 3.3 | Rabbits

Aflatoxin can cause damage to the liver and kidneys. Aflatoxin B1 has significantly ($p < 0.05$) genotoxic effects, resulting from its damaging impact on the DNA and RNA and disrupting protein synthesis. It was shown in rabbits that ZnO-NPs (25 $\mu$g/kg body weight) ameliorated the genotoxic effects of aflatoxicosis. ZnO-NPs showed hepatoprotective efficacy by scavenging and detoxifying free radicals and enhancing antioxidant capacities (Atef et al., 2016). Moreover, ZnO-NPs treatment (100 mg/kg body weight) significantly ($p < 0.05$) improved nutrient digestibility, semen volume, sperm motility, vitality and morphology, serum testosterone concentrations, and liver and kidney functions in male Californian rabbits (Abdel-Wareth et al., 2020) (Table 2).

## 4 | THE TOXICITY OF ZnO-NPs IN ANIMALS

The toxic properties of ZnO-NPs are believed to be caused by the release of $Zn^{+}$ ions from the nanoparticles. Therefore, a high number of ZnO-NPs in feeds, even for short durations, can cause Zn toxicity in animals (Underwood & Van Eps, 2012). In addition, ZnO-NPs caused haemolysis, lowering the erythrocyte parameters, decreasing platelet number and reducing serum haptoglobin concentration, and some histopathological lesions in the liver (Ibrahim et al., 2017).

### 4.1 | Lambs

In lambs, supplementing feed with ZnO-NPs (20 mg/kg body weight) for 25 days significantly ($p < 0.05$) decreased serum ALP and increased serum creatinine levels. In addition, there were cell swelling, hepatocytic necrosis, and multiple interstitial nephritides in these animals. Thus, ZnO-NPs are contraindicative in sheep with Zn deficiency (Najafzadeh et al., 2013) (Table 3).

## 4.2 | Mice

In mice, ZnO-NPs (50 and 300 mg/kg body weight) were toxic to the testicular germ cells. Based on the observation of multinucleated giant cells and releasing of immature germ cells from the seminiferous tubules, decrease in seminiferous tubule size, epithelium growth, and maturation impairment, it showed that ZnO-NPs also affected Sertoli cell functions (Talebi et al., 2013). While ZnO-NPs supplementation at a low amount (50 mg/kg body weight) caused minimal toxicity in mice; however, at high concentrations (500 mg/kg body weight), the nanoparticles significantly ($p < 0.05$) decreased bodyweight, increased the relative weights of the pancreas, brain, and lungs, serum ALT, and enhanced Zn metabolism-related genes such as metallothionein 1 and 2, ZIP8, ZIP14, ZnT1, ZnT2, and ZnT4. There was also a significant ($p < 0.05$) accumulation of Zn in the pancreas, hepatic tissues, and bones of ZnO-NP-treated mice (Wang et al., 2016). Similarly, ZnO-NPs (50 mg/ml) decreased related antioxidant enzymes and increased DNA adduct (8-OHdG) production in mice liver homogenate. The same study also showed that ZnO-NPs induced 50% death of the mouse connective tissue, L929 cells (Syama et al., 2013) (Table 3).

ZnO-NPs (100 $\mu$g/ml) also reserved DNA repair through depressing fen-1 and pol B proteins. The nanoparticles dose-dependently reduced the viability of and killed mouse macrophages. The effect of ZnO-NPs on the macrophage's viability results in G0/G1 phase cell cycle arrest with SOD, catalase, and reactive oxygen species (ROS) formation inhibition. Mice administered with ZnO-NPs (500 mg/kg body weight) exhibited severe DNA impairment in peripheral blood and bone marrow cells. Histopathologically, ZnO-NPs caused intense inflammation and injury to adult mice's liver, lungs, and kidneys and reduced body weight and increased mortality rate (Pati et al., 2016). Moreover, ZnO-NPs (10, 20, and 30 $\mu$g/ml) caused in vitro cytotoxicity in mouse ovarian germ cells through enhancing ROS generation, significantly ($p < 0.05$) increasing the expression of pre-meiotic germ cells markers, and decreasing in meiotic and post-meiotic markers (Saber et al., 2021) (Table 3).

On the other hand, in male Swiss albino mice, ZnO-NPs (25 mg/kg body weight) showed weak genotoxicity that significantly ($p < 0.05$) decreased mitochondrial membrane potential ($\Delta\Psi m$) and enhanced ROS generation, and eventually caused apoptosis. In bone marrow cells, ZnO-NPs specifically reduced $\Delta\Psi m$, increased oxidative stress, arrested G0/G1 cell cycle, aberrated chromosomes, and formed micronuclei. The nanoparticles caused DNA damage in the hepatic tissues, induced oxidative stress, and concurrently decreased antioxidant enzymes' inhibition (Ghosh et al., 2016) (Table 3). However, in adult male albino mice, ZnO-NPs (50, 300, and 600 mg/kg body weight) do not affect the anxiolytic exploits and item recognition (Zahra et al., 2017).

## 4.3 | Rats

ZnO-NPs (536.8 mg/kg body weight) significantly ($p < 0.05$) lowered the mean body weight gain in male Sprague Dawley rats. Simultaneously, both male and female rats showed significant ($p < 0.05$) alterations in anaemia-related blood tests and slight to sub-severe pancreatitis after oral administering with ZnO-NPs. The toxic effect of ZnO-NPs was primarily associated with the bio-persistence of ZnO-NPs in the body (Seok et al., 2013) (Table 3).

Another study suggested that ZnO-NPs (3.0 mg/kg or 30 mg/kg body weight) were not promptly absorbed from the GIT of rats after consumption and were mostly eliminated in faeces. However, the ZnO-NPs (30 mg/kg body weight) blood concentration peaks within 5 min and returns to normal by 48 h post-intravenous injection. Administered ZnO-NPs disseminated mainly to liver, kidneys, lung, and spleen, but not to thymus, brain, and testes. In these rats, intravenous ZnO-NPs enhanced the formation of mitotic figures in the hepatic tissues, while in the pulmonary tissues, multifocal acute damages with dark brown pigmentation were found. These manifestations were in rats orally treated with the nanoparticles (Choi et al., 2015).

Similarly, oral ZnO-NPs (500 mg/kg body weight) in Sprague Dawley rats caused pathological changes in the pancreas, including apoptosis of acinar cells, ductal cell hyperplasia, infiltration of periductal lymphoid cells, and increasing of regenerative acinar cells with inflammation and oedema in the gastric mucosa, excessive salivation, and retinal atrophy. Consequently, haematocrit, albumin, mean cell volume (MCV), mean cell haemoglobin (MCH), mean cell haemoglobin concentration (MCHC), total protein, and albumin were decreased significantly ($p < 0.05$). In contrast, the total RBC count was increased (Park et al., 2014) (Table 3).

Furthermore, ZnO-NPs (200 mg/kg body weight) significantly increased serum ALT and AST levels in male Wistar rats. In addition, the liver tissues of treated rats presented more Kupffer cells, congestion, parenchymal/port inflammations, ballooning, and chromatin condensation, which were evidence of apoptosis. In the kidneys, ZnO-NPs caused cell proliferation and congestion in the glomerulus and interstitial tissue inflammation. The nanoparticles also significantly ($p < 0.05$) impacted sperm quality and quantities in treated rats (Abbasalipourkabir et al., 2015) (Table 3).

Moreover, the toxicity of ZnO-NPs (3.0 mg/kg body weight) on the kidneys were also demonstrated in another study where the nanoparticles significantly ($p < 0.05$) reduced the body weight, kidney index, and the activities of catalase and SOD in the kidney cortex. The nephrotoxicity of ZnO-NPs is suggested to be attributed to the increase in oxidative stress in the renal tissues of treated animals (Xiao et al., 2016).

ZnO-NPs also showed toxicity to the central nervous system. IP treatment with ZnO-NPs (100 mg/kg body weight) significantly ($p < 0.05$) improved MDA and decreased catalase and SOD activities in the brain. The study suggested that the ZnO-NPs-induced prominent brain histological changes, including oedema and satellitosis, could cause behavioural changes (Rahdar et al., 2020). This was confirmed in another study that showed long-term (8 weeks) IP injection of ZnO-NPs (4.0 mg/kg body weight) resulted in attenuating the spatial learning and memory capacity through a change in synaptic plasticity in young Wister rats (Han et al., 2011) (Table 3).

ZnO-NPs-treated rats (500 mg/kg body weight) showed decreased number of born-alive pups and body weights of pups while enhanced

**TABLE 3** Toxicological adverse effects of Zinc oxide nanoparticles (ZnO-NPs) in some animal species

| Laboratory animal | ZnO-NPs dose | Toxicological adverse effect | References |
|---|---|---|---|
| Lambs | 20 mg/kg body weight | -Changed normal liver and kidney function tests -Altered normal liver and kidney histopathology | Najafzadeh et al. (2013) |
| Mice | 50 and 300 mg/kg body weight | -Acted as testicular toxicant that affected spermatogenesis and testicular histopathology | Talebi et al. (2013) |
| | 500 mg/kg body weight | -Decreased body weight, increased weights of the pancreas, brain, and lungs as well as serum alanine aminotransferase, enhanced expression of genes related to Zn metabolism, and accumulated significant amount of Zn in the liver, pancreas, kidneys, and bones | Wang et al. (2016) |
| | 50 mg/ml | -Induced marked changes in 8-OHdG formation<br>-Reduced viability of L929 cells in vitro | Syama et al. (2013) |
| | 100 $\mu$g/ml | -Inhibited DNA repair, killed macrophage, and inhibited superoxide dismutase, catalase, and reactive oxygen species | Pati et al. (2016) |
| | 500 mg/kg body weight | -Induced DNA damage in the bone marrow and blood cells, produced high inflammation and destruction of liver, lungs, and kidneys, and reduced body weight and induced mortality | Pati et al. (2016) |
| | 10, 20, and 30 $\mu$g/ml | -Caused in vitro cytotoxicity in ovarian germ cells through enhancing reactive oxygen species generation, significant increasing in the expression of pre-meiotic germ cells markers, and decreasing in meiotic and post-meiotic markers | Saber et al. (2021) |
| | 25 mg/kg body weight | -Decreased mitochondrial membrane potential, induced reactive oxygen species generation, and apoptosis<br>-In bone marrow cells, reduced mitochondrial membrane potential, increased oxidative stress, arrested G0/G1 cell cycle, chromosome aberrations, and micronuclei formation<br>-In the liver cells, caused DNA damage, induced oxidative stress, and decreased the inhibition of antioxidant enzymes | Ghosh et al. (2016) |
| Rats | 536.8 mg/kg body weight | -Decreased body weight and showed significant alterations in haematological tests especially those related to anaemia with various degrees of pancreatitis | Seok et al. (2013) |
| | 30 mg/kg body weight | -Increased the formation of mitotic figures in the liver with multifocal acute injuries and dark brown pigment in the lungs | Choi et al. (2015) |
| | 500 mg/kg body weight | -Caused pathological changes including acinar cell apoptosis and ductular hyperplasia, periductular lymphoid cell infiltration, and an increased number of regenerative acinar cells in the pancreas with inflammation and oedema in the stomach mucosa, excessive salivation, and retinal atrophy of the eye<br>-Decreased haematocrit, mean cell volume, mean cell haemoglobin and mean cell haemoglobin concentration<br>-Decreased total protein and albumin | Park et al. (2014) |
| | 200 mg/kg body weight | -Increased total oxidant status and decreased total antioxidant capacity significantly<br>-Impacted on sperm quality and quantity<br>-Induced histopathological changes in liver and kidney tissues | Abbasalipourkabir et al. (2015) |
| | 100 mg/kg body weight | -Significantly increased MDA and decreased catalase and superoxide dismutase activities in the brain<br>-Induced brain histological changes that caused behavioural changes | Rahdar et al. (2020) |

(Continues)

**TABLE 3** (Continued)

| Laboratory animal | ZnO-NPs dose | Toxicological adverse effect | References |
|---|---|---|---|
| | 4.0 mg/kg body weight | -Attenuated the spatial learning and memory capacity through alteration in synaptic plasticity | Han et al. (2011) |
| | 500 mg/kg body weight | -Reduced number of born-alive pups, decreased body weights of pups and increased fetal resorption | Jo et al. (2013) |
| | 200 mg/kg body weight | -Increased in the corpus luteum, follicular cysts, inflammatory cell infiltration, and fibrosis<br>-Induced epithelial destruction and hyperplasia of endometrial glands<br>-Decreased the serum concentrations of reproductive hormone, oestrogen, and progesterone | Mohammad et al. (2019) |
| Fish | 1000 mg/kg feed | -Induced accumulation of Zn in the gill, intestine, and liver of rainbow trout fish<br>-Developed oxidative stress and impaired the metabolism | Connolly et al. (2016) |
| | 2.16 g/aquarium | -Accumulated high amount of Zn in the liver and brain of fish, induced reactive oxygen species with a greater challenge to the antioxidant defense system of goldfish | Yin et al. (2017) |
| | 500 mg/kg feed | -Disturbed the homeostasis and proteins of the haematological and the immune system of juvenile common carp | Chupani et al. (2017) |
| | 10 mg/L | -Induced epicardial and yolk-sac oedema, Influenced inflammation and the immune system-related genes in the Zebrafish embryos | Choi et al. (2016) |
| | 760 $\mu$g/L | -Increased oxidative stress, behavioural changes, and genotoxic effects in grass carp | Estrela et al. (2021) |

fetal resorption. ZnO-NPs were also spread to mammary tissues of dams and hepatic/renal tissues of pups (Jo et al., 2013). ZnO-NPs (200 mg/kg body weight) dose-dependently increased the corpus luteum, follicular cysts, inflammatory cell infiltration, and fibrosis in the ovaries. In uterine tissues, the developed lesions after ZnO-NPs exposure include the destruction of epithelial tissues and endometrial gland's hyperplasia. Also, the nanoparticles decreased the serum concentrations of reproductive hormone, oestrogen, and progesterone (Mohammad et al., 2019) (Table 3).

Similarly, the effects of 250 nm ZnO-NPs (by inhalation in a whole-body exposure chamber) in male Sprague Dawley rats using nuclear magnetic resonance to advocate the metabolic reactions of the pulmonary system were reported. The tested bronchoalveolar lavage fluid of treated animals revealed a decrease in acetate, ascorbate, formate, glycerophosphocholine, glycine, and trimethylamine N-oxide, taurine, as well as an increase in isoleucine and valine. Metabolic enzyme alteration was also found in pulmonary tissues that might result from antioxidation, DNA damage, and cell membrane stability (Lee et al., 2016).

### 4.4 | Fish

Treatment of rainbow trout fish with ZnO-NPs (1.0 g/kg feed) resulted in the aggregation of Zn in gills, intestine, and liver. Among the effects of Zn's tissue accumulation are oxidative stress and impaired metabolism. However, the tissue Zn is rapidly cleared upon cessation of treatment (Connolly et al., 2016). Also, the toxicity of ZnO-NPs (2.16 g/aquarium) to goldfish (*Carassius auratus*) was investigated, and it was found that elevated $CO_2$ levels in a water-sediment ecosystem led to high Zn accumulation in the hepatic and brain tissues, induced more ROS and a great challenge to the antioxidant defence mechanism (Yin et al., 2017). In juvenile common carp (*Cyprinus carpio*) fish, ZnO-NPs (500 mg/kg feed) disturbed the homeostasis through the destruction of the proteins of the haematological and the immune system (Chupani et al., 2017). Additionally, post-fertilization exposure of ZnO-NPs (10 mg/L) leads to inflammation-causing pericardial and yolk-sac oedema at the embryonic/larval developmental stages of Zebrafish (*Danio rerio*) (Choi et al., 2016). Also, ZnO-NPs (760 $\mu$g/L) increased oxidative stress, behavioural changes, and genotoxicity in *C. idella* (grass carp) (Estrela et al., 2021) (Table 3).

## 5 | CONCLUSIONS

Nanotechnology provides the synthesis of novel nanodevices that could be used to improve human and animal health. Nanomaterials have several advantages over traditional compounds in that they offer better improvements to animal management, husbandry, and production. In human and veterinary medicine, nanomaterials are now widely used to detect and diagnose diseases and vaccine, drug, and gene deliveries. ZnO-NPs have long been used in veterinary medicine and animal production. For example, ZnO-NPs improved animal health and

improved the qualities and quantities in milk and meat production. Therefore, it is recommended that ZnO-NPs be used as supplements in animal feeds; however, the application of the compound must be regulated at safe doses to avoid the accumulation of Zn in tissues and the development of toxicity.

## ACKNOWLEDGEMENTS

The authors have not received any specific fund or grant to support this review article from any agency or organization.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## FUNDING INFORMATION

None.

## AUTHOR CONTRIBUTIONS

*Conceptualization*, *resources*, *supervision*, *validation*, *visualization*, *writing—original draft*, *and writing—review and editing*: Heshu Sulaiman Rahman. *Investigation*, *visualization*, *and writing—original draft*: Hemn Hassan Othman. *Supervision and writing—review and editing*: Rasedee Abdullah. *Validation*, *visualization*, *and writing—original draft*: Hareth Yahya.

## DATA AVAILABILITY STATEMENT

Not Applicable.

## PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1002/vms3.814.

## ORCID

*Heshu Sulaiman Rahman* https://orcid.org/0000-0003-0356-0399

## REFERENCES

Abbasalipourkabir, R., Moradi, H., Zarei, S., Asadi, S., Salehzadeh, A., Ghafourikhosroshahi, A., Mortazavi, M., & Ziamajidi, N. (2015). Toxicity of zinc oxide nanoparticles on adult male Wistar rats. *Food and Chemical Toxicology*, *84*, 154–160.

Abdel-Wareth, A. A. A., Al-Kahtani, M. A., Alsyaad, K. M., Shalaby, F. M., Saadeldin, I. M., Alshammari, F. A., Mobashar, M., Suleiman, M. H. A., Ali, A. H. H., Taqi, M. O., El-Sayed, H. G. M., Abd El-Sadek, M. S., Metwally, A. E., & Ahmed, A. E. (2020). Combined supplementation of nano-zinc oxide and thyme oil improves the nutrient digestibility and reproductive fertility in the male Californian rabbits. *Animals*, *10*(12), 2234.

Adegbeye, M. J., Elghandour, M. M., Barbabosa-Pliego, A., Monroy, J. C., Mellado, M., Reddy, P. R. K., & Salem, A. Z. M. (2019). Nanoparticles in equine nutrition: Mechanism of action and application as feed additives. *Journal of Equine Veterinary Science*, *78*, 29–37.

Alkaladi, A., Abdelazim, A. M., & Afifi, M. (2014). Antidiabetic activity of zinc oxide and silver nanoparticles on streptozotocin-induced diabetic rats. *International Journal of Molecular Sciences*, *15*(2), 2015–2023.

Amiri, A., Dehkordi, R. A. F., Heidarnejad, M. S., & Dehkordi, M. J. (2018). Effect of the zinc oxide nanoparticles and thiamine for the management of diabetes in alloxan-induced mice: A stereological and biochemical study. *Biological Trace Element Research*, *181*(2), 258–264.

Atef, H. A., Mansour, M. K., Ibrahim, E. M., El-Ahl, R. M. S., Al-Kalamawey, N. M., El Kattan, Y., & Ali, M. A. (2016). Efficacy of zinc oxide nanoparticles and curcumin in amelioration the toxic effects in aflatoxicated rabbits. *International Journal of Current Microbiology and Applied Sciences*, *5*(12), 795–818.

Bai, D. P., Lin, X. Y., Huang, Y. F., & Zhang, X. F. (2018). Theranostics aspects of various nanoparticles in veterinary medicine. *International Journal of Molecular Sciences*, *19*(11), 3299–3330.

Baltić, M. Ž., Bošković, M., Ivanović, J., Dokmanović, M., Janjić, J., Lončina, J., & Tatjana, B. (2013). Nanotechnology and its potential applications in meat industry. *Tehnologija Mesa*, *54*(2), 168–175.

Banumathi, B., Vaseeharan, B., Ishwarya, R., Govindarajan, M., Alharbi, N. S., Kadaikunnan, S., Khaled, J. M., & Benelli, G. (2017). Toxicity of herbal extracts used in ethno-veterinary medicine and green-encapsulated ZnO nanoparticles against *Aedes aegypti* and microbial pathogens. *Parasitology Research*, *116*(6), 1637–1651.

Batool, M., Khurshid, S., Qureshi, Z., & Daoush, W. M. (2021). Adsorption, antimicrobial and wound healing activities of biosynthesized zinc oxide nanoparticles. *Chemical Papers*, *75*(3), 893–907.

Biria, A., Navidshad, B., Aghjehgheshlag, F. M., & Nikbin, S. (2021). The effect of in ovo supplementation of nano zinc oxide particles on hatchability and post-hatch immune system of broiler chicken. *Iranian Journal of Applied Animal Sciences*, *10*(3), 547–553.

Bogdan, J., Pławińska-Czarnak, J., & Zarzyńska, J. (2017). Nanoparticles of titanium and zinc oxides as novel agents in tumor treatment: A review. *Nanoscale Research Letters*, *12*(1), 225.

Bonetti, A., Tugnoli, B., Piva, A., & Grilli, E. (2021). Towards zero zinc oxide: Feeding strategies to manage post-weaning diarrhea in piglets. *Animal*, *11*(3), 642.

Chen, J., Wang, W., & Wang, Z. (2011). Effect of nano-zinc oxide supplementation on rumen fermentation in vitro. *Chinese Journal of Animal Nutrition*, *23*(8), 1415–1421.

Choi, J. S., Kim, H., Kim, P., Jo, E., Kim, H. M., Lee, M. Y., Jin, S. M., & Park, K. (2015). Toxicity of zinc oxide nanoparticles in rats treated by two different routes: Single intravenous injection and single oral administration. *Journal of Toxicology and Environmental Health, Part A*, *78*(4), 226–243.

Choi, J. S., Kim, R.-O., Yoon, S., & Kim, W.-K. (2016). Developmental toxicity of zinc oxide nanoparticles to zebrafish (*Danio rerio*), a transcriptomic analysis. *PLoS One*, *11*(8), e0160763.

Chupani, L., Zusková, E., Niksirat, H., Panáček, A., Lünsmann, V., Haange, S. B., von Bergen, M., & Jehmlich, N. (2017). Effects of chronic dietary exposure of zinc oxide nanoparticles on the serum protein profile of juvenile common carp (*Cyprinus carpio* L.). *Science of The Total Environment*, *579*, 1504–1511.

Connolly, M., Fernández, M., Conde, E., Torrent, F., Navas, J. M., & Fernández-Cruz, M. L. (2016). Tissue distribution of zinc and subtle oxidative stress effects after dietary administration of ZnO nanoparticles to rainbow trout. *Science of The Total Environment*, *551*, 334–343.

Czyzowska, A., & Barbasz, A. (2020). A review: Zinc oxide nanoparticles—Friends or enemies? *International Journal of Environmental Health Research*, *32*, 885–901.

El-Maddawy, Z. K., & El Naby, W. (2019). Protective effects of zinc oxide nanoparticles against doxorubicin induced testicular toxicity and DNA damage in male rats. *Toxicology Research*, *8*(5), 654–662.

El-Sayed, A., & Kamel, M. (2020). Advanced applications of nanotechnology in veterinary medicine. *Environmental Science and Pollution Research*, *27*, 19073–19086.

Estrela, F. N., Guimarães, A. T. B., Silva, F. G., da Luz, T. M., Silva, A. M., Pereira, P. S., & Malafaia, G. (2021). Effects of polystyrene nanoplastics on *Ctenopharyngodon idella* (grass carp) after individual and combined exposure with zinc oxide nanoparticles. *Journal of Hazardous Materials*, *403*, 123879.

Faiz, H., Zuberi, A., Nazir, S., Rauf, M., & Younus, N. (2015). Zinc oxide, zinc sulfate and zinc oxide nanoparticles as source of dietary zinc: Comparative effects on growth and hematological indices of juvenile grass carp

(*Ctenopharyngodon idella*). *International Journal of Agriculture and Biology*, *17*(3), 568–574.

Faizan, M., Hayat, S., & Pichtel, J. (2020). Effects of zinc oxide nanoparticles on crop plants: A perspective analysis. *Sustainable agriculture reviews* (pp. 83–99). Springer.

Fathi, M., Haydari, M., & Tanha, T. (2016). Effects of zinc oxide nanoparticles on antioxidant status, serum enzymes activities, biochemical parameters and performance in broiler chickens. *Journal of Livestock Science and Technologies*, *4*(2), 7–13.

Ghazi, S., Diab, A. M., Khalafalla, M. M., & Mohamed, R. A. (2022). Synergistic effects of selenium and zinc oxide nanoparticles on growth performance, hemato-biochemical profile, immune and oxidative stress responses, and intestinal morphometry of Nile tilapia (*Oreochromis niloticus*). *Biological Trace Element Research*, *200*, 364–374.

Ghosh, M., Sinha, S., Jothiramajayam, M., Jana, A., Nag, A., & Mukherjee, A. (2016). Cyto-genotoxicity and oxidative stress induced by zinc oxide nanoparticle in human lymphocyte cells in vitro and Swiss albino male mice in vivo. *Food and Chemical Toxicology*, *97*, 286–296.

Han, D., Tian, Y., Zhang, T., Ren, G., & Yang, Z. (2011). Nano-zinc oxide damages spatial cognition capability via over-enhanced long-term potentiation in hippocampus of Wistar rats. *International Journal of Nanomedicine*, *6*, 1453–1461.

Hassan, A., Oraby, N., Mohamed, A. A., & Mahmoud, H. (2014). The possibility of using zinc oxide nanoparticles in controlling some fungal and bacterial strains isolated from buffaloes. *Journal of Applied Sciences Egypt*, *29*(3), 58–83.

Hill, E. K., & Li, J. (2017). Current and prospects for nanotechnology in animal production. *Journal of Animal Science and Biotechnology*, *8*(1), 26.

Hozyen, H. F., Ibrahim, E. S., Khairy, E. A., & El-Dek, S. I. (2019). Enhanced antibacterial activity of capped zinc oxide nanoparticles: A step towards the control of clinical bovine mastitis. *Veterinary World*, *12*(8), 1225–1232.

Huang, K.-L., Lee, Y.-H., Chen, H.-I., Liao, H.-S., Chiang, B.-L., & Cheng, T.-J. (2015). Zinc oxide nanoparticles induce eosinophilic airway inflammation in mice. *Journal of Hazardous Materials*, *297*, 304–312.

Ibrahim, D., Ali, H. A., & El-Mandrawy, S. A. (2017). Effects of different zinc sources on performance, biodistribution of minerals and expression of genes related to metabolism of broiler chickens. *Zagazig Veterinary Journal*, *45*(3), 292–304.

Jo, E., Seo, G., Kwon, J. T., Lee, M., Bc, L., Eom, I., Kim, P., & Choi, K. (2013). Exposure to zinc oxide nanoparticles affects reproductive development and biodistribution in offspring rats. *Journal of Toxicological Sciences*, *38*(4), 525–530.

Kesmati, M., Torabi, M., & Ghandizadeh, D. M. (2014). Nanoparticles of zinc oxide reduces acute somatic pain in adult female Wistar rats. *Zahedan Journal of Research in Medical Sciences*, *16*(2), 24–28.

Kujur, K., Ghosh, S., Batabyal, S., & Mukherjee, J. (2016). Effect of micronutrient supplementation on the hormonal profile of local goat and sheep breeds of West Bengal. *Indian Journal of Animal Sciences*, *86*(2), 224–225.

Lee, S. H., Wang, T. Y., Hong, J. H., Cheng, T. J., & Lin, C. Y. (2016). NMR-based metabolomics to determine acute inhalation effects of nano-and fine-sized ZnO particles in the rat lung. *Nanotoxicology*, *10*(7), 924–934.

Li, M. Z., Huang, J. T., Tsai, Y. H., Mao, S. Y., Fu, C. M., & Lien, T. F. (2016). Nanosize of zinc oxide and the effects on zinc digestibility, growth performances, immune response and serum parameters of weanling piglets. *Animal Science Journal*, *87*(11), 1379–1385.

Mahmoud, U. T., Darwish, M. H., Ali, F. A. Z., Amen, O. A., Mahmoud, M. A., Ahmed, O. B., Abd El-Reda, G., Osman, M. A., Othman, A. A., Abushahba, M. F. N., & El Shoukary, R. D. (2021). Zinc oxide nanoparticles prevents multidrug resistant *Staphylococcus*-induced footpad dermatitis in broilers. *Avian Pathology*, .

Mishra, A., Swain, R., Mishra, S., Panda, N., & Sethy, K. (2014). Growth performance and serum biochemical parameters as affected by nano zinc supplementation in layer chicks. *Indian Journal of Animal Nutrition*, *31*(4), 384–388.

Mohammad, H. S., Hossein, M. A., Amani, R., Vahid, R. S., Hasan, A. M., Sokouti, Z., & Babaei, H. B. (2019). Subchronic effects of different doses of zinc oxide nanoparticle on reproductive organs of female rats: An experimental study. *International Journal of Reproductive BioMedicine*, *17*(2), 107–118.

Najafzadeh, H., Ghoreishi, S., Mohammadian, B., Rahimi, E., Afzalzadeh, M., Kazemivarnamkhasti, M., & Ganjealidarani, H. (2013). Serum biochemical and histopathological changes in liver and kidney in lambs after zinc oxide nanoparticles administration. *Veterinary World*, *6*(8), 534–537.

Osmond-McLeod, M. J., Oytam, Y., Kirby, J. K., Gomez-Fernandez, L., Baxter, B., & McCall, M. J. (2014). Dermal absorption and short-term biological impact in hairless mice from sunscreens containing zinc oxide nano-or larger particles. *Nanotoxicology*, *8*(Supl), 72–84.

Park, H. S., Kim, S. J., Lee, T. J., Kim, G. Y., Meang, E. H., Hong, J. S., Kim, S. H., Koh, S. B., Hong, S. G., Sun, Y. S., Kang, J. S., Kim, Y. R., Kim, M. K., Jeong, J., Lee, J. K., Son, W. C., & Park, J. H. (2014). A 90-day study of subchronic oral toxicity of 20 nm positively charged zinc oxide nanoparticles in Sprague Dawley rats. *International Journal of Nanomedicine*, *9*((Suppl) 2), 93–107.

Pati, R., Das, I., Mehta, R. K., Sahu, R., & Sonawane, A. (2016). Zinc-oxide nanoparticles exhibit genotoxic, clastogenic, cytotoxic and actin depolymerization effects by inducing oxidative stress responses in macrophages and adult mice. *Toxicological Sciences*, *150*(2), 454–472.

Pati, R., Mehta, R. K., Mohanty, S., Padhi, A., Sengupta, M., Vaseeharan, B., Goswami, C., & Sonawane, A. (2014). Topical application of zinc oxide nanoparticles reduces bacterial skin infection in mice and exhibits antibacterial activity by inducing oxidative stress response and cell membrane disintegration in macrophages. *Nanomedicine: Nanotechnology, Biology and Medicine*, *10*(6), 1195–1208.

Pogribna, M., & Hammons, G. (2021). Epigenetic effects of nanomaterials and nanoparticles. *Journal of Nanbiotechnology*, *19*(1), 1–18.

Rahdar, A., Hajinezhad, M. R., Bilal, M., Askari, F., & Kyzas, G. Z. (2020). Behavioral effects of zinc oxide nanoparticles on the brain of rats. *Inorganic Chemistry Communications*, *119*, 108131.

Reda, F. M., El-Saadony, M. T., El-Rayes, T. K., Attia, A. I., El-Sayed, S. A., Ahmed, S. Y., Madkour, M., & Alagawany, M. (2021). Use of biological nano zinc as a feed additive in quail nutrition: Biosynthesis, antimicrobial activity and its effect on growth, feed utilization, blood metabolites and intestinal microbiota. *Italian Journal of Animal Science*, *20*(1), 324–335.

Saber, M., Hayaei-Tehrani, R. S., Mokhtari, S., Hoorzad, P., & Esfandiari, F. (2021). In vitro cytotoxicity of zinc oxide nanoparticles in mouse ovarian germ cells. *Toxicology in Vitro*, *70*, 105032.

Sahoo, A., Swain, R., & Mishra, S. K. (2014). Effect of inorganic, organic and nano zinc supplemented diets on bioavailability and immunity status of broilers. *International Journal of Advanced Research*, *2*(11), 828–837.

Saptarshi, S. R., Duschl, A., & Lopata, A. L. (2015). Biological reactivity of zinc oxide nanoparticles with mammalian test systems: An overview. *Nanomedicine*, *10*(13), 2075–2092.

Seok, S. H., Cho, W. S., Park, J. S., Na, Y., Jang, A., Kim, H., Cho, Y., Kim, T., You, J. R., Ko, S., Kang, B. C., Lee, J. K., Jeong, J., & Che, J. H. (2013). Rat pancreatitis produced by 13-week administration of zinc oxide nanoparticles: Biopersistence of nanoparticles and possible solutions. *Journal of Applied Toxicology*, *33*(10), 1089–1096.

Shaalan, M. I., El-Mahdy, M. M., Theiner, S., El-Matbouli, M., & Saleh, M. (2017). In vitro assessment of the antimicrobial activity of silver and zinc oxide nanoparticles against fish pathogens. *Acta Veterinaria Scandinavica*, *59*(1), 49–59.

Syama, S., Reshma, S., Sreekanth, P., Varma, H., & Mohanan, P. (2013). Effect of zinc oxide nanoparticles on cellular oxidative stress and antioxidant defense mechanisms in mouse liver. *Toxicological & Environmental Chemistry*, *95*(3), 495–503.

Talebi, A. R., Khorsandi, L., & Moridian, M. (2013). The effect of zinc oxide nanoparticles on mouse spermatogenesis. *Journal of Assisted Reproduction and Genetics*, *30*(9), 1203–1209.

Umrani, R. D., & Paknikar, K. M. (2014). Zinc oxide nanoparticles show antidiabetic activity in streptozotocin-induced Type 1 and 2 diabetic rats. *Nanomedicine*, *9*(1), 89–104.

Underwood, C., & Van Eps, A. (2012). Nanomedicine and veterinary science: The reality and the practicality. *Veterinary Journal*, *193*(1), 12–23.

Wang, C., Lu, J., Le Zhou, J. L., Xu, J., Li, W., Zhang, L., Zhang, L., Zhong, X., & Wang, T. (2016). Effects of long-term exposure to zinc oxide nanoparticles on development, zinc metabolism and biodistribution of minerals (Zn, Fe, Cu, Mn) in mice. *PLoS One*, *11*(10), e0164434.

Wang, C., Zhang, L., Su, W., Ying, Z., He, J., Zhang, L., Zhong, X., & Wang, T. (2017). Zinc oxide nanoparticles as a substitute for zinc oxide or colistin sulfate: Effects on growth, serum enzymes, zinc deposition, intestinal morphology and epithelial barrier in weaned piglets. *PLoS One*, *12*(7), e0181136.

Xiao, L., Liu, C., Chen, X., & Yang, Z. (2016). Zinc oxide nanoparticles induce renal toxicity through reactive oxygen species. *Food and Chemical Toxicology*, *90*, 76–83.

Xie, Y., Wang, Y., Zhang, T., Ren, G., & Yang, Z. (2012). Effects of nanoparticle zinc oxide on spatial cognition and synaptic plasticity in mice with depressive-like behaviors. *Journal of Biomedical Science*, *19*(1), 14.

Yin, Y., Hu, Z., Du, W., Ai, F., Ji, R., Gardea-Torresdey, J. L., & Guo, H. (2017). Elevated CO2 levels increase the toxicity of ZnO nanoparticles to goldfish (*Carassius auratus*) in a water-sediment ecosystem. *Journal of Hazardous Materials*, *327*, 64–70.

Youssef, F. S., El-Banna, H. A., Elzorba, H. Y., & Galal, A. M. (2019). Application of some nanoparticles in the field of veterinary medicine. *International Journal of Veterinary Science and Medicine*, *7*(1), 78–93.

Zaheer, T., Imran, M., Pal, K., Sajid, M. S., Abbas, R. Z., Aqib, A. I., Hanif, M. A., Khan, S. R., Khan, M. K., ud Din Sindhu, Z., & ur Rahman, S. (2021). Synthesis, characterization and acaricidal activity of green-mediated ZnO nanoparticles against Hyalomma ticks. *Journal of Molecular Structure*, *1227*, 129652.

Zahra, J., Iqbal, S., Zahra, K., Javed, Z., Shad, M. A., Akbar, A., Ashiq, M. N., & Iqbal, F. (2017). Effect of variable doses of zinc oxide nanoparticles on male albino mice behavior. *Neurochemical Research*, *42*(2), 439–445.

Zhao, C. Y., Tan, S. X., Xiao, X. Y., Qiu, X. S., Pan, J. Q., & Tang, Z. X. (2014). Effects of dietary zinc oxide nanoparticles on growth performance and antioxidative status in broilers. *Biological Trace Element Research*, *160*(3), 361–367.

**How to cite this article:** Rahman, H. S., Othman, H. H., Abdullah, R., Edin, H. Y. A. S., & AL-Haj, N. A. (2022). Beneficial and toxicological aspects of zinc oxide nanoparticles in animals. *Veterinary Medicine and Science*, *8*, 1769–1779. https://doi.org/10.1002/vms3.814