***Review Article***

# A Comprehensive Review of Nano Iron Supplementation in Piglets: Efficacy, Mechanisms, and Future Perspectives

# A Complete Review of the Efficacy, Mechanisms and Future Prospects of Nano Iron Supplementation in Piglet


**Abstract**

Nanotechnology is a promising avenue for innovative research and development, with recent applications such as the production of nutrients with enhanced bioavailability. The distinctive characteristics of nano metals such as their larger specific surface area, heightened surface activity, greater catalytic efficiency and stronger adsorption capabilities result in an enhanced bioavailability. Small particles are easily transported through the gastrointestinal tract and can be assimilated by the animal ~~organism~~ resulting in higher efficacy compared to larger particles. Nanoparticles have the potential to serve as a vehicle for the delivery of medication, nutrients, probiotics, supplements, and other substances to the feed of livestock and poultry. Iron (Fe) is an essential micronutrient that is indispensable for swine due to its critical function in regulating blood hemostasis and hemoglobin levels. Iron deficiency anemia (IDA) is a prevalent condition solely observed in swine. The susceptibility of iron deficiency in piglets is positively correlated with their size, owing to their increased blood volume and hemoglobin utilization capacity. Iron nanoparticles, also known as IONPs, have become a powerful tool in a variety of biomedical and environmental contexts. The enhanced surface area, surface activity and catalytic efficiency of nano minerals make them a promising option for animal mineral feed supplements, even at lower dosages relative to traditional sources. The objective of this review is to elucidate the effectiveness of nano iron fortification in piglets as a prophylactic measure against anemia.



**Key words:** ~~piglets; nano iron; anaemia; growth~~ Anaemia, Growth, Nano-iron, Piglet


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**Introduction:**

The nanotechnology field presents a promising avenue for innovative research and development, with recent applications including the production of nutrients with enhanced bioavailability. The field of nanotechnology pertains to materials that possess unique and enhanced physical, chemical, and biological characteristics as a result of their diminutive particle size, as stated by Wang (2000). The term "nano mineral particles" pertains to particles that possess a size ranging from 1-100 nm, as described by Thulasi et al. (2013) and Feng et al. (2009). Nanoparticles of minerals are extensively employed across a range of industries, encompassing agriculture, animal husbandry, and food production. The nano minerals exhibited noteworthy impacts even at lower dosages compared to traditional mineral sources. The nano minerals exhibit greater growth-promoting, immuno-modulatory, and antibacterial properties compared to their conventional counterparts. In addition, nano minerals are utilized to improve the reproductive performance of livestock and poultry. According to Sindhura et al. (2014) nano-sized particles exhibit greater potential than their conventional counterparts, resulting in a reduction in the required quantity. The potential of nano minerals to enhance bioavailability has been attributed to their increased surface area, heightened surface activity, superior catalytic efficiency, and enhanced adsorption capabilities. This finding has been documented in several studies, including those conducted by Chaudhry and Castle (2011), Albanese et al. (2012) and Rajendran et al. (2013). The fundamental characteristics of nano metals are primarily dictated by their dimensions, geometry, chemical makeup, crystal lattice arrangement, and physical form, as documented in various studies (Dickson et al., 2000; Zhang et al., 2001; Sheikh et al., 2016). The aforementioned particles exhibit stability even when subjected to elevated temperature and pressure. Furthermore, they can be readily transported through the gastrointestinal tract and assimilated by the animals ~~organism,~~ rendering them more efficacious than their larger counterparts. The particle size of nano minerals has a significant impact on their functional activities, including chemical, catalytic, and biological effects. According to previous studies conducted by Chithrani and Chan (2007), Zha et al. (2008), and Liao et al. (2010), it has been observed that nanoparticles exhibit unique properties in terms of transportation and absorption, and are capable of penetrating deeper into tissues. Additionally, nanoparticles have the capability to migrate through the lymphatic system and accumulate within the liver and spleen. The aim of this current review is to shed light on the effectacy of nano minerals in piglets to prevent anaemia.

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## ~~The characteristics of nanoparticles:~~ Characteristics feature of nanoparticles

A nanoparticle is operationally defined as a particle with a diameter of less than 100 nanometers (nm). The term "nano" originates from the Latin word "*nanus*," which translates to "*dwarf*." According to Buzea et al. (2004), the properties of nanoparticles exhibit significant differences in comparison to those present at a larger scale including physical, chemical, electrical, optical, mechanical, and magnetic properties. Nanoparticles exhibit distinct characteristics, primarily attributable to the following factors:

1. ~~1.~~ The stability of nanoparticles is comparatively lower than that of larger structures due to the reduced energy required for the bonding of adjacent atoms, leading to a change in the fusion point of the element (Hagan, 1996).
2. ~~2.~~ Quantum nanostructures exhibit behavior analogous to that of individual atoms due to quantum effects. The spatial configuration of nano particles enables them to exhibit characteristics that are not inherent to the constituent element. For instance, metals like gold or platinum can display magnetic properties in their nano form.
3. ~~3.~~ According to Buzea et al. (2007), the rate of a reaction can be increased by breaking a material into smaller particles, which leads to a significant increase in its surface area.

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## ~~The mechanisms by which nanoparticles exert their effects.~~ Mechanism of action of nanoparticles

Chen et al. (2006) delineated the discrete mechanisms of action demonstrated by nanoparticles as follows: Nanoparticles exhibit a proclivity to increase their surface area, thereby amplifying their interaction with biological substrates. Prolonged the retention time of the compound in the gastrointestinal tract for better absorption. Reduce the effects of gastrointestinal clearance mechanisms. The presence of fine capillaries enables the efficient and thorough infiltration of tissues. The cross-sectional fenestration of the epithelial lining. Enhance cellular uptake to achieve maximum efficacy. The effective delivery of bioactive molecules to targeted locations, leading to enhanced pharmacokinetics.

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The process of nanoparticles being absorbed by the gastrointestinal tract (GIT) involves various pathways, such as ingestion and inhalation, as well as oral pathway. The physiological processes of nanoparticle absorption, distribution, metabolism and excretion are contingent upon their physicochemical attributes such as their solubility, charge and size. Particles with a size smaller than approximately 300 nm are capable of entering the bloodstream, whereas particles with a diameter smaller than 100 nm are capable of penetrating diverse tissues and organs (Hett, 2004). Ultrafine particles can gain access to central nervous system through the inhalation pathway, circumventing the formidable barrier of the blood-brain barrier. However, the potential impact of their chemical reactivity with other substances on both human health and environment cannot be overlooked. Bio-functionalized nanoparticles (BN) have gained significant recognition in the field of enteric infection treatment as well as in the pre-transport and processing stages as pathogen purging agents (Taylor et al., 2004).

The utilization of conventional and biogenic metallic nanoparticles has gained significant global attention in recent years as a potential solution to combat the growing concern of antimicrobial resistance, as noted by Hemeg (2017). The unique physical and chemical properties of nano materials have yielded promising results, as documented by Pelgrift and Friedman (2013) and Beyth et al. (2015). Several studies have recognized the antibacterial characteristics of metal nanoparticles as demonstrated by the research (Khurana et al. 2016; Sportelli et al. 2016; -and Patra and Baek 2017).

**Intervention of nanotechnology in animal and poultry nutrition**

The utilization of nanotechnology in domain of animal and poultry nourishment has been a topic of interest. The application of nanotechnology in the field of animal nutrition involves utilization of diverse nanoparticles for purpose of administering medication, nutrients and supplements. In contemporary times, the utilization of feed additives, specifically trace minerals in the nanoparticle configuration, has emerged as a viable solution to meet the mineral requirements of livestock and poultry feed. It is anticipated that utilization of nano additives will confer benefits such as enhanced bioavailability, reduced dosage requirements, and consistent interaction with other constituents. Owing to their low dosage, they can function as a replacement for antibiotics as growth promoter agents, eliminate residual antibiotics in animal products and reduce environmental contamination

(Hett, 2004; Schmidt, 2009). The integration of nano-additives into capsules of natural feed constituents, such as proteins, is a feasible strategy.

**Effect of nano iron supplementation on the performance of piglets:**

Piglet health and nutrition are crucial factors in the swine industry. The early stages of a piglet's life are critical for its growth and development, and proper nutrition is essential for optimal health. Piglets require a balanced diet that meets their nutritional needs to ensure they reach their full potential. However, several factors can affect piglet health, such as disease outbreaks, environmental stressors, and inadequate nutrition. Therefore, it is essential to provide piglets with a healthy diet.

Minerals are a vital component in the nutritional requirements of animal production. According to Raje et al. (2018), minerals play a crucial role in facilitating the digestive and reproductive processes, as well as the growth of animals. Importance of iron supplementation is to prevent anaemia and support their growth and development. Iron is a crucial nutrient for piglets, as it plays a important role in the production of haemoglobin, which carries oxygen throughout the body. Without enough iron, piglets can develop anaemia, which can lead to poor growth, reduced immunity, and even death. Therefore, supplementing their diet with iron is critical to ensure their overall health and well-being. According to Uniyal et al. (2017), Iron (Fe) is a crucial trace element that is indispensable for pigs as it plays a vital role in maintaining appropriate blood hemostasis and hemoglobin count. Additionally, it serves as a constituent of vital antioxidant enzymes, including superoxide dismutase, which mitigates peroxide-induced damage in instances of stress (Zhao et al., 2014). The neonatal period is characterized by the prevalence of iron deficiency, which is the most frequently occurring nutritional disorder in mammals. Iron deficiency anemia (IDA), which is the most severe outcome of iron deficiency, is a common occurrence only in pigs (*Sus scrofa domestica*) among mammalian species (Svoboda and Drabek 2005; Kim et al., 2018; Szudzik et al., 2018). Suckling piglets frequently experience anemia, which can be attributed to inadequate Fe transfer from the placenta to the fetus and the insufficient Fe levels present in sow milk, as noted by Rincker et al. in 2004. As a result, weaning piglets may experience the lingering consequences of iron deficiency that originated during the suckling phase. According to Perri

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et al. (2016), the rapid expansion of contemporary swine farms has resulted in a heightened vulnerability of larger piglets to iron deficiency in comparison to their smaller and medium-sized counterparts. This is attributed to the greater blood volume and hemoglobin utilization capacity of the former. During the weaning period, there is a heightened need for dietary iron. However, the absorption efficiency may be reduced due to the unstable intestinal microbiota resulting from the transition from milk to solid feed.

The utilization of ferrous sulfate, an inorganic form of iron, has been extensively employed in the dietary regimens of swine. The inorganic type has been observed to exhibit reduced absorption or increased variability in bioavailability ratios, depending on the dietary source and content of ascorbic acid, pectin, phytate, protein, amino acid, and other mineral sources [(Feng et al., 2009; Yu et al., 2000)]. In order to address the issue of low absorption rates, researchers have introduced an organic form of mineral that exhibits higher bioavailability. This is due to its lower binding capacity with chelates, as noted in studies conducted by Feng et al. (2009) and Shinde et al. (2011). In addition to the intestinal interactions between minerals and chelates, the size of particles plays a crucial role in the absorption of nutrients through the gastrointestinal mucosa, as noted by Bunglavan et al. (2014). According to Desai et al. (1992), the absorption rate can be increased by at least 10 times when consuming nutrients with a particle size of 100 nm or smaller, as compared to larger particles. According to Qiu et al. (2018), the enhanced availability and accessibility of particles in the intestinal mucosa is attributed to the reduction in particle size.

Iron dextran (FeDex) is commonly administered to piglets in the pig industry between days 3-6 postpartum to prevent the onset of iron deficiency anemia, as noted by Egeli and Framstad (1999). However, this veterinary practice is associated with various adverse effects, including sudden cardiovascular collapse and respiratory failure, as reported by Ueberschar in (1966). Conversely, the ingestion of iron through oral means may be linked to intestinal disorders that have the potential to be hazardous, such as diarrhea, abdominal pain, and constipation. Iron overdose has been widely recognized as a potential cause of significant corrosive lesions in the upper gastrointestinal tract, including mucosal necrosis, ulceration, and ischemia, as reported by Bloor et al. (2021). The administration of oral iron supplements has the potential to disrupt the equilibrium of the intestinal microbiota, thereby affecting the assimilation of various micronutrients, including iron, as well as others (Yilmaz and Li, 2018).

According to Raje et al. (2018), the utilization of nano minerals in livestock has been found to enhance the bioavailability of minerals~~,~~ leading to improvements in animal growth, production, and health. Numerous research studies have indicated that the bioavailability of materials is considerably enhanced when they are prepared in nanometer size (Thakkar et al., 2010). It is postulated that the bioavailability of iron can be enhanced through the reduction of iron-containing compounds to nanometer size, akin to the effects observed with zinc phosphate-based nanoparticles and zinc supplements (Hilty et al., 2010). Liposomes, which are small vesicles surrounded by a lipid bilayer membrane~~,~~ are frequently employed as drug carriers to mitigate systemic toxicity and enhance drug delivery to specific sites within the body. This is in conjunction with the use of nanoparticles~~,~~ as noted by Alavi et al. (2017).

The effectiveness of supplements in addressing iron deficiency anemia is primarily influenced by the bioavailability of the iron they contain, as noted by Lopez and Martos ~~in~~ (2004). The diminished bioavailability of inorganic iron in neonatal piglets is attributed to the absence of iron transporters in the duodenum during the initial stages of neonatal life, as per the findings of Lipinski et al. (2010). Rafal et al. (2021) utilized hemoglobin as a dietary source of haeme, which is a highly bioavailable organic iron, to effectively counteract the onset of iron deficiency anemia in piglets. Iron nano particles (IONPs) have emerged as a potent instrument in various biomedical (Krishnan, 2010) and environmental applications (Kohler et al., 2019). The literature extensively reports that IONPs have the potential to function as drugs and/or gene carriers~~,~~ in addition to serving as contrast agents or hyperthermal mediators in anticancer therapy (Cochran et al., 2013). Nonetheless, the efficacy of iron oxide nanoparticles ~~(IONPs)~~ in addressing iron deficiency anemia (IDA) remains largely unexplored. The study conducted by Son et al. (2019) revealed that the administration of nano minerals resulted in the enhancement of piglet growth, as evidenced by a rise in live weight gain and a decrease in feed conversion ratio. The research findings indicate that the provision of nano minerals can enhance the immune system, decrease the occurrence of diarrhea, and stimulate the growth of pigs~~,~~ particularly those that have been recently weaned.

Pereira et al. (2015) conducted a study which demonstrates that nanoparticulate iron (III) oxo-hydroxide is a viable and secure source of iron for human consumption, given its high bioavailability and efficient utilisation by the human body. The authors Churio et al. (2019) have provided evidence that the use of iron oxide nanoparticles ~~(IONPs)~~ is more effective in treating iron deficiency anaemia in piglets compared to heme and non-heme iron micro particulate. This is attributed to the physicochemical properties of IONPs. The objective of the research carried out by Wegmuller et al. (2004) was to assess the effects of iron pyrophosphate size reduction and encapsulation on haemoglobin retention in rats suffering from anaemia. The results of the study indicate that the bioavailability of iron pyrophosphate, which had an average particle size of 2.5 µm, was 43%, whereas that of iron pyrophosphate with a particle size of 0.5 µm was 95%, when compared to ferrous sulphate. The study conducted by Lee et al. (2019) revealed that the utilisation of Fe nanoparticles via the hot melt extrusion method led to a significant elevation in the villus height observed in the duodenum and jejunum of piglets. According to Hosseindoust et al. (2017) and Kim et al. (2017), the evaluation of intestinal morphology is utilised as a means of gauging an organism's capacity to effectively process nutrients. The potential for improved digestive capacity of nutrients in weaned piglets can be attributed to an increase in villus height. The study conducted by Mazgaj et al. (2021) revealed that the oral administration of iron oxide nanoparticles to suckling piglets for a duration of 23 days resulted in a marginal therapeutic impact as compared to the administration of Sucrosomial® or FeDexiron. This finding is in contrast to previous research and is associated with decreased parameters of piglet growth. Whilst the administration of iron oxide nanoparticles ~~(IONPs)~~ appears to be a procedure of low toxicity for both piglets and their microbiota, the study's utilisation of a daily dose of 6 mg of iron does not permit the integration of this compound into supplementation strategies.

The relatively elevated expense associated with nanoparticle and organic sources has limited their utilization in comparison to the more prevalent inorganic source. Not ~~with standing~~withstanding the financial aspect, it is imperative to consider the environmental concerns. The utilization of highly absorbable Fe is imperative for the promotion of sustainable swine industry, as it aids in the reduction of environmental pollution, as noted by JunHyung Lee et al in 2019.

With regard to "Regulations of Nanotechnology" authored by Gopi et al. in 2017 discusses the regulatory framework surrounding the field of nanotechnology. The utilization of nanotechnology in the realm of animal nutrition necessitates particular attention to risk assessment, regulatory measures, and oversight. Therefore, a meticulous evaluation of potential, technical, societal and policy implications of these nascent applications must be conducted promptly. Numerous countries worldwide have accredited regulatory frameworks and diverse approaches to guarantee the safety of nano products in agriculture~~,~~ or food. The Food Safety and Standards Act is primary regulatory framework governing food safety in India. In October of 2001, the Government initiated a program known as the Nano Science and Technology Initiative (NSTI), which was subsequently followed by "Nano Mission" program in 2007. Several research activities have been conducted within the framework of this program and only recently have some measures been initiated to tackle risk-related concerns. The matter of standardisation continues to be a subject of apprehension, given that India has merely embarked upon preliminary measures to tackle standardisation concerns. The current state of legislation in the country regarding nano hazards is insufficient, as noted by Sharma and Chugh (2009). Additionally, there is a need for additional resources and expertise to effectively manage the risks associated with nanotechnology~~,~~ as highlighted by Barpujari (2011).

## Conclusion~~:~~

Nanotechnology provides innovative approaches to augment the growth and productivity of livestock. Nanoparticles of minerals have been found to mitigate the antagonistic effects of minerals in the intestine, leading to a decrease in excretion and environmental contamination. Nano minerals exhibit significant potential as mineral feed supplements for animals, even at lower doses compared to conventional sources. This is attributed to their ability to enhance bioavailability in biological systems, which is facilitated by their increased surface area, surface activity, and catalytic efficiency. The current review suggests that the administration of nano iron supplements may enhance the growth, digestive efficiency, and immunity of piglets.



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