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Antioxidant Properties and Toxic Risks of Using Metal Nanoparticles on Health and Productivity in Poultry

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ABSTRACT

Metal nanoparticles (NPs) are introduced into various fields of science, particularly poultry farming. Supplementation of metal salts in nanoform can increase the profitability of poultry farming by enhancing meat and egg production. Although their toxic parameters pose limitations on their use, many studies have evaluated the effects of using metal NPs in modern poultry farming on health, productivity, metabolism, and especially antioxidant properties. In addition, the peculiarities of their toxicokinetic and recommended doses that meet safety criteria in practical activities are highlighted. Zinc oxide NPs are one of the most studied compounds in the poultry industry. Their pronounced antioxidant properties, positive effect on productivity and homeostasis of poultry, egg quality, and immune status have been experimentally confirmed. Copper oxide NPs have similar properties but are limited in usage due to their toxicokinetics. Silver and gold NPs emerge as potential alternatives to antibiotics and could solve the resistance problem of microorganisms to antibiotics. Other important NPs used in poultry are Iron and Calcium. In their nanoform, these NPs exhibit high bioavailability, which allows for efficient absorption and utilization by poultry. The methods used to synthesize these nanoparticles make it economically viable to incorporate them into poultry diets, reducing overall expenses compared to similar macroergic compounds. Manganese and chromium NPs positively affect sperm survival in turkeys during refrigerated storage and contribute to increasing the resistance of the broiler chickens' body to heat stress and normalizing the metabolism of sex hormones. In conclusion, the application of metal nanoparticles to poultry is a promising research direction, aiming at the development of feed additives, antibiotics, and growth stimulants due to their antioxidant, bactericidal, and immunomodulatory effects.

Keywords: Antioxidants, Health, Metal Nanoparticles, Poultry, Productivity, Toxicology

INTRODUCTION

The poultry industry is a part of the agri-food sector, playing a vital role in ensuring food security (Ahmad et al., 2022). Advancements in technology have led to the development of innovative feed additives based on nanomaterials, as well as the introduction of nano vaccines and diagnostics to increase the efficiency of the final poultry product (Skliarov et al., 2021a). Modern science, specifically nanobiotechnology, is actively engaged in improving diagnostic and therapeutic measures and addressing the solution of nutritional problems in animal husbandry and poultry farming using nanotechnological means (Patra and Lalhriatpuii, 2020).

Nanoparticles (NPs) are becoming widely used in poultry farming due to their advantageous characteristics, such as low toxicity, high bioavailability, significant surface area compared to macroergs, and prolonged action (Rana, 2021). Various mineral NPs have become a significant focus of research in animals, including poultry. It should be noted that mineral NPs are characterized by small sizes and exhibit a wide range of properties due to increased digestibility in the gastrointestinal tract and the effect on target tissues of the body (Patra and Lalhriatpuii,

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2020).

Nanoparticles have a positive effect on the health, productivity, quality, and safety of their products due to the regulation of hematopoietic vascular, digestive, and excretory. One of the most significant benefits is their ability to protect against free radical oxidation and their immunomodulatory properties (Michalak et al., 2022). Although there are numerous publications on the effects of NPs on animals and poultry, research specifically focused on the impact of trace elements in nanoform on farm animals remains limited. However, several studies have pointed out the positive changes (feed digestibility and live weight gain) occur due to the use of trace elements in feeding various types of poultry. Of particular importance is the use of silver (Ag), copper (Cu), and zinc (Zn) NPs as an alternative to antibiotics against the main pathogens of poultry infectious diseases, such as *Salmonella* and *Campylobacter* (Hassan et al., 2020). In addition, the use of NPs with an enzyme-like effect (for example, similar to glutathione peroxidase) will contribute to preventing infertility and improving the qualitative indicators of various species of poultry sperm (Koshevoy et al., 2021).

It should be noted that the results of some studies have indicated that metal NPs *in vivo* and *in vitro* experiments can negatively affect the intestinal function and health of poultry (Kolba et al., 2020). Another application of NPs in poultry lies in developing nano vaccines to replace traditional viral vector vaccines. This highlights the significant antiviral potential of NPs, which can be attributed to their unique physical properties and pharmacokinetics (Fawzy et al., 2021). Metal NPs play a notable role in stimulating the immune system, especially its humoral link. It should be noted that the use of NPs as immunomodulators will prevent an increase in the resistance of poultry to infectious diseases (Ren et al., 2021).

The authors of the current study opine that a promising direction of research for modern poultry farming involves using NPs of metal oxides and salts with antioxidant properties and low toxicity as well as developing safe regulations for their use. Therefore, the aim of this study was to explore the toxic risks and antioxidant properties of metal NPs, and their impact on health and productivity when applied to poultry.

Metal nanoparticles in poultry farming

Regarding the use of metal NPs in poultry farming, many studies indicate that nanometals exhibit increased bioavailability compared to their macroergic counterparts. Of particular significance are their unique antioxidant properties, which are not commonly found in traditional forms of metals (Koshevoy et al., 2022).

Metal NPs are widely used in treating, diagnosing, and preventing diseases of various etiologies (Koshevoy and Naumenko, 2023). It is known that the deficiency of some essential metals leads to the occurrence of many pathological disorders. It is shown that most diseases are accompanied by significant changes in the balance of metals and trace elements, and the introduction into the body leads to therapeutic results (Skliarov et al., 2021b).

It has been established that NPs have a high biological activity, and it is necessary to take into account the factors (form-factor, geometry, solubility, dimensions) the design of which, in turn, will allow to adjust the activity of NP metals if necessary. For the synthesis and application of NPs, it is necessary to use a comprehensive, safe, and effective approach to assess possible health and environmental risks. The unique parameters (physical and chemical) of metal NPs allow for obtaining special modulations of absorption mechanisms, which will solve the problem of mineral antagonism in the poultry intestine (Patra and Lalhriatpuii, 2020). The NPs can improve the immune response of the chicken’s body and digestion due to the normalization of the digestibility of nutrients from feed, contributing to effective feeding and decreased rate of early embryonic mortality (Givisiez et al., 2020).

Their bioavailability usually decreases when passing through the gastrointestinal barriers, the intestinal mucosa, and the liver (Skliarov et al., 2021c). Depending on the size, NPs can transit through the digestive tract without being absorbed by the body, or penetrate through the intestine and enter the organs and tissues with the bloodstream. The addition of metal NPs to the diet of broilers improved the hatchability of chickens and their growth, optimized immune responses, and reduced oxidative stress due to NPs effects on the antioxidant defense system (Michalak et al., 2022).

Statistical analysis

In conducting a comprehensive review of the scientific literature to assess the toxic risks associated with using metal NPs for poultry, as well as evaluating their antioxidant properties, the authors of this study analyzed the results presented in 70 articles sourced from the scientific databases Scopus and PubMed. The selection of these articles focused primarily on publications from the last 10 years, utilizing specific metal NPs, poultry, antioxidants, health, and productivity. Following the compilation of relevant data, the results were processed and organized based on the metal-forming principle.

Zinc nanoparticles

Zinc oxide nanoparticles (ZnO-NPs) are considered safe and stable antimicrobial agents that can inactivate bacteria through several potential mechanisms of action (Hakeem et al., 2020). In addition, ZnO-NPs serve as an alternative source of the mineral zinc in poultry diets. Depending on the dosage, form factor, and size, they can increase productivity, normalize hormonal balance, and exert an antioxidant effect. The toxicological parameters of zinc and its compounds can cause an oxidative imbalance, and initiate oxidative modifications of lipids and proteins, leading to damage to cell membranes and mitochondria, as well as negative effects on DNA. The toxic effect of NPs depends on the dose, size, and shape, and is sometimes more toxic than similar macro compounds.

According to Mahmoud et al. (2020), the use of ZnO-NP in low doses accelerates the weight gain of the bird and improves the digestibility of all dietary components, without compromising their resistance to diseases. Different doses of ZnO-NP could affect the change in the relative weight of the stomach, compared to the intact bird. At the same time, a low dose (10 ppm) of ZnO-NP increased the weight of the spleen and the weight of the bursa (in all groups of poultry), compared to the control group. It should be noted that a high dose (40 ppm) of ZnO-NP contributes to the increase in pH, reduced meat color, and improved broilers' resistance to Newcastle disease (Mahmoud et al., 2020).

The use of dietary supplements containing ZnO-NPs at doses ranging from 20 to 60 mg/kg is beneficial for broiler chickens, especially under heat-stress conditions. These supplements have demonstrated significant improvements in body weight gain, feed digestibility, and carcass characteristics of the birds. Notably, ZnO-NP supplementation enhances the functions of the digestive tract and the excretory system. The administration of ZnO-NPs at these doses does not lead to a toxic effect on serum levels of trace elements and thyroid hormones compared to intact controls (Abdel-Wareth et al., 2022).

The antioxidant properties of these NPs depend on their quantity in the diets of broilers, leading to a compensatory effect on the redox status of the serum of birds and their tissues. In high doses (40-60 mg/kg body weight), ZnO-NPs cause intensification of lipoperoxidation (an increase in the content of thiobarbiturate-active products) in the femoral muscles of broiler chickens 7 days after death, indicating that ZnO-NPs induces a system of antioxidant protection in muscle tissues. The use of ZnO-NP reveals antioxidant properties and an anti-stress effect, evidenced by a decrease in the level of the stress hormone (corticosterone) in blood when the bird is kept in conditions with increased environmental temperature. At the same time, ZnO-NPs can mitigate the negative effects of thermal stress, as a result of which further research is necessary for introduction into poultry diets (Ramiah et al., 2019).

Zhao et al. (2014) found that total antioxidant capacity (TAC) in the serum and liver tissue of broilers was significantly higher in the ZnO-NPs (20 mg/kg) group at all time points, as compared to the intact control group. Additionally, in the 60 mg/kg and 100 mg/kg ZnO-NPs groups, the TAC was significantly higher in blood serum on days 28 and 35, and in liver tissues on days 21 and 28. Compared to the control, the activity of copper-zinc superoxide dismutase (SOD) was significantly higher in the blood on days 28 and 35, and in the liver tissues after 21 days, specifically in the 60 mg/kg and 100 mg/kg ZnO-NPs groups. The malondialdehyde (MDA) content in blood serum and liver tissues decreased significantly in the 20, 60, and 100 mg/kg ZnO-NPs groups, compared to the control group.

The SOD activity in the liver, pancreas, and blood plasma increased significantly in the chickens treated with ZnO-NPs. The MDA content in eggs was significantly reduced in the ZnO-NPs treated groups. It was found that ZnO-NPs as a dietary supplement could improve the productivity of laying hens, and levels of 40 to 80 mg/kg ZnO-NP are optimal concentrations (Abedini et al., 2018b).

Dietary supplementation to broiler chicks ZnO-NPs increased TAC, and 80 mg/kg ZnO-NPs decreased MDA content in the small intestinal mucosa, compared to the $ZnSO_4$ group. In contrast, dietary ZnO-NPs did not alter the mRNA expression of superoxide dismutase, catalase, glutathione peroxidase, glutathione S-transferase, heme oxygenase-1, and NADPH plus quinone oxidoreductase 1. No significant difference was found in individual mineral concentrations (Mn, Cu, Fe, and Zn) in the liver among the $ZnSO_4$ and ZnO-NPs groups. However, 160 mg/kg ZnO-NPs increased fecal Zn, Fe, and Cu, but did not affect fecal Mn (Zhang et al., 2022). Generally, the use of these NPs as correctors of antioxidant protection and scavengers of oxygen radicals is an effective alternative to macroergic antioxidants. It should be noted that the oral administration of ZnO-NPs does not have a negative effect on the immune status and DNA integrity in broilers. The study by Mahmoud et al. (2021) indicated minor liver histopathological changes and DNA damage. However, the treatment did not significantly affect the levels of IgG, IgM, and interferon-gamma. Results of a study conducted by Ramiah et al. (2020) indicated that dietary ZnO-NPs altered the gene expression of *cholecystokinin* (ileum), heat stress proteins (HSP) 70 (jejunum and ileum), and HSP 90 (duodenum, small intestine, and ileum). The interaction between ZnO-NPs concentration and temperature in the duodenum and stomach influenced ghrelin gene expression.

It was also found that 20 ppm ZnO-NPs increased calcium (Ca), low high-density cholesterol, and decreased urea and triglyceride levels. Moreover, 40 ppm ZnO-NPs increased creatinine. Hematological and immunological parameters showed significant dose-dependent modulation by ZnO-NPs supplementation. The phagocytic activity, phagocytic index, and levels of IgM and IgG were all influenced by the dosage of ZnO-NPs. The best values for these parameters were observed in broilers that received 5 and 10 ppm ZnO-NPs/kg diet, followed by the 20 ppm group. So, to eliminate the risk of heat stress of broilers in the summer season, ZnO-NPs should be added to the diet in a dose of no more than 10 ppm/kg of diet (Dosoky et al., 2022).

For the first time, Zhang et al. (2017) reported that intact NPs had a different effect on the egg yolk proteome, compared to Zn^{2+}. A total of 37 proteins were specifically regulated by ZnO-NPs (50 mg/kg), 22 proteins were altered exclusively by $ZnSO_4$ (similar dose), and 17 proteins were regulated by both ZnO-NPs and $ZnSO_4$. In addition, changes in protein levels due to ZnO-NPs in egg yolk may affect the nutritional value of egg yolk and embryonic development. The ZnO-NPs only slowed the laying rate at the beginning of the laying period. The ZnO-NPs did not affect egg protein or water content, slightly reduced egg physical parameters, such as shell thickness and porosity (12-30%) and trace elements (20-35%) after 24 weeks of treatment. However, the lipid content in the yolk significantly decreased under the influence of ZnO-NPs (from 20 to 35%). The mechanism of action of yolk lipid-lowering ZnO-NPs is that they decrease lipid synthesis and increase lipid digestion (Zhao et al., 2016).

Egg laying and egg weight were significantly higher in the ZnO-NPs treated groups. In addition, eggshell thickness and shell strength increased in the ZnO-NPs group, compared to the other groups. Furthermore, the addition of Zn reduced egg loss. There were significant differences between zinc deposition in the tibia, liver, pancreas, eggs, and feces. The addition of ZnO-NPs supplements to the diet of broiler increased SOD activity in the liver, pancreas, and plasma, but decreased MDA content in eggs (Abedini et al., 2018a).

According to the results of Mesak et al. (2018), ZnO-NPs did not affect the locomotor activity of chicks and did not cause anxiolytic or anxiogenic effects on birds in an open-field test. However, based on the lowest cluster score recorded during the social aggregation test, chicks exposed to ZnO-NPs failed to recognize predatory threats, compared to the control group. The findings highlighted the challenges in evaluating the effects of introducing NPs on the behavioral characteristics of birds. While these indicators play a crucial role in regulating higher nervous activity, their complexity makes the assessment process difficult. The higher concentration of Zn in the brains of animals exposed to ZnO-NPs indicates the ability of these NPs to cross the blood-brain barrier even at low concentrations. Between 1 and 42 days of age, broiler chickens fed 100 mg/kg ZnO-NPs showed lower feed intakes and feed conversion ratios than controls. The amount of Zn accumulation in the liver was significantly higher in all treatment groups than in breast and thigh muscle tissues regardless of temperature conditions (both at normal temperature (control group) and under conditions of heat stress (experimental group, Ramiah et al., 2020).

Adding ZnO-NPs to the sperm storage medium can be introduced as an effective method to preserve the quality of rooster sperm during the cooling period. Extender supplementation with 100 μg/ml ZnO-NPs showed higher total motility, progressive motility, activity mitochondria, viability, membrane integrity, and lower lipid peroxidation, compared to other groups during 22 and 45 hours of refrigerated storage. The fertility rate of 22-hour chilled sperm samples was higher in the ZnO-NPs groups, compared to the control group (Khodaei-Motlagh et al., 2022).

A positive effect of metal oxide NPs, such as ZnO-NPs, ZnO_2-NPs, and TiO_2-NPs, against multi-resistant and/or pan-resistant strains of *staphylococcus (S.) aureus* has been observed. ZnO_2-NPs exhibited higher inhibitory activity against *S. aureus* strains, compared to ZnO_2-NPs and TiO_2-NPs. The anti-inflammatory activity results suggest that ZnO_2-NPs are a lead compound for developing an alternative antimicrobial agent against drug-resistant and virulent *S. aureus* isolates (Ali et al., 2021).

Copper nanoparticles

Copper is an important vital element playing a role in different physiological processes, such as hemoglobin synthesis, hematopoiesis, bone formation, and functions of the nervous system. It also is a part of the enzymes tyrosinase and cytochrome oxidase (El-Sabry et al., 2021).

Copper nanoparticles (CuO-NPs) have a small size and high surface-to-volume ratio, so they are relatively bioavailable. Sharif et al. (2021) demonstrated the potential effects of CuO-NPs on growth, antioxidant status, immune system, nutrient digestibility, and feed conversion ratio in poultry. Using small concentrations of CuO-NPs as a feed supplement does not negatively affect probiotic strains, and important normal microflora of poultry (*Lactobacillus, Enterococcus, Enterobacterium*). The positive effect of Cu is related to the low level of dissociation of NPs since biologically active ions are released more slowly, creating a prolonged effect of exposure (Sizentsov et al., 2018).

A comparative analysis of the influence of Cu sources on the improvement of energy and nitrogen use has indicated the dominance of the influence of CuO-NPs over $CuSO_4$ (Scott et al., 2018). Blood cholesterol, urea, and glucose levels were reduced by CuO-NPs treatment, compared to other groups. With the addition of Cu supplement to the diet, the relative weight of the liver was reduced, and the Bursa of Fabricius was enlarged. The Cu excretion decreased only in chicks (using as a water supplement in a dose of 50 mg/kg CuO-NPs with 20 mg/kg of water). Immune genes were not affected by the treatment. However, the administration of CuO-NPs *in ovo* is more effective for broiler performance than the administration of CuSO4 or using CuO-NPs and/or CuSO4 as a water supplement (Scott et al., 2018).

Morsy et al. (2021) showed a dose-dependent increase in the levels of MDA, Cu content, percentage of DNA fragmentation, and microscopic estimations of different organs of the chickens treated with CuO-NPs. The histopathological changes, decreasing weight gain, food conversion ratio, catalase activity, and antibodies titers of both New Castle and Avian Influenza viruses were observed in birds treated with CuO-NPs with variation in severity.

CuO-NPs used as a feed supplement for poultry, affected the assimilation of mineral elements. Thus, the oral administration of CuO-NPs to chickens in doses of 5, 10, and 15 mg/l leads to its accumulation in the intestinal walls. The highest level of Cu NPs application increased the content of Cu in the blood plasma of birds. An *in vitro* study showed that Cu accumulated in the intestine reduced Ca and Zn absorption but had no effect on iron absorption (Ognik et al., 2016).

CuO-NPs exhibit superior pro-angiogenic capabilities, compared to $CuSO_4$ salt. Its significant effects on the mRNA concentration and on the mRNA gene expression of all pro-angiogenic and proliferative genes at the molecular level have been confirmed by Mroczek-Sosnowska et al. (2015).

According to Sawosz et al. (2018), using CuO-NPs instead of traditional CuSO4 supplements, the amount of Cu provided to the animals is decreased by 75 %, but this reduction does not negatively impact their growth. At the same time, it increasingly reduces the release of Cu into the environment. The CuO-NPs supplement linearly increases body weight, average daily weight gain, and feed intake in broiler chickens. The levels of uric acid, blood glucose, and feed conversion ratio decrease linearly with the addition of CuO-NPs to the diet.

Using CuO-NPs supplement increases weight, length, diameter, weight/length index of the leg, and tibiotarsal index in broiler chickens. It also improves the muscle parameters of broilers, pH, fiber diameter, fiber cross-sectional area, bundle diameter, and bundle cross-sectional area. The concentrations of Cu, iron, Ca, and phosphorus increased in the blood after administration of the CuO-NPs (Abdullah et al., 2022).

The results of Kozłowski et al. (2018) showed that reducing Cu levels from 10 mg/kg to 2 mg/kg in the diet of turkeys did not worsen their growth performance, but weakened the antioxidant protection. Dietary supplementation of Cu at a dose of 20 mg/kg induced an oxidation reaction and inhibited antioxidant protection to a greater extent than at 2 mg/kg. The CuO-NPs dietary supplements also have a more positive effect on carbohydrate metabolism and antioxidant status in turkeys, compared to $CuSO_4$. The analysis of the antioxidant and metabolic status of young turkeys showed that Cu at the dose of 10 mg/kg was an optimal level.

The high level of phagocytic activity, serum lysozyme activity, and activation of immunomodulatory genes, including NF-κβ, PGES, IL-1β, TGF-1β, IFN-γ, *BAX*, and *CASP8* demonstrate a significant enhancement of the immune response in chickens treated by CuO-NPs under the normal temperature (El-Kassas et al., 2018). The responses between two tested broiler strains (Ross 308 and Cobb 500) were different, especially in terms of gene expression. CuO-NPs reduced heat stress-induced inflammatory conditions in broilers. This is evidenced by low gene expression, the absence of degenerative changes in the spleen, and an altered ratio of heterophils and lymphocytes. Supplementing chickens' feed diets with CuO-NPs is recommended, particularly when feed is supplemented with 50% of the required Cu amount. This addition is especially beneficial at normal housing temperatures as it enhances the immune response of birds, particularly during heat stress. The use of CuO-NPs helps reduce degenerative changes induced by heat stress (El-Kassas et al., 2018).

According to Mroczek-Sosnowska et al. (2017), the femurs from the CuO-NPs group exhibited increased weight and volume, and they displayed significantly higher resistance to fracture when compared to the control group. CuO-NPs helped the proliferation of PCNA-positive cells in the long bones of chickens. A higher number of PCNA-positive cells in the bones of chickens treated by CuO-NPs compared to the control group (137 and 122, respectively) suggested a stimulating effect during embryogenesis.

Silver nanoparticles

Argentum is necessary for the functioning of the endocrine glands, brain, liver, and other organs (Hassan et al., 2020). It is the most deficient trace element and the best conductor of heat and electricity among metals. Argentum is a heavy metal with a negative effect on the body. With prolonged use, Ag accumulates in the body and causes toxic reactions. Silver nanoparticles (Ag-NPs) have antimicrobial activity and are potential candidates for replacing antibiotics in animal husbandry (Gallocchio et al., 2017).

The Ag-NP is a precipitated form of metal ions constantly generated and removed from surfaces when they bind to biological substrates. High concentrations of ions are locally created at the surface of the particles. They are harmful to microbes, but harmless to the organism. At the same time, it provides a milder, prolonged action of Ag cluster and colloid product (Shaikh et al., 2021).

Ag-NPs have a positive effect on the integrity of the intestine without affecting the immune organs. However, some residue of these particles remains in chicken muscles, necessitating further studies on the concentration and size of NPs, as well as the route of administration and withdrawal time to prevent any potential harm to the chicken muscles (Salem et al., 2021).

The supplementation of Ag-NPs improves the growth performance of broiler chickens, as evidenced by higher body weight, increased muscle mass, and enhanced feed efficiency. Notably, acid-insoluble ash digestibility increases significantly, and there is a tendency for increased Ag digestibility. In addition, various indicators have indicated significant improvements, including triiodothyronine content in blood plasma, muscle Ag and nitrogen content, and mRNA levels in muscle tissue such as insulin-like growth factor-1, glucose transporters, citrate synthase, and glutathione peroxidase (GSH-Px). However, no changes have been observed in mRNA levels of atrogin-1, fatty acid synthase, acetyl-CoA carboxylase, lactate dehydrogenase, and carnitine palmitoyl transferase 1A (Saleh and El-Magd, 2018). In a 22-day *in vivo* investigation involving oral administration of 20 nm spherical Ag-NPs coated with polyvinylpyrrolidone to chickens, Ag was found to accumulate in the liver and yolks, while no significant accumulation was observed in muscles, egg protein, and kidneys of the experimental group (Gallocchio et al., 2017).

The surface of Ag NPs is easily oxidized in biological systems, leading to the release of the toxic Ag^+ ion. These ions interact with nucleic acids, lipid molecules, and proteins, inducing oxidative stress and DNA damage. Consequently, the antioxidant systems are depleted as a result of this process (Siddiqi et al., 2018).

A study by Dosoky et al. (2021) indicated no toxicity in broiler embryos after administration of a solution containing 50 mg/kg of Ag-NPs. Moreover, Ag-NPs had no effect on the activity of liver transferases (ALT, AST), alkaline phosphatase, and serum cholesterol, glucose, and triacylglycerol concentrations. Ag-NPs were not detected to cause genotoxicity in liver DNA, as indicated by the concentration of 8-oxo-2'-deoxyguanosine, a biomarker of oxidative stress and associated DNA damage. The results demonstrate that low doses of Ag-NPs are safe for poultry with limited or zero toxicity (Xu et al., 2013). However, further research is needed to identify potential toxic effects and safe doses of nano-Ag supplements for different poultry species.

Another study revealed that Ag-NPs could cause oxidative reactions in the blood, wall of the small intestine, liver, and pectoral muscles of chickens, especially at doses exceeding 9.47 mg/bird (Kulak et al., 2018). A study by Pineda et al. (2012) examined the effects of using water solutions with varying concentrations of Ag-NPs on nitrogen utilization and blood plasma IgG concentration in chickens. The microbial population in the digestive tract, energy metabolism, and growth performance of the chickens remained unaffected by the addition of Ag-NPs to their diet. Moreover, the excretion and nitrogen utilization efficiency were not altered, and there were no changes in the bacterial populations in the intestinal samples. However, there was a significant finding regarding the blood plasma IgG concentration in the experimental broilers. On day 36 of Ag-NPs administration, the concentration of immunoglobulin (IgG) in the blood plasma decreased.

On the other hand, Vadalasetty et al. (2018) have discovered that the administration of Ag-NPs at a concentration of 50 ppm via drinking water reduced the growth of broilers, depressed the immunity, and had no antibacterial effect on different intestinal bacteria. It limits the usage of Ag-NPs against *Campylobacter jejuni* in broiler chickens. Different clinical and biochemical effects were observed after using various Ag-NPs concentrations (1-5 ppm). The most efficient and safe dose of Ag-NPs (up to 2 ppm) was confirmed for the growth traits (body weight, body weight gain, and feed conversion ratio) as well as hematological parameters. On the contrary, higher concentrations (3-5 ppm) caused dose-dependent mild to moderate adverse effects regarding the hematological, biochemical, and oxidative parameters (MDA, T-AOC, and GSH-Px; Fouda et al., 2021).

The serious cardiovascular problems with a decrease in myocardial contractility and an increase in the internal diameter of the left ventricle could occur due to high doses of Ag-NPs (Raieszadeh et al., 2013). Therefore, it is necessary to determine the amount of NPs introduced to the chickens carefully. Experimental studies (Husseiny et al., 2021) have shown that *in ovo* injection of 20 ppm Ag-NP improved muscle development in chick embryos, compared to a 40 ppm administration. This confirms the effectiveness of using Ag-NPs to improve poultry productivity.

SiO_2-Ag-NPs have no negative effect on the growth performance and hematological, biochemical, and oxidative parameters of broiler chickens. In addition, immunohistochemistry revealed minimal inflammatory reactions and lymphoid depletion at the 8 mg/kg dose. Therefore, SiO_2-Ag-NPs can be considered a promising and safe nano-growth stimulator in broilers during its introduction to the poultry diet at a dose of 4 mg per kg of food (Dosoky et al., 2021).

Gold nanoparticles

Gold nanoparticles (Au-NPs) have been extensively studied, but there is still a lack of comprehensive information regarding their immunogenic potential, meaning their ability to trigger immune responses in the body. Au-NPs are non-ionic, nanocrystalline, chemically pure particles of 5 nm in size that are synthesized by the photochemical method. When Au-NPs are ingested, they tend to accumulate in the intestinal wall. The extent of this accumulation depends on the dose and duration of exposure. Au-NPs negatively affect the absorption of Ca, iron, and potassium in the jejunum *in vitro* (Sembratowicz et al., 2016). The interaction between Au-NPs and chitosan involves several mechanisms, including the antioxidant effect, the strengthening of the protective effects of antioxidants in the deactivation of free radicals, and the activation of electron transfer in redox reactions. Au-NPs with a size of 15 nm inactivate nitroxyl free radicals by oxidation to carboxyl derivatives. These systems stimulate the immune system and are practically non-toxic (Suchomel et al., 2018).

Chickens treated by Au-NPs for a shorter period, had an increase of the respiratory activity of leukocytes and a decrease of the lysozyme activity of the blood. Higher doses (1.5 and 2.0 mg/kg body weight/day) of Au-NPs with longer duration of taking caused an increase of the interleukin 6 level and ceruloplasmin activity, as well as erythrocyte sedimentation rate. These are signs of a pro-inflammatory effect. In addition, Au NPs increased the content of IgA and IgY in the blood, but the immune response of chickens depended on both the dose and the duration of feeding. Long-term administration of high doses of Au NPs causes an inflammatory response, which could be avoided if the dose does not exceed 1.0 mg/kg body weight/day (Sembratowicz and Ognik, 2018).

Hassanen et al. (2020) confirmed that the addition of 15 ppm Au-NPs to drinking water caused significant blood damage due to oxidative stress, histopathological changes, increased IL-6, Nrf2 gene, and DNA fragmentation in the studied immune organs of broiler chickens. The study results showed a significant decrease in antibodies against Newcastle and avian influenza viruses. On the other hand, the 5 ppm Au-NPs group showed better growth performance with an increase in the final feed conversion ratio without any differences in the preliminary toxicological and immunological parameters, compared to the control groups.

The implementation of Au-NPs has a high potential for application in poultry farming when coated with bacterial outer membrane proteins. This combination enhances their ability to induce an immune response, making them promising candidates for vaccine development against poultry salmonellosis. (Anwar et al., 2021).

Iron nanoparticles

Iron is one of the most important trace elements. Iron deficiency can lead to various growth retardation and pathological conditions, such as anemia and disorders of the skin and feathers (Rehman et al., 2020). Ferrum (Fe), commonly known as iron, is an essential element for living organisms and plays a crucial role in various biological processes. It is a component of many important proteins and enzymes that are involved in key cellular functions. Some examples of iron-containing proteins and enzymes include cytochrome, peroxidase, oxidase, catalase, hemoglobin, and myoglobin. Iron preparations, in their conventional macroergic form (e.g., iron salts or chelates), are commonly used to supplement iron in cases of iron deficiency or related conditions. However, these preparations have certain limitations, including limited bioavailability and a low toxic threshold. Therefore, iron nanoparticles (Fe_2O_3-NPs) can contribute to the solution of this problem.

The physical, biological, and pharmacological properties of Fe_2O_3-NPs depend on the particle size. Larger particles are better captured by macrophages, but smaller ones, as a rule, circulate longer in the bloodstream and penetrate the capillary wall. There were no accumulations of Fe_2O_3-NPs in the liver, spleen, as well as in chyme of duodenum. Iron levels in the liver and duodenal villi reflect the bioavailability of the released iron due to the transformation of Fe_2O_3-NPs in the acidic environment of the stomach. A duodenal gene expression study associated with iron uptake from Fe_2O_3-NPs indicates enhancement of the iron-over-iron pathway, supporting a role for mucins. As a result, oral administration of iron oxide nanoparticles is a safe way to deliver drugs in low doses of NPs (Chamorro et al., 2015).

Based on the physicochemical properties, Fe_2O_3-NPs have diverse applications, such as detoxifying biological fluids, antimicrobial therapy, and tissue regeneration. However, their properties can lead to significant biodegradation of Fe, resulting in the release of its ions. In a study involving Fe_2O_3-NPs supplement plus xylanase, a significant weight gain (54.5%) was observed by the fifth week compared to the control group of chickens. Despite the supplementation, there was no notable rise in iron concentration in the muscles, and no morphological changes were observed in liver cells (chickens were injected with 40 ncat/mg endoxylanase and 15 ppm Fe_2O_3-NPs). Nevertheless, these experimental findings show promising potential for utilizing Fe2O3-NPs in poultry farming to produce safe and high-quality meat (Rehman et al., 2020).

The pollution caused by metal nanoparticles is on the rise due to their increased utilization in industrial and domestic applications. These NPs are toxic to established microorganisms, potentially impacting their associated functions and nutrient cycling in agroecosystems. A study conducted by Kamran et al. (2020) showed the toxic effect of Fe2O3 NPs on soil microbes, affecting carbon and nitrogen mineralization in applied manure, consequently influencing the nitrogen cycle within the manure-substrate-plant continuum on the farm.

Ferroptosis is a form of cell death associated with iron-dependent lipid peroxidation. Basaki et al. (2021) used a chick embryo model to investigate whether ferroptosis was involved in the molecular mechanism underlying the potential effects of Fe_2O_3-NPs on maternal brain development. Ferroptotic cells appeared in cerebral tissue after exposure to low doses. Oxidative stress and ferroptotic cells were more evident. Low doses caused stronger oxidative stress in cerebral tissue. The TAC and MDA increased, and GSH-Px expression and activity decreased in the Fe_2O_3-NPs treated groups. According to the results of a study by Basaki et al. (2021), maternal exposure to Fe_2O_3-NPs was associated with ferroptosis in the brain.

Calcium nanoparticles

The widest group of NPs is characterized by Ca compounds, as one of the main elements in poultry nutrition. It should be noted that the use of Ca macroergic salts, particularly in the form of carbonates and phosphates, is common in the rations of both layer and broiler poultry. However, recent studies (Ganjigohari et al., 2018; Abo El-Maaty et al., 2021; Gutiérrez-Arenas et al., 2021) have proven the clinical effectiveness of using various Ca salts in nanoform-calcium carbonate ($CaCO_3$-NPs), dicalcium phosphate (Ca_2PO_4-NPs), and complex Ca particles with an extract of *Sargassum latifolium algae* (SL-Ca-NPs).

The results of studies addressing the effects of CaCO3-NPs on the performance of laying hens have indicated that $CaCO_3$-NPs can replace $CaCO_3$-NPs in lower amounts while reducing the concentration of Ca in the diet (up to 1.43 %) and decreasing the productivity of laying hens, egg quality, shank thickness, and Ca content in the blood. At the same time, laying hens treated by $CaCO_3$-NPs had a better average feed conversion rate and increased relative eggshell mass and eggshell mass/surface area (Ganjigohari et al., 2018).

Nano dicalcium phosphate (Ca_2PO_4-NPs) produced by co-precipitation can be used as a substitute for dicalcium phosphate (DP), a mineral involved in poultry metabolism and development. The digestibility of dietary sources of phosphorus improved in the group receiving 0.35% Ca_2PO_4-NPs. The study conducted by Gutiérrez-Arenas et al. (2021) revealed that the dietary source of phosphorus ash and diameters exhibited significant increases when supplemented with additional Ca2PO4-NPs, as compared to the control treatment. Consequently, the utilization of 0.35% Ca2PO4-NPs was identified as the optimal dosage for chickens in terms of enhancing digestibility, absorption rates, and the amount of phosphorus from the diet that gets deposited in the breast tissue.

In a study investigating the effects of feed supplements containing *Sargassum latifolium* combined with Ca-NPs, researchers observed that laying hens fed with these supplements exhibited higher rates of egg weight and shell weight. All groups of laying hens treated with SL-Ca-NP showed the most significant improvements in shell thickness and shell weight per unit surface area. Supplementing SL-Ca-NP into the chicken diet, up to a dosage of 1.5 g/kg of feed, resulted in increased levels of calcium and inorganic phosphorus in the blood serum The ultrastructure of the eggshell in laying hens showed well-developed palisade and mastoid layers when treated with SL-Ca-NP. Additionally, the number of apical cells along the branched tubular gland was greater in SL-Ca-NP-treated hens compared to those not receiving the treatment. Importantly, electron microscopic examination did not indicate any negative effects on the quality of eggshells (Abo El-Maaty et al., 2021).

Therefore, the development of nanostructured Ca compounds can become an effective alternative to commonly used feed additives and increase the profitability of the poultry industry.

Manganese nanoparticles

The British United Turkeys recommended introducing Mn supplement into the diet of young turkeys (Jankowski et al., 2019). The reduction of the Mn2O3-NPs dose from 100 to 50 and even 10 mg/kg did not negatively affect the antioxidant defense of young turkeys. In addition, using Mn supplement increases the Mn content in the bloodstream. Moreover, 50% reduction of the recommended level of MnO-NPs increased lipid oxidation processes. It can be assumed that replacing MnO-NPs with Mn2O3-NPs in turkeys' diet will increase cell apoptosis in young turkeys. On the other hand, the reduction of Mn supplement amount in the turkey diet reduces apoptosis, regardless of Mn form (Jankowski et al., 2018).

As stated by other researchers, reducing Mn supplementation at rational rates decreases ileal absorption and Mn accumulation in the liver, pectoral muscles, and skin. The reduction in dietary Mn supplementation in turkeys could potentially lead to an increase in intestinal Zn absorption and a decrease in the accumulation of Zn and Cu in the liver, breast muscle, and skin. Additionally, this reduction in Mn supplementation stimulated B-cells to produce immunoglobulin M and release cytokine IL-6. However, it is worth noting that apoptosis and oxidation in the liver cells and pectoral muscles of turkeys were not intensified by this dietary change (Jankowski et al., 2019).

In a study by Ognik et al. (2019), experimental investigations were conducted using two forms of Mn (MnO-NPs and Mn_2O_3-NPs) added to turkeys' diet at three doses of 100, 50, and 10 mg/kg. The results showed that the most effective form was Mn_2O_3-NPs at a dose of 10 mg/kg, which significantly induced lipid oxidation. Regardless of the dose of Mn2O3-NPs, this supplement reduced protein nitration more effectively, compared to MnO-NPs. However, reducing the dietary dose of Mn from 100 to 50 mg/kg, and then to 10 mg/kg, led to increased oxidation of proteins and DNA in cells, decreased the activity of antioxidant enzymes, and lowered the level of glutathione. At the same time, it caused an increase in global DNA methylation. Therefore, any reduction in the dietary dose of both forms of Mn was found to be unfavorable in terms of the observed effects on oxidative stress and DNA methylation.

Another study by Orzołek et al. (2021) investigated the improvements in turkey sperm parameters during long-term storage. The researchers evaluated several sperm parameters after 2, 24, and 48 hours of storage, including motility, activity of the cell membrane, mitochondrial membrane potential (MMP), and the percentage of sperm showing NO and SOD activity. The addition of Mn_2O_3-NPs to sperm diluent increased the mitochondrial membrane potential and activity of the plasma membrane. As a result, all spermatozoa showed good motility during the storage period.

Chromium nanoparticles

Lin et al. (2015) found that the addition of CrPic-NPs and CrPic to the diet of broiler chickens was more effective than the addition of $CrCl_3$. It significantly increased the concentration of chromium in blood serum. However, it was observed that the triglyceride level in the blood serum was lower with the addition of $CrCl_3$, compared to CrPic. It was established that CrPic-NPs supplement improved chromium utilization and reduced serum cholesterol in broiler chickens more effectively than the CrPic supplement. Additionally, NPs supplementation was found to be beneficial in reducing the negative effects of heat stress in broiler chickens. This was attributed to changes in the immune system, including the expression of IFN-γ immune. The addition of Cr and CrPic-NPs improved the weight gain and feed conversion ratio of heat-stressed chicks. The CrPic and CrPic-NPs dietary supplements enhanced antibody titers of heat-stressed broilers as well as antibody titers against avian influenza and infectious bronchitis (supplements of CrPic-NPs at 1000 ppb and CrPic at 1500 ppb from days 21 to 42 of age (Hajializadeh et al., 2017).

Berenjian et al. (2018) compared quails' diet with CrPic-NPs and a diet without CrPic-NPs. At 23 days of age, there was a positive linear relationship between dietary CrPic-NPs levels, feed intake, and average daily gain. The increase of CrPic-NPs in quails' diet led to a general increase in white blood cells and hematocrit levels. In 35-day-old quails, indicators of body weight gain, energy use, and the number of leukocytes in the blood increased due to the addition of CrPic-NPs to the diet. Thus, the optimal concentration of CrPic-NPs in the quails' diet facilitated the negative consequences of physiological stress in quails.

The Cr supplements in both forms (salts and nanoforms) in a dose of 3 mg/kg were found to increase serotonin levels and decrease norepinephrine levels. These supplements also regulate the levels of hormones involved in carbohydrate metabolism, leading to an increase in insulin secretion and a decrease in glucagon secretion. However, it was observed that Cr supplements at this dose had a negative impact on the antioxidant potential of the liver and pectoral muscles of chickens. Therefore, further research is needed to identify new doses of these supplements that would avoid compromising the antioxidant defense system (Stępniowska et al., 2019).

It became obvious that Cr accumulates in the wall of the ileum, liver, pectoral muscles, bones, skin, and feathers of chickens. According to *in vivo* research by Stępniowska et al. (2020), the deposition of Cr in the chickens' ileum did not affect the intestinal absorption of the mineral. However, the introduction of Cr to the chickens' diet reduced the level of phosphorus in the femur. Hamidi et al. (2022) noted the positive effect of CrPic and CrPic-NPs supplementation on the status of heat-stressed broilers, namely on their growth, hormonal changes, immune biomarkers, and IFN-γ gene expression.

Summarizing the obtained results, the authors of the current study note that the use of metal NPs in feed additives for poultry is an urgent scientific task and requires further detailed research, especially in the field of nanotoxicology. The main parameters of the positive effect of metal NPs on the poultry body, a combination of antioxidant, antibiotic, and immunomodulatory impact, are shown in Figure 1.

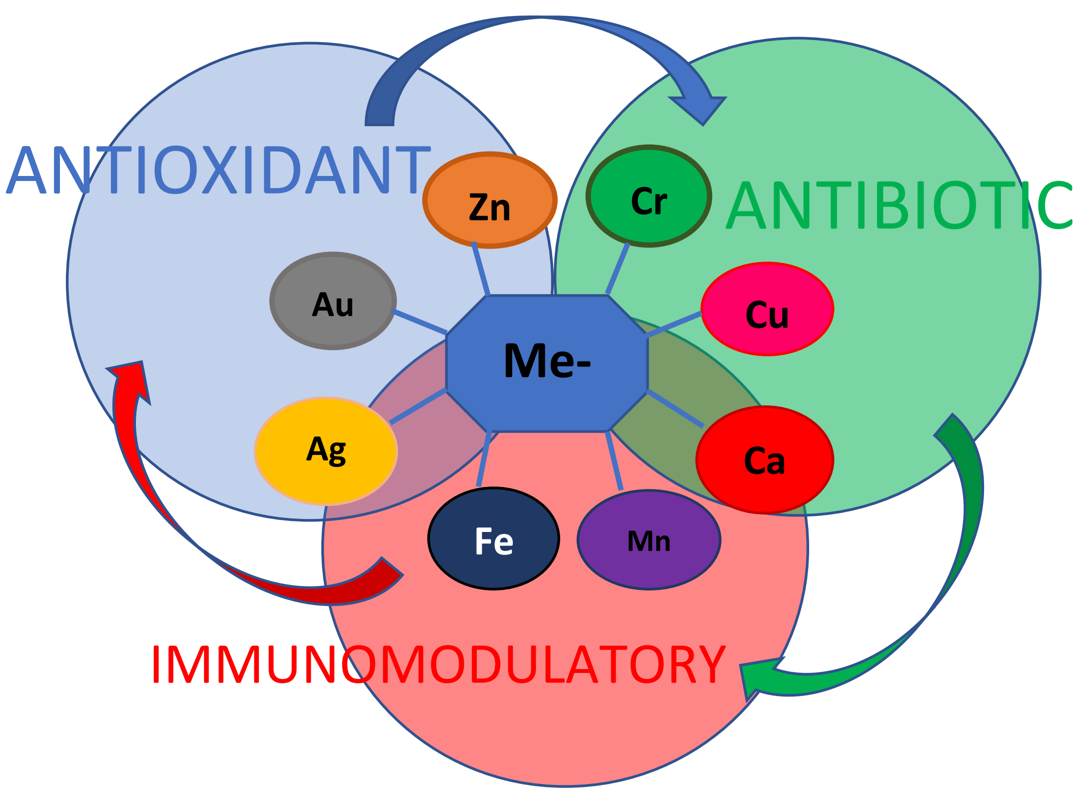

Figure 1. Effect of metal nanoparticles (including Ag, Au, Ca, Cu, Cr, Fe, Mn, and Zn) on the poultry body using safe doses

Table 1. Dose-dependent effects of metal nanoparticles on increasing feed digestibility, growth performance stimulating, influencing gene expression, and maintaining hormonal balance

Parameters	**Me-NPs**							
	Ag	**Au**	**Ca**	**Cu**	**Cr**	**Fe**	**Mn**	**Zn**
IFD	↓↓	↑↑	↑	↑↑↑	–	↑	↑	↑↑↑
GPS	↓	↑	↑	↑↑↑	↑↑	–	↑↑	↑↑↑
IGE	↑↑	–	–	↑↑	–	–	–	↑↑
MHB	↑	–	–	–	↑	–	–	↑↑

Me-NPs: Metal nanoparticles, including Ag, Au, Ca, Cu, Cr, Fe, Mn, and Zn, IFD: Increasing feed digestibility, GPS: Growth performance stimulating, IGE: Influencing gene expression, MHB: Maintaining hormonal balance, ↑↑↑: Pronounced positive effect in therapeutic doses, ↑↑: Positive effect in medium doses; ↑: A positive effect is observed only when administered in low doses, ↓↓↓: Pronounced negative effect in low doses, ↓↓: Negative effect in medium doses, ↓: Negative reactions are noted for the introduction of high doses of NPs, – : There is no information about the presence of influence on this parameter.

In addition, the obtained data indicate a pronounced dose-dependent effect of the introduction of metal NPs (in particular, nanoparticles of zinc, copper, and chromium have pronounced redox properties; nanoparticles of silver and gold exhibit an antibiotic effect, while nanoparticles of manganese, calcium, and iron have a positive effect on the immunity of poultry); therefore, feed additives based on these nanoparticles can lead to a complex antioxidant, antibacterial, and immunomodulatory effects (Table 1).

CONCLUSION

Metal NPs have become widely used in the poultry industry and have attracted the interest of numerous researchers. These bioavailable and effective compounds possess unique properties, but their study has been ongoing for more than a decade. A comprehensive analysis of specialized literature revealed a substantial volume of experimental studies exploring the impact of metal NPs on birds' bodies and their products, as well as a comparative analysis with macroergic compounds.

Zn-NPs offer a broad spectrum of effects on various types of poultry, including antioxidant, antimicrobial, and immunomodulatory properties, which contribute to enhanced productivity and increased resistance against internal diseases. Introducing these NPs into diets at a dose of 20-80 mg/kg of body weight allows for a comprehensive beneficial effect on the body. Similarly, Cu-NPs demonstrate comparable properties and, at the same time, exert a pronounced impact on mineral homeostasis, immune protection, and bone tissue, with an effective dose ranging from 5-50 mg/kg of body weight.

Ag-NPs and Au-NPs serve as potential alternatives to antibiotics due to their antioxidant properties. Their comprehensive impact on antioxidant protection helps in preventing cardiovascular and nervous diseases and also improves fertility. Introducing these nanoparticles into diets at appropriate doses (Ag-NPs at 20-40 mg/kg of body weight and Au-NPs up to 1 mg/kg of body weight) can effectively reduce the occurrence of infectious diseases and bolster the immune system.

Fe-NPs can serve as viable substitutes for macroergic agents in the treatment of anemia and diarrhea; however, their use should be limited due to their pro-oxidant properties. On the other hand, Ca-NPs can be safely introduced into diets in the form of various salts at a dose of up to 1.5 g/kg of body weight.

Mn-NPs play a vital role in turkey feed, and their high bioavailability and low toxicity make them excellent replacements for pharmacopeial drugs. Moreover, their properties contribute to preserving rooster sperm during refrigerated storage. Cr-NPs serve as effective anti-stressors, enhancing the bird's resistance to thermal and other physiological stresses. It is noteworthy that they can regulate hormonal balance and impact the antioxidant status.

As a result, the poultry industry should prioritize the implementation of nanotechnological advancements, including metal NPs. However, special attention should be paid to NPs with strong antioxidant properties and a low toxicity threshold. When conducting studies related to nanoform compounds, careful consideration should be given to combining assessments of toxicological parameters with the effects on redox status. This approach is crucial for the safe and beneficial integration of metal NPs in poultry feed additives.

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Authors' contributions

Svitlana Naumenko and Vsevolod Koshevoy conceptualized the research idea, developed the structure of the work, and reviewed and edited the manuscript. Olena Matsenko, Olha Miroshnikova, Iryna Zhukova, and Iryna Bespalova took part in the selection of literature sources and drafting of the manuscript. All authors have read and approved the final version of the manuscript for publication in this journal.

Competing interests

The authors have declared that no competing interest exists.

Ethical consideration

Ethical issues under current regulations, including plagiarism, consent to publication, misconduct, data fabrication and/or falsification, double posting and/or submission, and redundancy, have been verified by the authors and warranted against the aforementioned violations.

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