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Nanoformulated Treatments for Iron Deficiency Anemia

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ABSTRACT: Iron deficiency anemia is one of the most common nutritional disorders, impacting more than 30% of the world. IDA is extremely prevalent, especially in third-world countries. Some leading causes of IDA are poor diet intake and heavy blood loss. Many conventional medications include oral ferrous sulfate, ferrous gluconate, and intravenous injections. However, IDA still persists as a leading deficiency. This is due to the severe gastrointestinal side effects, which impact patient compliance. New emerging nanoformulations can mitigate side effects while maintaining or even increasing absorption. In this literature review, this paper examines numerous studies on conventional therapies and nanoformulations. Comparing dosages, efficiency, and general reception, it was found that nanoformulations are superior to traditional medications. Specifically, nanoferric pyrophosphate was found to be superior to other nanoformulations. This is beneficial for IDA in both first and third-world countries. However, more clinical research needs to be done in order to better understand the full range of nanoformulations on humans.

KEYWORDS: Biomedical and Health Sciences, Nanomaterials, Iron Oxide Nanoparticles, Iron Deficiency Anemia, Iron Supplementation.

Introduction

Iron deficiency anemia (IDA) is one of the most common blood conditions that impacts one's red blood cells. According to the World Health Organization (WHO), IDA is one of the most common dietary deficiencies in the world, with over 30% of the population being affected by this condition.[1] In the United States, around one in four adults suffers from inadequate iron absorption or intake.[2] Without enough iron, the human body cannot produce sufficient hemoglobin. Hemoglobin is the protein contained in red blood cells that is responsible for the delivery of oxygen to the tissues.[3] Symptoms associated with IDA include, but are not limited to, excessive tiredness, dizziness, fatigue, lethargy, hair loss, and lightheadedness.[4,5] Iron deficiency anemia has shown outcomes of poor pregnancy outcomes, poor motor and mental performance in children, and low work productivity in adults.[5] On society as a whole, this impacts several factors, including significant economic losses, reduced quality of life, and impaired human development. Impaired human development is one of the most critical impacts of IDA. Due to the cognitive losses, the work capacity of adults also significantly decreased.[6]

In order to treat IDA, traditional medication includes oral iron supplements and intravenous iron injections.[5] However, these traditional routes are associated with major gastrointestinal (GI) side effects such as nausea, constipation, and diarrhea, which impact up to 50% of patient compliance.[5] New technologies, such as nanoformulated technologies, aim to mitigate risks. Nanoscience is an emerging field in science with many new opportunities for applications, especially in medicine. It can be defined as the science involving the design of materials on a nanometer scale, or one billionth of a meter. Nanoformulated iron is hypothesized to be a better approach compared to conventional iron due to its larger surface area, which enhances absorption.[7]

Conventional oral iron supplements, like ferrous sulfate, are effective and commonly used in increasing iron levels. However, the absorption of iron is dependent on food intake and dosage. While an empty stomach is optimal for iron absorption, many side effects are present: gastrointestinal side effects such as nausea, constipation, and diarrhea are common.[5] In comparison, nanoformulated iron supplements such as liposomal iron, sucrosomial iron, and iron oxide nanoparticles, when used properly, address traditional concerns. These formulations enhance iron bioavailability by increasing its solubility and using alternatives.[5]

There are many conventional medications meant to treat IDA. Yet, IDA remains the largest nutritional deficiency in the world. Nanotechnology is an emerging field that can reduce the significant number of patients with IDA. The close evaluation between nanoformulated iron supplements and conventional therapies is crucial for advancing both science and public health sectors. Addressing this topic allows for new mechanisms in iron absorption. Additionally, it allows physicians a broader scale of pharmaceuticals to address iron deficiency anemia, reduce the side effects, especially in areas with populations with histories of low immunity or tolerance, which has led to poor adherence. Widespread use of solutions in high-risk groups like young children or pregnant women can reshape policy decisions regarding iron supplementation protocols in resource-poor areas. This bridges the gap in nutritional health worldwide, making therapies more accessible and acceptable worldwide.

Methodology

The primary aim of this study was to examine the recent advancements in nanoformulations in IDA. The objective of this literature review was to explore how nanoformulated iron delivery systems enhance iron bioavailability and absorption

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while reducing gastrointestinal side effects compared with conventional medications. Specifically, this literature review aims to synthesize existing research studies in clinical studies to identify both technological innovations and gaps in current studies addressing iron absorption challenges in anemic patients. Through this synthesis of the literature, this paper aims to understand nanoformulations, such as different iron particles, and how they compare to conventional medications. The research relied on digital tools and databases to gather data. PubMed served as a primary search engine for gathering biomedical papers due to its vast collection of data. Supplementary databases such as Google Scholar and ScienceDirect were used in limited cases to ensure comprehensive coverage. The search strategy was carefully refined through specific keywords such as "Nanomedicine," "Nanotechnology," "Iron oxide nanoparticles," and "Bioavailability enhancement." Data gathering was organized through a filtered approach. An initial screening stage eliminated duplicates and irrelevant studies by assessing titles and abstracts. The remaining articles were assessed through a full-text read. Studies with insufficient data and unclear methodologies were excluded. Literature from PubMed from 2015 to 2025 was filtered. Focusing on studies with strong clinical or animal evidence, we gathered around 41 sources for our main consideration. Using several sources and their patient data, quantitative comparisons between conventional treatments and nanoformulated medications were conducted. Both primary and secondary sources were included in this review. The primary sources consisted of peer-reviewed experimental research articles, clinical trial publications, and animal studies. These sources provided both qualitative and quantitative data. The inclusion of secondary sources provided additional, deeper insight. Data on iron absorption levels, dose equivalencies, and side effects were explored. Throughout the entire process, no physical tools or materials were used in this study.

Biological Importance of Iron:

Biologically, life relies on many different metals, and iron is one of them. Iron is needed by most species. Iron is essential for many important cellular processes, including gene regulation, metabolism, bioenergetics, and hormone synthesis. Both deficiency and overload can disrupt these functions and can lead to serious diseases.[4] About 60-70% of iron in the body is incorporated into the main circulating protein hemoglobin in red blood cells. This binds and transports from the lungs to the tissue. Another portion of the iron is then stored in myoglobin in the muscle, where it stores oxygen to support muscle contraction. Without enough iron in the body, hemoglobin levels fall, resulting in IDA with symptoms ranging from weakness and fatigue to hair loss.[4,8]

Iron is the metal in active sites of redox enzymes, enzymes that can catalyze a reduction or oxidation of their substrate, in the mitochondrial electron transport chain. This is critical for ATP production.[9] It is part of heme and non-heme enzymes in oxidative metabolism. Iron absorption uses heme iron from meats such as poultry and seafood. Heme iron is readily available for iron absorption rather than non-heme iron. Nonheme iron can be found in plants, and only about 17% or less is absorbed. When there is a lack of heme iron, IDA can impair metabolism, impacting physical health.[4,10]

Additionally, iron interacts in DNA replication and repair. DNA replication initially starts with the unwinding of the DNA helicase, which includes iron-dependent DNA. The iron-sulfur (Fe-S) cluster of DNA is used for DNA binding and helicase activity. After the DNA unwinds, the RNA primer is deposited for DNA replication initiation. Primase, which contains 2 units that are iron-dependent. DNA polymerases and then combine complementary DNA strands. Iron-containing enzymes supply the iron-containing DNA strands. An Fe-S protein (PPAT) starts purine synthesis.[11] Ribonucleotide reductase (RNR), an enzyme used for DNA synthesis, uses an iron-based cofactor that converts ribonucleotides to deoxyribonucleotides.[12] This is then used by polymerases.[4] Many DNA replications and protein repair depend on iron clusters. A deficiency of iron can slow DNA replication and cellular division. Iron is essential for human life because even small disruptions of iron levels can severely impact oxygen transportation, metabolism, and DNA replication.[4,13]

Diagnostic criteria for Iron Deficiency Anemia:

The diagnosis of IDA is established by assessing hematological and iron biomarkers. In a healthy individual, ferritin can show iron levels. However, they are rarely beneficial in order to find the actual iron availability for erythropoiesis. For this reason, additional criteria are evaluated. Transferrin saturation (TSAT), soluble transferrin receptor (sTfR), percentage of hypochromic erythrocytes (%HYPO), and reticulocyte hemoglobin content (CHr) are all used to identify IDA.[14] The World Health Organization explains that IDA is standardized by a hemoglobin level of less than 130 g/L in men, less than 120 g/L in nonpregnant women, and less than 110 g/L in both pregnancy and children less than 5 years of age.[14]

Global Epidemiology of IDA:

Iron Deficiency Anemia is the leading cause of worldwide anemia, affecting up to 30% of the world. Women of reproductive age and children are the highest risk groups of IDA due to the increased need for iron, blood loss due to menstruation, and, most often, an inadequate diet.[15] The most common regions impacted by IDA are South Asia and sub-Saharan Africa. Many countries report anemia in more than half of women and children. Additionally, tropical Latin America and part of Oceania exhibit high anemia rates, though slightly lower than South Asia and sub-Saharan Africa.[16] Especially in South Asia, anemia in women of reproductive age is highly prevalent, and rates frequently exceed 50% with particularly high rates in countries such as India, Pakistan, and Bangladesh. Low dietary nutrients, menstrual and pregnancy-related blood loss, and cereal-based diets with low iron bioavailability drive these high rates of IDA. Sub-Saharan Africa also shows similar patterns of IDA, especially among children and women. With rates surpassing 60%, IDA often overlaps with malaria and other inflammatory conditions that cause blood loss and increase the need for iron.[17] In comparison, higher

income areas such as North America, Western Europe, and parts of East Asia have overall lower rates of anemia; still, IDA remains prevalent in the same high-risk groups of young children, menstruating, and pregnant women.[18] In high-income settings, the main cause of IDA surrounds heavy menstrual bleeding, poor diet choices, bariatric surgery, and gastrointestinal disorders such as celiac disease. Instead of widespread food insecurity, these criteria cause bleeding.[5] Globally, IDA still progresses as a nutritional barrier and causes many burdens, especially for women and young children. Although there are many conventional therapies aimed at decreasing IDA rates, it remains prevalent in third-world countries. Nanoformulations of iron can improve bioavailability without the gastrointestinal side effects. Novel nano-iron systems hope to overcome the limitations of conventional medications and provide scalable solutions for food fortification.

Discussion

Iron Deficiency Anemia Overview:

Johns Hopkins Medicine defines Iron Deficiency Anemia (IDA) as low hemoglobin levels due to insufficient iron levels. This can result from diets low in iron, body changes, growth spurts in children and adolescents, gastrointestinal tract abnormalities, and blood loss.[19]

As shown in Figure 1, the human body absorbs iron through the stomach and duodenum. Iron absorption and regulation involve the hormone hepcidin and the iron transporter ferroportin. During this process, oxygen combines with iron and is transported into the plasma portion of blood by binding to transferrin.

From there, iron and transferrin are used in the production of hemoglobin, stored in the liver, spleen, and bone marrow, and utilized as needed by all body cells. Disruptions in this process can result in anemia.[20]

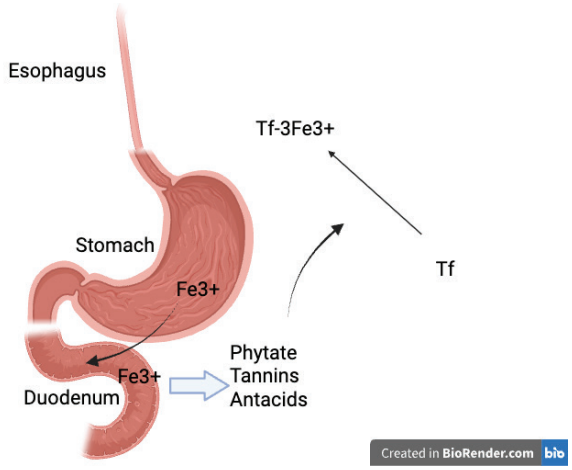

Figure 1: Iron Absorption. This image reflects iron absorption. Iron can be found in food; particularly, heme iron is found in poultry and seafood. During digestion, iron travels through the stomach to the duodenum, where it is absorbed into the bloodstream and used by cells as needed. Iron is oxidized to the Fe3+ state. Molecules like transferrin facilitate the absorption of iron, while phytates, tannins, and antacids block absorption.[21] Created using BioRender.

Heme Vs. Non-Heme Iron:

There are two types of iron: Heme and non-heme iron, which differ significantly in their absorption from dietary sources. Heme iron is found in animal products and is absorbed more efficiently. About 25% of heme iron is absorbed. In comparison, non-heme iron is from plant-based foods such as beans, nuts, dark chocolate, legumes, spinach, and fortified grains. Less than 17% of non-heme iron is absorbed. Non-heme iron is regulated by the body, so the bioabsorption tends to be less. Other foods can influence absorption. For instance, foods with vitamin C can enhance absorption. However, there are iron absorption inhibitors, such as calcium in dairy products. On the other hand, heme iron is absorbed regardless of the body's iron status, which can potentially lead to iron overload. Vegetarians rely solely on non-heme iron, so they need to consume more iron than an omnivore. Failure to meet iron requirements leads to IDA.[10]

Conventional Overview:

Conventional supplements such as ferrous sulfate and ferrous gluconate are used for the management and treatment of iron deficiency anemia. Iron supplements are available and cost-effective for the general population.[5] Oral iron supplements replace iron stores and encourage erythropoiesis: formation of red blood cells, which is essential for oxygen transport throughout the body.[22]

Oral Iron Supplementation:

Iron supplements such as ferrous sulfate (20% elemental Fe), ferrous gluconate (12% elemental Fe), and ferrous fumarate (33% elemental Fe) are the most common prescriptions for IDA.[20] Many formulations, such as ferrous sulfate, ferrous gluconate, and ferrous fumarate, are readily available over the counter.[5] For the best absorption, it is recommended to take Fe at least 30 minutes before a meal or 2 hours before taking other medications. Iron transportation occurs through the process of divalent metal transporter 1 (DMT1) across the basolateral membrane through the protein ferroportin, where it is stored as ferritin in the M1 macrophages. Then it is converted to absorbable Fe2+ ions. Before finally being separated by transferrin to various sites in the body, including the bone marrow for RBC synthesis. The absorbed iron is then incorporated with other components, such as porphyrin and globin chains, to form hemoglobin, which transports oxygen from the lungs to other organs in the body, entering systemic circulation.[20]

Intravenous Iron Injections:

Intravenous iron injections are effective in the treatment of IDA and are considered when oral supplementation fails. Situations where IV is preferable are patients who cannot tolerate oral iron due to side effects, pregnant women who already have significant nausea and vomiting, patients who have a gastric bypass, where reduced gastric secretion impairs iron absorption, and patients who have malabsorption conditions that prevent adequate absorption into the body (such as Whipple's disease, SIBO, celiac disease, pernicious anemia).[20] Intravenous iron injections are useful when there are substantial iron losses, such as menstrual bleeding, chronic gastrointestinal bleeding, and impaired intestinal absorption (such as celiac disease, inflammatory bowel disease, or after gastric/duodenal surgery).[5]

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There are many types of IV iron injections, which include iron sucrose and ferric carboxymaltose. All IVs can differ in doses and infusion time.[23]

Table 1: Comparative Efficacy of Various IV Treatments.

IV Formulations	Mechanism of release	Typical Dose	Infusion time	Safety
Iron sucrose[24]	Binds with transferrin[24]	100mg[24]	Multiple sessions[24]	Well tolerated[24]
Ferric Carboxymaltose[25]	Slow, RES uptake[25]	~750mg[25]	1–2 short infusions[25]	Larger doses, risk of hypophosphatemia[25]

Table 1 demonstrates the comparative efficacy of two types of IV iron formulation and how they vary in dose, infusion time, and safety.

Iron sucrose is a type of IV that is made up of a complex of ferric oxyhydroxide and sucrose. During transfusion, it releases iron that binds with transferrin. Then it's transported through target cells, such as erythroid precursors, which are located in the bone marrow. There, it is incorporated into hemoglobin.[26] The iron is rapidly absorbed in the bloodstream with peak serum levels within around 10 minutes.[24] However, iron sucrose is less stable than other complexes, so it releases iron more quickly. This means it is generally well tolerated and can be used in patients with chronic diseases.[26]

Studies have shown that pharmacologically relevant concentrations of iron sucrose can significantly inhibit phagocytic function in neutrophils. This impact can be facilitated by elemental Fe rather than the carbohydrate shell.[27] Ferric carboxymaltose is another type of IV that is made up of a macromolecular complex of ferric hydroxide and carboxymaltose.[28] Ferric carboxymaltose is used in symptomatic patients to help reduce HF symptoms and improve quality of life. The high molecular weight allows for slow and controlled release. Ferric carboxymaltose is taken up by endocytosis by the M1 macrophages of the reticuloendothelial system. Since this slow release has larger doses, there are lower risks of infusion reactions, but it is associated with a higher risk of hypophosphatemia, defined as an adult serum phosphate level of fewer than 2.5 milligrams per deciliter (mg/dL).[29]

Pitfalls of Conventional Medications:

While conventional medications are widely used, they pose side effects for the patient. These side effects hinder patient compliance and overall effectiveness of the treatment. The most common oral medications, such as ferrous sulfate, ferrous gluconate, and ferrous fumarate, have GI side effects of nausea, abdominal pain, vomiting, heartburn, diarrhea, constipation, and discolored stools. All of these side effects inhibit patient compliance. Up to 50% of patients have reported experiencing discomfort leading to poor adherence to treatment plans.[5] There are many adverse effects as intestinal iron absorption is limited. For example, the maximum absorption of 100mg of oral iron only leads to up to 20% to 25% absorption rates and is reached in the late stage of iron deficiency.[5] This rate can even decrease further depending on certain foods that inhibit iron absorption. Additionally, uptake may be impaired in a disease setting, such as celiac disease, anemia of chronic disease, or autoimmune gastritis. Within patients with inflammatory bowel disease, mucosal injury and possible exacerbation of disease activity may occur.[5] Thus, conventional medications are only effective when intestinal absorption is not impaired by conditions such as celiac disease, autoimmune gastritis, duodenal resection, or menorrhagia.

Intravenous (IV) Injections, such as iron sucrose and ferric carboxymaltose, are used when oral medications fail. IV iron injections have their own set of side effects. With IV, there is a potential for iron overload, which can occur from repeated infusions. Additionally, there are rare risks of severe allergic reactions, such as anaphylactic reactions with dextran-containing formulations. More common side effects of IV include bloating or swelling of the body, blurred vision, chest pain or tightness in the chest, confusion, headache, and dizziness.[30] Overall, there are many pitfalls of conventional iron medications that limit patient compliance and reduce efficacy in patients with GI disorders. These challenges underscore the need for emerging innovative solutions, such as nano-iron, that reduce side effects while improving absorption.

Nanoformulations of Iron Deficiency Anemia:

Recent innovations in the field of nanotechnology have resulted in a wide array of new nanoformulated IDA solutions, such as iron oxide, ferric phosphate, iron oxo hydroxide, and ferric pyrophosphate. These nanoformulations are used for the treatment of IDA rather than the frequently used iron salts due to their efficiency. Research has been ongoing to increase the efficacy of Iron Nanoparticles (IONPs) based treatments, and these nanoformulations aim to close the gap of IDA. These tiny nanosized iron oxide particles have proven to increase bioavailability and absorption in addition to lowering the risk of gastrointestinal side effects.[31] For example, nanoformulated ferric phosphate demonstrates more than 72% increase in absorption rates compared to conventional ferrous sulfate. Additionally, the nanoformulation demonstrates better safety in both mice and human subjects.[32]

Table 2: Comparative Efficacy of Various Nanoformulated Treatments.

Nanoformulated IDA treatments	Dosage(animal)	Relative Efficiency	Findings
Iron Oxide + multivitamin mixture[33]	2.57-4 mg/kg rat(single dose)[33]	Rapid Efficiency- fast hemoglobin recovery (4.4 → 14.6 g/dL, 4 days)[33]	Fast correction for IDA; had minimal toxicity[33]
Iron Oxide NP + folic acid coat[33]	2–4 mg/kg rat	Improved hemoglobin compared to ferrous sulfate[33]	Better than traditional medication, but there are better nanoformulated solutions[33]
Magnetite (Fe_3O_4) NP + vitamin C[33]	~8.3 mg (rat, equivalent dose)[33]	Faster anemia correction(within 4 days)[33]	High absorption yet minimal side effects[33]
Iron oxo-hydroxide NP + tartaric/adipic acid tail[33]	20 mg/kg rat; humans tested[33]	~80% as efficient as iron sulfate[33]	Enhanced bioavailability, but not as efficient[33]
Nano-ferric pyrophosphate [31]	10–30 mg/kg (rat model)[31]	103.2% relative to ferrous sulfate[31]	Superior bioavailability and efficiency, the best out of all[31]
Hybrid iron NP (amyloid fibril bound)[31]	2.5 mg/100g food product (rat)[31]	More efficient in comparison to ferrous sulfate, high bioavailability[31]	Good for food fortification[31]
Iron phosphate NP ($FePO_4$)[31]	10–20 mg/kg (rat model)[31]	Similar to ferrous sulfate[31]	Improved absorption; not as good as other solutions[31]
Commercial iron salts (ferrous sulfate, gluconate)[34]	10–200 mg daily (humans, oral)[34]	Standard: ~10–20% absorption[34]	High dose required, GI side effects[34]

Table 2 summarizes the comparative efficacy of various nanoformulated treatments relative to the most commonly used conventional iron salts for the treatment of iron deficiency anemia (IDA). The table highlights key studies that compare different iron nanoparticles, including hybrid iron nanoparticles alongside conventional iron salts such as ferrous sulfate and gluconate. For each formulation, the dosage and animal model are listed. The relative efficiency of the formulation and its results are compared with conventional medications, and the main findings regarding hemoglobin levels, side effects, and overall absorption are presented. The data demonstrate that nanoformulated iron treatments are often superior to conventional medications. This table serves as a concise reference for evaluating the advantages of Iron NPs in IDA treatment.

Among the various solutions, iron oxide nanoparticles have been widely studied. Oftentimes, iron (Fe) NPs are encapsulated with multivitamins or coated with folic acid to improve bioavailability and minimize toxicity. These NPs are synthesized through co-precipitation and are designed to rapidly correct IDA (Iron Deficiency Anemia). Several reports, specifically in rats, have shown fast hemoglobin recovery with minimal side effects. The multivitamin model demonstrates enhanced iron metabolism, and the folic acid coating reduces direct contact with the intestinal lining, therefore reducing gastrointestinal side effects.[33]

Magnetite nanoparticles, especially when capped with vitamin C, can demonstrate higher absorption rates than conventional medications while maintaining minimal side effects and no cytotoxic effects. Vitamin C enhances iron solubility, and experiments in albino rats have shown that this formulation corrects IDA faster than most commercially available solutions, such as ferrous sulfate.[33]

Iron oxo-hydroxide NPs (nanoparticles), which are modified with tartaric and adipic acids, can mimic the structure of ferritin, which is the body's natural iron storage protein. This NP has been shown to reduce toxicity and enhance bioavailability. Tests from both human and animal clinical studies have demonstrated having a greater bioavailability and being approximately 80% as efficient as ferrous sulfate in terms of absorption.[33]

Nanoformulated ferric pyrophosphate, synthesized through titration, is shown to have superior bioavailability and absorption. Studies have indicated it is more than 103.2% more efficient than ferrous sulfate.[31] Nano-ferric pyrophosphate is designed for the rapid correction of IDA, while maintaining minimal side effects. Hybrid iron nanoparticles have shown a high level of bioavailability, making them effective for food fortification. These NPs have proven stable tolerability, but long-term data are still limited.[31]

Iron phosphate NPs are synthesized through flame spray pyrolysis. These NPs have shown improved absorption compared to conventional iron salts, while still maintaining minimal side effects, making them a good option for food fortification. However, other nanoformulations are superior, as they require less dosage in comparison for an optimal effect.[31] Commercial iron salts such as ferrous sulfate remain the standard medication for IDA; they come with many significant gastrointestinal side effects, including nausea, constipation, and diarrhea. These side effects have led to poor compliance from patients.[34] In comparison, nanoformulations require fewer doses but achieve better tolerability.

Nano-Ferric Pyrophosphate:

Nano-ferric pyrophosphate is an especially small-sized iron nanoparticle developed as a food fortificant. The particles are typically 10-30 nanometers. It is used to address IDA throughout daily dietary intake rather than high-dose medicinal supplementation. Nanosizing Ferric Phyrophosphate, which is usually poorly soluble (Fe^{3+}) salt, allows the water-insoluble iron salt to sharply increase solubility in acidic environments, which improves gastrointestinal absorption and hemoglobin regeneration. In bulk form, ferric pyrophosphate is white and almost tasteless, which makes it convenient for adding it to cereals, dairy, and other foods without it causing a metallic taste or dark discoloration.[31] In the rat model, nano-ferric pyrophosphate achieved a relative bioavailability of roughly 103% when compared with ferrous sulfate.[31] This indicates that nano-ferric pyrophosphate can match or even surpass standard oral iron salt while avoiding many of the GI side effects that limit use of other fortificants in food products.[35] On a functional level, nano-ferric pyrophosphate is more of a "stealth" nutritional fortification than a high-dose drug. For example, it can be blended into foods such as infant cereals, dairy products, and other daily staples so that populations at risk of IDA can receive repeated doses of highly bioavailable iron without noticeable changes in taste or appearance and side effects.[35, 36] Past preclinical work indicates that at a nutritionally relevant dosage, nano-ferric pyrophosphate can replenish hemoglobin levels with minimal toxicity through proteomic changes such as shifts in proteins like Fetuin-B.[35]

In a recent randomized controlled trial in children ages 2-12, Liposomal SunActive was compared with conventional iron for the treatment of IDA. Liposomal iron is a novel oral formulation of ferric pyrophosphate. After one month of therapy, 96 pediatric patients demonstrated higher hemoglobin levels. After six months of oral iron therapy, the patients on the liposomal iron still showed greater HB levels.[37] Liposomal iron and nano-ferric pyrophosphate are both similar, and their efficacy is comparable if not superior to traditional iron salts. Both can be used as a food fortification for children, as there are undetectable changes in taste and easy incorporation due to their size.[35, 37]

Side Effects and Tolerability:

Nanoformulations have consistently outperformed conventional medications, while maintaining superior safety and tolerability. Compared to traditional iron salts, nano-iron supplements have shown fewer gastrointestinal side effects, with lower rates of nausea, constipation, diarrhea, and abdominal discomfort; these being the most common side effects reported with conventional medications such as ferrous sulfate and ferrous gluconate.[38, 39] However, the field of nano-iron is relatively new, so there are some potential side effects and safety concerns to consider.[37]

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One notable side effect that was seen was the risk of local reactions at the site of administration, especially with intravenous nano-iron products. Leakage of the solution outside of the vein can lead to discoloration of the skin, which can persist over several months but usually resolves over time. Rapid infusion of some nano-iron formulations can trigger complement activation-related pseudoallergy (CARPA). CARPA can be shown as flushing, back/chest pressure, or itching. However, these reactions are more common with older formulations or those that release more free iron and are not usually life-threatening, unlike true anaphylaxis, which is extremely rare with modern formulations.[40]

Oral Nano-Iron supplements are less likely to cause systemic side effects. However, some individuals may experience mild gastrointestinal side effects, such as a change of color in stool or a metallic taste in the mouth. Typically, these effects are less severe compared to conventional medications. In extremely rare cases, extravasated iron products lead to granulomas, dermatitis, or local fibrosis. There is still ongoing research about the long-term side effects of nano-iron accumulation in tissues, but current evidence shows nano-iron is generally safe. Compared to conventional medications, nanoformulations have significantly better tolerability due to fewer GI side effects.[41]

The findings of this literature review highlight the potential of the future of biomedical nanotechnology in iron supplementation for the management of iron deficiency anemia (IDA). By synthesizing multiple sources from recent clinical studies, this review demonstrates that nanoformulated iron supplements consistently outperform conventional iron salts such as ferrous sulfate and ferrous gluconate in terms of bioavailability and patient compliance. The most notable formulation among the nanoformulations is nano-ferric pyrophosphate, as it is 103.2% more effective than conventional salts.[12] Nano-ferric pyrophosphate provides superior absorption rates as well as reduced gastrointestinal side effects compared to traditional therapies like ferrous sulfate and ferrous gluconate. These results are significant as they provide better solutions for weaker communities with persistent challenges associated with conventional medications, including vulnerable populations such as children, pregnant women, and individuals with gastrointestinal disorders.

One of the most interesting findings is the enhanced bioavailability of nanoformulated iron supplements. Studies have shown that nano-ferric pyrophosphate achieves bioavailability rates exceeding those of ferrous sulfate, with minimal side effects and rapid correction of anemia. This is due to the physicochemical characteristics of nanoparticles, such as size and release mechanisms, which facilitate increased iron uptake. Similarly, iron oxide nanoparticles encapsulated with multivitamins or coated with folic acid have shown rapid hemoglobin recovery while reducing toxicity, demonstrating the advantages of nanoformulations in clinical practices.

Additionally, another key finding was its increased tolerability. Conventional iron salts are notorious for their gastrointestinal side effects, such as nausea, constipation, or diarrhea, resulting in poor patient compliance. In comparison, nanoformulations are associated with reduced side effects, which can result in higher adherence rates as well as patient satisfaction. Nano-ferric pyrophosphate has been shown to have superior absorption rates. This is essential for the future. In order to close the nutritional gap between populations with a history of lower tolerability, the reduced side effects not only improve quality of life for patients but also enhance the effectiveness of anemia management.

Future Directions and Limitations:

The implications of this finding are far-reaching for clinicals, future research, and public policy. Through a clinical perspective, nano-iron supplements can improve patient outcomes in the management of iron deficiency anemia (IDA). As for public policy, the integration of nanoformulations both internationally and nationally could decrease the global burden of Iron Deficiency Anemia (IDA), especially in areas where access to conventional therapies is limited. The versatility of nanoformulations is suitable for not only individual treatment but also large-scale food fortification programs. This provides a practical solution for improving iron bioavailability in populations with limited access to healthcare.

Some theoretical implications show a deeper understanding of the mechanisms of iron absorption and the role of nanotechnology in improving drug delivery. The success of nanoformulations shows the importance of particle size. These insights benefit the development of future nanomedicine applications, not only for iron deficiency but also for other micronutrient deficiencies. Despite the promising findings, several limitations must be acknowledged. The majority of studies are from animal models such as rats and small-scale human trials. Additionally, the cost of these nanoformulations can pose barriers to their widespread adoption, especially in poorer communities. Further research is required to observe the immune response as well as the long-term effects of repeated exposure to iron nanoparticles.

■ Conclusion

Based on current research, the field of nanotechnology can enhance iron absorption through nano-iron with significantly fewer gastrointestinal side effects. Notably, nano-ferric pyrophosphate outshines conventional medications and has a promising impact on food fortification. Overall, Nanoformulations offer greater bioavailability and absorption compared to conventional medications. However, current research mostly uses animal models. Future research needs to focus more on clinical trials on humans to see the full capacity of nanoformulations. By addressing these gaps, nanoformulations of iron supplements can transform the global epidemiology of iron deficiency anemia and maximize its accessibility.

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References

1. Kumar, A.; Sharma, E.; Marley, A.; Samaan, M. A.; Brookes, M. J. Iron Deficiency Anaemia: Pathophysiology, Assessment, Practical Management. BMJ Open Gastroenterology 2022, 9 (1), 1–9. https://doi.org/10.1136/bmjgast-2021-000759.
2. About 1 in 4 Americans may have inadequate iron intake or absorption. NHLBI, NIH. https://www.nhlbi.nih.gov/news/2024/about-1-4-americans-may-have-inadequate-iron-intake-or-absorption.
3. Billett, H. Hemoglobin and Hematocrit. National Library of Medicine. https://www.ncbi.nlm.nih.gov/books/NBK259.
4. Teh, M. R.; Armitage, A. E.; Drakesmith, H. Why Cells Need Iron: A Compendium of Iron Utilisation. Trends in Endocrinology and Metabolism 2024, 35 (12). https://doi.org/10.1016/j.tem.2024.04.015.
5. Jimenez, K.; Kulnigg-Dabsch, S.; Gasche, C. Management of Iron Deficiency Anemia. Gastroenterology & Hepatology 2015, 11 (4), 241.
6. Horton, S.; Ross, J. The Economics of Iron Deficiency. Food Policy 2003, 28 (1), 51–75. https://doi.org/10.1016/s0306-9192(02)00070-2.
7. Saini, R.; Saini, S.; Sharma, S. Nanotechnology: The Future Medicine. Journal of Cutaneous and Aesthetic Surgery 2010, 3 (1), 32. https://doi.org/10.4103/0974-2077.63301.
8. Briguglio, M.; Hrelia, S.; Malaguti, M.; Lombardi, G.; Riso, P.; Porrini, M.; Perazzo, P.; Banfi, G. The Central Role of Iron in Human Nutrition: From Folk to Contemporary Medicine. Nutrients 2020, 12 (6), 1761. https://doi.org/10.3390/nu12061761.
9. Prier, C. K.; Kosjek, B. Recent Preparative Applications of Redox Enzymes. Current Opinion in Chemical Biology 2019, 49 (46), 105–112. https://doi.org/10.1016/j.cbpa.2018.11.011.
10. Moustarah, F.; Mohiuddin, S. S. Dietary iron. PubMed. https://www.ncbi.nlm.nih.gov/books/NBK540969/.
11. Abbaspour, N.; Hurrell, R.; Kelishadi, R. Review on Iron and Its Importance for Human Health. Journal of Research in Medical Sciences: The Official Journal of Isfahan University of Medical Sciences 2014, 19 (2), 164.
12. Dagnell, M.; Schmidt, E. G.; Elias S.J. Arnér. The A to Z of Modulated Cell Patterning by Mammalian Thioredoxin Reductases. Journal of Biological Chemistry 2018, 115, 484–496. https://doi.org/10.1016/j.freeradbiomed.2017.12.029.
13. Zhang, C. Essential Functions of Iron-Requiring Proteins in DNA Replication, Repair and Cell Cycle Control. Protein & Cell 2014, 5 (10), 750–760. https://doi.org/10.1007/s13238-014-0083-7.
14. Achille Iolascon; Immacolata Andolfo; Russo, R.; Sanchez, M.; Fabiana Busti; Swinkels, D.; Patricia Aguilar Martinez; Rayan Bou-Fakhredin; Muckenthaler, M. U.; Unal, S.; Porto, G.; Ganz, T.; Antonis Kattamis; Lucia De Franceschi; Maria Domenica Cappellini; Munro, M. G.; Taher, A. Recommendations for Diagnosis, Treatment, and Prevention of Iron Deficiency and Iron Deficiency Anemia. HemaSphere 2024, 8 (7). https://doi.org/10.1002/hem3.108.
15. GBD 2021 Anaemia Collaborators. Prevalence, Years Lived with Disability, and Trends in Anaemia Burden by Severity and Cause, 1990–2021: Findings from the Global Burden of Disease Study 2021. The Lancet Haematology 2023, 10 (9). https://doi.org/10.1016/s2352-3026(23)00160-6.
16. Liu, Y.; Ren, W.; Wang, S.; Xiang, M.; Zhang, S.; Zhang, F. Global Burden of Anemia and Cause among Children under Five Years 1990–2019: Findings from the Global Burden of Disease Study 2019. Frontiers in Nutrition 2024, 11. https://doi.org/10.3389/fnut.2024.1474664.
17. Goodarzi, E.; Beiranvand, R.; Naemi, H.; Darvishi, I.; Khazaei, Z. Prevalence of Iron Deficiency Anemia in Asian Female Population and Human Development Index (HDI): An Ecological Study. Obstetrics & Gynecology Science 2020, 63 (4), 497–505. https://doi.org/10.5468/ogs.19196.
18. National Institutes of Health. Iron: Fact Sheet for Health Professionals. National Institutes of Health. https://ods.od.nih.gov/factsheets/Iron-HealthProfessional.
19. Johns Hopkins Medicine. Iron-Deficiency Anemia. Iron-Deficiency Anemia. https://www.hopkinsmedicine.org/health/conditions-and-diseases/irondeficiency-anemia.
20. Nguyen, M.; Tadi, P. Iron supplementation. PubMed. https://www.ncbi.nlm.nih.gov/books/NBK557376/.
21. Joint Center for Sickle Cell and Thalassemic Disorders at Brigham and Women's Hospital. Iron Absorption. Harvard.edu. https://sickle.bwh.harvard.edu/iron_absorption.html.
22. Cha, H. J. Erythropoiesis: Insights from a Genomic Perspective. Experimental & Molecular Medicine 2024. https://doi.org/10.1038/s12276-024-01311-1.
23. Short, M. W.; Domagalski, J. E. Iron Deficiency Anemia: Evaluation and Management. American Family Physician 2013, 87 (2), 98–104.
24. Macdougall, I. C.; Comin-Colet, J.; Breymann, C.; Spahn, D. R.; Koutroubakis, I. E. Iron Sucrose: A Wealth of Experience in Treating Iron Deficiency. Advances in Therapy 2020, 37 (5), 1960–2002. https://doi.org/10.1007/s12325-020-01323-z.
25. Cada, D. J.; Levien, T. L.; Baker, D. E. Ferric Carboxymaltose. Hospital Pharmacy 2014, 49 (1), 52–69. https://doi.org/10.1310/hpj4901-52.
26. PubChem. Iron Sucrose. Nih.gov. https://pubchem.ncbi.nlm.nih.gov/compound/Iron-Sucrose (accessed 2025-11-30).
27. Ichii, H.; Masuda, Y.; Hassanzadeh, T.; Saffarian, M.; Gollapudi, S.; Vaziri, N. D. Iron Sucrose Impairs Phagocytic Function and Promotes Apoptosis in Polymorphonuclear Leukocytes. American Journal of Nephrology 2012, 36 (1), 50–57. https://doi.org/10.1159/000339285.
28. Bhandari, S.; Pereira, D. I. A.; Chappell, H. F.; Drakesmith, H. Intravenous Irons: From Basic Science to Clinical Practice. Pharmaceuticals 2018, 11 (3). https://doi.org/10.3390/ph11030082.
29. Sharma, S.; Hashmi, M. F.; Castro, D. Hypophosphatemia. PubMed. https://www.ncbi.nlm.nih.gov/books/NBK493172/.
30. Mayo Clinic. Iron Sucrose (Intravenous Route) Description and Brand Names - Mayo Clinic. www.mayoclinic.org. https://www.mayoclinic.org/drugs-supplements/iron-sucrose-intravenous-route/description/drg-20075836.
31. Kumari, A.; Chauhan, A. K. Iron Nanoparticles as a Promising Compound for Food Fortification in Iron Deficiency Anemia: A Review. Journal of Food Science and Technology 2021, 79 (10). https://doi.org/10.1007/s13197-021-05184-4.
32. Baumgartner, J.; Winkler, H. C.; Zandberg, L.; Tuntipopipat, S.; Mankong, P.; Bester, C.; Hilty, F.; Zeevaart, J. R.; Gowachirapant, S.; Zimmermann, M. B. Iron from Nanostructured Ferric Phosphate: Absorption and Biodistribution in Mice and Bioavailability in Iron Deficient Anemic Women. Scientific Reports 2022, 12 (1), 2792. https://doi.org/10.1038/s41598-022-06701-x.
33. Shukla, A.; Dasgupta, N.; Ranjan, S.; Singh, S.; Chidambram, R. Nanotechnology towards Prevention of Anaemia and Osteoporosis: From Concept to Market. Biotechnology & Biotechnological Equipment 2017, 31 (5), 863–879. https://doi.org/10.1080/13102818.2017.1335615.

DOI: 10.36838/IJHSR813.81

34. Pantopoulos, K. Oral Iron Supplementation: New Formulations, Old Questions. Haematologica 2024, 109 (9). https://doi.org/10.3324/haematol.2024.284967.
35. Srinivasu, B. Y.; Mitra, G.; Muralidharan, M.; Srivastava, D.; Pinto, J.; Thankachan, P.; Suresh, S.; Arun Shet; Rao, S.; Ravikumar, G.; Thomas, T. S.; Kurpad, A. V.; Mandal, A. K. Beneficiary Effect of Nanosizing Ferric Pyrophosphate as Food Fortificant in Iron Deficiency Anemia: Evaluation of Bioavailability, Toxicity and Plasma Biomarker. RSC Advances 2015, 5 (76), 61678–61687. https://doi.org/10.1039/c5ra07724a.
36. Ghosh, R.; Arcot, J. Fortification of Foods with Nano-Iron: Its Uptake and Potential Toxicity: Current Evidence, Controversies, and Research Gaps. Nutrition Reviews 2022, 80 (9). https://doi.org/10.1093/nutrit/nuac011.
37. Mohammed, N. I.; Wason, J.; Mendy, T.; Nass, S. A.; Ofordile, O.; Camara, F.; Baldeh, B.; Sanyang, C.; Jallow, A. T.; Hossain, I.; Faria, N.; Powell, J. J.; Prentice, A. M.; Pereira, D. I. A. A Novel Nano-Iron Supplement versus Standard Treatment for Iron Deficiency Anaemia in Children 6–35 Months (IHAT-GUT Trial): A Double-Blind, Randomised, Placebo-Controlled Non-Inferiority Phase II Trial in the Gambia. eClinicalMedicine 2023, 56. https://doi.org/10.1016/j.eclinm.2023.101853.
38. Philippa Skett. Iron supplements in nano form are gentler on the gut. New Scientist. https://www.newscientist.com/article/dn25975-iron-supplements-in-nano-form-are-gentler-on-gut/ (accessed 2025-11-30).
39. Singh, K.; Sethi Chopra, D.; Singh, D.; Singh, N. Nano-Formulations in Treatment of Iron Deficiency Anaemia: An Overview. Clinical Nutrition ESPEN 2022, 52 (1). https://doi.org/10.1016/j.clnesp.2022.08.032.
40. Daldrup-Link, H. E. Ten Things You Might Not Know about Iron Oxide Nanoparticles. Radiology 2017, 284 (3), 616–629. https://doi.org/10.1148/radiol.2017162759.
41. Li, J.; Wang, L.; Li, S.; Liang, X.; Zhang, Y.; Wang, Y.; Liu, Y. Sustained Oral Intake of Nano-Iron Oxide Perturbs the Gut-Liver Axis. NanoImpact 2023, 30 (1), 100464–100464. https://doi.org/10.1016/j.impact.2023.100464.

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