REVIEW PAPER

Role of nanotechnology in iron deficiency

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ABSTRACT

Micronutrients are one of the major groups of nutrients required by the body. Vitamins and minerals are considered micronutrients that are vital for growth, immune function, brain development, and many other important functions. they also play a role in preventing and fighting diseases. Malnutrition (undernutrition) is caused by a lack of nutrients and is the leading cause of death in the world. Biofortification of staple crops with micronutrients has been proposed as a potential technique for combating malnutrition by enriching target food crops. Iron deficiency is one of the most frequent dietary problems worldwide, affecting both industrialized and developing nations. Iron deficiency anemia is a condition in which the blood doesn't have enough healthy red blood cells. It may be due to blood loss, lack of red blood cell production, and high rates of red blood cell destruction, but it leads to reduced oxygen flow to the body's organs and causes fatigue, skin pallor, shortness of breath, light-headedness, dizziness, or a fast heartbeat. Nanotechnology is the creation and use of innovative structures, materials, and systems in a variety of disciplines, including agriculture, food, and medicine. The study and management of matter at sizes of 1 to 100 nanometers is known as nanotechnology. It can help with everything from food production to manufacturing, and it can make a big impact on food quality and safety, and also the health benefits of foods. While nanotechnology may be the greatest technique to reduce anemia's effects while also boosting iron bioavailability in the blood, it has some negative effect on the body that depends on the duration of exposure and the level of intake. In this paper, we discuss how micronutrient deficiencies and anemia can be prevented by using nano techniques as well as how they impact the human body.

Keywords: *Iron complex, Iron deficiency anemia, Nanoparticles, Nano-encapsulation, Pharmaceuticals*

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INTRODUCTION

Deficiency affects the body's ability to function properly. Micronutrient deficiencies are estimated to contribute to roughly 7.3% of the global burden of disease, with iron and vitamin A deficiency ranking among the 15 top causes of global disease burden [1], contributing to the deaths of almost one million children per year [2]. Around 2 billion people affected by Iron, iodine, and zinc deficiency are from developing nations. Impaired brain development, impaired immunity poor pregnancy results, poor growth, and blindness can all result from this deficiency.

Anemia is a common disease caused by iron deficiency in which the amount of red blood cells or their oxygen-carrying capacity is insufficient to meet the body's physiological needs. The severity of anemia varies according to age, gender, altitude, smoking habits, and the stage of pregnancy. Many iron complexes have been tested and combined into food vehicles to get an optimal iron fortifier based on the needs of anemic people [3]. These issues had not been fully resolved and their chemistry is the cause of the problem. Ferrous and ferric iron are the most prevalent types of iron utilized in food fortification. Both forms of iron have an empty d-block and are attempting

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to find a stable location, forming compounds with anthocyanins, flavonoids, tannins, and phenolic chemicals found in food. Several typical problems result from this process, including a negative influence on texture and color, metallic aftertaste, off-flavor due to lipid peroxidation, vitamin (ascorbic acid and carotenoid) degradation, and decreased iron absorption [4]. Now researchers and enterprises are interested in employing nanotechnology for the successful delivery and enhancement of the bioavailability of iron in the body. The nanomaterial's properties can be exploited to create formulations that deliver iron complexes to the body that enhance the bioavailability and absorption of iron for the prevention of anemia.

HISTORY

In the 1930s and World War II, significant attempts were made in the United Kingdom and the United States to fortify meals with various micronutrients and to make people healthy. Fortification was not a novel concept. Bakers in France enriched bread with cod-liver oil as early as 1873 to promote the health of hospitalized youngsters. Helen Mackay [5], a British researcher, discovered that iron-fortified milk could help newborns to prevent anemia. By the late 1920s, some margarine in Europe had been fortified with vitamin A, and several patented techniques for adding cod-liver oil, liver oil, or cod-liver oil extracts to the margarine had been created [6].

Rice, potatoes, wheat, lentils, and millet are among the staple food of India, which vary by area; the eastern and southern regions of the country rely primarily on rice, while the northern and western parts rely on wheat. In 2016, India produced 158.8 million tonnes of rice, making it one of the top producers. According to the global scenario, rice provides 30% of calories on average, and in some low-income countries, it can reach 70% [7]. Domestic milled rice consumption is predicted to be at 97.6 MMT (million metric tonnes) in 2017/18, while wheat consumption is estimated to be over 93 million, as per the GAIN research. Furthermore, milling removes practically all vitamins and minerals from the foods that are important for human nutrition [8]. As a result, rice and wheat can play an excellent role as delivery vehicles of micronutrients. Although iron, folic acid, and Vitamin B12 fortification are advised in the Indian context, rice fortification with other micronutrients such as Vitamin B1, niacin, zinc, and in rare cases, selenium and Vitamin A and E are also used. Oil is a nearly indispensable food item of daily life, with use by 99% of homes in India. Edible oil is consumed in the country at a rate of 12–18 kg per person per year, and vitamins A and D are fat-soluble vitamins, so oil delivers the micronutrients effectively [7]. The addition of vitamins and minerals to normal meals is a public health technique for increasing nutritional intake without increasing caloric intake. Food fortification is a medium to long-term remedy to the population's alternative nutrient deficits [9].

Since the 20th century, large-scale food fortification programs have been launched in industrialized countries, helping to eliminate deficiency disorders in high-income countries, primarily in North America and Europe [10]. Food fortification has lately acquired popularity in LMICs, and its influence on health in these nations is expanding. However, the effectiveness of fortification programs is determined not only by the biological efficacy of fortified foods, but also by their effective implementation, which includes, among other things, monitoring, quality assurance (QA)/quality control (QC), and industry compliance with fortification standards [11].

As a result, biofortification of staple crops with micronutrients has been proposed as a potential technique for combating malnutrition by enriching target food crops to address the gap in micronutrient absorption by humans and animals [12]. The insufficiency of micronutrients is going up due to the growth in the global population. Around 3 billion people are affected by zinc and iron deficiency which is caused by low-nutrition staple food-based diets. Mineral insufficiency causes a reduction in the gross national product due to its low work productivity. In the United Kingdom, for example, anemia affects 11% to 38% of children before they reach the age of two. Zn deficiency affects 10% of the population in Canada and the United States [13].

According to WHO mortality data, iron insufficiency causes roughly 0.8 million fatalities (1.5% of all deaths) each year, and vitamin A deficiency causes a comparable proportion. Iron deficiency anemia causes 25 million DALYs (Disability Adjusted Life Years) lost (or 2.4% of the global total), vitamin A deficiency causes 18 million DALYs lost (or 1.8% of the global total), and iodine deficiency causes 2.5 million DALYs lost (or 0.2% of the global total) [3].

Micronutrient deficiencies are far more difficult to assess in terms of scale and impact, while it is believed that several forms of micronutrients, such as zinc, folate, and vitamin D deficiency, contribute significantly to the global disease burden. However, there are limited data on the prevalence of these micronutrient deficiencies, and because their negative health impacts are often non-specific, the public health implications are unclear [7]. Mineral deficiencies, caused by a lack of calcium, iron, or zinc in the diet or absorption, are linked to a variety of human health issues, including stunted growth in children, weak bones, and immune system abnormalities. Food fortification could be a crucial component in resolving this issue.

Food fortification: changing the nutritional value of food

Fortification in food

The word "food fortification" refers to the process of increasing the necessary micronutrient content of foods to improve their nutritional value and provide health advantages (Fig. 1).

Mass fortification

One or more micronutrients widely used in food that is regularly consumed by the general population, such as cereals, condiments, and milk, are referred to as Mass Fortification. The government is in charge of its regulation.

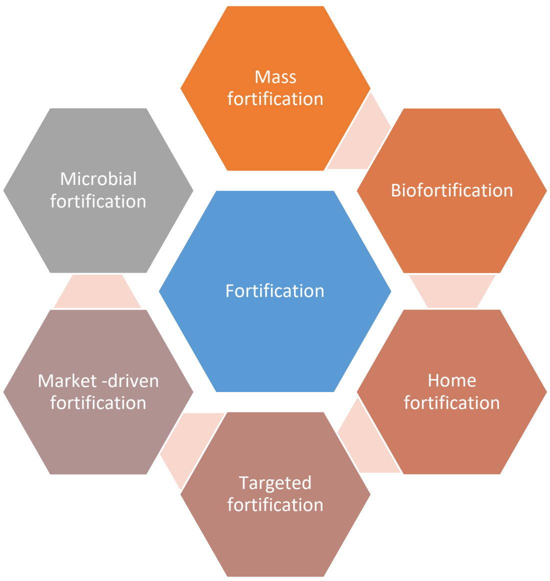

Fig. 1. Techniques of fortification.

Targeted fortification

In this program, fortification is done on a specific group, for example infants and young children's complementary foods.

Market-driven fortification

This sort of fortification is used in the food industry, where food makers take a commercial effort to manufacture food products containing one or more micronutrients.

Household fortification

In this fortification, only at the household or community level, practical methods of increasing micronutrients in food are used.

Microbial fortification

Microbial fortification entails the release of micronutrients by bacteria, which is frequently accomplished through fermentation. For example, the bacterial release of carotene by fermentation is an example of these tactics.

Bio-fortification

Bio-fortification is accomplished through biotechnology or breeding procedures aimed at boosting the nutrition of the food. For example, the production of transgenic "Golden rice" for the enrichment of vitamin A.

The goal of food fortification is to promote health by decreasing the effects of micronutrient shortages. Although iron, zinc, and vitamin A deficiency are common worldwide, sub-Saharan Africa (SSA) accounts for 80% of all cases. Furthermore, with metabolic issues and reduced infection resistance, this region has a higher prevalence of physical and mental developmental disabilities, as well as other physiological illnesses linked to micronutrient deficiency. To prevent micronutrient malnutrition in SSA, basic foodstuffs such as rice, maize, and wheat flour have already been fortified. Furthermore, in SSA and other developing regions, industrial food fortification, which has made fortified supplemental foods commonly accessible in developed countries, is conspicuously absent [3, 14]. This is because commercially fortified food products are too expensive for most people in these areas. The delivery vehicle influences the bioavailability of micronutrients in fortified foods [15]. This shows that in SSA, fortification of a variety of staple meals, as well as foods that have been forgotten

Table 1. Fortified foods and their fortificants

Name of fortified food	Addition of fortificants
Oils	Vitamin A, Vitamin D, Vitamin E, omega -3,
Curd	Probiotic curd, flavors
Juices	Calcium, Vitamin D, iron
Bread	Vitamin B, iron, folic acid, Vitamin 12, oats, whole grain wheat
Milk	Vitamin A, Vitamin D, soymilk, calcium
Biscuit	Vitamin A, iron, calcium, folic acid, and Vitamin D
Rice	Vitamin A, B6, B3 and B12

or undervalued, could be crucial in combating micronutrient deficiency. Perspectives on food fortification's benefits and problems, as well as the required technology in reducing the risk of micronutrient deficiencies in SSA, have also been discussed (Table 1) [7].

Impact of fortification in different regions

Food fortification is a low-cost, tried-and-true method for enhancing diets and avoiding and treating micronutrient deficiencies**.** In 2008 and 2012 [16], the Copenhagen consensus identified food fortification as one of the most cost-effective development targets. While mandatory food fortification has been used to avoid micronutrient malnutrition since the 1920s in high-income countries (HIC) in Europe and North America, when the first salt was iodized, it is still less popular in LMICs where food systems are unable to deliver a nutritious diet due to the production and consumption of a few massive starchy food crops (maize, rice, and wheat) with low micronutrient content or biocompatibility (phytate). Food fortification has been more popular in LMICs over the last two decades for a variety of purposes, including increasing urbanization and expanding household buying power, which has resulted in a higher proportion of people relying on processed foods [2]. Food fortification programs aim to reduce nutritional deficiencies in populations and are assumed to have one of the highest benefit-to-cost ratios of any nutrition intervention [16], but this is only correct if fortified foods are produced by centralized and comparatively well-developed industry sectors, according to a regional expert. Foods fortified with micronutrients include staples (such as cereal flour and grains such as rice), sauces, and processed market food [17]. Latin America has a long history of fortification of cereal flours and salt, going back to the 1950s, and it is the developing region with the greatest access to fortified staples; almost every country, for example, has guidelines and regulations for fortifying wheat flour, maize flour, and rice. Food fortification is preferred in Latin America compared with impoverished Asian and African nations for a variety of reasons. The region has a high degree of urbanization, literacy, and real wealth, as well as a specialized food sector and broad commercial food consumption, allowing for a wide spectrum of food fortification. Sub-Saharan Africa and South Asia, on the other hand, are poor and more rural, with lower commercial food intake and a large number of small producers of staples such as wheat or maize flours. Latin America already has a long tradition of public-private-civil-society partnerships, as well as a willingness to address nutritional challenges. Industry and several academic research organizations in the region also have considerable technological skills that can be leveraged to manufacture fortified products and establish and implement programs. In contrast, the public sector's technical skills and resources for monitoring and evaluating programs vary greatly. Because of the large amount of regional trade and the presence of numerous multinational firms in the region, uniformity in regulations and standards for fortification is a must. Although Latin America has various food fortification initiatives, there is little evidence that they are effective in solving vitamin deficiencies. There have been a few studies; the results are inconsistent, but they all point to the impact of vitamin deficiencies [18-21]. Bioavailable fortificants were not employed in some circumstances. Because of inadequate fortification levels and/or poor fortification intake, not too much of the "nutrient gap" might be addressed, especially in the case of iron [22]. Poor quality control, regulation, and monitoring systems may have further contributed to the program's failure and inefficiency. Some initiatives, however, may be successful, albeit impact evaluations have not yet been completed. Latin American programs uncover the qualities that underlie their effectiveness and obtain assistance for fortification efforts across the board. We considered it a success if we could show that it had a positive influence on micronutrient deficiencies. We chose three programs based on our understanding of the region, all of which used mass, required fortification, and for which effect analyses had been conducted. In Guatemala, sugar fortification with vitamin A affects the vitamin A status of the population. The impact of iron and other micronutrient fortifications on intake and anemia in mothers and children in Costa Rica [23], as well as fortification of wheat flour with folic acid in Chile, has been shown to reduce the incidence of numerous chronic illnesses (NTDs) [7,24].

Iron deficiency

Iron deficiency is a very common dietary problem worldwide, affecting both industrialized and developing nations. Iron deficiency anemia is attributed to a lack of iron levels in the blood for an extended period. Low iron levels in the blood can be caused by several things, including food that has a deficiency of iron, worm infestation hemorrhage, digestive illnesses, and so on. The World Health Organization (WHO) estimates that 48% of children between 5 and 14 years of age and 52% of pregnant women in underdeveloped nations have anemia [25].

Table 2. Based on the WHO report number of women suffering from anemia, the global prevalence of anemia in 2011

WHO region	Affected women
Africa	79.1
America	40.5
South East Asia	202
Europe	50.2
Eastern Mediterranean	59.1
Western Pacific	96.2

Dietary iron comes in two forms: nonheme iron is found in both plants and animals, and heme iron is derived from hemoglobin and myoglobin in animal diets. In meat-eating countries, heme iron is projected to provide 10–15% of total absorbed iron, but due to its larger and more uniform absorption (estimated at 15–35%), it could contribute up to 40% of total absorbed iron [26, 27]. Non-heme iron absorption is more affected by an individual's iron status than heme iron absorption [28]. The prevalence of anemia among women from various parts of the world is depicted in Table 2. Non-heme iron is abundant in plant-based diets, in comparison with heme iron present in animal tissues; it is weakly absorbed in the body [29]. In underdeveloped nations, another reason for iron deficiency is the reliance on plant-based diets and food crops. Some of the iron deficiency effects and causes are given in Table 3 for the various age groupings in the population.

To prevent iron deficiencies, food must have iron content mentioned in Table 4. Food can be enriched by different techniques and meet the target amount of iron.

Table 3. Factors of Iron Deficiency Anemia (IDA) in people of various ages.

Stages	Causes	References
Infancy	Due to low birth weight, iron stores are deficient at the moment of birth	30
Childhood	Unidentified blood loss may be linked to malnutrition and persistent diarrhea. Inflammatory bowel illness, according to Miller (2013)	31
Adolescence	Growth spurt with insufficient hematopoiesis	32
Pregnancy	It requires 1200 mg of iron from conception to birth; IDA Lee and Okam were caused by insufficient iron storage prior to pregnancy (2011). Increased dietary requirements, yet poor iron, vitamin, and copper absorption	33
Old age	Nutrient insufficiency and poor absorption, as well as the usage of nonsteroidal anti-inflammatory medicines (NSAIDs), are all factors	34
Adults	Chronic infections, such as tuberculosis, cancer, and chronic diarrhea Leonardo and his colleagues (2019) GI surgery, during severe stages of IDA, histologic defects of the GI tract mucosa, such as blunting of villi, emerge, resulting in blood leakage and poor absorption of iron, further compounding the condition	35–37
Common Causes	Excessive blood loss due to hookworm infestation. Bernstein, Wu, and Lesperance (2017). Folate absorption is reduced. West, Bailey, and Black (2015) Bias Against Women	38,39

Table 4. Iron content in different foods.

Plant-based Food	Common iron content (µg/g)	Iron after biofortification (mg/g DW)	Reference
Brown rice	15		40
Polished rice	2	15	41
Wheat, wholemeal	30	59	40
Wheat, flour, white	7		42
Maize, whole	30	60	40
Common bean	50	107	41
Dried peas	50		41
Pearl millet	47	88	43
Cassava root	5	45	41
Sweet potato	6	85	44
Irish potato	3		45
Cabbage, broccoli	17		
Tomatoes	5		
Beefsteak	35		

Evolution of nanotechnology

Nanometre-scale technology uses atoms or molecules with a size of 1–100 nm to create and use new materials. The created nanomaterials have one or more exterior dimensions and an interior structure in the size range of 1-100 nanometres, allowing nanoscale observation and modification. These materials exhibit distinct qualities compared with their macroscale counterparts because of their surface-to-volume ratio and other new physiochemical traits such as color, solubility, strength, diffusivity, toxicity; and magnetic, optical, and thermodynamic properties [46, 47]. Nanotechnology has appeared in a new era of industrialization, with both developed and emerging countries keen to invest more in that technology [48]. As a result, nanotechnology brings up several new opportunities for the creation and use of innovative designs, materials, and technologies in industries like agriculture, food, and medicine, to name a few. Awareness among consumers about food standards and medical benefits is driving academics to create a method for improving food quality while preserving it and the possible extent of the nutritional content of the product. Because many nanoparticle-based products include essential nutrients and are non-toxic, the food industry has increased its demand for them [49]. They've also been proven to be resistant to high temperatures and pressures [50]. From food manufacturing to processing and packaging, nanotechnology can assist. Food quality and safety, as well as the medical benefits that food delivers, are all affected by nanomaterials. Many organizations, researchers, and businesses are developing new nanotechnology-related techniques, procedures, and products [51, 52].

Innovative science and technology start with dreams and creativity. Aspirations like these gave birth to nanotechnology, a 21st-century challenge. Nanotechnology is defined as the study and management of matter at sizes ranging from 1 to 100 nanometers, where unique phenomena enable innovative applications [53]; although humans have long been exposed to nanoparticles. Nanoparticle studies are not new, they grew in popularity as the world became more industrialized. The 1925 Nobel laureate in chemistry, Richard Zsigmondy, was the first to propose the notion of a "nanometer." He first used a microscope to measure the size of particles like gold colloids, and he coined the term "nanometer" to define particle size. Modern nanotechnology was established by Richard Feynman, the Nobel Laureate in Physics in 1965. He suggested the notion of altering matter at the atomic level during a speech titled "There's Plenty of Room at the Bottom" at the 1959 American Physical Society meeting at Caltech. Feynman's assumptions have since been proven correct, and his original concept has opened up new avenues of thought. As a result, he is considered the founder of contemporary nanotechnology. Over 15 years after Feynman's discussion, Japanese scientist Norio Taniguchi was the first to adopt the word "nanotechnology" to define semiconductor operations on the order of a nanometer. He asserted that nanotechnology involved the processing, separation, consolidation, and alteration of materials by a single atom or molecule. Eric Drexler of MIT integrated concepts from Feynman's "There is Plenty of Room at the Bottom" and Taniguchi's term nanotechnology in his 1986 book, "Engines of Creation: The Coming Era of Nanotechnology." Drexler proposed the idea of a nanoscale "assembler" that could make copies of itself and other complicated objects. Drexler invented the phrase "molecular nanotechnology," which summarizes his approach to nanotechnology. The science of nanotechnology advanced even further when Iijima [54,75], a Japanese scientist, developed carbon nanotubes. Nanotechnology's emerging disciplines received a lot of interest around the turn of the 21st century. The renown of Feynman and his notion of influencing matter at the atomic level affected US research goals. President Bill Clinton supported research investment for innovative technologies through a speech at Caltech on January 21, 2000. President George W. Bush signed the twenty-first-century Nanotechnology Research and Development Act three years later. The measure established a National Technology Initiative (NNI) [55], which prioritized nanotechnology research at the federal level. Today, the NNI is overseen by the President's Cabinet-level National Science and Technology Council (NSTC) [56] and its Committee on Technology. The NNI's planning, funding, execution, and review are overseen by the Committee's Subcommittee on Nanoscale Science, Engineering, and Technology (NSET). Participants from 20 US departments, as well as independent bodies and commissions [53], make up the group.

Nano fortifier

It's critical to select the right combination of food carriers and iron supplements when designing iron-fortified foods. To add iron to foods, a variety of iron salts are available.

Iron salts are classified into three categories based on their solubility:

(a) Highly water-soluble

(b) Poorly water-soluble but soluble in dilute acid

(c) Water-insoluble but poorly acid-soluble.

Except for ferrous chloride, the high water-soluble iron complex has often more bioavailability. After solubilization, ferrous chloride is rapidly oxidized, as seen by the rapid emergence of the orange color. It explains the reason for less bioavailability of ferrous chloride. Iron absorption is influenced by the type of iron fortifier used in the human metabolic process. The taste, color, and sensory evaluation of food products are all influenced by the water-soluble iron component [4, 57]. The most critical issue is finding a long-lasting iron compound, that has more bioavailability and does not alter food pH or organoleptic qualities.

New iron fortifiers are currently being developed. Nanotechnology engineering creates nano-form iron that is easily absorbable by the human body [58]. However, because biological systems cannot have too much free iron, industrial production must be conducted under strict safety standards [59]. Fe (III) nanoparticles were shown to be transported by the ferric pathway in an animal model and had no negative hematological or organ consequences [60], implying that tailored iron forms and fractions can be produced to adjust iron solubility and absorption as desired. Ferritin nanoparticles are another solution. Ferritin is a big protein that has the ability to store a considerable amount of iron. It might be an excellent source of iron. As a result, synthetic ferritin-mimetic nanoparticles were made and several duodenal loops or cultured cells were investigated [61,62]. Some food vehicles are used to transfer the nano complexes given in Table 5.

Techniques analysis

Anemia arose the interest of scientists and technologists of food all around the world, and several nanotechnology-based iron delivery technologies are being developed or explored. For food fortification, only iron water-soluble forms are allowed, but they cause undesired color changes and an off-taste in the meal, preventing them from being used directly as food fortifiers [69]. Because a smaller particle size enhances dispersion via the gastrointestinal tract, encapsulation offers better bioavailability and absorption. The nanoscale reduction also enhances chemical solubility and absorption. This is supported by the findings that Anchovy muscle protein hydroxylate (AMPH) enhances nonheme iron absorption by forming nano-sized ferric hydrolysis products. They looked at how AMPH affected nonheme iron bioavailability and intestinal absorption in rats, as well as the *in vitro* cellular absorption mechanisms in Caco-2 cells. Bioavailability was improved, and the efficiency of

Table 5. Recent research on iron fortification in foods.

Approached by Fortification	Food carrier	Reference
Increase Ferrous sulfate and ferrous gluconate	Infant formula	63
Iron pyrophosphate in microencapsulation	Fruit juice, dairy products	64
Cold plasma treatment	Rice	65
Increase Ferrous sulfate, ferrous fumarate, and NaFeEDTA	Curry powder	66
Increase Microencapsulation of ferrous sulfate	Liposomes	67
Ferritin	Nanoparticles	68

hemoglobin regeneration was improved [70]. Several investigations have been done to solve the iron deficit, researchers are working on nanomaterials for iron or ferrous salt encapsulation and effective transit into the body. Scientists [71], to generate the ferritin core of the mimic, created 5–10 nm iron oxo-hydroxide nanoparticles and transformed them with tartaric and adipic acid tails. Plants, animals, and humans all have ferritin, which is an iron-storage and detoxifying protein. They tested the effectiveness and iron oxo-hydroxide nanomaterial absorbed by cells using animal and cellular models. Rats and the human intestine Caco-2 cell line were also involved in the investigation of the toxicity. The nanomaterial was discovered to exhibit little cytotoxicity in cells and had no negative impacts on the rats' intestinal mucosa or fecal microbiota. Because it has no negative impacts on intestinal cells and bacteria and has good solubility in stomach juices, such a formulation offers a lot of potential for treating iron deficiency anemia. Furthermore, the ligand-transformed nano-particle Fe molecule closely resembles ferritin present in the human body, causing an increase in blood absorption. The accessibility of ligand-doped Fe (III) oxo-hydroxide nanomaterials was shown to be 80% as effective as ferrous sulfate, which is often used in iron supplementation, in studies on somewhat iron-deficient menopausal female subjects. In addition, this form was three times more absorbable than a conventional ferric chloride complex treated with the same ligand. Furthermore, after 14 days of feeding, in rats, iron oxo-hydroxide nanoparticles were generated, with no structural or functional modifications, and there was no abnormal Fe deposition [71]. As a result, it may be argued that such a formulation is both safe and more effective. Zariwala et al. [72] used the double emulsion solvent evaporation procedure to make ferrous sulfate-loaded solid lipid nanoparticles. Because of the numerous benefits they give, the utilization of solid lipid nanoparticles is common in therapeutic applications and administration. Unlike liposomes, which are generally unstable, solid lipid nanoparticles have high absorption, biocompatibility, and stability. The researchers used human intestinal Caco-2 biomaterials to determine the nanomaterial's absorption and used ferritin production as an indicator for iron absorption. Iron absorption was shown to be 13.42% greater in ferrous sulfate-loaded lipid nanocomposites than in free ferrous sulfate. The inclusion of lipids in the nanomaterials accounts for greater absorption. Lipids have been shown to improve encapsulated drug or molecule intestinal absorption by boosting particle delivery across the gut's bimolecular lipid membrane [73]. Lipids have bio-adhesive properties and attach to the gastrointestinal tract lining, boosting cellular absorption [72, 74]. By functioning as permeability enhancers, lipids can alter the protective barrier of the gastrointestinal tract [75]. Using the MTT (methylthiazolyldiphenyl-tetrazolium bromide) assay, in Caco-2 cell lines, the cytotoxic effect of lipid nanoparticles was examined. On the Caco-2 cells, solid lipid nanoparticles had no harmful effects. Solid lipid nanoparticles may become a remarkably efficient iron delivery technique, despite the fact that lipids are suitable for biological systems. It would be able to overcome practically all the drawbacks of current iron supplementation medicines. Hosny et al. [76], generated solid lipid nanoparticles loaded with iron, and carried out another work on solid lipid particles. Modifying synthesis factors including surfactant type and concentration, homogenization duration, and ultrasonication had an effect on nanoparticles, zeta potential, and encapsulation efficiency. By using hot emulsification and ultrasonication, iron solid lipid nanoparticles were made. A dialysis bag approach was used to assess drug release, and *in vivo* pharmaco-kinetic research was conducted on male albino rabbits who had been fasted for 24 hr before the trial. The iron solid lipid nanoparticles were tested against commercially available iron tablets. Iron bioavailability and drug release efficiency were shown to be more in solid lipid nanoparticles than is available commercially in iron capsules. By incorporating iron into solid lipid nanoparticles, bioavailability was raised fourfold. Because iron salts are water-insoluble, they were transformed into solid lipid nanoparticles, that improved solubility, and tissue permeability. Lipid absorption can be increased in several ways, involving intracellular or paracellular absorption via Peyer's patches and direct absorption into the lymphatic system, bypassing the liver. There are other ways, including tropical, oral, ophthalmic, rectal, and parenteral [76]. As a result, lipid nanoparticle delivery systems like these can significantly improve iron release and bioavailability in the body. Lipids, on the other hand, have a proclivity for clogging the pores and channels of cell membranes, a phenomenon that has yet to be fully examined. A. Shukla et al. Iron absorption is improved by ferric pyrophosphate, a water-insoluble iron component found in chocolate beverages and infant cereals. It is less accessible for absorption since it dissolves poorly in stomach acids due to its reduced solubility in dilute acids. Srinivasu et al. [69], by reacting a solution of sodium pyrophosphate using ferric chloride in the presence of ethylene glycol at 65 °C with constant stirring to minimize particle agglomeration, created a nano-size of ferric pyrophosphate ($FeO_4(P_2O_7)3$). The bioavailability of nano-sized ferric pyrophosphate was investigated by feeding iron-depleted rats a meal supplemented with nano-sized ferric pyrophosphate for 15 days. To compare the levels of availability in the two groups, a fraction of the treated rats was administered the same dosage of $FeSO_4$ for the same period of time. The hemoglobin regeneration capacity to quantify the bioavailability of ferric pyrophosphate was assessed. In comparison with ferrous sulfate, its relative bioavailability was found to be 103.2%. Oral toxicity tests on rats showed that nano-sized ferric pyrophosphate has no harmful effects. The higher solubility of ferric pyrophosphate in weak acids, owing to molecular size reduction, can be attributed to the greater bioavailability of nano-sized molecules of ferric pyrophosphate above ferrous sulfate. Metal solubility rises as particle size decreases [69], which is widely known. Some iron complexes and their characteristics are shown in Table 5 [4]. Salah et al. another nano-based therapy option for iron deficiency has been investigated. Because vitamin C increases iron absorption throughout the intestinal lumen, they developed magnetite (Fe_3O_4) nanoparticles encapsulated with it. Albino rats were used to assess the formulation's efficiency. It was discovered that administering the same medicine intraperitoneally or orally can effectively improve iron deficiency anemia. Experimental rat bone marrow tests revealed that magnetite nanoparticles encapsulated with vitamin C enhanced erythropoiesis while having little effect on hemostasis. After 10 days concentration of hemoglobin climbs from 7 to 14 g/dl, and red blood cell counts raised [77] from 3.2 £ 106 to 6.5 £ 106 / mm³. European Egyptian Pharmaceutical Companies (EEPI) have been granted a patent for development of iron-based nanoparticles for the treatment of anemia. On iron oxide (magnetite) nanoparticles, vitamins, folic acid, nicotinic acid, and ascorbic acid were encapsulated. Iron absorption requires vitamin C, but cell growth requires folic acid and nicotinic acid.

According to the authors, the drug was created in two forms: gel-based and liquid solution for oral ingestion. By extracting blood out from the canthus of the eyes, anemia was discovered in five-week-old albino rats, and the formulation was tried on them. The control group consisted of healthy, non-anemic animals. The rats were starved for six hours before receiving the medications. Depending on their physique, the rats were given varying amounts of nano iron oxide, ferric chloride, or magnetite nanoparticles treated with a multivitamin cocktail. A single dosage of 0.8 mg nanomaterials encapsulated with a vitamin supplement mixture was demonstrated to heal iron-deficient anemia and repair erythrocytes in less than four days. In seven days, hemoglobin levels climbed from 4.4 to 14.6 g/dl, then stabilized at 13.6 g/dl 80 days later. This is substantially faster than ferric chloride. Although the vitamin mixture was effective in treating anemia, it fell short of magnetite nanoparticles. Thus, iron-deficient anemia in albino rats may be treated with a single dosage of magnetite nanoparticles encapsulated with a micronutrient combination, equivalent to 8.3 mg, in less than four days. Most commercially available treatments are slower and less effective. Furthermore, unlike traditional iron pills, which have several negative side effects, this product has none. Moreover, unlike standard iron supplements, which come with so many undesirable side effects, the medicine has no hazardous side effects on the body due to the lower amount of nano iron oxide required to dramatically treat anemia [78]. Vitamin C, in addition to nanosized magnetite particles, improves Fe absorption through the intestinal villi. As a result, this combination can improve iron bioavailability and has the potential to be commercialized as an iron deficiency treatment. Although such a product has a lot of potential for treating iron deficiency, certain parameters, such as nanoparticle solubility in stomach acids, biocompatibility, and availability in the human body, as well as long-term implications of their consumption, still need to be investigated. Because the phenomenon of the human body differs from that of rats, the impacts of magnetic particles must be studied in humans before they can be used as a therapeutic agent. As a result, using nanostructures to transport iron salts gives benefits not found in traditional iron-deficient treatments. Nanomaterials may be able to reduce the negative effects of iron salts, particularly ferrous sulfate, on the gastrointestinal tract and normal gut flora. It also has a higher bioavailability and absorption rate than traditional iron salt [3].

Nanomaterials can help to decrease the adverse effects of iron salts, specifically ferrous sulfate, on the intestinal tract and normal gut flora. As previously stated, food fortification is now the most cost-effective method of reducing iron deficiency within the population without resorting to pharmaceuticals. Insoluble iron salts,

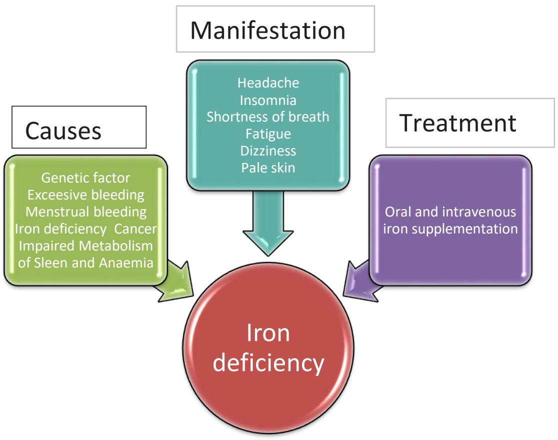

Fig. 2. Iron deficiency in humans has several causes, symptoms, and therapies

such as elemental iron, ferric pyrophosphate, and ferric phosphate, could be used as a substitute for soluble iron salts, which are highly bioavailable but have a disagreeable smell and color and cause gastrointestinal damage. The sensory characteristics of food are unaffected by insoluble iron salts. Iron salts' poor solubility in gastric juices results in decreased bioavailability and thus they have poorer nutritional value [78].

Nanotechnology in the prevention of anemia

There are several techniques to consider when creating a successful iron food fortification strategy, and nanotechnology can meet all of them. Nanotechnology has changed the medical, agricultural, and food industries during the last few decades. The length of a nanoparticle is typically 1–100 nm. Food additives, anti-caking agents, carriers for effective nutrition delivery, antibacterial agents, and fillers have all been employed as nanoparticles in the food business [79, 80]. Improved nutritional accessibility and delivery of minerals, nutrients, chemicals, and pharmaceuticals to their targets is one of the numerous applications of nanotechnology. The bioavailability of certain compounds rises when they are manufactured in nanoscale form, according to researchers [81, 82]. For subtleties, food technologists and scientists are turning to nanotechnology, which is gaining traction as a viable technique for iron treatment of anemia with dietary fortification and medicine delivery. Verma et al. [83] findings, the notion is supported by studies that show that in rats, lowering the size of the particles of elemental iron by 50–60% to 7–10 mm increases iron absorption by 50%. Another investigation by Harrison et al. used data from five commercial ferric orthophosphate samples, varying the material particle size (1–15 lm) and absorption in 0.1 N HCl (11.6%–63.4%). According to the study, the smaller and better dissolving in HCl had a higher bioavailability value (RBV). These findings show that reducing particle size is a viable technique for increasing iron bioavailability. Iron compounds have more surface area due to particle size reduction methods, improving their solubility in gastric acid and resulting in increased absorption. Many nanomaterials are used based on the result of research to prevent IDA in Table 7.

The main difficulty of pharmaceutical businesses is drug delivery since most of the compounds are insoluble in water (when

Table 7. Recent research has suggested new nanotechnology-based iron deficiency anemia remedies

Nanomaterial	Details of research	Reference
Nanoparticles of Magnetite	In albino rabbits, magnetite nanoparticles treated with vitamin C may elevate Hb levels from 7 to 14 g/dl in just 10 days	77
Nanoparticles of Iron	Accessibility and iron absorption are increased when mineral water is enriched with nano-iron	80
Nano-suspension of Iron	The ultrasonic approach was used to create a suspension of nano-disperse iron, in which the iron crystal lattice fractures and the number of active surface atoms rises	84
Nanoparticles of ferric pyrophosphate	Pyrophosphate's bioavailability is boosted in the nano-form because its size is reduced, making it more soluble	87
Nanoparticles of Iron	In murine models, a tartrate-modified, nano-disperse ferrihydrite was effectively employed to transport Fe (III) into the gastrointestinal tract without the risk of free radical production	85
Nanocomposite	For therapy of anemia in albino rats, iron oxide nanoparticles coated with a combination of vitamins and supplements such as folic acid, nicotinic acid, and ascorbic acid were produced	84
Nanoparticles of boron, calcium, chromium, copper, iodine, iron, magnesium, manganese	Commercial supplement that promises to increase the body's trace element bioavailability	84

medicine is dissolved in water, it is more effective). Furthermore, as discussed, [77] traditional iron deficiency anemia treatments have drawbacks.

As a result, nanotechnology may be the greatest technique to reduce anemia's effects while also boosting iron bioavailability in the blood. The reason for this is that, at the nanoscale, the surface area is much increased, resulting in a faster rate of disintegration. Furthermore, the nanoparticle can be tailored to meet individual requirements, resulting in increased stability and longevity [86]. Furthermore, the medicine is released more quickly, lowering the dosage and negative effects [87]. Some of the most well-known uses of nanotechnology in medicine, notably in treatment and therapies, are as follows:

As medication delivery systems with a specific target: to be target-specific, nanoparticles can have their transport mechanism and pharmacokinetic properties altered. Carbon nanotubes, for example [88-90].

As theranostics: nanoparticles that can be used for diagnostic and therapeutic purposes. For example, plasmonic nanobubbles [91-93].

As lipoplexes: To self-assemble an efficient drug delivery system, anionic nucleic acids and cationic lipids are used [94-97]. As a result, we look at potential nano-technological solutions that might greatly assist in the treatment of iron deficiency anemia, taking into account the benefits of nano-size technology.

A. Nano-encapsulation

Iron nanoencapsulation has been

demonstrated to be useful in the delivery of medications. The drug's stable and regulated release is ensured through nano-encapsulation, which reduces adverse effects. In general, medications are encapsulated in solid lipid nanoparticles to optimize absorption by increasing iron bioavailability in the blood by offering a higher solubility rate. Encapsulation has the effect of reducing gastrointestinal side effects while also enhancing bioavailability. The human Caco-2 cell line (which is used as an *in vitro* model of small intestine mucosa to estimate drug absorption) was used to evaluate these cells and rats, yielding a minimal cytotoxic impact with no negative effects on the rats' intestinal mucosa or fecal microbiota. As a result, this implies that when drugs are encapsulated in a form that is highly like a naturally occurring chemical, the body accepts it.

Bioactive substances/drugs are enclosed in a barrier of protection using nano-encapsulation in Fig. 3. This system uses a variety of delivery techniques, such as association colloids, nano-particles, nano-emulsions, nano-fibers/nano-tubes, nano-laminates, and nano-carriers that are resistant to enzyme degradation, especially in the gastrointestinal tract, to encapsulate bioactive substance/drugs [98].

B. Nano-ionization

The process of modifying or creating chemicals in the Nano form is known as nano-ionization. Nanostructures such as Nanocapsules, Nanoparticles, Nanocrystals, and Nanospheres, among others, are frequent Nano forms. By influencing the bioavailability of iron in the blood, this approach can be used to treat anemia. According to research, when the medicine is converted into a Nano form, the body absorbs it more efficiently in the gastrointestinal tract. This method can be used by anyone. The authority that drug producers have during the medicine development process is a fundamental benefit of this technique. They have the ability to control particle size distribution, allowing them to create a wide range of medications for different applications.

C. Nano-sized iron-oxyhydroxide particles

An iron-oxyhydroxide nanoparticle was produced and compared with a commonly used ferrous sulfate supplement in a case study involving human female participants. To assess the bioavailability of different ligand-modulated iron oxyhydroxide nanoparticles, moderately iron-deficient menopausal female participants were administered the produced nanoparticle and also the ferrous sulfate supplement. The absorbance of ligand-doped Fe (III) oxo-hydroxide nanoparticles was shown to be 80% as effective as ferrous sulfate, which is routinely used in iron supplements. A normal ferric chloride salt prepared of the same ligand was three times more available for absorption than the former. Furthermore, after 14 days of feeding, in rats, iron oxo-hydroxide nanoparticles had no structural or physiological

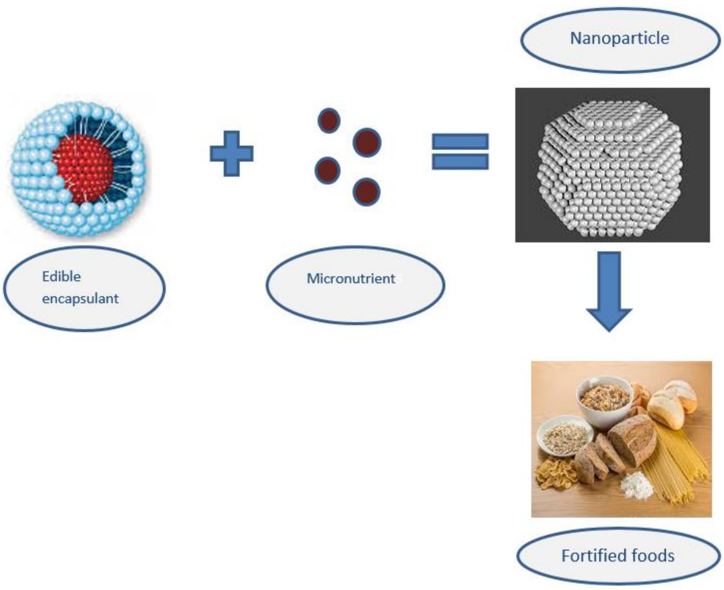

Fig. 3. Nanoencapsulation

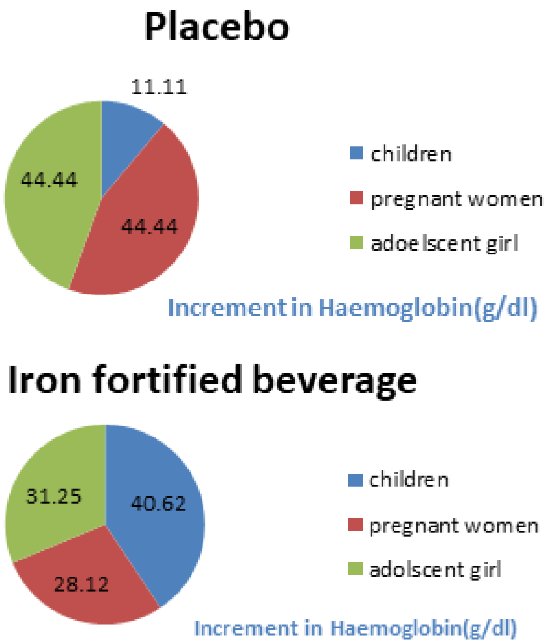

Fig. 4. Effects of iron-fortified beverages on hemoglobin levels in schoolchildren, pregnant women, and teenage females

changes, and no aberrant Fe deposition was discovered. This demonstrates the value of small-scale research on nano-based therapies for iron insufficiency in producing good results [99].

The changes in hemoglobin concentration among patients who were anemic at the start are shown in this graph (Fig. 4). In all experiments, the groups that got the powdered beverage enriched with redox-stabilized iron had significantly higher hemoglobin levels than those who received the placebo [100].

Adverse effects

INPs raise a lot of safety issues, particularly when used orally or as a fortifier. Therefore, research into all toxicological and clinical practice factors is necessary. Because iron nanoparticles persisted in the body for a longer period of time after degrading, *in vivo* and *in vitro* hazardous studies of these materials typically require lengthy research and monitoring for months or even years. The toxicity investigations are complicated by the varying pharmacokinetics and decomposition kinetics of the iron nanoparticles and their coating molecules. The most often reported side effects in clinical research include gastrointestinal problems such as nausea, vomiting, stomach discomfort, diarrhea, and constipation. Overall, the report found that taking iron nanoparticles orally is a secure method of low-dose drug delivery. Some researchers still maintain that the potential long-term safety implications of these INPs have not been sufficiently assessed [101].

Conclusion and future perspectives

Anemia is one of the major problems that is caused by iron deficiency, and it affects all age groups. Many researchers conducted trials with fortified foods in India and other countries mostly were found to have positive results to increase the nutritional status of the subjects included in the study. Nanosized iron salts can be a potential tool for this context. By creating iron complexes at the nanoscale, it is possible to boost iron bioavailability and solve issues with food carriers' undesirable color, flavor, metallic taste, and rancidity. Thus, the fortification of food and food products for the treatment of IDA uses nanosized iron powder, which really is significant. In this way, nanotechnology plays an important role in the fortification of food and gives health benefits. On the other hand, excess amounts of iron cause different diseases related to the body's organs, and nanoparticles have the ability to overcome physiological boundaries, harm cells, and tissues, and cause health problems. As a result, several technical concerns like characterization, safety evaluations, and the influence of iron nanoparticles on food and the human body should be investigated before being addressed.

In recent years, the combination of diagnosis and treatment (theranostic), using cancer as an example of disease, has drawn a lot of interest in the advancement of nanomedicine. Some excellent examples include using oleic acid-coated iron oxide nanoparticles for near-infrared diagnostic applications, using alginate and folic acid-based chitosan nanoparticles for photodynamic colorectal cancer detection, using cathepsin B as a metastatic process fluorogenic peptide probe conjugated to glycol chitosan nanoparticles as a biopolymeric material in cancer therapy and dextran. Nanoparticles have already transformed the way we identify and administer pharmaceuticals in biological systems, even though regulatory mechanisms for nanomaterials and risk assessments will be the focus of further advancement in the future. Our ability to detect diseases and even combine diagnosis with treatment has become a reality due to advances in nanotechnology [102].

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