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REVIEW ARTICLE

Importance of Nano-Sized Feed Additives in Animal Nutrition

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ABSTRACT

"Nano", which derives from the Latin word *nanus* and means dwarf, refers to a very small unit of measurement equal to one billionth of a meter. Nanotechnology, which deals with the manipulation of matter at the atomic and molecular level, has an application area in animal husbandry as well as in many fields. Nano-sized feed additives, which have come to the forefront in the livestock sector in recent years, have become an innovative application used to increase the nutritional value of feeds and optimize animal health and performance. Since these additives are nano-sized particles with increased specific surface area, they can have a positive effect on a number of factors such as digestibility, nutrient absorption, immune system, growth and development. Minerals in the form of nanoparticles used as feed additives can increase bioavailability by passing through the intestinal wall to body cells faster compared to larger particles. The nano level of the substance not only increases the productivity of animals, but also brings the potential to improve the functionality of feed molecules. Nano feed additives increase the digestion and absorption of feed, allowing animals to benefit from feed more effectively. However, there are several challenges associated with this approach. These include the potential for endotoxin production, reduced nutrient absorption due to interaction with natural nutrients, the possibility of nanoparticle accumulation in the animal body, health risks, ethical considerations, environmental concerns and some negative effects such as interference with natural nutrients that can be avoided by encapsulation. This article discusses recent studies on nano-sized feed additives that offer potential benefits in animal nutrition.

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1. Introduction

Consumer demand for high-quality, safe, diverse, functional, or nutritious food in animal production is increasing every day (Bölükbaşı et al., 2023). Increasing consumer demands and economic growth have brought animal production to a significant position (Latino et al., 2020). This is getting stronger due to urbanization and rising incomes. Increased demand triggering a higher global demand for animal feed, which requires large quantities of grain to feed livestock. This trend has important implications for the future sustainability of the livestock sector and resource management. Global feed demand is projected to almost double after 2050. It is estimated that 1.3 billion tons of grain will be needed to feed livestock alone (Valin et al., 2014; Rajendran et al., 2022). To meet these expectations, sustainable agricultural practices, feed processing, and animal nutrition techniques need to be developed. Biotechnological approaches are needed to obtain relatively cheap, high-quality products with reduced environmental impact to meet the nutritional needs of a global population expected to reach 9 billion by 2050 (Pirgozliev et al., 2019).

Following the ban on the use of ionophore group antibiotics in animal nutrition, interest in biotechnological methods for animal health and productivity has increased in recent years (Gilbert, 2012). As a result, increased awareness of feed additives has led to a trend towards sustainable practices in the

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livestock sector (Pandey et al., 2019). Animal nutrition is a fundamental element of modern agriculture. It has a direct impact on healthy animal growth, productivity, and product quality. In recent years, there has been a shift away from antibiotics, traditionally used as growth promoters, towards natural feed additives (Özdemir et al., 2022). This shift both ensures the safety of products intended for human consumption and improves performance by minimizing the environmental impact of antibiotic additives. It is also positively changing the balance of the animal production industry (Schmidt, 2009). Feed additives play a very important role in animal nutrition. In particular, they increase the efficiency of nutrients in animal feed. These additives, which are used to promote animal growth by improving the quality and flavor of feed, exert their effects on the intestines or intestinal cell walls of the animal (Bai et al., 2022). Feed additives are also added to animal feed in non-therapeutic amounts to help protect the animal from various environmental stresses (Ban & Guan, 2021). These additives, which can include various substances such as crystalline amino acids, antioxidants, antifungals, etc. help to increase the production of animal protein for human consumption and reduce the cost of animal products. Conventional feed additives have long been used to provide animals with the nutrients they need. However, the use of these additives is sometimes limited in terms of efficiency, cost-effectiveness, and environmental impact. In this context, the use of biotechnology in agriculture has emerged as a revolutionary innovation in animal nutrition. One of these new technologies is the science of nanotechnology, which enables the use of materials at the atomic and molecular levels (Tona, 2017; Placha et al., 2022a, 2022b). Nanoparticles (NPs), which have the potential to provide innovative solutions to current problems in agriculture, can offer significant benefits to the sector (Usman et al., 2020). Manipulation of matter at the nanoscale offers the potential to enhance the functionality of feed molecules as well as increase animal productivity (Bunglavan et al., 2014; Nabi et al., 2020; Rajendran et al., 2022). Nano-sized feed additives such as NPs are extremely small particles that can provide various benefits in animal nutrition (Yadav et al., 2022). These additives can improve both the quantity and quality of safe, healthy and functional animal products. The results of the latest research show that incorporating nanomaterials into animal feed can lead to improved animal growth, better-feed utilization and more efficient nutrient conversion (Seven et al., 2018; Abdelnour et al., 2021). In addition, nanomaterials can help improve digestion and absorption of nutrients in animals, resulting in better overall metabolism and physiology (Abdelnour et al., 2021). The use of nano-sized feed additives in animal nutrition is an emerging field with the potential to revolutionize the livestock industry due to their potential benefits in improving animal health and performance (Dubey et al., 2017; Abdel-Rahman et al., 2022). Nano-sized feed additives, especially nanominerals, have superior bioavailability compared to conventional minerals. Nanominerals, with their low doses and enhanced bioavailability, are a viable substitute for antibiotics and can be incorporated into natural feed components (Schmidt, 2009; Gelaye, 2024). This means that animals require less of these additives to obtain the same nutritional benefits. Nano-sized feed additives have the effect of increasing growth, removing residues, reducing environmental pollutants, contributing to the production of non-polluting animal products, improving the immune function of animals, and reducing the risk of disease (Dei, 2021). This review article discusses the role, benefits and application challenges of nano-sized feed additives in animal nutrition and highlights future research directions. Firstly, the basic properties of nano materials and their potential effects on animal nutrition will be examined, and then the impact of this technology on animal health, feed efficiency, and environmental sustainability will be discussed in detail.

2. What is Nanotechnology?

The word "nano" is derived from "*nanus*", a Latin term meaning "dwarf", and represents a tiny unit of measurement that is one-billionth of a meter (Singh, 2016; Joudeh & Linke, 2022). It was introduced by the renowned physicist Richard Feynman in 1959 and was first employed as a concept of nanotechnology by Norio Taniguchi in 1974 (Feynman, 1959; Mulvaney, 2015; Singh, 2016; Ijaz et al., 2020). In principle, nanomaterials are defined as materials with a length of 1-1000 nm and a diameter of usually 1 to 100 nm. Today, there is various legislation in the European Union (EU) and the USA that contains specific references to nanomaterials. An internationally recognized definition for nanomaterials has not been universally agreed upon. Different organizations have different views on the definition of nanomaterials. NPs are substances composed of a minimum of 50% of components with dimensions in the range of 1-100 nanometers, occurring naturally or synthetically, as outlined by the EU Commission. A nanometer (nm) is a unit included in the International System of Units (Système International d'unités, SI), which represents a length of $1x10^{-9}$ meter (Jeevanandam et al., 2018). Nano-sized feed additives are based on the manipulation and use of materials at the nanometer scale (billionths of a meter). This scale can alter the physical, chemical and biological properties of materials, greatly enhancing the efficacy and functionality of feed additives. Thanks to the small size, high surface area and increased reactivity properties of NPs, such additives can be more effective on the digestive system of animals and maximize the absorption of nutrients (Peters et al., 2016). Nanotechnology, as a field focusing on the regulation and control of matter at the molecular level, involves the process of investigating physical, chemical and biological phenomena at nanometer dimensions (Tüylek, 2021). These studies aim to create impacts in a wide range of science and technology fields, from materials science to biology, electronics to medical applications. The main goal of nanotechnology is to control properties by manipulating nanometer-scale structures and to enable the design of new and advanced products by using these properties in the desired way.

The science of nanotechnology, which has a common application area with biotechnology, which brings together natural sciences and engineering disciplines and deals with the manipulation of matter at the atomic and molecular level, has found a field of study in the field of animal nutrition as well as in many fields with the development of technology.

3. Nano Size Feed Additives

Feed additives used in animal nutrition can be classified in two ways as feed additives that are nutrients such as amino acids, minerals and vitamins, and non-nutrients such as antibiotics, hormones, prebiotics, enzymes, pellet binder, yeast culture, antioxidants, etc. (Tasho & Cho, 2016). The main reasons for the use of feed additives are protecting animal health, increasing productivity, increasing the nutritional content of feeds, preserving the quality of nutrients and feed, as well as giving a certain form to feeds. Integrated into feed formulation and production processes, these additives are strategically used in the animal feed industry to contribute to the healthy growth and development processes of animals and to optimize production efficiency (Mantovani et al., 2022).

The difference between nanomaterials and larger materials is that due to the surface effects of nanomaterials, the energy required for atoms to combine is low, which causes the atoms to be less stable. For example, the melting point of gold NPs of a given size is lower than the melting point of the same element of a larger structure. Quantum effects, on the other hand, involve nanostructures at the nanometer scale behaving like a single atom (Singh, 2016). There are three approaches to the synthesis of NPs: physical methods (such as high-energy ball milling and vapor deposition), chemical methods (including colloid formation), and biological techniques. Two primary strategies are used for nanoparticle synthesis: the top-down approach, which includes methods such as thermal decomposition, ball milling, lithography, laser ablation, and sputtering, and the bottom-up approach, which includes techniques such as chemical vapor deposition (CVD), sol-gel processes, spinning, pyrolysis, and biological synthesis. In the top-down approach, starting materials are transformed into larger structures and then further reduced to nanoparticles. On the other hand, in bottom-up synthesis, nanoparticles are built at the molecular or atomic level and then assembled to achieve the desired properties. These methods require different synthesis conditions and control mechanisms, and they find applications in various fields such as nanotechnology and materials science (Ijaz et al., 2020). Apart from these, methods such as reactive precipitation, microemulsion, sono-chemical, and supercritical chemical processes are also included (Prakash et al., 2022). NPs can be prepared by a variety of methods. Among these methods, precipitation is made using nanotools used in nanotechnology such as emulsion crosslinking, spray drying, and emulsion-drop combination. NPs can be broadly classified into several types, including inorganic (such as nanominerals), organic (including nanomolecules of proteins, fats, and sugars), emulsions, dispersions, and nanopolymers such as nanoclay (Al-Beitawi et al., 2017). Inorganic NPs are preferred in packaging, treatment, storage, and antimicrobial applications for use in feeding and irrigation (Bunglavan et al., 2014). Inorganic NPs include substances such as titanium dioxide, which is used in the feed industry as a UV protection barrier. Organic NPs, on the other hand, have various applications, such as nanocapsules, which can be used to increase nutritional value. These NPs can transport vitamins or other nutrients without affecting the taste or appearance of the feed. Nanotechnology is used in feed processing to deliver nutrients directly to specific organs without altering taste or color, using various techniques such as encapsulation, chelation, packaging and the use of nanotubes (Gelaye, 2024). Overall, the use of nanomaterials in the feed industry includes a variety of applications, such as biosensors, diagnostic markers, shelf-life extenders, and antimicrobials (Ahmadi & Rahimi, 2011). NPs increase nutrient absorption by reducing the antagonistic effect of divalent cations, especially in small minerals. These properties make them useful in the nutrition of livestock and poultry and improve the use of feed and supplements (Marappan et al., 2017).

Nanometer-sized NPs have a larger specific surface area, which differs from conventional-sized particles, higher surface efficiency, high catalytic efficiency, and greater absorbing ability. In addition, nanoparticles have unique physical, chemical, and biological properties, such as enhanced material strength, improved solubility, increased conductivity, optical properties, thermal dynamics, and catalytic efficiency (Alhashmi Alamer & Beyari, 2022; Khan & Hossain, 2022). The increased surface area of nano-sized particles can have a positive effect on many factors such as digestibility, nutrient absorption, immune system, growth and development (Hatab et al., 2022; Hussain et al., 2023). These advantages are used to increase the bioavailability of feeds through the size effect and high surface reactivity. Minerals in NP form used as feed additives can increase absorption rates by penetrating the gastrointestinal barrier and entering the body's cells faster than larger particle sizes (Bunglavan et al., 2014; Jafari & McClements, 2017).

Feed additives are very important to improve the growth performance of the animals. However, it also presents challenges such as endotoxin production and the potential for reduced nutrient absorption due to interaction with natural nutrients. With this reduction in nutrient absorption, many macronutrients can be metabolized or converted by microbes in the rumen (Patra et al., 2019). However, the preservation of nutrients for absorption in the small intestine is very important in this regard. When feed additives are combined with encapsulation at the nano scale, they are better recognized and utilized by the animals' bodies (Albuquerque et al., 2020). Encapsulation involves coating or trapping one material (in this case, feed additives or nutrients) inside another material to protect it from the surrounding environment. This technology is already widely used in various scientific fields, especially in animal nutrition researches. These additives work to increase the feed's resistance to spoilage, heat and light, and protect it from degradation by proteases and various digestive enzymes (Wang et al., 2022a) by using encapsulation, nutrients can be protected against premature spoilage in the rumen and made available for absorption in the small intestine. This can increase the efficacy of feed additives and improve overall animal health and growth.

Nano-encapsulation technique ensures that feed additives are transported to specific target sites and released under control. This is aimed at ensuring that animals get the most out of the feed by preventing substances from entering into undesirable chemical reactions (Shah et al., 2016; Pateiro et al., 2021; Tolve et al., 2021). In short, encapsulation and nanotechnology can be used together to improve the efficacy and safety of feed additives used in animal nutrition. The integration of these approaches can improve the growth and health performance of animals and bring significant innovation to animal feeding strategies. As a result, it increases the bioavailability of feed additives.

4. Increasing Feed Efficiency with Nano-Sized Additives

The challenges facing modern agriculture are multifaceted and complex. One of the main problems is the low efficiency of converting plant products, which are primarily used as animal feed, into animal products. This inefficiency intensifies the pressure on agricultural systems, leading to an increase in demand for crop production. As the world grapples with this problem, there is a growing consensus that agriculture needs to develop in a more productive and diversified way. This evolution is forced not only by the growing global population but also by the changing climate and the declining availability of natural resources. The call for sustainable food production resonates around the world (Jararweh et al., 2023; Azlan et al., 2024). It's not just about increasing the amount of food produced; the point is to do this in a way that uses fewer resources, reduces environmental impact, and at the same time improves farmers' livelihoods. This balancing act presents a significant global challenge that requires a thoughtful and strategic approach to how we produce and consume food. Technology, on the other hand, is at the forefront of this agricultural revolution. Feed additives produced by preventing pollution and utilizing waste products are included in feed technology (Dumlu & Bölükbaşı, 2023). From precision farming techniques that optimize resource use and reduce waste, to biotechnology that can increase crop yields and resilience, technology offers a range of solutions for modernizing farming practices. The application of these technologies can lead to significant improvements in the efficiency of food production systems, enabling more food to be produced with a lower environmental footprint (Evcim et al., 2012; Qayyum et al., 2023).

There is evidence that nano-sized feed additives significantly improve feed efficiency in animals. These additives, which optimize nutrient absorption and utilization, help animals convert feed into energy more effectively, leading to improved growth rates and feed conversion rates (Kah et al., 2019). Incorporating nano-sized additives into animal feeds is a key approach to improving feed efficiency and in turn, the profitability of animal agriculture. Thanks to the use of nano feed additives to improve feed efficiency, it can both reduce feed costs and increase the quality and quantity of animal products (Poddar & Kishore, 2022).

Increasing feed efficiency means indirectly increasing the quantity and quality of the product. As a matter of fact, studies have shown that meat and egg quality in chickens and meat, milk and other yield parameters in cattle and sheep were mostly positively affected by the inclusion of nano feed additives in the ration through water and feed (Dong et al., 2022; Gelaye, 2024).

4.1. Advantages of Nano-Sized Feed Additives

Nanostructures developed with rational approaches are among the most impressive artificial materials and have unique chemical, physical, and/or biological properties (Khan et al., 2022). Nanominerals and nanoemulsion technologies offer low-cost, reduced additives, growth-promoting and immunomodulating properties in the production of cattle and poultry feed (El-Sayed & Kamel, 2020). Nanominerals can suppress harmful pathogens in feed, control the rumen fermentation process, and provide solutions to reproductive problems in cattle and sheep populations. At the same time, nano-zinc oxide used in treating animal diseases can improve the growth rate, immune response and reproductive efficiency of livestock and poultry; it can also reduce the incidence of diarrhea in piglets (Mishra et al., 2014; Hassan et al., 2021). Thanks to liquid vitamins prepared with nanotechnology, nutrients are mixed directly into the blood through the gastrointestinal tract, and their bioavailability increases (Shabani et al., 2019).

NPs also help to reduce the need for preservatives in feed and eliminate odours in feed that are unpleasant to animals (Reddy et al., 2020). Nanotechnology plays an important role in the treatment of animal diseases, including therapy, diagnostics, tissue engineering, vaccine development, and many other areas. The application areas include a wide range of fields such as animal health and production, animal breeding, reproduction, animal nutrition (Wang et al., 2022a).

Nano-sized feed additives offer several advantages in animals. Thanks to their very small size, these additives increase the nutritional value of the feeds and enable the animals to digest these nutrients more effectively. In addition, nanoadditives have positive effects on animal health and productivity by delivering targeted nutrients directly to specific organs or tissues. Nano-sized additives can increase nutrient bioavailability, thereby leading to improved growth, feed conversion, and overall animal health (Sharif et al., 2021). In addition, these additives can be more stable than traditional feed supplements and have a longer shelf life without deteriorating their quality due to their concentrated form (Mortensen et al., 2022). Firstly, their small size and large surface area in the intestinal lumen allow for easier absorption and can be utilized by animals, maximizing their nutritional benefits (Kumari & Chauhan, 2022). By leveraging advanced nanotechnology, farmers will now have a powerful impact on optimizing nutrient absorption and promoting sustainable livestock production. NPs have long been used in human and veterinary medicine for diagnostic and therapeutic purposes, although they are a new application in animal production. These applications encompass disease diagnosis, targeted drug delivery systems, vaccine administration, and nutrition management (Sertova, 2020).

While high doses of mineral feed additives as inorganic salts can improve animal growth performance, their low bioavailability may also pose environmental risks. This necessitates the addition of nano-sized additives to animals as a more effective alternative to mineral applications. Metal NPs such as zinc, silver, copper, gold, selenium and calcium are suggested to be effective alternatives due to their higher bioavailability and absorption (Michalak et al., 2022). Studies have shown that calcium NPs form denser bone in mice and turkeys compared to microcalcium (Jia et al., 2018; Wang et al., 2022b).

Nano enzymes have several advantages such as stability, biocompatibility, conductivity, and susceptibility, improving surface area to improve enzyme-based sensor performance (Song et al., 2019). In order to prevent denaturation and loss of function due to protein/enzyme binding of NPs, enzyme molecules are combined and cross-linked together to form NPs in a prearranged manner. This method has succeeded in unlocking the manufacturing potential of biosensors with increased analytical performance (Riley & Narayan, 2021; Liu et al., 2022; Thapa et al., 2022). In addition, recent research indicates that enzyme NPs exhibit high catalytic efficiency and thermal stability, which enhances both the temperature resistance and cellulose degradation capacity of these NPs (Khizar et al., 2021; Gu et al., 2022; Liu et al., 2022).

Another purpose of using NPs is to reduce the number of harmful bacteria and to be able to improve the growth performance of animals by promoting the growth of beneficial bacteria. These effects include a reduction in the production of bacterial toxins, an increase in the production of vitamins and growth factors, improved nutrient absorption through thinning of the intestinal epithelium, and a reduction in the turnover and motility of intestinal mucosal epithelial cells (Hill et al., 2017).

Giving a definitive answer about the impact of nano-sized feed additives on shelf life is challenging, as the May vary depending on the specific type of nanomaterial used, the composition of the feed, and the storage conditions. Research on the effects of nano-sized feed additives on safety, efficacy, and shelf life has reported that engineered and deliberately added NPs to feeds provide the food industry with innovative methods to improve the quality, shelf life, safety, and health of foods (McClements et al., 2017; Siemer et al., 2018).

Nano additives increase feed efficiency by enabling animals to use the nutrients they consume more effectively (Gopi et al., 2017). This means higher growth and more production with less feed. Another advantage is that nano additives can strengthen the immune system of animals and make them more resistant to diseases (Gelaye, 2024). Furthermore, improved feed efficiency helps reduce environmental impact because less feed production means less farmland and lower carbon emissions (Kah et al., 2019; Wang & White, 2022).

4.2. Potential Risks in Animal Nutrition

Although nano-sized feed additives have shown promising benefits in improving animal nutrition, it is crucial to consider the potential risks and safety implications. Because NPs are often used in end products, they typically do not interact with humans, animals or the environment (Hemathilake & Gunathilake, 2022). However, some concerns include the potential for undesirable accumulation in animal tissues, environmental impact, and the need for rigorous testing and regulation (Dupuis et al., 2022).

When incorporating these additives into animal diets, it is essential to prioritize the safety and welfare of animals and consumers.

In vitro and in vivo studies have been conducted on certain organisms on the limitations and risks of the use of nano-sized feed additives. NPs that have a particularly toxic effect can be listed as silver, gold, zinc oxide, titanium dioxide, silicon dioxide, copper oxide (Jamuna & Ravishankar, 2014). Studies on silver nanoparticle (AgNP), one of the NPs with common toxicity, have shown cytotoxicity and increased membrane permeability at the in vitro level, while at the in vivo level it has not shown any effect other than at high doses. In addition, effects such as DNA damage, functional degradation, cell death, apoptosis and cytotoxicity, cytotoxic effect due to ROS, and cell cycle diversity independent of ROS, mitochondrial damage have been reported as a result of some studies (Chairuangkitti et al., 2013; Ferdous & Nemmar, 2020; Li & Wang, 2021; Wang et al., 2021). Studies on gold NPs, on the other hand, have indicated that symptoms such as deterioration of the actin cytoskeleton, intracellular GSH depletion as a result of interaction with glutathione (GSH), mitochondrial membrane depolarization and apoptosis can be seen (Lopez-Chaves et al., 2018; Talarska et al., 2024). It has been reported that inflammation and bleeding in the lung, ROS accumulation and increased lipid peroxidation, decreased antioxidant capacity (Manzoor et al., 2024) can be seen in titanium dioxide NPs, and oxidative stress can be seen in silicon dioxide and copper oxide NPs (Alruwaili et al., 2022; Zhang et al., 2022). Dose and material size are among the main causes of all these adverse effects. The size of NPs can alter toxicity, and smaller-diameter NPs are more dangerous to cells than larger-diameter NPs, as smaller particles are more likely to reach intracellular sites such as mitochondria and nucleus (Kumar et al., 2017; Li & Lee, 2020). In addition, the cytotoxicity of NPs may be increased when they are mixed with different types of compounds. Therefore, attention should be paid to interactions in the selection of nanomaterials (Jurj et al., 2017).

The long-term health effects of nano-sized additives are not fully known. There are concerns that these substances may accumulate in the body or have side effects (Miller & Senjen, 2008). The effects of nano additives on the environment are not fully understood. Their introduction into soil and water resources can have negative effects on ecosystems (Boxall et al., 2007). Recent in vitro and animal studies have shown that excessive accumulation of NPs can damage cellular organs such as the liver, spleen, kidneys, and respiratory tract and cause toxic effects (Surendhiran et al., 2020). Further research is needed to assess the potential risks to human and animal health and the environment from exposure to NPs (Liu et al., 2022).

The dominant processes of nanoparticle-mediated toxicity include oxidative stress, inflammation, DNA damage and inhibition of cell division and death (Gatoo et al., 2014). While the toxicity of bulk copper is largely dependent on its salt composition, for Cu-NP, other physicochemical characteristics such as size, surface area, surface chemistry, surface texture, dispersion medium, and agglomeration capacity significantly influence the level of toxicity.

Although nano-sized feed additives have many benefits, there are challenges in their application to animal nutrition. In analyses on different species, Cu-NP used as a feed additive caused Cu accumulation in liver and lung tissues, decreased body weight, and dose-dependent lesions in the lung and liver. In addition, smaller Cu-NPs have been reported to be more toxic to zebrafish embryos than larger Cu-NPs. Cu-NP caused membrane damage, ROS generation and DNA strand breaks in lung cells and mammalian cell lines (Zhang et al., 2012; Hua et al., 2014; Song et al., 2014; Sadiq et al., 2015; Hedberg et al., 2016).

Nanotechnology faces many obstacles, including environmental hazards from the release of NPs into the environment, worker and consumer health and safety concerns, questions about the self-replication of nanomachines and their impact on human development, business challenges in commercializing nanotech-enabled products, and concerns about protecting intellectual property rights.

As with nano minerals, there are limitations in the use of nano enzymes in terms of animal nutrition. Enzymes used in animal feed can break down random components in feed products. Thus, it can potentially lead to a decrease in meat or egg production, low feed efficiency and digestive problems. In this respect, the use of nano is not preferred (Islam et al., 2023). It is important to ensure proper dosage and avoid over-supplementation to prevent any adverse effects. The cost of nano-sized additives can also be a limiting factor for some farmers. Furthermore, comprehensive research is required to fully grasp the long-term implications and possible hazards of incorporating these additives in animal feed (Seaton et al., 2010).

4.3. Nanotechnology in Animal Nutrition

As a novel approach to animal nutrition, nanotechnology offers the opportunity to improve nutrient bioavailability, production efficiency and the health and immune status of animals. Nanometer-sized feed additives have a stronger absorption capability thanks to their expanded specific surface area. In this way, it reveals its ability to increase the bioavailability of feeds (Budak, 2018).

By incorporating nano-sized additives into animal diets, positive effects on overall animal health and productivity can be achieved by optimizing nutrient intake. Various nano-sized feed additives can be used in animal nutrition. These include nanominerals, nano-vitamins, nano-enzymes, nano-antioxidants, nano-probiotics, and nano-herbs (Fesseha et al., 2020; Zaheer, 2021). Studies on nanotechnology applications in the field of animal nutrition have mainly focused on evaluating the effects of effects of mineral supplementation with NPs.

4.4. Activities Conducted

The addition of nano-sized feed additives has emerged as a game-changing development in the effort to increase the efficiency of animal nutrition. With the ability to deliver essential nutrients in precise doses, these additives play a critical role in improving animal health and performance.

Each nanoparticle has a different mechanism of action. Zinc oxide and selenium NPs increase the overall nutritional value and digestibility, while also increasing the production of volatile fatty acids. Zinc oxide, in particular, helps minimize environmental impact by reducing fecal mineral loss. It is also beneficial to the gut and has the potential to improve villus height, crypt depth and villus surface area. Magnesium oxide, along with silver and copper NPs, demonstrate strong antimicrobial effects against both gram-positive and gram-negative bacteria, offering effective microbial management. In addition, these NPs aid in microbial control by weakening the biofilm formation of microbial communities. Iron oxide and copper NPs support intestinal health by improving microbial growth in the digestive tract. The nanoform of calcium can be used effectively against periodontal disease and gastrointestinal parasites. (Singh, 2016; Adegbeye et al., 2019).

Zinc oxide nanoparticles have gained popularity as an alternative feed additive in poultry due to their impact on the metabolic activity and health status of birds, attributed to their antibacterial and immunostimulatory effects (Sagar et al. 2018; Akhavan-Salamat & Ghasemi, 2019).

Abedini et al. (2018) investigated the effects of zinc oxide NPs on egg quality, immune response, zinc retention, and blood metrics in laying hens during the later stages of production. As a result of this study with a total of 288 laying hens aged 64 weeks, it was reported that dietary supplementation with ZnONPs increased zinc absorption in laying hen intestines and improved performance. It was reported that NPs to be used in laying diets may be a more suitable zinc source than normal zinc oxide. According to this study, ZnONPs can be used as a substitute for antibiotic growth promoters in the diet of broilers due to their inclusion in the diet.

Hatab et al. (2022) investigated the effects of zinc oxide NPs (ZnONPs) synthesized by *Alternaria tenuissima* on reproductive performance, carcass characteristics and biochemical parameters of chickens. It was observed that ZnONPs supplementation resulted in higher body weight, improved feed intake and performance index compared to the control group. In addition, serum cholesterol, triglyceride, low-density lipoprotein, and uric acid concentrations were decreased, while high-density lipoprotein and liver enzyme concentrations were increased. Zinc accumulation in serum, liver and muscle showed a linear increase with the increase in zinc supplementation. In conclusion, it has been reported that supplementation with 40 or 60 mg/kg ZnONPs can improve productive performance and that low levels of Zn supplementation give positive results.

In another study conducted by Fawaz et al. (2019) on the yield performance of laying hens with zinc oxide NPs administered to 120 laying hens in four groups containing 0, 20, 40, or 60 mg/kg zinc oxide NPs. It was observed that the feed conversion ratio improved in correlation with the level of supplementation, resulting in a significant increase in both egg production and egg mass ($P<0.05$). The inclusion of ZnO NPs at concentrations of 20, 40 or 60 mg/kg in the diet of laying hens was found to improve several aspects of their productivity and health. These include improvements in overall production performance, egg quality as measured by Haugh units, shell strength, nutrient digestibility and reduction in cholesterol levels. In addition, these NP supplements have been shown to have a positive effect on liver and kidney function. In conclusion, ZnO NPs can be considered as an effective feed additive in diets used to optimize the health and productivity of laying hens.

Chromium picolinate (CrPic) NPs have been reported to reduce heat stress in broiler chickens, improve feed conversion, increase mineral concentrations including Cr, Ca, and P in the livers of the subjects, and also induce increased lymphocyte counts in broiler chickens (Sirirat et al., 2012). In research where chromium nanoparticles were added to pig diets, it was found to improve skeletal muscle mass and meat quality in pigs by reducing fatty acid synthase activity compared to the control group (Poddar & Kishore, 2022; Xiong et al., 2022).

As phosphorus (P) in poultry feces causes environmental problems, a study was conducted by Hassan et al. (2016) for the regulation of poultry diets to reduce phosphorus waste so that it does not negatively affect the performance of birds. The study investigated the effect of replacing conventional dicalcium phosphate (DCP) with nanodicalcium phosphate (NDCP) on the performance of broiler chickens and the reduction of calcium (Ca) and phosphorus excretion in their feces. Birds fed NDCP gained significantly more body weight and utilized feed more efficiently than the control group (1.75% CDCP). Body weight gain and feed consumption increased by approximately 25% and 10%, respectively, while feed conversion ratio improved by approximately 12% compared to chickens fed CDCP. Hassan et al. (2016) determined that the use of 0.44% NDCP in diets reduced excreted Ca and P by 50.74% and 46.24%, respectively, compared to the control group. In conclusion, the use of nanoparticle-sized dicalcium phosphate can mitigate the environmental impact of poultry farming by reducing excreted Ca and P by approximately 50%.

Another study was conducted in broilers to investigate the effect of nanodicalcium phosphate (NDCP) versus conventional dicalcium phosphate (CDCP) on carcass characteristics and bone measurements. The diets contained three different levels of either CDCP or NDCP: %1.75, %1.31, and %0.88, and a lower level of NDCP at %0.44. These levels were equivalent to providing 100%, 75%, 50%, or 25% of the recommended dietary phosphorus requirement. It was concluded that substituting NDCP for CDCP improved all measured bone parameters. Diets containing 25% NDCP can be successfully used instead of 100% CDCP, and when used in nanoparticle size, the level of dicalcium phosphate can be successfully reduced from 1.75% to 0.44%. Nanoparticle-sized dicalcium phosphate can be used approximately 400% more effectively than traditional dicalcium phosphate (Mohamed et al., 2016).

AgNPs, another element added to the diet of monogastric animals, have antibacterial activity (Fondevila et al., 2009; Pineda et al., 2012). Furthermore, AgNPs have been reported to potentially improve muscle morphology without affecting embryo growth in broiler performance (Sawosz et al., 2012). In another study conducted by the same researchers on quails, it was reported that 25 mg/kg Ag-nano supplementation in their water significantly increased the population of lactic acid bacteria (Sawosz et al., 2008). Nevertheless, it has been reported that a concentration of 50 mg/kg of AgNPs chelated with the amino acids threonine and cysteine could serve as potential agents to enhance the immune capacity in embryos and chickens (Bhanja et al., 2015).

A study on turkeys investigated the effects of reducing the amount of manganese (Mn) in their diet on their growth, antioxidant status and immune system. The researchers used two different sources of Mn: manganese oxide (MnO) and manganese NPs (NP-Mn2O3). They also tested three different levels of Mn (100, 50 and 10 mg/kg). According to the results of the study, reducing the amount of Mn did not have a negative impact on the health of the turkeys. Specifically, Mn in the form of NP-Mn2O3 allows young turkeys to reduce the amount of Mn in their diet without compromising their antioxidant defenses. Reducing Mn in the form of MnO can increase lipid oxidation, while replacing it with NP-Mn2O3 can increase apoptosis (cell death). In general, however, reducing the amount of Mn in the diet tends to reduce apoptosis, regardless of the form. This study shows that the form and amount of manganese used in turkey diets can have important effects (Jankowski et al., 2018).

Copper (Cu), zinc (Zn) and manganese (Mn) NPs were used to study their effect on aminopeptidase activity in turkey meat. 144 Hybrid Converter turkeys were fed standard and nanoparticle-supplemented diets containing 100%, 50% and 10% of the physiological requirement of these minerals, respectively. The study was conducted to investigate the effect of mineral supplementation on the activity of aminopeptidases (alanyl: AlaAP, leucyl: LeuAP, and arginyl: ArgAP) in both turkey breast and thigh muscles. The results showed that even at the lowest dose (2 mg/kg), nano-Cu had a significant effect on aminopeptidase activities in bud muscle. Moreover, at doses of 20 mg/kg (100% requirement) and 10 mg/kg (50% requirement) of nano-Cu, the activity of all aminopeptidases in the bud muscle was inhibited. Aminopeptidase activities indicated that the addition of nano-formed Cu and Zn to the diet, especially at doses meeting 10% of the requirement, is important for maintaining homeostasis in turkey muscle (Jozwik et al., 2018).

In a study conducted by Nguyen et al. (2015) Metal NPs added to chicken diets as metal nanoparticle additives in a feed premix consisting of Fe, Cu, ZnO, and Se, which replaced the inorganic mineral component due to the nanocrystalline metal content, reduced the inorganic mineral content by at least four times, reduced environmental pollution, and allowed animals to utilize these minerals more efficiently in the body.

Radi et al. (2021) investigated the comparative effects of zinc oxide ZnO and zinc oxide nanoparticles ZnO NPs as feed additives on growth, feed selection tests, tissue residues and histopathologic changes in broiler chickens. Observations showed that birds receiving a diet containing ZnO NPs at a dietary dose of 90 mg/kg from 2 to 20 days of age showed an increase in body weight compared to the zinc oxide treated group.

Hussan et al. (2022) conducted a study to evaluate the effect of supplementing zinc in the form of nano zinc oxide (nano ZnO) on broiler performance. In the study, nano ZnO was added to the basal diet at the ppm level and fed to a total of 6 groups. Results showed that 2.5 ppm nano ZnO supplementation led to a significantly higher increase in live weight, greater feed intake, and an improved feed conversion ratio (FCR) at 42 days of age compared to the control and other treatment groups.

Zinc NPs have a positive effect on growth, immunity, and reproduction in poultry and monogastric animals such as pigs, while improving feed efficiency (Swain et al., 2016; Milani et al., 2017). In a study involving 200 1-week-old Japanese quails, one group was fed a basal diet while the other groups were fed diets supplemented with nano-zinc (Zn-NPs) at increasing levels (0.1, 0.2, 0.3, and 0.4 g/kg diet). The study reported significant ($p \leq 0.0001$) improvements in body weight, weight gain, feed intake and feed conversion efficiency in quails fed diets supplemented with 0.2 g/kg Zn-NPs. In the groups where 0.1-0.3 g/kg was added to the diet, it was reported that ALT, AST, and LDH activities showed a positive result. Furthermore, within the same range (0.1-0.3 g/kg), Zn-NPs also showed a positive effect on parameters such as superoxide dismutase (SOD), glutathione peroxidase (GPX), malondialdehyde (MDA), immunoglobulin G (IgG), and immunoglobulin M (Reda et al., 2021).

In another study broilers were fed with zinc oxide NPs (ZnO NPs) added to the diets at specific ratios. At the end of the experiment, broilers fed diets containing ZnO NPs exhibited significantly higher zinc retention compared to those in the control group, which was statistically significant ($p < 0.05$). This increased zinc uptake subsequently led to a decrease in zinc excretion in their feces. This resulted in increased Zn absorption and bioavailability, decreased zinc excretion, and demonstrated potential antibacterial activity against the tested pathogens. It was also reported that the addition of different levels of ZnO-NP did not affect broiler growth performance ($p > 0.05$). However, the study observed a significant antibacterial effect when ZnO-NPs were included in the diet at a concentration of 100 mg per kg. This effect was reported by Yusof et al. (2023) which was characterized by a significant reduction in the number of *Enterococcus* species, while the population of beneficial partner bacteria such as *E. coli* lactic acid bacteria remained unaffected. In a similar study, Cu silicate NPs altered the intestinal microbiota in chickens, increasing the number of Lactobacillus species and decreasing *E. coli*. It has been reported that the inclusion of Cu silicate Nps can modulate the intestinal microflora, stimulate the growth of beneficial bacteria, suppress harmful bacteria, improve nitrogen metabolism, and reduce fecal ammonia emissions (Minglei et al., 2013).

Studies on the addition of Cu-NPs to the diets of marine organisms have yielded very successful results. It has been reported that administration of Cu-NPs to fish resulted in increased body weight, improved feed efficiency, increased protein retention, enhanced immune response and antioxidant defence system compared to the control group. In another study on shrimp, Cu-NPs were reported to improve growth, digestive enzyme activity, biochemical component concentrations and hemocyte counts (El Basuini et al., 2016; Muralisankar et al., 2016). In a separate study, El Basuini et al. (2017) reported that a mixture of Cu-NPs and vitamin C added to the red sea bass diet increased feed intake and consequently increased body weight. It was also reported to have a significant effect on body protein and lipid content, protease and bactericidal activity, and tolerance to stress compared to the control group.

Tomaszewska et al. (2017) compared the effects of administering two different chemical forms of copper, CuCO3 and Cu-NP (carbonate and NPs), through dietary mixtures on geometric and structural parameters of bones in young rats. Although there were no changes in body weight and bone morphology depending on Cu-NP dose, significant changes in geometric and mechanical parameters were found. It was reported that Cu-NP administered at low dose increased mechanical strength by increasing bone tissue density and ash content in bones, without changes in strain and stress compared to a low dose of Cu administered in conventional form.

Gao et al. (2014) supplemented culture media containing Caco-2 cells with different concentrations of copper sulphate (CuSO4), micron-sized copper oxide (micron-CuO), and nano-sized copper oxide (nano-CuO) and then examined their effects on the expression of Ctr1, ATP7A/7B, MT, and DMT1 genes and proteins. The results showed that nano-CuO significantly increased Ctr1 mRNA expression in Caco-2 cells compared to micron-CuO and CuSO4. In addition, at the same concentration, nano-CuO was found to be more effective than CuSO4 and micron-CuO in enhancing Ctr1 protein expression.

Studies have shown that in ovo administration of nano copper (Cu-NP) in broiler chicken eggs increases body weight, improves feed conversion ratio, and improves breast and leg muscles by promoting blood vessel development during embryogenesis (Mroczek-Sosnowska et al., 2015a, 2015b). Furthermore, it has been reported that in ovo injection of Cu-NPs stimulated proliferating cell nuclear antigen (PCNA) positive cells in the long bones of broiler chickens, demonstrating a stimulating effect during embryogenesis. (Mroczek-Sosnowska et al., 2017). Miroshnikov et al. (2015) reported that intramuscular CuNp administration in chickens supported development and increased hemoglobin levels, especially in red blood cells. In addition, serum Cu and protein levels increased, and the arginine content of the liver also increased.

The effect of highly dispersed copper particles on the metabolism of broiler chicks was studied after a single intramuscular injection. Preparations containing copper NPs, agglomerates, and microparticles were used in the study. It was observed that copper NPs triggered rapid growth and metabolic changes, while agglomerates and microparticles provided a similar effect but over a longer period. These results provide important findings that can be used to improve microelement preparations (Miroshnikov et al., 2015).

El-Nile et al. (2023) used nanosized and natural zeolite as a feed additive in a study on rumen fermentation, blood metabolites, milk yield, feed intake and fatty acid profile in dairy goats. Damascus goats in late pregnancy were used in this study and both forms of zeolite increased blood serum albumin and calcium levels. In contrast to natural zeolite, the nano zeolite-added group increased milk production and short-chain fatty acids, decreased ruminal ammonia-N concentration, and somatic cell count. It was also reported to have a positive effect on kidney function.

Elemental nano-selenium (NSe) was added to the diet as a feed additive in a study to investigate its effect on feed digestion, rumen fermentation and urinary purine speciation in sheep. Sheep were fed a basic diet and supplemented with 0 (control), 0.3, 3, and 6 g nano-Se/kg per dry matter (DM). It has been reported that supplementation of nanoselenium in the basal diet improves rumen fermentation and feed utilization, possibly by stimulating rumen microbial activity, digestive microorganisms, or enzyme activity. This supplementation resulted in a significant decrease in rumen pH (ranging from 6.68 to 6.80) and ammonia concentration (ranging from 9.95 to 12.49 mg/100 ml), along with an increase in total volatile fatty acid (VFA) concentration. The optimal dose of nanoselenium was determined to be approximately 3.0 g per dry matter of the diet in sheep (Shi et al., 2011).

In a study on broiler chickens, the selenium uptake of nano-elemental selenium (Nano-Se) and sodium selenite was compared. Nano-Se was retained more efficiently in the body, providing a wider optimal-toxic dietary range than sodium selenite. Nano-Se was able to increase growth performance and selenium concentration better than sodium selenite (Hu et al., 2012).

Lee et al. (2020) conducted a study to evaluate the effects of dietary selenium (Se) concentration and source on performance, nutrient digestibility, plasma Se levels, glutathione peroxidase (GPx) activity, and thiobarbituric acid reactive substances (TBARS) in broiler chickens. The experimental diets were administered in two phases (phase 1, days 0 to 14, and phase 2, days 15 to 32) for a total of 32 days. Treatments included a control group (no Se supplementation), sodium selenite (SeS; at 0.15, 0.30, or 0.45 ppm), and hot-melt-extruded sodium selenite (SeHME; at 0.15, 0.30, or 0.45 ppm). Significant linear responses ($P < 0.01$) were observed for the expression of SelW, GPx1, GPx3, and GPx4 genes in the liver and spleen in response to SeS and SeHME treatments. In conclusion, it has been reported that SeHME may enhance antioxidant activity and Se absorption, thus potentially serving as a more suitable source of Se compared to standard sodium selenite.

In a study on the effects of dietary nano-selenium on tissue selenium accumulation, antioxidant status, and immune functions in laying hens, inorganic sodium selenite and nano-Se were administered to diets for comparison. The study reported that Nano-Se was nutritionally superior. In another study in broiler chickens, Nano-Se supplementation was found to have a positive effect on body weight gain (BWG) and feed conversion ratio (FCR). A supplementation of 0.3-0.4 mg nano-Se kg-1 was reported to be the optimal level for inclusion in broiler diets (Ahmadi et al., 2020).

Overall, the usage of NPs as feed supplements has the potential to improve growth performance and feed efficiency, increase total protein and albumin levels in serum, and significantly enhance total antioxidant capacity. Furthermore, this approach can contribute to optimizing many biological processes such as digestion, metabolism, and nutrient uptake, increasing the efficiency of production processes and reducing environmental contamination.

5. Conclusion and Recommendations

Research on nano-sized feed additives in animal nutrition offers a transformative approach toward enhancing agricultural productivity and sustainability. In this research, the unique properties of nanoparticles are exploited to highlight their potential to significantly improve nutrient delivery and absorption, facilitate feed efficiency, and reduce the environmental footprint of livestock production with lower feed inputs. These small but powerful substances are critical for improving animal health and producing high-quality animal products. By striking the critical balance between technological innovation and sustainable, environmentally friendly food production systems, it is crucial to meet the growing global demand for food and contribute to future food security.

However, these advantages, as well as the potential risks and environmental concerns associated with nanomaterials, require the need for careful application. Rigorous scientific research, strict regulations and ethical considerations are vital to ensure the safety and effectiveness of nano-sized feed additives for both animals and the wider ecosystem.

As we move forward at the dawn of a nanotechnological revolution in animal nutrition, it is imperative to embrace innovation with a balanced perspective, ensuring that technological advances are compatible with environmental and ethical standards. This effort aims not only to harness the vast potential of nano-sized feed additives to transform livestock management, but also to combine these innovations with an unwavering commitment to ecosystem and public health. The promise of transforming livestock management and food production systems with nano-additives is significant. But they require scientific rigor, sustainability, efficiency and a commitment to health. Future research should look more closely at the effects nano-sized feed additives on different animal species, their specific applications, economic aspects of their use, and sustainability implications. Such a review will open new avenues of research in the field of animal nutrition and nanotechnology and enrich the achieved results. As research progresses, nano-sized feed additives will continue to revolutionize animal nutrition and herald a new era by enabling stakeholders to adopt these innovations with confidence.

Conflict of Interest

The author has no conflict of interest to declare.

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