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REVIEW ARTICLE
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Assessing the Dual Impact of Zinc Oxide Nanoparticles on Living Organisms: Beneficial and Noxious Effects

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ABSTRACT

Nanotechnology is gaining popularity in the realm of animal management, husbandry, and production. Zinc oxide nanoparticles (ZnO NPs) have been under scrutiny for a considerable duration. These NPs have contributed to advancements in animal agriculture, aquaculture, and veterinary medicine. Consequently, ZnO NPs have emerged as promising antimicrobial agents, especially in the context of rising multi-drug-resistant bacteria. Their heightened effectiveness in addressing a broad spectrum of infections has garnered significant attention. Moreover, Zn, recognized as an essential trace element for numerous biological functions in animals, plays a pivotal role in their overall well-being. These NPs have found utility in sunscreens, and there are assertions that they could serve as supplementary treatments to mitigate the adverse effects of chemotherapy. While ZnO NPs hold promise as anti-inflammatory, anti-diabetic, and anti-cancer agents, it is crucial to be cautious regarding alterations in their dosage, as they can entail significant hazards to multiple organs in animals, including the liver, lungs, and kidneys. In the field of biomedicine, ZnO NPs are widely utilized for disease diagnosis and monitoring owing to their substantial potential. However, their widespread adoption in biomedical applications encounters obstacles because of sporadic toxicity concerns. Indeed, they have been identified as carrying toxicological risks, affecting various bodily organs and systems, such as the liver, spleen, kidney, stomach, pancreas, heart, and lungs. Moreover, adverse effects on the nervous system, lymphatic system, hematological indices, sex hormone levels, and fetal development have been linked to these NPs. In this review, we aim to evaluate the utilization of ZnO NPs in various animal-related applications, considering both their promising benefits and potential risks.

Keywords: Ruminants, Pulmonary Infection, Neurotoxicity, Anti-inflammatory, Antibacterial.

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INTRODUCTION

Nanoparticles (NPs) have a large surface area and other significantly distinct physical, chemical, and biological characteristics when compared to their bulk counterparts, their widespread use of nanomaterial-based technologies has opened a new horizon in material science throughout the previous several decades (Mandal et al. 2022; Ali et al. 2023; Khan et al. 2023; Saif et al. 2023.). The food industry stands to benefit greatly from the rapidly developing science of nanotechnology, which has applications in everything from mechanics to medicine. Nanotechnology is the study of controlling and manipulating matter at the atomic and molecular level, often on a size from 1 to 100nm (Sahoo et al. 2021; Khan et al. 2022; Ullah et al. 2023**;** Naeem et al. 2023).

Because of its low-temperature production, varying morphologies, high crystallinity, powerful optical capabilities, and excellent electrical properties, ZnO NPs are rising in popularity. These NPs have a broad band-gap semiconductor (Khataee et al. 2020). Zinc is an essential trace element that plays a role in many facets of cell metabolism by acting as a catalyst, structural element, and gene expression regulator (Tsang et al. 2021).

Zinc lactate, Zn amino acid, and chelate are examples of organic zinc sources, while zinc sulfate and ZnO are examples of inorganic zinc sources. It is needed for a variety of enzyme-based reactions, metabolic functions, and oxidation-reduction processes (Al Jabri et al. 2022). Organic Zn trumps inorganic Zn in terms of bioavailability (Khataee et al. 2020). It is a powerful antioxidant that inhibits the formation and reactive response of free radicals (Youn and Choi 2022). Damage to cells and degenerative disorders may result (Narayanam et al. 2021).

ZnO NPs are among the most researched NPs because of their many practical applications in the manufacturing of things like ceramic compounds, transparent materials, elastic polymers, ointments,

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lubricants, dyes, and adhesives (Iqbal et al. 2021). In addition, ZnO NPs are cytotoxic, meaning they alter the nucleo-skeleton and cytoskeleton of germ cells, which can lead to DNA damage (Hong et al. 2022). Because of its low-temperature production, varying morphologies, high crystallinity, powerful optical capabilities and excellent electrical properties, ZnO NPs are rising in popularity. ZnO is a broad band-gap semiconductor (Khataee et al. 2020). However, some organic molecules can cause oxidative reactions with ZnO NPs (Pogribna and Hammons 2021).

Rubber, paint, coating, and cosmetics are just a few of the many industrial goods that make use of ZnO NPs. In the recent two decades, these NPs have been more popular in biological applications due to their high biocompatibility, low toxicity, and low cost (Jiang et al. 2018). Cytotoxicity, genotoxicity, photo-genotoxicity, acute toxicity, and carcinogenicity tests on ZnO NPs were all negative (Chauhan et al. 2022). The use of nanotechnology to generate particles in the nanoscale range is partially responsible for the widespread interest in ZnO NPs for their antibacterial activity (Sirelkhatim et al. 2015; Altaf et al. 2023).

ZnO NPs are the most extensively used metal oxide NPs in electrical and optoelectronics due to their unique optical and chemical characteristics, which can be readily modified by modifying the shape and the large band gap (Mandal et al. 2022). Polluted settings, such as those found in mines, electronic waste dumps, and agricultural soils, pose a threat due to the presence of ZnO NPs and heavy metals (Xiao et al. 2022). Due to their biocompatibility, low cytotoxicity, and cost-effectiveness, ZnO NPs have lately been identified as a viable choice for several sectors, including optics, electrics, packaged foods, and medicine (Alhujaily et al. 2022). Using high temperature and pressure conditions, a high price tag and a lack of environmental friendliness are all downsides of the chemical and physical methods now in use-to-use ZnO NPs (Gomaa 2022). Fig. 1 demonstrates the different pathways through which exposure to ZnO NPs can occur, including dermal, oral, and inhalation routes.

Beneficial Effects of ZnO NPs in different Animals

ZnO NPs are one of the most widely used metal oxide NPs because of their high biocompatibility, high economic value, and low toxicity in a wide range of applications (Rahman et al. 2022; Batool et al. 2023). These versatile ZnO NPs find utility in a diverse spectrum of areas, as depicted in Fig. 2, including but not limited to biomedical imaging, antioxidant properties, antibacterial characteristics, drug and gene delivery systems, biosensors, food packaging enhancements, anti-cancer interventions, and antifungal applications.

Ruminants

ZnO NPs have been shown to improve animal performance, feed utilization, antioxidant status, and immunological response as mentioned in Table 1 (Abd El Rahim et al. 2023). In dairy cattle with sub-clinical mastitis, adding ZnO NPs to the feed reduced the somatic cell count (SCC), improved the situation, and increased milk output (Hozyen et al. 2019). Recently, the cattle sector has begun using ZnO NPs as a feed additive because to their significant benefits over regular ZnO, including better antibacterial and bioavailability (Qi et al. 2021). Zn deficiency in Lambs may be treated with small doses of ZnO NPs, which also improves the hemato-biochemical picture and trace element profiles of the plasma and wool. While having very small effects, it also caused developing lambs to acquire weight faster and grow at a faster rate as shown in Table 1 (Elgayed et al. 2022). With no adverse effects on liver functions, total serum proteins, or selenium level, the addition of nano-Zn particles to Livestock feeding regimens boosted growth rate and weight gain performance status in growing Barki lambs. Additionally, iron levels and antioxidant status also increased as a result of it (Abd El Rahim et al. 2023).

Poultry

Birds with increased body weight thanks to nanoparticles. In the diets of poultry, ZnO NPs are a trace mineral that is essential. By administering ZnO NPs to poultry, one can improve growth and performance while simultaneously treating infections with an antibacterial agent (Mohd Yusof et al. 2021). In comparison to birds given the control meal, animals given nutritional supplements containing ZnO NPs at 20, 40, and 60mg/kg food significantly increased body weight, body weight growth, and feed conversion ratio with linear effects ($P \leq 0.05$). ZnO NPs added to the meal at doses of 20, 40, and 60mg/kg linearly enhanced significantly ($P<0.05$) the nutritional digestibility of crude protein, crude fiber, and ether extract as compared to the control group (Abdel-Wareth et al. 2022a) as shown in Table 1.

Furthermore, in Broilers, dietary ZnO NPs may have boosted mRNA expression of insulin-like growth factor 1 (IGF-1) and growth hormone genes (Rahman et al. 2022). ZnO NPs (40mg/kg) added to the feed significantly modulated the immune system of the Broilers, leading to better gut health as measured by an increase in intestinal microarchitecture and cellular count (Ali et al. 2017). ZnO NPs (0.2g/kg meal) also have a cumulative impact on the growth and physiological performance of Japanese Quails, as evidenced by an improvement in the animals' body weight, food intake, and food adaption ratio. In addition, ZnO NPs raise the concentrations of superoxide dismutase, glutathione peroxidase, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, triglyceride, and low-density lipoprotein (Reda et al. 2021) as described in the Table 1. The productivity of laying hens can be enhanced by adding ZnO NPs (80mg/kg) to their diet. Therefore, ZnO NPs may be a more effective source of Zn in food than regular ZnO and can increase zinc absorption in the intestines of older individuals (Abedini et al. 2018).

Fish

The current study found that supplementing the feed of Tilapia (*Oreochromis niloticus*) with ZnO NPs at a dose of 40mg/kg significantly improved the fish's overall health, immunological function, and resistance to illness. It may also have a beneficial effect on hematological profile, oxidative stability, and resistance to viral infections. Our findings suggest that supplementing a natural diet with ZnO NPs at a concentration of 40mg/kg feed will improve tilapia (*O. niloticus*) health, immunity, and disease resistance (Yaqub et al. 2023; Mwafy,et al. 2023). Nano-ZnO improves Tilapia (*O. niloticus)* immune function, health, and disease resistance more than other common inorganic zinc forms diet (Ibrahim et al. 2023). Antibacterial activity of ZnO NPs (15.75g/mL) against fish infections Salmonella aeromonads with *Aeromonas hydrophila* (*A. hydrophila*) (Shaalan et al. 2017). The development of nanotechnology has made available safe and non-toxic ZnO NPs and products that can have beneficial effects in the aquafeed business, such as greater nutritional availability, improved intestinal nutrient absorption, and higher bioactivities (Ibrahim et al. 2023). ZnO NPs improved fish survival and resistance to disease when dosed at 30 and at 60g/g. When ZnO NPs are added to the diet of *O. niloticus,* the fish have a stronger immune response and are less susceptible to sickness caused by *A. hydrophila* (Sherif et al. 2023).

Table 1: Beneficial effects of ZnO nanoparticles in different animals

Animal's species	Doses of ZnO NPs	Effects	References
Ruminants	0.015 to 0.06mg	Improved zinc deficiency, Improved plasma, Body weight gain, Growth rate in lambs	Elgayed et al. (2022)
	15mg/kg and 30mg/kg	Weight gain, Enhanced growth rate, Improvement in antioxidant status in Barki lambs Improved digestibility	Abd El Rahim et al. (2023)
	0.04mg	Reduced clinical mastitis in cows	Hozyen et al. (2019)
Poultry	20, 40, 60mg/kg	Enhanced nutrient digestibility of fibers and proteins in broiler chicken	Abdel-Wareth et al. (2022a)
	0.1, 0.2, 0.3, 0.4mg/kg	Increase in beneficial microbial population	Reda et al. (2021)
Fish	20, 40, 60mg/kg	Immunomodulation Resistance to bacterial disease	Yaqub et al. (2023)
Pigs	400, 800, 3000mg/kg	In weaned piglets, Weight gain, diarrhea rate decreased, plasma zinc level increased, intestinal morphology improved	Wang et al. (2018)
	150,300,450,3000mg/kg	Improved growth performance, intestinal morphology and microbiota, and immunity	Pei et al. (2019)

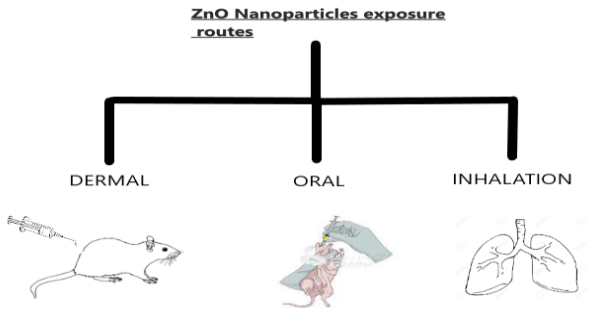

Fig. 1: Exposure Routes of ZnO NPs in Living Organisms: Through the Skin, Oral Ingestion, and Inhalation.

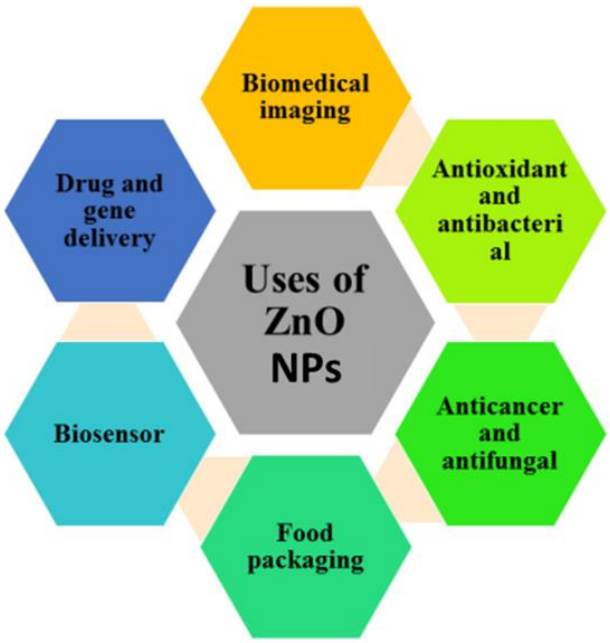

Fig. 2: Beneficial effects of ZnO NPs in the Medical Field industry (Ajay Jyothis 2021).

Pigs

Growth performance of pigs, intestinal morphology and microbiota, and immunity are all affected by ZnO NPs levels much below those used in typical ZnO therapeutics. The ability of nano-ZnO to minimize mineral excretion may be beneficial in solving environmental issues which is mentioned in Table 1 (Wang et al. 2018). ZnO NPs were found to be efficacious at lowering inflammation and improving mucosal barrier function, enterobacterial composition, and intestinal bacterial core in a pig model (Liu et al. 2021). Growth performance, intestinal morphology microbiota, and immunity can all see boosts from exposure to nano-ZnO in Weaned Pigs as indicated in Table 1 (Pei et al. 2019).

Beneficial effects of ZnO Nanoparticles in Experimental Animals

Mice

ZnO NPs (1, 3, and 5mg/kg) alleviate inflammation caused by carrageenan in Mice at all three doses as reflected in Table 2 (Keerthana and Kumar 2020) ZnO NPs anti-diabetic effects in Mice with diabetes mellitus produced by intra-peritoneal (IP) injections. Significant anti-diabetic characteristics of ZnO NPs were demonstrated by their ability to enhance pancreatic islet area volume while decreasing serum TG, LDL, TC and blood glucose (0.1mg/kg) (Amiri et al. 2018). ZnO NPs (0.03mg) remarkably minimize wound size and expedite skin regeneration in mice (Batool et al. 2021) as illustrated in Table 2. Anti-diabetic effects of ZnO NPs induction (40mg/kg) in diabetic Mice (Siddiqui Shafayet et al. 2020).

Rats

ZnO Nanoparticles have positive effects on the heart and neurons of rats. ZnO NPs were shown to prevent diabetes-induced cardiopathy in streptozotocin-induced diabetic Wistar rats at 1, 3, and 10mg/kg (Alkazazz and Taher 2021). In male Wistar rats with streptozotocin-induced diabetes, ZnO NPs (10 mg/kg) exerts anti-diabetic effects as shown in the Table 2 (El-Behery et al. 2019). Blood glucose and insulin levels are improved in diabetic rats after therapy with a modest dosage of ZnO NPs taken orally (1mg/kg bw) (Alasadi 2020). ZnO NPs significantly raised testosterone levels in male Rats, which in turn enhanced reproductive indices. ZnO NPs mitigated doxorubicin-induced testicular toxicity and genotoxicity due to their antioxidant and androgenic attributes (El-Maddawy and Abd El Naby 2019), as detailed in Table 2.

Rabbits

Nano-ZnO can outperform conventional Zn sources at 60 mg/kg in rabbit diets while indirectly reducing environmental effects (Raslan et al. 2020). Supplementing the diet with dietary ZnO NPs (20 to 80mg/kg) can lessen the negative effects of heat stress on Rabbit performance and health. When White New Zealand Rabbits were supplemented with ZnO NPs, growth performance, meat's physical and chemical characteristics, and blood biochemistry parameters all improved according to Table 1 (Abdel-Wareth et al. 2022b).

Table 2: Beneficial effects of ZnO NPs in experimental animals

Animal species	Dosages of ZnO NPs	Effects	References
Mice	1, 3, 5mg/kg	Anti-inflammatory effects	Keerthana and Kumar (2020)
	0.03mg	Wound healing	El-Maddawy and Abd El Naby (2019)
Rats	10mg/kg	Anti-diabetic effects	El-Behery et al. (2019)
	0.02mg	Anti-diabetic activity Maintain cell structure and functions	Alkazazz and Taher (2021)
	3.0mg	Decreased testicular and genotoxicity	Batool et al. (2021)
Rabbits	20, 40, 60, and 80mg/kg	Body weight gain Feed intake increased.	Abdel-Wareth et al. (2022b) Abdel-Wareth et al. (2020)
	100mg	Improved kidney, liver functions Enhanced fertility	

Table 3: Toxic effects of ZnO Nanoparticles in different animals

Animal species	Dosages of ZnO NPs	Effects	References
Goat	0.05mg	Oxidative stress Endoplasmic reticulum stress Autophagy	Wang et al. (2023)
	20mg/kg	Altered liver, kidney histopathology in lambs	Najafzadeh et al. (2013)
Mice	• 0.01, 0.02, and 0.03mg • 5, 50, 300mg/kg • 100,200, 400mg/kg/day	• Cytotoxic effect in ovarian germ cell • Seminiferous tubule diameter, epithelial height and maturation arrest all decrease. • Maternal toxicity	Saber et al. (2021) Talebi et al. (2013) Lee et al. (2016)
Rabbit	0.001-0.1mg	Expression of apoptosis	Abdel-Aziz et al. (2018); Lee and Park (2019); Taha and Ismail (2023)
Fishes	0, 2, 4, 6, 8, 10mg/L	Alterations in hematological parameters and Oxidative stress in *C. Carpio*	Rajkumar et al. (2022)
	0.76mg	Genotoxic effects and increase in oxidative stress in *Grass Carp*	Estrela et al. (2021)

Nano-ZnO at 50mg/kg in the diet of Male Californian Rabbits exposed to high temperatures has been shown to increase their CP and EE digestibility, lactic acid bacteria growth, ALT, AST, creatinine, and testosterone concentrations (Abdel-Wareth et al. 2023). Maximizing productive performance and enhancing FCR in developing New Zealand White Rabbits with the addition of 50mg/kg ZnO NPs food in the premix has been shown to have no detrimental effects (Massoud et al. 2021). ZnO NPs (25g/kg bw) have been proven to mitigate the genotoxic effects of aflatoxicosis in rabbits. ZnO NPs have shown hepatoprotective advantages by scavenging free radicals and boosting the body's antioxidant defenses (Abdel-Wareth et al. 2020).

Beneficial Effects of ZnO Nanoparticles in Vivo Studies

The anticancer effects of ZnO NPs (100,200,300mg/kg) in male Wister rats treated with 1mL of NPs solution for 28 days were validated by the increased expression of P53 and Bax genes, which suggested apoptotic induction in the HUH7 cell line (Rahimi et al. 2019). ESC-bearing Mice induced with three different doses of ZnO Nanoparticles (50, 300, and 500mg/kg bw) alone or in combination with NAC for seven consecutive days act as a protective method for the healthy normal tissue against ZnO NPs' toxicity, without affecting its antitumor activity (El-Shorbagy et al. 2019; El-Hamaky et al. 2023).

ZnO NPs induced in Balb c Mice show that ZnO: Eu NPs lead to increased sperm hyperactivity and is also able to overcome the Blood-testis barrier (BTB) with their subsequent accumulation in testes (Kielbik et al. 2019). Adult male albino rats were separated into three groups: control, CP treated, and CP + ZnO NPs treated. The CP group received CP (5mg/kg/day), whereas the CP + ZnO NPs group received both CP and ZnO NPs (5mg/kg/day). ZnO NPs successfully reduced CP-induced testicular histological, biochemical, and genetic changes (Anan et al. 2018). Nano-ZnO particles have antimicrobial properties, due to its bactericidal effects on a wide spectrum of bacteria and fungi, ZnO NPs may find application as therapeutic agents. Therefore, conventional antibiotics, which frequently lead to the development of multidrug-resistant bacteria, may be superseded (Mohd Yusof et al. 2019; Samy et al. 2022; Umair et al. 2022; Shnawa et al. 2023; Akhtar et al. 2023).

In adult male rats, ZnO NPs show a protective effect against cyclophosphamide-induced testicular damage (Anan et al. 2018). Lipid peroxidation, oxidative stress, and liver fibrosis are all reduced in DMN (2µL/100g bw) treated Rats when ZnO NPs (50mg/kg) are administered thereafter. Serum levels of ALP, AST, and LDH are all reduced (Rani et al. 2018). Nano-ZnO has been found to have anti-diabetic and antioxidant properties, making them a novel Zn delivery agent also treatment with ZnO NPs, restores the architecture of the seminiferous epithelium and Leydig cell (El-behery et al. 2019).

Beneficial effects of ZnO NPs in Vitro Studies

The in vitro chemotherapeutic efficiency of ZnO NPs suggests that they are useful for treating triple-negative and drug-resistant breast tumors (Abu-Huwaij et al. 2022; El-Dawy et al. 2022; 2023). The use of ZnO NPs (20nm to 90nm) has an antifibrotic medication in glaucoma filtration surgery by efficiently enhancing collagen lattice contraction in HTFs (Yin et al. 2019). The antibacterial activity of ZnO NPs (<50 nm) was also described by Singha et al. against murine fibroblast 3T3 cells (Singha et al. 2019). ZnO NPs inhibit the development of *Aeromonas salmonicida, Yersinia ruckeri*, and *Aeromonas invadans* when tested in vitro at concentrations of 15.75, 31.5, and 3.15g/mL, respectively. This demonstrates the antimicrobial properties of ZnO NPs (Shaalan et al. 2017). The in vitro release of Biocompatible ZnO Nanoparticles (70 to 100nm in size)laden nano hydrogel with high encapsulation efficiency show antibacterial action under in vitro conditions (Chopra et al. 2015) as shown in Table 3.

Toxicity of ZnO NPs in Animals

The organs most affected by ZnO NPs exposure were the liver, kidneys, lungs, and spleen, and this was true independent of the route of administration. ZnO NPs are specific to certain tissues and organs (Fujihara and Nishimoto 2023). As a result of the hemolysis brought on by ZnO NPs, erythrocyte parameters, platelet count, serum haptoglobin content, and some pathological lesions in the liver were all negatively impacted (Ibrahim et al. 2017). ZnO NPs have been shown to reduce spermatozoa parameters, especially at higher doses. The sperm toxicity of ZnO NPs is time and dosage-dependent (Halo Jr et al. 2021).

Mice

By increasing ROS production and significantly ($P \leq 0.05$) upregulating the expression of pre-meiotic germ cell markers while downregulating the expression of meiotic and post-meiotic markers, ZnO NPs (10, 20, and 30g/mL) produced in vitro cytotoxicity in mouse ovarian germ cells according to Table 3 (Saber et al. 2021). There is evidence that ZnO NPs are harmful to the brain and nervous system. When ZnO NPs (100mg/kg bw) were given IP, catalase and SOD activity were considerably reduced, whereas MDA levels were elevated ($P \leq 0.05$). ZnO-Nanoparticles were hypothesized to cause behavioral issues due to severe histological changes (edema and satellitosis) in the brain (Rahdar et al. 2020). ZnO NPs have been shown to induce apoptosis and autophagy through the production of oxidative stress in vitro experiments. Reducing cell viability and increasing apoptosis by blocking autophagy in Mouse Leydig TM3 cells (Shen et al. 2019).

Goats

Since ZnO NPs are toxic to normal mammalian cells in Goats, it is crucial to investigate its safe use in the feed and food industries (Wang et al. 2023). Cells exposed to ZnO NPs develop reactive oxygen species (ROS), leading to oxidative stress. Meanwhile, the expression of death receptor-related genes (TNF, TNFR1, FADD, Caspase 8, and Caspase 6) increases, indicating that the death receptor-mediated extrinsic apoptotic pathway was active as described in Table 2.

Rabbits

The spermatozoa parameters were reduced at higher doses of ZnO NPs (Halo Jr et al. 2021). Kidney tissue has been exposed to the harmful effects of ZnO NPs. Proximal convoluted tubules were destroyed, resulting in cytoplasm vacuolation, intratubal protein accumulation, and brush border loss. Additionally, there was congestion and glomerulus enlargement in the renal corpuscles (Abdel-Aziz et al. 2018), as shown in Table 3. The cerebral cortex, hippocampus, and cerebellum of Rabbits receiving ZnO NPs (600mg/kg) treatment displayed degenerative, necrotic alterations in neurons along with a vascular and inflammatory response (Taha and Ismail 2023).

Fish

Superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione S-transferase (GST), and glutathione (GSH) activity all increase in *C. carpio* after exposure to ZnO NPs, as do other antioxidant enzymes (Raza et al. 2022) as mentioned in Table 3 (Rajkumar et al. 2022) ZnO NPs have negative effects on *O. niloticus*, including growth inhibition, hepato-renal toxicity, protein depletion, immunotoxicity, and oxidative damage (Hamed et al. 2022). *Grass Carp* are susceptible to the oxidative stress and genotoxic effects caused by exposure to ZnO NPs (760g/L) (Estrela et al. 2021). Bighead carp have sudden anomalies in behavior after being exposed to high concentrations of zinc oxide Nanoparticles, and they die as a result. Sub lethal ZnO NPs exposure results in oxidative stress, manifested as decreased SOD and increased TBARs levels due to an overabundance of ROS (Aziz et al. 2022).

Rats

SOD activities are upregulated, and histological changes are induced in the brains of Wister rats due to exposure to ZnO NPs, leading to aberrant behaviors (Rahdar et al. 2020).

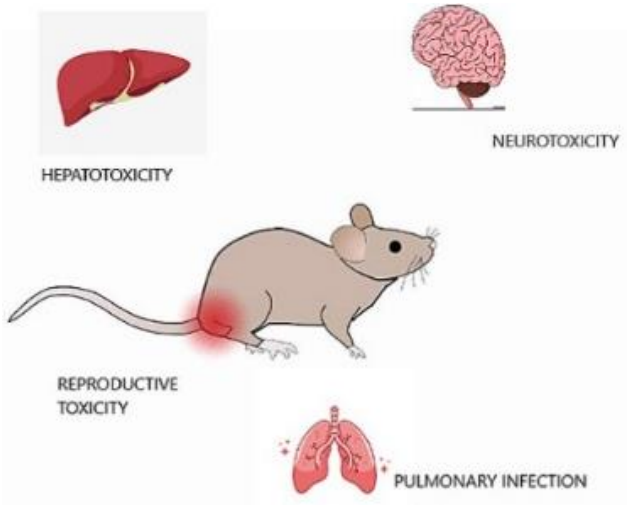

Fig. 3: Hepatoxicity, Neurotoxicity, Reproductive toxicity, and Pulmonary Infection by induction of ZnO NPs.

The BTB proteins are disrupted, and sperm DNA is damaged due to the increased production of ROS caused by ZnO NPs (Akram et al. 2021; Rani et al. 2023). Morphological shifts in the structure and ultrastructure (Hamam et al. 2022). The total number of cells, total protein content and hydroxyproline content were all raised, but body weight was decreased, when ZnO NPs were injected intratracheally into Mice at 200, 400, and 800mg/kg (Wang et al. 2017). Fig. 3 illustrates the adverse toxicological impacts on rats resulting from their exposure to ZnO NPs, including hepatotoxicity, neurotoxicity, reproductive toxicity, and pulmonary effects. Developmental harm occurs in pregnant female rats exposed to 100, 200, or 400mg/kg/day of ZnO NPs from gestational day 5 to 19. Embryo-fetal development and maternal toxicity are both affected by ZnO NPs at 200mg/kg/day (Hong et al. 2014).

ZnO Nanoparticles Induced Toxicity in Vivo Studies

Studies of ZnO NPs in mice at three different doses (orally administered 10, 50, and 300mg/kg) reveal hepatotoxicity and nephrotoxicity (Srivastav et al. 2019). ZnO NPs increase GGT and LDH activity, oxidative stress, inflammation, and capillary-trophic insufficiency in male Wister rats (Sizova et al. 2019). The expression of the aryl hydrocarbon receptor (AhR) and its downstream target cytochrome P450 1A1 (CYP1A1) in macrophages in Mouse lung epithelia is upregulated in response to ZnO NPs (5, 20 and 80µg /mice suspended in 30 µL of distilled water) exposure in vivo (Ho et al. 2017).

Lung and systemic inflammation, dyslipidemia, raised serum HO-1 and PECAM-2 levels, and aortic pathological damage are the results of intratracheal injection of ZnO NPs (0, 12.5, 25, 50, 100, and 200µg/mL) suspension in male Wister rats with a high-fat diet (as a positive control). Atherosclerotic alterations, such as NPs phagocytosis and lung inflammation are the result of exposure to ZnO NPs

(Yan et al. 2017). Testicular weights, testosterone levels, sperm quality, and morphometric parameters were all drastically reduced in ZnO-intoxicated animals (Rafiee et al. 2019). Degeneration, growth and survival were negatively affected by ZnO NPs (100nm as 10mg/mL sol) in a dose- and time-dependent way in mice. It causes reproductive toxicity and infertility (Huang et al. 2022).

ZnO Nanoparticles Toxicity in Vitro Studies

The cytotoxicity of ZnO Nanoparticles (measuring 20nm or 90 to 200nm as 1mg/mL) was seen in a variety of cell lines inducing, increased mitochondrial dysfunction caused by newly synthesized ZnO NPs was the primary cause of the acute cytotoxicity they produced (Wang et al. 2019). In vitro studies have shown that even at modest concentrations of ZnO NPs (12.5ppm), they are genotoxic. Additionally, ZnO NPs are lethal to lymphocytes at high concentrations (500ppm and beyond) (Akbaba and Türkez 2018). It has also been found that ZnO NPs (67nm as 1mg/mL) are toxic to the nervous system. Autophagy and apoptosis are triggered by ZnO NPs, and the generation of inflammatory cytokines is prompted (Song et al. 2019). The in vitro investigations showed that ZnO NPs is toxic to developing oocytes in the fetus. ZnO NPs injected intravenously 16mg/kg bw in 12.5 dpc pregnant mice on two consecutive days causes DNA damage in pachytene oocytes in fetal ovaries, as well as decreases primordial follicle construction and folliculogenesis dynamics in offspring ovaries (Zhai et al. 2018).

Conclusion

Nanotechnology has opened up exciting possibilities for improving human and animal health. Nanomaterials offer numerous advantages over traditional compounds, enhancing animal management, husbandry, and production. ZnO NPs have a well-established history in veterinary medicine and animal production, contributing to improved animal health and enhanced milk and meat production. Their use as supplements in animal feeds is recommended, but strict regulation is essential to prevent Zn accumulation and associated toxicity. However, caution is vital, as systemic distribution of ZnO NPs can lead to toxicity in various organs and systems, depending on factors such as concentration, dosage, administration route, and exposure duration. Therefore, ZnO NPs hold significant therapeutic promise, their safe and controlled application is crucial to maximize benefits while minimizing potential harm in both human and animal health contexts.

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