SVU-IJAS
SVU-International Journal of Agricultural Sciences
Volume 4 Issue (3) pp.: 203-222, 2022
Print ISSN 2636-3801 | Online ISSN 2636-381X
Doi: 10.21608/svuijas.2022.166077.1238
RESEARCH ARTICLE

Green synthesis of copper oxide nanoparticles in broiler nutrition: Present perspectives and strategic future in climate change conditions

Doha A. Mohamed [1], M.S. Abd El-sadek [1] and A.A.A. Abdel-Wareth [2]*

[1] Nanomaterial Laboratory, Physics Department, Faculty of Science, South Valley University, 83523 Qena, Egypt
[2] Department of Animal and Poultry Production, Faculty of Agriculture, South Valley University, 83523 Qena, Egypt.

Abstract

Under tropical and subtropical climates, global warming and climate change have a negative impact on the output of cattle and poultry. In hot temperature zones, heat stress is one of the most important stressors affecting chicken productivity, leading to huge financial losses for the poultry sector. The harmful effects of overheating have been reduced by the adoption of several pragmatic approaches. One of these is food manipulation, which is gaining popularity as a natural source of antioxidants, minerals and electrolytes in many parts of the world. According on size, dose, and animal, research in recent years have suggested copper nanoparticles as a possible substitute for antibacterial medicines and a growth booster. An essential element known as copper (Cu) is important for the organism's defense against oxidative stress. Nevertheless, there is little study on the application of The CuO nanoparticles in the poultry sector. The use of plant extracts in the synthesis of metal nanoparticles is a very promising green synthesis technique. One of the most significant issues in the production of poultry is heat stress. The copper oxide nanoparticles may improve bird performance, lower bird temperature, and increase bird tolerance to the harmful effects of high temperature when added to the diet, particularly at 50% of the birds' suggested requirement during heat stress. In the context of current perspectives and a strategic future under conditions of climate change, this review and case study provides an overview of the mode of action, recommended levels of Nano-CuO, and effects on growth performance, nutrient digestibility, carcass criteria, and blood biochemical of broilers.

Keywords: Broiler, Climate Change, Production, Nanotechnology, Nutrition

1. Introduction

An increase in environmental temperature, which produces heat stress in birds, is one of the most serious issues that could restrain the growth of the poultry business. According to the Intergovernmental Panel on Climate Change (IPCC, 2007), by the year 2100, the average world surface temperature would have risen by 1.4°C to 5.8°C, which will have a significant impact on the poultry industry. This constraint is anticipated to be severe, especially in the tropics and subtropics, as weather change alleviation measures have failed to meet the IPCC (2014) recommendations. High temperature negatively affects homeostasis and consequently the endocrine system. These factors have a negative impact on egg production, ovulation, and oviposition in the ovary and reproductive tract (Oguntunji and Alabi, 2010) as well hatched broiler chicks are susceptible to various

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***Corresponding author:** **Ahmed A.A. Abdel Wareth**
Email: a.wareth@agr.svu.edu.eg
Received: September 14, 2022; Accepted: September 28, 2022; Published online: September 30, 2022.

infectious diseases, oxidative stress, and high ambient temperature, which lead to increased mortality and economic losses (Ghanima *et al.*, 2020; Ibrahim *et al.*, 2020). Heat stress increases the spread of infectious diseases and endangers the host's ability to grow, absorb nutrients, digest food, and perform other physiological processes (Saleh *et al.*, 2020; Alagawany *et al.*, 2017; Abdel-Moneim *et al.*, 2020). Moreover, prolonged exposure to heat stress suppresses the innate immune response and induces immune disorders via altering the organs' immune functions (Ghanima *et al.*, 2020; Ma *et al.*, 2019) and circulating antibody levels (Tang *et al.*, 2016).Heat stress also induces oxidative stress by damaging the membrane of immune cells, leading to apoptosis (Habashy *et al.*, 2019) and increased intestinal barrier permeability and consequently translocation of toxic agents into the body (Hirakawa *et al.*, 2020; Koch *et al.*, 2019). As a result, it's critical to put mitigation techniques in place for environmental stressors and climate change that can lessen their negative impacts on broiler chicken growth performance, immunological functions, and antioxidant capacity, particularly in situations of heat stress. Several mitigation measures, such as feed additives like trace elements, have been employed in the past. (Harsini *et al.*, 2012; Ibrahim *et al.*, 2020), vitamins (Khan *et al.*, 2012), probiotics (Abdel-Moneim *et al.*, 2020; Abd El-Moneim *et al.*, 2019; Abou-Kassem *et al.*, 2021; Elbaz, Ibrahim *et al.*, 2021; Saleh *et al.*, 2021; Abd El-Hack et al., 2020), and herbal products (Ghanima *et al.*, 2020; Abd El-Hack *et al.*, 2019; Abd El-Hack *et al.*, 2020; Badran *et al.*, 2020). Previous studies demonstrated that high ambient temperatures may cause heat stress in the production environment, which may have a negative impact on welfare, meat quality, carcass features, productivity, egg mass, and egg quality (Fiza *et al.*, 2021). Animal and veterinary sciences are now seeing the emergence of the field of nano-biotechnology for a number of useful applications, including nutritional, medicinal, and diagnostic ones. (Prasad *et al.*, 2018; Amlan and Lalhriatpuii, 2020; El-Maddawy *et al.*, 2022). Nanoparticles (NPs) of essential minerals, which size from 1 to 100 nm, could be used as an alternative to conventional forms of elements in animal diet (Mohamed *et al.*, 2016; Swain *et al.*, 2016; Scott *et al.*, 2018; Abdollahi et al., 2020; Kociova *et al.*, 2020; Szuba-Trznadel *et al.*, 2021). It is assumed that much smaller doses of nanoparticles will be required to cover animal requirements for elements than bulk minerals (Vijayakumar and Balakrishnan, 2014; Refaie *et al.*, 2015; El Basuini et al., 2017; Scott *et al.*, 2018; Youssef *et al.*, 2019; Abdollahi *et al.*, 2020; Szuba-Trznadel *et al.*, 2021; Ouyang *et al.*, 2021) and thus the environmental impact caused by the high concentration of inorganic salts will be alleviated (Vijayakumar and Balakrishnan, 2014; Ouyang *et al.*, 2021). Reduced mineral supplementation to animal diets may also result in lower feed costs. Additionally, due to their attributes like small size, good homogeneity, high surface area, and physical reactivity, nano-forms of elements can increase bioavailability to animals (Vijayakumar and Balakrishnan, 2014; Hill and Li, 2017; Youssef *et al.*, 2019; Hidayat *et al.*, 2021). Animals may also benefit from the biological features of nanoparticles like lower dose, lower antagonistic, greater absorption rate, and better tissue dispersion. The immense potential of nanoparticles, even at very low dosages, is well established related animal nutrition research on nanoparticles for growth efficiency, feed efficiency, and health status. The body weight, average daily gain, and feed conversion ratio (FCR) are regularly increased and improved by nano-forms of micro- and macroelements (Bkowski *et al.*, 2018; Yusof *et al.*, 2019). NPs are utilised to meet an animal's nutritional needs, increase productivity, improve immunological function and microbial profile, and lower the risk of disease. NPs are known for their antibacterial, antifungal, antiviral, antiprotozoal, antioxidative properties, etc. Silver, copper, selenium, and zinc nanoparticles can constitute alternative health and growth promoting additives to antibiotics (Sawosz *et al.,* 2007; Pineda *et al.,* 2012; Bąkowski *et al.,* 2018; Kumar and Bhattacharya, 2019; Yusof *et al.,* 2019; Nabi *et al.,* 2020; Sheiha *et al.,* 2020; Hidayat *et al.,* 2021; Morsy *et al.,* 2021; Ouyang *et al.,* 2021; El-Maddawy *et al.,* 2022). Cu nanoparticles (Nano-Cu) have received a lot of attention in recent years as a potential replacement for antibacterial drugs and a growth stimulant. Depending on size, shape, dose, and animal species, Nano-Cu can have a variety of impacts on animal performance. Reports have noted that Nano-Cu Toxicological Effects have growth-promoting, antimicrobial, and immune-modulating properties in addition to being highly bioavailable. Animals require copper as a trace metal and as a cofactor for various biological activities. It can strengthen immunity, increase immunity, increase resistance to external diseases, and increase antioxidant capacity. It can also support participation in hematopoiesis. Furthermore, copper is involved in various physiological and biochemical processes (Gangadoo *et al.,* 2016; Scott *et al.,* 2018). Nano-Cu physical, chemical, and biological characteristics as well as their significance in animal diets have been discussed in reviews, such as those by (Scott et al., 2018; Amlan and Lalhriatpuii, 2018). When added to animal feed, copper nanoparticles stimulate the immune system, boost growth, and function as an antibacterial and antifungal agent. The green synthesis of Nano-CuO has recently also surfaced as a unique technique and is becoming increasingly significant among researchers. To avoid agglomeration, however, the synthesis of Nano-Cu requires a range of stabilizers, including donor ligands, polymers, and surfactants. The copper oxide nanoparticles may improve bird performance, lower bird temperature, and increase bird tolerance to the harmful effects of high temperature when added to the diet, particularly at 50% of the birds' suggested requirement during heat stress. Accordingly, based on their biological effects, the dose and duration of Nano-CuO supplementation for broilers must be optimised. Furthermore, more research is still needed to validate the bioavailability of Nano-CuO in broilers. In this review, we summarise the advantages, mode of actions, recommended level, risks, and potential applications of nano-CuO as a feed additive for broiler chickens.

2. Mode of action of Nano-CuO

Numerous elements like size, shape, solubility, and charge affect how NPs function (Hett, 2004; Abd El-Ghany, 2019). The mechanisms of NPs are primarily exerted by increasing surface area for higher interaction and biological support, prolonging the residence time in the gastrointestinal tract (GIT), decreasing intestinal clearance mechanisms, increasing tissues' penetration and distribution, efficient cells uptake and effective delivery to target sites, and consequently efficient bioavailability (Chen *et al.,* 2006). One benefit of adding mineral NPs to poultry diets is that it prevents mineral dissociation, which reduces mineral-mineral antagonistic interactions in the intestine, increases intestinal absorption, and decreases mineral excretion and environmental pollution (Gopi *et al.,* 2017; Scott *et al.,* 2018a; Patra and Lalhriatpuii, 2019). It can be concluded that Cu is present within chicken tissues in very small and regular amounts, but it plays an essential role in chicken growth, acting as a catalyst in enzyme systems within cells (Prashanth *et al.,* 2015). Schematic diagram of different methodologies for CuO NMs synthesis (Fig.1). However, a relatively constant concentration of copper (Cu) in chicken bodies shows that the amount of Cu in the animals' bodies rises as their weight does. A lack of copper will undoubtedly hinder the growth of chickens, while too much copper is not advisable because it will either be expelled or negatively impact performance. At lower doses, Nano-Cu can be more effective than bulk Cu due to their tiny size, which can improve GIT uptake (Civardi *et al.*, 2015). Due to their greater surface area, Nano-Cu interacts with organic and inorganic components in the mammalian body more effectively. The Nano-Cu has the ability to diffuse into and traverse the small intestine. Sustainable green nanotechnology Fig. 2).

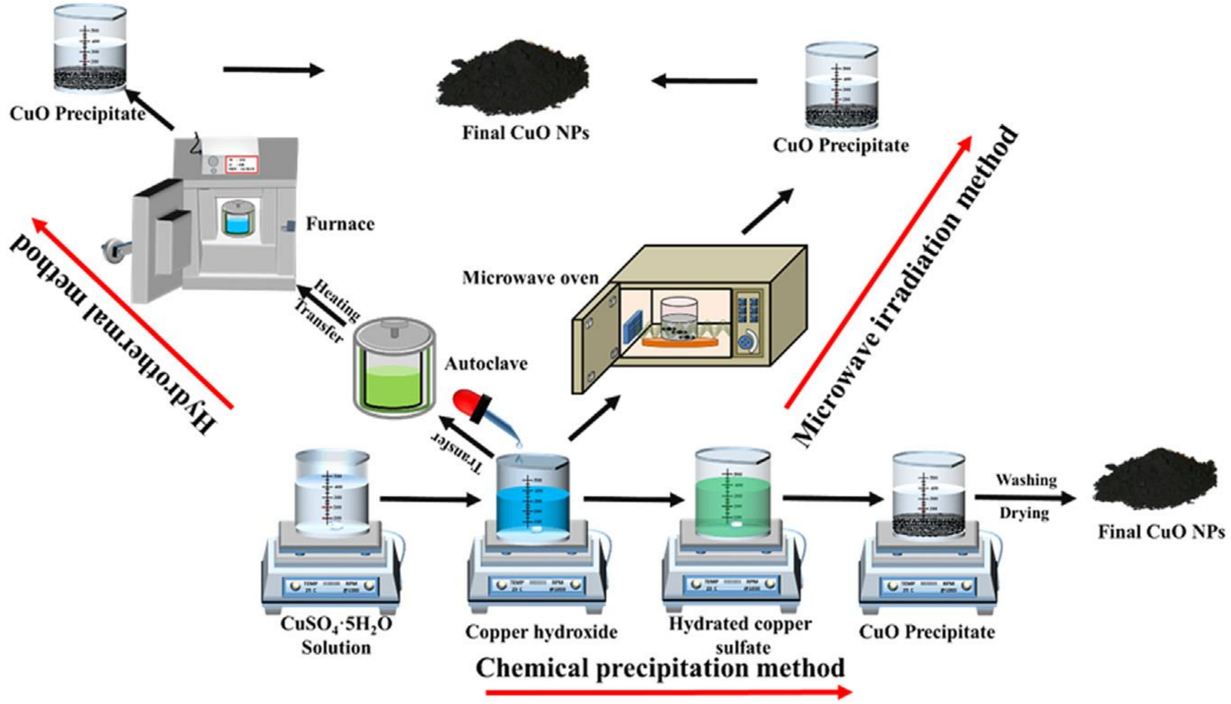

Figure 1. Schematic diagram of different methodologies for CuO NMs synthesis

The Nano-Cu will first interact with the GIT's defences before moving on to the target organs. As a result, the characteristics of the nanoparticles and the physiological barriers themselves play a significant role in determining which nanoparticles pass through them. Nano-Cu uptake may take place through one of the various kinds of endocytosis, with research (scoot *et al.*, 2018) indicating that Nano-Cu is superior to CuSO4 in promoting animal development and performance. In general, nanoparticles can enter the GIT by a variety of routes, including direct ingestion from food and liquids, administration of therapeutic nanodrugs, and oral delivery.

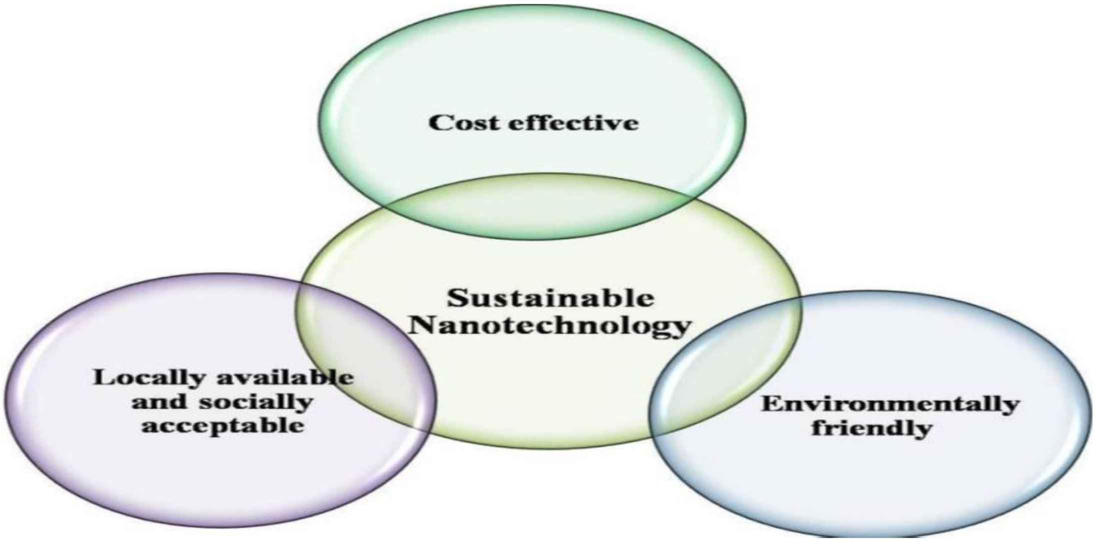

Figure 2. Sustainable green nanotechnology

Inhaled nanoparticles can also be eaten and enter the GIT after passing through the respiratory system. The diffusion and accessibility of particles through mucus and interaction with GIT cells determines their uptake in the GIT. The Cu is used as a growth promoter in the poultry feed industry, and immune function (Fig. 3).

Smaller particles will more quickly diffuse through the GIT mucus to the intestinal lining cells before being absorbed through the GIT barrier to the circulation. According to O' Hagan (1996), uptake might take place intercellularly, by active transport processes, or passive diffusion across the mucosal cells.

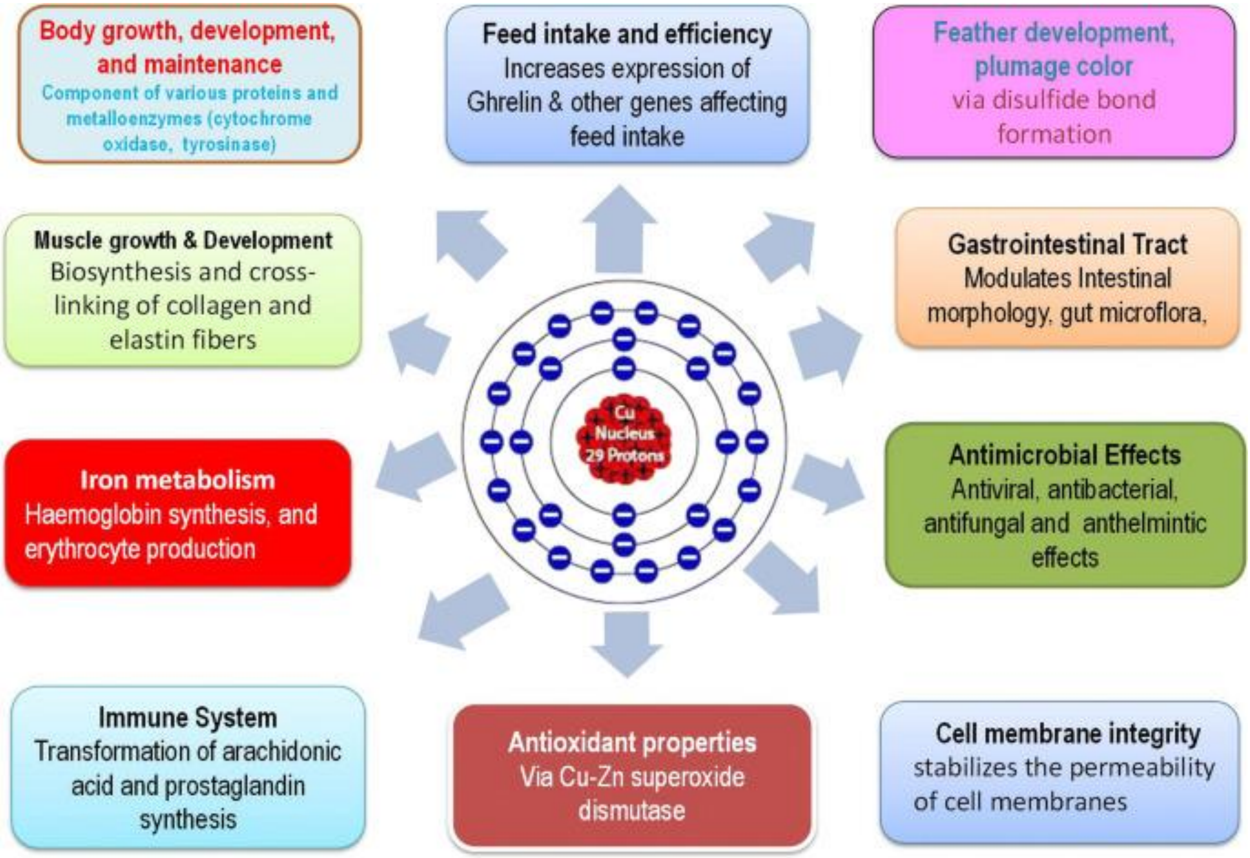

Figure 3. The Cu is used as a growth promoter in the poultry feed industry, and immune function (Sharif *et al.*, 2021).

It has been suggested that smaller particles that are capable of being taken up by the villus epithelium may directly enter the bloodstream, thereafter, being predominantly scavenged by the liver and the spleen (Hillery *et al.*, 1994). Cu is involved in the stimulation of the immune system to combat infections and repair injured tissues (Failla *et al.*, 2003). Additionally, it encourages the neutralisation of free radicals that seriously harm cells. It has been shown that the stomach can only absorb a limited amount of copper; the remainder is taken up by the small intestine (Tapiero *et al.*, 2003). A little amount of Cu is reabsorbed by intestinal cells, while the majority of Cu is expelled via bile that enters the gastrointestinal tract (GIT) (Magaye *et al.*, 2012). Cu has an impact on the control of ceruloplasmin levels, superoxide dismutase (SOD) activity, and dietary fat digestion. The SOD enzyme facilitates the dismutation of two superoxide radicals into hydrogen peroxide and oxygen, hence assisting in the removal of reactive oxygen species (ROS) induced damage (Lin *et al.*, 2008). Finally, it follows the uptake of nanoparticle-derived metal ions into cells By depleting intracellular ATP production and disrupting DNA replication (Sondi *et al.*, 2004; Kim *et al.*, 2008). Nano-Cu-mediated depolarization of the cell membrane induces filamentation, and Nano-Cu-mediated ROS production in cells results in lipid oxidation and deterioration of protein and DNA oxidation (Chatterjee *et al.*, 2014). For S. aureus, E. coli, and Bacillus subtilis, Nano-Cu coated with linoleic acid is highly bactericidal, indicating that Nano-Cu can be employed as efficient growth inhibitors in diverse Microorganisms, making it usable in a variety of medical devices and antimicrobial control systems (Das, Gang *et al.*, 2010).

3. Recommend levels of copper in poultry diets

The Recommended levels of Cu sources in broiler chickens diets presented in table 1. National Research Council (NRC, 1994) recommended copper content in the diet of chickens about 4 mg/kg in the case of layers and 8 mg/kg in the case of layers broiler chicken.

Also, it has been demonstrated that supplementation with 4 mg/kg feed of Cu as a cupric chelate of amino acid hydrate may be sufficient for normal broiler growth to 29 days of age (Bao *et al.*, 2007), while (Jegede *et al.*, 2011) demonstrated a significantly higher daily weight gain in broilers fed Cu proteinate compared to cupric sulphate supplementation. Additionally, supplementing with Cu glycine chelate (4–8 mg/kg) decreased the Cu concentration in broiler faeces compared to CuSO4 but had no effect on the Cu concentration in the liver (Kwiecie *et al.*, 2015).

On the basis of the levels of copper in the liver, Ledoux *et al*. (1991) demonstrated the relative bioavailability of cupric oxide, cupric carbonate, and cupric sulphate using supplementation levels of 150, 300, and 450 mg Cu/kg feed. The relative biological availability was calculated to be 88.5%, 54.3%, and 0% for the sulphate, carbonate, and oxide, respectively.

Tribasic Copper Chloride (TBCC) has a relative value of 134% compared to CuSO4 according to feeding supplementation up to 390 mg/kg feed (Liu *et al.,* 2005), although Miles RD *et al.* (1998) proposed a value of 112% for TBCC. According to Luo *et al.* (2005), TBCC was 109% as valuable as sulphate in terms of hepatic Cu buildup, indicating that it is less detrimental to vitamins in both feed and the bird itself. When birds were provided TBCC using a 36 IU/kg diet, their liver and plasma vitamin E levels were higher than when they were fed sulphate. Additionally, the carcass weight of broilers was increased similarly by TBCC and cupric sulphate (220 and 180 mg Cu/kg feed, respectively).

Growth by intramuscular injection of a 20 mL solution containing nanoparticles (42.9%) and microparticles (37.9%) of copper in broiler chickens (Scott *et al.,* 2016). Nano-CuO also showed strong antibacterial activity against Salmonella and Campylobacter isolates from poultry (Duffy *et al.*, 2018). Supplementation of Nano-CuO (2, 10, and 20 ppm) in turkey hens significantly increased the activity of aminopeptidases in turkey hens fed lowest dose (2 ppm) of copper in thigh muscles than other groups. In another study, supplementation of Nano-CuO (5, 10, and 15 ppm) through drinking water revealed a dose-dependent increase serum Cu concentration (Ognik *et al.*, 2016) It has also been reported that intestinal copper accumulation did not affect iron absorption but it reduced the absorption of Ca and Zn. Supplementation of Nano-CuO increased weight and volume ratio of femoral bones and their resistance against fracture in chicken. It also enhanced proliferating cell nuclear antigen (Scott *et al.,* 2017). The effects of feeding Nano-CuO in ovo on hatchability, immunity, and performance after hatching have also been studied. It has been documented that broilers perform effectively after receiving a Nano-CuO injection in ovum. However, there was no discernible impact on the expression of immune-related genes (Lee *et al.,* 2016). Although nan-Cu *in ovo* feeding did not affect hatchability, it did increase FCR and the percentage of breast meat in broilers (Joshua *et al.,* 2016). To fully utilize the advantageous properties of copper nanoparticles, additional research is needed to optimize the right level and form of Nano-CuO in both meat and egg type birds.

Table 1. Recommended levels of Cu sources in broiler chickens diets

Animals and age	Concentration and size	Effect and conclusion	References
Broiler chickens (1–7 weeks old)	5, 10 and 15 mg/L of drinking water (5 nm)	Increased content of Cu in the blood; decreased absorption of Zn and Ca; No effect on Fe absorption	Ognik *et al.* (2016)
Chicken embryo (1st day of incubation)	50 mg/kg (15–70 nm)	Positive effect on chicken growth performance and improved percentage of breast and leg muscles	Mroczek-Sosnowska *et al.* (2015a)
Broiler chickens injection (1st day of incubation)	50 mg/kg	Increased accumulation of Cu in the liver and spleen organs	Mroczek-Sosnowska *et al.* (2014)
Broiler chickens (1–32 days old)	100 mg/kg	No effect on the growth performance and digestibility of nutrients	Sarvestani *et al.* (2016)
Chicken embryo injection (1st day of incubation)	50 mg/kg (2–15 nm)	Improved metabolic rate and no harmful effect on embryo development	Scott *et al.* (2016)
Chicken embryo injection (1st day of incubation)	50 mg/kg (37.3 nm)	Pro-angiogenic properties at a systemic level to a greater degree than inorganic form of copper (CuSO4)	Mroczek-Sosnowska *et al.* (2015b)
Broiler chickens in ovo	0.3 mL of 50 mg/L of drinking water	A positive effect on broiler chickens' performance (e.g., body weight) as compared to the control group	Mroczek-Sosnowska *et al.* (2015b)

The liver, spleen, and kidneys experience morphological and functional alterations as a result of the systemic toxic effects of copper nanoparticles. Cu nano-particles' overall higher solubility in physiological milieu and their bio-distribution, as compared to their ionic form, are most likely responsible for their in vivo toxicity (Wang *et al.*, 2014). Growth metrics decreased as a result of Nano-CuO toxicity, although malonaldehyde concentration—a sign of cellular oxidation—as well as total SOD activity, total GHS-Px concentration, and Na (+)/K(+)-ATPase activity increased (Suttle, 2010). On the brain, however, the opposite effects were seen. However, there is a lack of toxicological information regarding the effects of feeding Nano-CuO to diverse poultry species, necessitating additional research.

4. Immunological effects of Nano-CuO

Future applications of Nano-CuO in animal feed and treatment will be influenced by its interactions with the immune system.

Nanoparticle exposure can cause immune stimulation or suppression; unintentional immunological function suppression results in infectious illnesses. Autoimmune illnesses, on the other hand, can be brought on by an improperly enhanced immune response (Shannahan *et al.,* 2014). Due to their physicochemical characteristics, Nano-CuO has been implicated in numerous studies to date in triggering inflammatory reactions. Smaller nanoparticles (less than 70 nm) can potentially be translocated across capillary blood flow since they cannot be recognised as foreign particles, as has been shown (Moghimi *et al.,* 2001) and the lymphatic system (Geiser *et al.*, 2005) to the lymph nodes for antigen presentation (Manolova *et al.,* 2008). While the recognized nanoparticles will be cleared by macrophage-mediated clearance, phagocytosed nanoparticles may be destroyed within the lysosomes of phagocytic cells (Chono *et al.,* 2006). If the nanoparticles exceed the size of the engulfing phagocyte, they take inflammatory response, including cytokines, chemokines and ROS, which can result in inflammation (Borm *et al.,* 2004) and DNA damage (Li *et al.,* 2008).

From the lymphatic and circulatory systems, nanoparticles may distribute to organs including the kidneys, from where partial or total clearance may occur. The Cu is also engaged in immune system activation to battle infections and heal wounded tissues (Failla *et al.,* 2003). Furthermore, it promotes the neutralisation of free radicals, which cause serious cell harm (Tapiero *et al.,* 2003). Cu has been demonstrated to be somewhat absorbed by the stomach, although the vast majority is absorbed in the small intestine. Also, Cu is primarily eliminated in the gastrointestinal tract (GIT) through bile, with just a little amount reabsorbed by intestinal cells (Magaye *et al.,* 2012). Likewise Cu's biological roles are linked to its participation in metalloenzyme active sites. In addition Cu may be present in several metalloenzymes, including cytochrome oxidase, SOD, lysyl oxidase, dopamine hydroxylase, and tyrosinase (Makarski *et al.,* 2006).

The cu is necessary for the production of antioxidant enzymes, white blood cells, and antibodies (Sharma *et al.,* 2005). Additionally Cu is transported to cells through the protein ceruloplasmin, which also functions as an oxidative enzyme (Lin *et al.*, 2008). Also, Cu is essential for the body since it is a part of the enzyme systems involved in the creation of red blood cells, the metabolism of iron, and immune system activity. Furthermore, Cu stimulates the manufacture of dopamine, which helps the neurological system develop as well as connective tissues like collagen and elastin (Mroczek-Sosnowska *et al.,* 2013).

5. Effects of Nano-CuO on growth performance

Animal growth and health may be impacted if Nano-CuO uptake in the GIT is increased. When added to feed for piglets, poultry, and fish, Nano-CuO has been shown to boost growth performance and feed utilisation when compared to CuSO4 (Gonzales *et al.,* 2009; Mroczek-Sosnowska *et al.,* 2015b; El Basuini *et al.,* 2016). The enhancement was credited to Nano-CuO 's superior bioavailability when compared to CuSO4 salts. The mechanism underlying this improvement is still unclear, though. Studies have suggested that the antimicrobial characteristics of Nano-CuO may be responsible for their effects (Arias *et al.,* 2006), while others have proposed that enhanced energy and fat digestion may be the cause (Gonzales *et al.,* 2009; Scott *et al.,* 2016). Furthermore, some studies demonstrated that the activity of SOD was enhanced with Nano-CuO supplementation in animal diet (Lien *et al.,* 2009; Refaie *et al.,* 2015). Nanoparticles in animal nutrition are explored for growth performance, feed utilization and health status (Abd El-Hack *et al.,* 2017; Amlan and Lalhriatpuii, 2020; Dawood *et al.,* 2021). The most frequently observed increases in body weight, average daily gain, and feed conversion ratio (FCR) are caused by nano-forms of micro- and macroelements(FCR) (Ba *et al.*, 2018; Yusof *et al.*, 2019). NPs are used to cover the animal's demand for elements, improve their productivity.

6. Effects Nano-CuO on physiological response

Due to its numerous biological actions, copper is a crucial trace metal in the diet of chickens. It functions as a constituent of numerous proteins and metalloenzymes, including as cytochrome oxidase, superoxide dismutase, ascorbate oxidase, and tyrosinase. It is essential for the production of erythrocytes, iron metabolism, and hemoglobin. Additionally, it participates in the biosynthesis, crosslinking, and production of keratin and melanin as well as collagen and elastin fibers (Tapiero *et al.*, 2003). It plays key role in hemoglobin synthesis, iron metabolism, and erythrocyte formation. It is also involved in biosynthesis and crosslinking of elastin fibers and collagen and of keratin and melanin synthesis (Miroshnikov *et al.*, 2015). Makarski *et al.* (2006) reported that a large number of metallic enzymes contain copper such as cytochrome oxidase, superoxide dismutase (SOD and tyrosinase. Furthermore Cu also aids in the production of connective tissues like collagen and elastin, as well as the development of the nervous system through dopamine synthesis Myeloid tissue and spinal cord tissue McDowell (1992) explained that Cu is involved in cellular respiration, energy generation, collagen synthesis, absorption and use of other trace minerals, antioxidant activity, heart function, bone growth, keratosis and pigmentation, and antioxidant action, among other things. Cu's essentiality is determined by the capacity of Cu atoms to gain and lose electrons in order to generate cuprous Cu+1 and cupric Cu+2 states. As a result, this change is critical for enzymes to support the metabolism of all main substrates, including proteins, lipids, and carbohydrates (EFSA, 2016). The Cu is involved in cellular respiration, energy production, synthesis of collagen, uptake and utilisation of other trace minerals, antioxidant activity, cardiac function, bone formation, keratinisation and pigmentation of tissue and myelination of the spinal cord (McDowell *et al.*, 1992). In addition, it contributes to the regulation of glucose and cholesterol metabolism (Mroczek-Sosnowska *et al.*, 2013). A deficiency Cu supplementation in the diet can cause disturbances in reproduction and development of sperm, high mortality of embryos during hatching, poor pigmentation of feathers, slow growth and a reduction in body weight (Mroczek-Sosnowska *et al.*, 2013). Furthermore, it may result in muscle weakness, anaemia, bone alterations that resemble scurvy, defective connective tissue synthesis, impaired myelinisation of nerve tissues and neurological defects, altered lipid metabolism and cardiac malfunction (Mroczek-Sosnowska *et al.*, 2013). Numerous studies have shown that Cu plays a significant and erythrocyte production (Tapiero *et al.*, 2003; Sharma *et al.*, 2009; Samanta *et al.*, 2011), which transports about 95% of Cu contained in blood, also takes part in iron metabolism (Meyer *et al.*, 2001; Zerounian & Linder, 2002; Cherukuri *et al.*, 2004). Cu increased haemoglobin, decreased plasma cholesterol and triglyceride significantly, decreased plasma proteins and its fraction did not change due to Cu supplementation (Rahman *et al.*, 2001). It can be determined that Cu supplementation has an effect on the blood levels and erythropoietic system of the chicken which could be used as an indicator of the impact of its toxicity in chickens. Furthermore, changes in the peripheral blood enable more accurate evaluation and explanation of the effect of Cu on the chicken's body (scoot et al., 2018). Agglomerates of nano- and micro-particles not only promoted growth performance but also extended the duration of deposition of the minerals in the body. Nano-CuO , a day after injection, increased the red blood cells, hemoglobin, protein, and copper in serum. However, non-significant effects of hematological parameters were observed in another study (Sosnowska et al., 2017). They investigated the effects of Nano-CuO and CuSO4 injections in fertilized broiler eggs. Chick development was observed by weighing body and relative organ weights after 24 h of hatching. Different sources of Cu exhibited non-significant effect on oxygen consumption but higher level (50 ppm) of Cu increased oxygen consumption.

7. Effects Nano-CuO on antioxidant capacity

Copper is one of the micronutrients considered essential to the growth, development and function of living organisms. Copper is involved in numerous biochemical processes as it has ability to easily accept and donate electrons which it occurs in the oxidation states Cu+ and Cu2+ (Angelova *et al.,* 2011; Maltais *et al.,* 2013). Such as Cu is part of the active sites of many enzymes, including copper-zinc superoxide dismutase (CuZn-SOD), cytochrome c oxidase, L-lysine oxidase, ascorbate oxidase, tyrosinase and dopamine beta-hydroxylase (Gaetke and Chow, 2003). These enzymes play an important role in antioxidant defense, melanin synthesis, formation of connective tissue, dopamine metabolism and mitochondrial respiration (Maltais *et al.,* 2013; Brewer, 2007; Angelova *et al.,* 2011; Palumaa, 2013). Moreover, Cu can bind directly with thiol groups of sulfur-containing amino acids (cysteine), leading to their oxidation and the formation of crosslinks between proteins, which may result in inactivation of enzymes or damage to the cell's structural proteins (Letelier *et al.,* 2005; Wu *et al.,* 2010; Dusek *et al.,* 2012). Similarly, specialized proteins are involved in intracellular transport of Cu and incorporation of this element into enzyme molecules (Ognik *et al.,* 2016). In the last decade numerous nutritional experiments have also been carried out using metal nanoparticles, showing that the biological response of the organism depended on the size of the particles the method by which they were produced, the dosage applied and the length of administration (Zhao and Riediger, 2014). It has also been shown most often in vitro using established cell lines (mainly murine macrophages and human dendritic cells) (Małaczewska, 2014), that Cu nanoparticles can exert an immunotropic effect, that is react with components of the immune system and thereby stimulate or inhibit it. The Cu affects the regulation of ceruloplasmin concentration, SOD activity and the digestion of dietary fat. The SOD enzyme helps in removing the damage caused by ROS by catalysing the dismutation of two superoxide radicals to hydrogen peroxide and oxygen (Lin *et al.,* 2008).

8. Conclusion

Broiler diet should incorporate green synthesis of Nano-CuO at a lower risk to consumers because it can improve bird health and performance. However, a lot more research is still needed to prove that using green synthesis of Nano-CuO in poultry nutrition is safe and won't affect people, the environment, or animals. Although the usage of Nano-CuO is still in its early stages, promising findings from recent studies are motivating more research. It appears that the inclusion of green synthesis of Nano-CuO supplements in chicken feed will be feasible in the near future.

Authors' Contributions

All authors are contributed in this research.

Funding

There is no funding for this research.

Institutional Review Board Statement

All Institutional Review Board Statements are confirmed and approved.

Data Availability Statement

Data presented in this study are available on fair request from the respective author.

Ethics Approval and Consent to Participate

Not applicable

Consent for Publication

Not applicable.

Conflicts of Interest

The authors disclosed no conflict of interest starting from the conduct of the study, data analysis, and writing until the publication of this research work.

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