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The crucial influence of nano-copper (nano-Cu) on rumen function, ruminant productivity, and reproduction

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ABSTRACT

The requirements and factors that affect dietary requirements for various trace minerals and vitamins in ruminants remain poorly defined. Copper (Cu) is recognized for its pivotal role in the cellular osmotic balancing system, thereby contributing to numerous metabolic mechanisms in livestock. However, the provision is still often neglected to be given. Nanoparticle technology has emerged as promising approach to pursuit of optimizing the functionality and efficacy of feed mineral consumption. The objective of this article was to review the criteria and effects of supplementary feeding of nanomineral copper (nano-Cu) on rumen function, productivity and reproductive ability in ruminants. Additionally, the manufacturing process of nano-minerals was also briefly discussed that has not been widely published. The primary source of information reviewed for this article is published scientific literature.

Introduction

Minerals, a category of micronutrients, are frequently disregarded, despite their crucial significance. Minerals are integral to the metabolic processes of livestock, exerting a distinct influence on growth patterns, reproductive activities, and the overall health of livestock (Pandey *et al*., 2023). Copper (Cu) is recognized for its role in the cellular osmotic balancing system, hence contributing to growth, reproduction, blood cell formation, cell metabolic processes, and particularly female livestock in the reproductive proces (Ognik and Krauze, 2016).

Furthermore, Cu assumes a significant function as a precursor in a multitude of enzymatic processes, encompassing superoxide dismutase (SOD), ceruloplasmin, cytochrome oxidase, L-lysine oxidase, ascorbate oxidase, tyrosinase, dopamine beta-hydroxylase, superoxide dismutase cofactor, tyrosinase, and reactive protein activity. High levels of Cu are found in antioxidant enzymes, specifically ceruloplasmin (Cp) and superoxide dismutase (SOD). Cu is involved in a range of metabolic processes, encompassing iron metabolism, cellular respiration processes (by enabling electron transport), connective tissue development, antioxidant mechanisms, and pigmentation (Gaetke and Chow, 2003; McDowell, 2003).

Nanoparticle technology has been employed in the pursuit of optimizing the functionality and efficacy of feed mineral consumption. The utilization of nanomineral copper (nano-Cu) in feed products has gained significant traction and has emerged as a viable renewable technology within the livestock industry (Ogen-Shtern *et al*., 2020; Hajjami *et al*., 2021). Nano-Cu has reduced dimensions while possessing an expanded surface area, hence enabling enhanced biological functionality through the utilization of lower concentrations (Strauch *et al*., 2020; Liu *et al*., 2022).

Prior studies have shown evidence indicating that the application of nano-Cu 7.68 mg/kg DM in dairy cows can enhance milk production by promoting feed efficiency through heightened cellulose and protease enzyme activity in the rumen while simultaneously preserving the rumen amylase metabolic proces (Shang *et al*., 2020). Other studies have also shown an increase in the efficiency of rumen performance in ruminants, such as improving the process of protein deamination, the efficiency of carbohydrate ingestion by rumen microbes, and others after adding some level of nano-Cu (Yanguo *et al*., 2020). This review study provided a comprehensive examination of the impact of utilizing nano-Cu at various feeding levels on the efficacy of rumen digestion, ruminant productivity, and reproduction. Additionally, it provided short insights into the manufacturing process of nano-Cu.

Manufacturing and production of Nano-Cu

The particle size distribution of nanominerals impacts their functional activities, such as biological, chemical and catalytic. Therefore, an efficient method is needed for nanomineral synthesis (Chauhan *et al*., 2016).Three ways are available for carrying out nano-Cu synthesis: physical, chemical, and biological (or "green synthesis") methods. Evaporation-condensation, physical vapor precipitation, gas phase synthesis, electric arc discharge, laser ablation, chemical vapor deposition, and ball milling-annealing are examples of physical processes. Inert gas condensation, chemical reduction, and the sol-gel method are examples of chemical techniques. Plants, algae, fungi, bacteria, and viruses can all be used in biological (or "green synthesis") processes (Abdelnour *et al*., 2021). During the physical method's process, large particle distribution and contamination can occur (Rajendran *et al*., 2013). Chemical techniques can provide a uniform particle size distribution using chemical-based materials, but they require strict adherence to strict guidelines before being given to animals (Swain *et al*., 2021). Biological techniques, also known as green synthesis, utilize components derived from natural sources, resulting in reduced toxicity and enhanced environmental friendliness (Murugan *et*

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al., 2014; Huston *et al*., 2021). Testing of nanoparticles can be done in various ways, including using a particle size analyser (PSA), scanning electron microscope (SEM), transmission electron microscope (TEM), X-ray diffraction (XRD) patterns and others (Rajendran *et al*., 2013). The utilisation of nano minerals can increase the bioavailability of each mineral and increase the bioavailability of each mineral by increasing cellular uptake and avoiding mineral antagonism. However, attention must be paid to its metabolism in the ruminant`s body (Abdelnour *et al*., 2021). Research on Nano-Cu formulations as supplements indicated that the nano mineral produced was in the form of a fine powder, a yield concentration of 68 per cent, observations under a transmission electron microscope were spherical in diameter between 30-80 nm, a zeta potential value of -22.8 mV, and a selenium concentration using X-ray dispersive energy analysis of 98.57±0.48 (Arulnathan *et al*., 2017). As mentioned above nano-Cu can be synthesised chemically or physically and can even be obtained by the biological method involving microorganisms or plant extracts, called green synthesis (Hosnedlova *et al*., 2017).

Application of Nano-Cu supplementation to rumen fermentation and digestibility

The trace mineral, copper (Cu), represents an important mineral in animal feed as it has essential physiological benefits: component or enzyme activator; involves in the synthesis of keratin, collagen and elastin and plays an essential function for the defense mechanisms and production. In ruminant animals, in addition to its metabolic functions, Cu has several effects on the ruminal microflora, such as positive effects on ruminal fermentation acting directly on microbial enzyme activity (Hilal *et al*., 2012; Jankovská *et al*., 2017; Sloup *et al*., 2017). Cu is required for the activity of several enzymes, cofactors, and reactive proteins, include caeruloplasmin, cytochrome c-oxidase, lysyl oxidases, superoxide dismutases, and tyrosinase. In addition, it helps with iron metabolism, connective tissue growth, defense mechanisms, and skin color (McDowell, 2003; Clarkson and Kendall, 2022). According to previous study Cu plays a part in the activity of many bacteria by acting as a cofactor for vital enzymes such as cytochrome oxidase, NADH dehydrogenase, and superoxide dismutase (Kenney and Rosenzweig, 2012). Although Cu is necessary for animal health, the effects of administration and concentration on rumen fermentation need to be considered. In order for many enzymes to function properly during the body's biological processes, copper, a trace mineral, needs to be a cofactor (Johnston *et al*., 2014).

Nano-Cu has higher bioavailability than copper sulphate, according to published findings (Gonzales-Eguia *et al*., 2009; Wang *et al*., 2012). Based on the results of the investigation of references regarding conventional Cu supplementation in feed, only a few references were obtained using Cu supplementation in the form of nanoparticles, so research using nano-Cu supplementation is an opportunity to produce research that has novelty. In vitro studied with nano-Cu indicate though that high levels of inorganic Cu (such as CuSO4) negatively influence rumen fermentation and reduced VFA production (Vigh *et al*., 2023). Multiple investigations conducted have focused on the significant enhancement of mineral bioavailability in ruminants when minerals are administered in nanoparticle form, however, little literature has addressed the effects of nano-Cu (Xun *et al*., 2012; Pelyhe and Mézes, 2013).

The study which added of 10 mg nano-Cu/kg DM to the base feed dramatically decreased the pH of rumen fluid and increased rumen VFA production than the control (Jamadi *et al*., 2022). The molar concentration of acetate in the high dose nano-Cu supplementation was found to be not significantly different from the treatment group supplemented with 30 mg nano-Cu/kg DM, but significantly higher in the groups supplemented with 10 and 20 mg nano-Cu/kg DM compared to the control. The supplement had no significant impact on the molar concentrations of propionate and butyrate (Zhang *et al*., 2007). Increased VFA production could sugested due to reflux carbon occurs in the rumen (Shete, 2023). Different data were reported by Zhao *et al*. (2022) who reported that Cu levels did not affect rumen pH, total VFA content, total gas, or CH_4 after addition of nano-Cu. However, other studies have shown that high levels of nano-Cu can reduce ruminal CH_4 production (Hernández-Sánchez *et al*., 2019) or slow down the trend of enteric CH_4 production (Sánchez-Sánchez *et al*., 2021), only the addition of nano-Cu as feed additives is still very limited and the available data is still very variable. Variations in VFA profiles are most likely due to variations in digestive enzyme activities caused by varying concentrations of nano-Cu additives. According to lastest research, nano-Cu have significant levels of antibacterial activity and microbial characteristics. When added to vegetable and animal proteins, they enhance some of the bactericidal effects of these proteins, which reduces gas production. Due to the chemical alteration of certain proteins, the addition of copper nanoscale particles increases gas production (Jamadi *et al*., 2022). Addition of nano-Cu was increased microbio population due to improved pH, higher availability of nitrogen, and higher energy of fermentable sources in lasted study (Shete, 2023). Nano-Cu also leading on defaunation of rumen ciliated protozoa then also affect on decreased of metanogenic bacteria which had symbiotic mutualism with protozoa then leads on decreased of methan production (Shete *et al*., 2023).

The intestinal tract absorbs nano-Cu, with a little amount in the abomasum and colon. Under rumen conditions, food nano-Cu, breakdown into Cu2+ ions. These ions can interact with ammonium thiomolybdate, volatile fatty acids, and lignin in the rumen fluid (Ghodrat *et al*., 2015; Chen *et al*., 2018). Cu may create intractable or inedible compounds that are expelled in feces, solvents that are carried into the abomasum, or unbound Cu. Cu oxide, which is viscous in rumen fluid, penetrates the acidic abomasum without Cu antagonists (Spears and Weiss, 2014). Cu2+ ions form in acidic conditions and time spent in the acidic the abomasum before reaching the gut affects Cu dissociation. Several previous studies have described the effect of nano-Cu supplementation on rumen fermentation activity (Table 1).

Application of Nano-Cu supplementation to ruminant productivity

Copper or nano-copper (Nano-Cu) is essential for the development of the neuro system (Gaier *et al*., 2013; Zhao *et al*., 2022), growth, including coat and hair, bone and connective tissue development (Suttle, 2010), fur pigmentation (Waldner *et al*., 2023), and fertility (Hemalatha and Makeswari, 2018; Narasimhaiah *et al*., 2018; Williams *et al*., 2002). Cu shortage can adversely influence the nervous, immune, cardiovascular and reproductive systems of animals (da Silva *et al*., 2022). Nano-Cu is an artificial material that has been widely used in animal feed additives and brings a technological revolution to livestock development although there has not been much research on the use of nano-Cu itself. Deficiency of Cu concentration in the blood, due to low supply from feed (forage) may lead to metabolic disorders in blood parameters and antioxidant function in small ruminants (Shen *et al*., 2021; Min *et al*., 2022). Cu deficiency affects antioxidant function and causes various diseases in goats (pica, anaemia, suppressed appetite, growth retardation, rough coat, and emaciation) (Rong *et al*., 2011). Therefore, supplementation with nano-Cu in feed is needed.

Goats supplemented with nano-Cu (2g/head once/week) for 30 days showed a significant increase (0.25 µg/g per 10 days) in blood Cu content (Shen *et al*., 2021). Sheep supplemented with nano-Cu (2g/head once/week) for 20 days showed a significant increase (1.72 µg/g) in blood Cu content (Min *et al*., 2022). Nano-Cu particles have a very active role in biological systems due to their nanoscale. Nano-Cu supplementation can enhance antioxidant function, reduce lipid peroxide production, protect the integrity of cell membrane structure and function, and improve the function of various tissues and organs in goats and sheep (Shen *et al*., 2021; Min *et al*., 2022). While in dairy cows reported that dietary sup-

plementation of nano-Cu improved the health status of dairy calves by increasing immunity and antioxidant status, especially against the incidence or symptoms of diarrhoea in calves (Pandey *et al*., 2023). Meanwhile, in young cattle (heifers) it was reported that dietary supplementation of nano-Cu improved health status, namely on immune response and increased antioxidant status (Vaswani *et al*., 2018; Kushwaha *et al*., 2021). However, there are still few studies that explain the role of nanominerals, especially nano-Cu as feed supplements on animal performance. Therefore, a brief review was conducted with the literature study presented in the Table 2.

Application of Nano-Cu supplementation to ruminant reproduction

Copper (Cu) deficiency in sheep will, to a certain extent, slow down the growth rate, which will, in turn, lower the economic advantage of sheep breeding (Zhao *et al*., 2022), as the Cu of the lamb is deficient, its development is severely stunted, and as it walks, its hindquarters swing and it is easier for them to tumble down. In severe circumstances, the livestock may experience paralysis in their hindquarters. In mature ewes, a Cu shortage can frequently be seen as an inconspicuous estrus, infertility,

Table 1. Effect of copper nano mineral supplementation on rumen fermentation activity

Treatment/element	Dosage/treatment	Livestock	Effect	Reference
Nano-Cu	0, 30, and 60 ppm/kg feed	Cattle	In sacco analysis showed Canola meal and soybean meal both produced more gas at 48 and 72 hours after the addition of 30 ppm of copper oxide nanoscale particles. At 12, 24, 48, and 72 hours, the amount of gas produced by poultry offal meal is dramatically reduced by the addition of 30 and 60 ppm of copper oxide nanoscale particles.	Jamadi *et al.* (2022)
Nano-Cu	0, 10, and 20 mg/kg feed	Cattle	The addition of nano-Cu to alfalfa can reduce rumen microorganisms (protozoa). The addition of nano-Cu reduces gas production and methane emissions.	Palangi *et al*. (2024)
Nano-Cu	Not mentioned	Gir cows	Increased ammonia nitrogen than control Improved VFA production Increased rumen methane production Higher total microbia rumen but decreased methanogenic bacteria (*Methanobrevibacter* sp) and protozoa	Shete (2023)
Nano-Cu	15 mg/day/head	Holstein calves	Increased VFA production	Vahedi *et al*. (2018)

Table 2. Effect of copper nano mineral supplementation on ruminant productivity

Element	Dosage/treatment	Livestock	Effects	References
Nano-Cu	2 g/head	Guizou Black goats	a significant increase in blood Cu content by 0.25 µg/g per 10 days, which is:	Shen *et al*. (2021)
Nano-Cu	5 g/ head	Kazakh sheep	a significant increase in blood Cu content by	Min *et al*. (2022)
Nano-Cu	10 mg/ head	Cattle	Increase in ADG by 11 g/day/head in supplemented calf	Pandey *et al*. (2023)
Nano-Cu	5 and 10 mg/kg DM	Sahiwal cows (heifers)	Nano-Cu supplementation at 5 mg increased ADG by 18 g/head/day, while the 10 mg group increased ADG by 29g/head/day compared to the control. Nano-Cu supplementation of 5 mg increased feed BK consumption (DMI) by 0.13 kg/head/day, while the 10 mg group by 0.16 kg/head/day compared to the control. Nano-Cu supplementation of 5 mg reduced feed conversion (FCR) by 0.35, while the 10 mg group by 0.40 compared to the control. Nano-Cu supplementation of 5 mg increased feed efficiency (FCE) by 0.07, while the 10 mg group by 0.08 compared to the control.	Vaswani *et al*. (2018)
Nano-Cu	8 mg/kg DM basis	Hariana cows/ heifers	Increased ADG by 9 g/head/day compared to the control. Reduced feed BK consumption (DMI) by 0.03 kg/head/day, while the 10 mg group by 0.16 kg/head/day compared to the control. Increased feed conversion (FCR) by 0.25 compared to the control. Increased the body condition score (BCS) to 2.68 compared to the control which was 2.57.	Kushwaha *et al*. (2021)
Nano-Cu	Not mentioned	Gir cows	Increased feed intake than the control Increased milk production up to 10% than control Increased gene expression on SLC2A8 as the glucose metabolism precursor on milk production process	Shete (2023)
Nano-Cu	15 mg/day/head	Holstein calves	Increased final weight up to 10% than control groups Increased ADG to 600 g/day Decreased diarrhea potential Increased blood Cu, glucose, total protein and albumin Increased GPx as natural antioxidant	Vahedi *et al*. (2018)

or abortion. These symptoms might be caused by a lack of copper.

Nano-Cu is a potent antioxidant compound, thus the provision of it either through feed or as an additive to the culture media is highly significant. However, research on this subject, especially on semen extenders in ruminants, has yet to be found, although significant results have been found in other species (Bastidas *et al*., 2019; Kowalska-Góralska *et al*., 2019; Garncarek *et al*., 2022; Yang *et al*., 2022). According to the research carried out in previous study, the effects of nano-copper oxide (nano-Cu_2O) are superior to those of CuSO4 and Cu_2O. This compound possesses a powerful biological effect, a good growth encouraging effect, and a high bio-availability (Min *et al*., 2022). Nano-Cu and their combination were effective in reducing the survivability of mastitis-borne pathogens without having any harmful effects on the tissues of the mammary gland (Radzikowski *et al*., 2020). The use of nano-Cu as pharmaceuticals for the treatment of osteoporosis, antibacterial and antifungal agents, contraceptives, in cancer imaging and therapy, and as food supplements for farm animals has shown a lot of promise (Zhou *et al*., 2016; Verma and Kumar, 2019; Mor *et al*., 2020). The data that are now available on the action of copper and CuNP on reproduction continue to be limited and contradictory. There is a body of evidence that was obtained on rodents that demonstrated the capability of copper and CuNPs to reduce gonadotropin and blood gonadal steroid hormones levels, to induce degenerative changes in gonads, to induce ovarian follicular atresia, and to suppress gamete and embryogenesis (Roychoudhury *et al*., 2016). Several previous studies have described the effect of nano-Cu supplementation on ruminant reproduction (Table 3).

Table 3. Effect of copper nano mineral supplementation on ruminant reproduction

Element	Dosage/treatment	Livestock	Effect	Reference
Nano-Cu	5g/head	Chinese Merino sheep male	Significantly improve physiological and biochemical parameters, increase the growth rate and wool yield	Zhao *et al*. (2022)
Nano-Cu	10mg/ml	Shami goat kid	A significant increase in the percentage of fat for the second treatment compared to the control and third treatments,	Alsamarrai *et al*. (2022)
Nano-Cu	10mg/ml	Granulosa cells	Directly affecting ovarian cells and their basic functions-viability, proliferation, apoptosis and release of hormones.	Sirotkin *et al*. (2020)

Conclusion

The administration of copper nanomineral in specific dosage is very important. Nano-Cu serves as an important role as the main precursor of antioxidants and various cellular activities of cells. The particle size distribution of nanominerals impacts their functional activities, such as biological, chemical and catalytic. Nano-Cu plays a role in the activity of many bacteria by acting as a cofactor for important enzymes such as cytochrome oxidase, NADH dehydrogenase, and superoxide dismutase, making it an important ingredient for maintaining rumen microbial activity. Feeding up to >10 mg nano-Cu has a positive effect on growth, productivity and reproductive function of livestock.

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Conflict of interest

The authors declare that there is no conflict of interest in this manuscript.

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