**Ferritin core nanoparticulate: A source of iron fortification**

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**Abstract**

To keep serum iron levels stable in the human body by recycling damaged erythrocytes and red blood cells, dietary iron is absorbed by duodenum enterocytes and the proximal jejunum before being absorbed in the serum. Traditional definitions of ID, which rely on low serum ferritin or iron levels as diagnostic thresholds, fail to account for changes in these parameters caused by chronic inflammation. The treatment of iron-deficiency anaemia includes addressing the underlying cause, such as gastrointestinal bleeding, as well as taking iron orally. To improve absorption, iron supplements should be taken without food. Treatment often produces a rapid response in 14 days. Although intravenous iron is more consistently and quickly delivered to the reticuloendothelial system than oral iron, it does not result in a faster increase in haemoglobin levels. Food fortification is a long-term and cost-effective technique for preventing iron deficiency anaemia. Iron supplements, on the other hand, frequently cause unwanted organoleptic changes and limit food acceptance and use. As a result, the fundamental difficulty in developing iron-fortified foods is to insert iron fortification more effectively in food to boost iron absorption without affecting the sensory features. It is an iron storage protein that consists of a spherical polypeptide shell which encloses a 6 nm core of the inorganic ferrihydrite hydrochloride, different ferritins have different amino acid sequences, but they all have the same structure. Spherical proteins consist of 24 subunits of mass 450, 500 kDa and a diameter of about 12 nm and an inner cavity of about 8 nm are part of the ferritin family. In the treatment of infectious diseases of the intestine, this mechanism is also promising. The iron in the protein shell does not touch the food ingredients and/or digestive tract cells. The food should be safe from oxidation or sensory alteration. In addition, oxidative damage can also be limited to intestine cells. The slow release of iron from the ferritin protects the cells of other iron supplements against oxidative damage. There are other difficulties with the production of bioactive food with high ferritin iron content. The concentration of ferritin iron in food of plant origin varies with the botany of the seeds or grains used. However, it also results from crop cultivation conditions and food processing. Since ferritin is a protein, food should be processed with non-thermal denaturation conditions. The method of iron speciation in plant samples was shown to have survived some thermal treatment, although the temperatures were above those which were known to degrade protein.

**Keywords:** Ferritin core nanoparticulate, iron fortification, traditional definitions

1. **Introduction**

Many physiological functions, including erythropoiesis, circulatory oxygen delivery and transfer, growth, development, and antioxidant capability of many organs, require iron. Ferric iron (Fe3+) and ferrous iron (Fe2+) are the most frequent types of iron existing in the human body (Brisset et al., 2018) [1]. To keep serum iron levels stable in the human body by recycling damaged erythrocytes and red blood cells, whereas dietary iron is absorbed by duodenum enterocytes and the proximal jejunum before being absorbed in the serum (Ganz and Nemeth., 2012). The heart, as a high-energy-consuming organ, has stringent iron homeostasis criteria. For example, adequate iron is required for oxidative phosphorylation and redox signalling, however, iron overload can result in excessive reactive oxygen species (ROS) formation, lipid peroxidation, and organ damage through the Fenton reaction (Drakesmith et al., 2015) [3]. Iron deficiency (ID) with or without associated anaemia is relatively common in chronic diseases with inflammatory aspects, such as obesity. Traditional definitions of ID, which rely on low serum ferritin or iron levels as diagnostic thresholds, fail to account for changes in these parameters caused by chronic inflammation (Ramakrishnan et al., 2015) [4]. The treatment of iron-deficiency anaemia includes addressing the underlying cause, such as gastrointestinal bleeding, as well as taking iron orally. To improve absorption, iron supplements should be taken without food. Iron absorption is aided by a low gastric pH. Treatment often produces a rapid response in 14 days.
It is characterised by an increase in haemoglobin levels. Iron supplementation is required for at least three months to replenish tissue iron stores and should continue for at least one month after haemoglobin levels have returned to normal (Anderson et al., 2013) [9]. Ferrous sulphate is a low-cost and effective therapy that is typically administered in two to three divided doses per day. Constipation, nausea, decreased appetite, and diarrhoea is all side effects of taking iron orally. If the patient is intolerant to oral iron, has malabsorption such as celiac disease, post-gastrectomy, or achlorhydria, or the losses are too great for oral therapy, intravenous iron may be required. Although intravenous iron is more consistently and quickly delivered to the reticuloendothelial system than oral iron, it does not result in a faster increase in haemoglobin levels (Berdoukas et al., 2015) [9].

Food fortification is a long-term and cost-effective technique for preventing iron deficiency anaemia (Lakhal et al., 2015) [12]. Iron supplements, on the other hand, frequently cause unwanted organoleptic changes and limit food acceptance and use (Triner et al., 2017) [7]. As a result, the fundamental difficulty in developing iron-fortified foods is to insert iron fortification more effectively in food to boost iron absorption without affecting the sensory features (Xue et al., 2014) [8]. The addition of Mg or Ca to ferric oxide-based nano-structured compounds boosted solubility and contributed to improved iron fortification. They are highly soluble in dilute acid and are likely to be absorbed effectively in the gut without causing significant colour changes (Qiao et al., 2012) [9]. Various forms of iron nanoparticles, such as zero-valent iron nanoparticles, iron phosphate nanoparticles (FePO4 NPs), and magnetite nanoparticles (Fe3O4 NPs), have recently been used to replace commonly used iron salt in food fortification due to their high biocompatibility and toxicological safety (Mancias et al., 2015). However, when utilized alone, these iron nanoparticles oxidize quickly and agglomerate, limiting their applicability in food systems (Ross et al., 2012) [11].

Ferritin was first discovered by Laufberger in the year 1937. It is an iron storage protein that consists of a spherical polypeptide shell (Apoferitin) which encloses a 6 nm core of the inorganic ferrihydrite hydrochloride (5Fe2O3·9H2O), different ferritins have different amino acid sequences, but they all have the same structure. Spherical proteins consist of 24 subunits of mass 450, 500 kDa and a diameter of about 12 nm and an inner cavity of about 8 nm are part of the ferritin family (Vannucci et al., 2015). In the treatment of infectious diseases of the intestine, this mechanism is also promising. The iron in the protein shell does not touch the food ingredients and/or digestive tract cells. The food should be safe from oxidation or sensory alteration (Hosny., 2015). In addition, oxidative damage can also be limited to intestine cells. The slow release of iron from the ferritin protects the cells of other iron supplements against oxidative damage. There are other difficulties with the production of bioactive food with high ferritin iron content. The concentration of ferritin iron in food of plant origin varies with the botany of the seeds or grains used. However, it also results from crop cultivation conditions (especially soil iron concentration) and food processing (Izquierdo., 2016). Since ferritin is a protein, food should be processed with non-thermal denaturation conditions. Therefore, the temperature or the exposure period should be restricted to elevated temperatures. The method of iron speciation in plant samples was shown to have survived some thermal treatment, although the temperatures were above those which were known to degrade protein, i.e. more than 80°C. Samples spike with labelling ferritin bean and mass ionisation of thermal ionisation spectrometry isotope dilution (IDMS) enables ferritin iron quantification. The colourimetric analysis of the various iron shapes taken from food samples, organically and inorganically complex as well as the ionic form of iron are another approach that is worth considering (Zhang et al., 2015).

Nanoparticles (NPS) are a wide class of materials containing at least one dimension of particulate matter less than 100 nm (Lui et al., 2018). NPS are not simple molecules alone and therefore consist of three layers, i.e. (a) the surface layer that can operate with various molecules, metal ions, surfactants, and polymers. (b) Shell Layer that, in all respects, is chemically different from the core material and (c) the core is basically the central part of the NP and refers generally to the NP itself (Kornienko et al., 2018). Also, recently ferritin has been used to produce nanoparticles for electronics with conduction and magnetic properties based on magnesium, cobalt, and copper (Wang et al., 2018). But the regulation of sizes and mineral loads is becoming increasingly clear to manufacture nanomaterials like memory devices and for fluorescent labelling of biomolecules (Chen et al., 2018).

2. Iron deficiency anaemia
Iron deficiency anaemia is the most common and easily treated of all anaemias. There is a growing understanding that iron deficiency can cause symptoms unrelated to anaemia and can be linked to a variety of diseases (Evstatiev and Gasche., 2012) [13].
2.1 Iron metabolism

Iron can be found in a variety of foods, with meat being the most abundant source. Iron in food is mostly in the ferric form (Fe³⁺), which is reduced to ferrous by stomach acid (Fe²⁺). Two receptors on the mucosal cells of the jejunum absorb iron (Levi et al., 2016) [23]. One receptor is specific for heme-bound iron and absorbs 30-40% of ingested heme iron. The other receptor, divalent metal transporter (DMT1), also absorbs inorganic iron but is 1 to 10% less efficient. Iron is exported from the enterocyte by ferroportin and delivered to plasma transferrin, the primary iron transport molecule. Transferrin, by binding to the transferrin receptor on the red cell membrane, can deliver iron to the marrow for use in red cell production or to the liver for storage. Ferritin is an iron storage protein (Porwal et al., 2012) [24]. The ferritin protein is made up of 24 ferritin subunits that work together to form a shell that can hold up to 4500 iron molecules (Evstatiev and Gasche, 2016). Iron from senescent red cells' haemoglobin is recycled by binding to ferritin in the macrophage. It is then either transferred to transferrin for recycling into developing red cells or stored. This system is extremely efficient, losing less than 5% of the iron in total red cell mass. Hepcidin, a protein, regulates iron absorption and iron release from the store (Hudak et al., 2016) [14, 26]. Hepcidin binds to ferroportin, causing it to degrade. Iron cannot be released from enterocytes or hepatocytes when hepcidin degrades ferroportin, resulting in both a lack of iron absorption and a halt in iron release to developing red cells. Not only does iron stimulate hepcidin synthesis, but so does inflammation (Pavord et al., 2012) [25]. Hypoxia increased erythropoiesis, and iron deficiency is all lower levels. Men should consume 8 mg of iron per day, while premenopausal women should consume 18 mg, increasing to 27 mg per day during pregnancy (Hershko and Camaschella, 2014) [27]. Meats are high in heme iron, which allows iron to be absorbed much more effectively. Nonmeat iron sources have lower iron stores, are less effectively absorbed, and are difficult to consume in sufficient quantities to meet iron requirements (Hudak et al., 2016) [14, 28]

2.1.1 Symptoms

Iron deficiency can cause symptoms due to both the lack of iron and the resulting anaemia. Anaemia symptoms include fatigue, tachycardia, and a lack of endurance. Pica, or strange cravings for ice or clay, can occur (Hershko and Camaschella, 2014) [27]. Symptoms in iron-depleted but nonanemic patients are becoming more widely recognised. Given the importance of iron in many cellular proteins and enzymes, particularly cytochromes and myoglobin, it is not surprising that symptoms can appear before anaemia. The most severe symptom is fatigue, which can occur even with minor reductions in iron stores (Weng et al., 2015) [28]. Two studies show that oral iron supplementation improves fatigue in iron-deficient but not anaemic women with ferritins less than 50 ng/ml (Vaucher et al., 2012) [16] while a third study shows that parenteral iron improves fatigue in women with ferritins less than 15 or iron saturation less than 20% (Sharma et al., 2016) [17]. Another recent study found that iron supplementation improved fatigue in iron-deficient but nonanemic fatigued adolescents (Leclercq et al., 2014) [18]. These studies, along with the previously mentioned improvements in athletic performance, clearly demonstrate the role of iron in well-being that extends beyond haemoglobin levels. Cold intolerance is another common symptom of iron deficiency (Von et al., 2015) [19]. Some of these symptoms are caused by anaemia, and they usually go away when the anaemia is treated. However, some patients with nonanemic iron deficiency experience cold intolerance. This could be due to a decrease in thyroid hormone efficacy. Because the effectiveness of the intracellular thyroid is dependent on iron stores, a lack of iron reduces the hormone's effectiveness (Ruz et al., 2012) [20]. Patients with heart failure have a higher prevalence of both overt and functional iron deficiency. Iron deficiency can affect anywhere from 13% to 42% of people, with a higher percentage having functional iron deficiency (Qian et al., 2016) [20]. Replacing depleted iron stores has been shown to improve cardiac function and quality of life, as well as to decrease hospitalisation (Robinson et al., 2014) [21]. Patients with pulmonary hypertension are another group in which iron deficiency may be harmful. Iron chelation mimics hypoxia by upregulating genes that control the hypoxic response, so the cellular response to hypoxia is iron-dependent (Frise et al., 2016). Iron is important in the regulation of pulmonary vascular resistance. When compared to healthy controls, iron-deficient patients had an exaggerated hypoxic. DeLoughery rise in pulmonary artery pressures. Low iron stores have been observed in patients with pulmonary hypertension, and repletion has been found to lower pulmonary artery pressure (Buro et al., 2015). restless leg syndrome is a condition in which patients experience leg cramps, unpleasant leg sensations, and the need to move their legs during the night. Many of these patients have low iron stores, as evidenced by studies of brain iron. Iron repletion alleviates symptoms in many patients, implying that low iron stores are pathogenic in at least some RLS patients (Moretti et al., 2015).

2.1.2 Treatment

Eating a diet rich in bioavailable iron can help treat iron deficiency, but it is unlikely to replenish iron stores on its own, though it can help maintain them. Meat is the iron-richest food. Cooking with iron skillets can also boost dietary iron, though the amount of iron enrichment varies (Rampton et al., 2014). Ferrous sulphate, taken three times a day, has been found to improve fatigue in iron-deficient but not anaemic women (Vaucher et al., 2012) [16]. While a third study shows that parenteral iron improves fatigue in women with ferritins less than 15 or iron saturation less than 20% (Sharma et al., 2016) [17]. Another recent study found that iron supplementation improved fatigue in iron-deficient but nonanemic fatigued adolescents (Leclercq et al., 2014) [18]. These studies, along with the previously mentioned improvements in athletic performance, clearly demonstrate the role of iron in well-being that extends beyond anaemia. It is important to note that concurrent calcium and fibre intake can reduce iron absorption, but this can be mitigated by taking vitamin C (Crabol et al., 2014). Importantly, tea is a powerful inhibitor of iron absorption; ingestion can reduce absorption by 90%.
Coffee also reduces iron absorption by roughly two-thirds the amount that tea does. A reasonable approach to oral iron replacement is, to begin with, a single ferrous sulphate taken with a meal that contains meat (if not vegetarian). Avoiding tea and coffee, as well as taking 500 mg of vitamin C with that meal, will help iron absorption (Zhu et al., 2010). If ferrous sulphate is not tolerated, ferrous gluconate, which contains less elemental iron per tablet, can be used instead. The reticulocyte count should increase in one week, and haemoglobin levels should begin to rise by the second week of therapy.

3. Iron fortification
Fortification is the common practice for increasing the content of an essential micronutrient like vitamins and minerals in foods, to improve the nutritional quality of the food, and to provide public health benefits at minimal risk (Bacanli et al., 2015) [30]. The main aim of food fortification is to improve the nutritional content of the food. A major criterion in deciding the best way of delivering micronutrients either by fortification or supplementation depends on the target population group. Food fortification aids in easy access to achieving daily nutritional needs for rural communities without dependency on pharmaceutical supplements and has the potential to impact a large number of people cost-effectively. Iron supplementation involves the oral administration of pharmaceutical iron compounds while fortification of iron involves the delivery of iron through foods. Supplementation of iron can be practised when immediate action is required for increasing the level of iron in the human body as orally administered haem iron easily enters into the bloodstream (Chandrasekara et al., 2018) [31]. Whereas iron fortification helps target a specific group by supplying iron through foods that follow the regular absorption mechanism as that of the diet, resulting in a gradual increase in the iron status of the population. Although the effect of fortification of foods is not as quick as supplementation in targeting nutrient deficiency, fortification is an effective approach for sustainable benefits in the long run (Khan., 2015) [30]. This review provides unambiguous evidence that iron concentration in the human bloodstream can be improved through iron-fortified foods. Considering all age groups, the pooled positive intervention can result in reductions in anaemia and iron deficiency owing to the interference of fortified iron from the food in the various pathways of iron absorption. Although food fortification has several benefits, there exist certain limitations such as deterioration of the colour and flavour of food vehicles, determination of optimal delivery systems and the assurance of health impact and acceptability of biofortified foods (Ansari et al., 2017) [31]. However, fortification remains to be attractive in terms of cost, since the costs of conventional medications remain high, but fortified foods remain harder to reach the poorest; those who are most price sensitive. The study on the economics of fortification showed that the effectiveness of fortification in terms of cost ranges from $22 to $60/day, remaining comparatively favourable to values of other healthcare interventions for children. Another study on the benefits of investment in iron fortification estimated a rise in benefit: cost ratio from 6:1 to 36:1, because of the combined effects of cognitive ability and physical productivity. In comparing food supplementation, fortification, and dietary diversification, food fortification is known to be cost-effective (cost of $66 per Disability-Adjusted Life Year - DALY), while supplementation and dietary diversification had a cost of $179 and $103 per DALY, respectively (Bamzai and Bhat., 2015) [30]. Therefore, for effective implementation of the fortification process, more studies are required, considering public awareness and acceptability.

![Fig 2: Benefits of food fortification across the life cycle](https://www.thepharmajournal.com)

3.1 Different types of iron fortificants
3.1.1 Wheat and maize flours
Wheat and maize millers are equipped with the same processes (Zimmerman et al., 2018) [35]. The fortification method of the two flours is well and reasonably straightforward, as both food and micronutrient Premix are in powder form and fortified by wheat and maize flour for many decades. However, considerable development was needed in selecting sufficiently bioavailable iron compounds which do not trigger any sensory changes. The key sensory issue with cereal meals was iron-catalyzed oxidative rancidity that could be caused by soluble iron compounds such as iron sulfate, particularly in long-term flour storage under warm and moist conditions (Tsang et al., 2018) [36]. Unacceptable colour
reactions in iron-fortified cereal when fruit was added were also dangerous. The iron fortification compound for cereal meals was initially made of organoleptically inert elemental powders made from iron ferrous sulfate, ferrous fumarate, NaFeEDTA and electrolytic iron powder are the 4 iron fortification compounds recommended. Sensory tests, efficacy studies in women and children in LMIC (Low Middle Income Economies), the relative bioavailability of iron compounds, and approximate daily intake of iron were all found in the proposed fortification levels (Hackl et al., 2016) [37]. For high phytate wheat and corn flour, NaFeEDTA is the only WHO-recommended iron compound. The absorbance in NaFeEDTE-fortified whole grain wheat rolls was 4 times higher than for iron, and in school foods, Indian children’s iron status was improved by the NaFeEDTA-fortified whole grain atta flour. (Diosady et al., 2019) [38].

3.1.2 Rice
As rice is mainly consumed as grain, it is technically more difficult to fortify rice than wheat or maize. Coating and extrusion are the two key rice fortification technologies, and they both involve the production of rice kernels that are micronutrient-fortified and then blended with rice kernels that are not fortifiable. Rice fortification has gained momentum in recent years with the advancement of fortified kernel technology (Cercamondi et al., 2016) [37, 39]. Extrusion may be done at various (cold, mild and hot) temperatures. Warm hot extrusion gelatinises the starch, partially or fully, to keep the kernel together and improve clarity and gloss, to look more precisely like non-fortified, equally clear rice grains. Cold extrusion involves a binder to hold the kernel and can be produced with special paste presses like warm extrusion (Namaste et al., 2017) [40, 41]. Hot extrusion involves a more costly, single or twin-screw extruder and additional investment in capital. A recent invention of rice fortification is the discovery of a new Ferric pyrophosphate iron absorption (FPP) enhancer (Rohner et al., 2017) [40, 41]. In rice extrusion, when trisodium citrate and citric acid were added with isotopically labelled FPP, the absorption of iron from FPP in humans almost doubled to a degree close to that of ferrous sulphate, and the hot extrusion process suggested converting the insoluble FPP to more soluble FPP citrate complexes. No colour changes were registered (Ganz., 2018) [42].

3.1.3 Milk products
To enforce milk with micronutrients, no special equipment is required. The fat-soluble vitamins are initially homogenized with an aliquot of milk, while the water-soluble vitamins and minerals are directly added by hand or by measuring (Hurrell., 2018) [35, 36]. Until packaging, the fortified milk is then agitated, pasteurized, homogenized, and heat-treated. Either before or after spray drying, dried milk can be strengthened. Reconstituted dried milk can provide iron for young children as a useful fortifying vehicle (Keats et al., 2019) [44]. But because of its relatively high concentrations of calcium and casein, it is a moderate inhibitor of iron absorption. Ascorbic acid is standard practice and can resolve milk-based inhibition and increase iron absorption and effectiveness in young children with the addition of acid to commercial, powdered milk formulas or dried cow’s milk fortified with ferrous sulfate (Darton., 2018) [45]. However, the combination of soluble iron compounds with ascorbic acid results in undesirable fluid milk taste changes; the iron strengthening of liquid milk was therefore not widely implemented (Glinz et al., 2017) [46].

4. Ferritin
Ferritin was first discovered by Laufberger in the year 1937. Ferritin, the primary iron storage protein was isolated from a horse spleen. The mammal, plant and microbial kingdoms contain ferritins (Zeth et al., 2016) [50]. Ferritin is an iron storage protein that consists of a spherical polypeptide shell (Apoferritin) which encloses a 6-nanometer core of the inorganic ferrihydrite hydrochloride (5Fe2O3·9H2O), a variety of amino acid sequences, but the similarity in architecture, are possessed by various ferritins. Spherical proteins consist of 24 subunits of mass 450, 500 kDa and a diameter of about 12 nm and an inner cavity of about 8 nm are part of the ferritin superfamily (Vannucci et al., 2015). In contrast to most other high-temperature and pH-sensitive proteins, ferritins can withstand high temperatures up to 75 °C for ten minutes and are stable with different denaturants including urea, sodium hydroxide, and guanidine chloride. The fact that ferritin contains many salt bridges and hydrogen connections forming between subunits makes these unique features possible (Steinman., 2017). Nanoparticles (NPS) are a wide class of materials containing at least one dimension of particulate matter less than 100 nm (Gemede et al., 2018). NPS are not simple molecules alone and therefore consist of three layers, i.e. (a) the surface layer that can operate with various molecules, metal ions, surfactants, and polymers. (b) Shell Layer that, in all respects, is chemically different from the core material and (c) the core is basically the central part of the NP and refers generally to the NP itself (Yang et al., 2018). Also, recently ferritin has been used to produce nanoparticles for electronics with conduction and magnetic properties based on magnesium, cobalt, and copper (Wang et al., 2018). But the regulation of sizes and mineral loads is becoming increasingly clear to manufacture nanomaterials like memory devices and for fluorescent labelling of biomolecules (Chen et al., 2018). Ferritin is an intracellular universal protein that keeps iron and releases it under control. Almost every living organism, including archaea, bacteria, algae, higher plants and animal is responsible for the production of protein. It works as an iron defect buffer and an iron overload in humans (Yang et al., 2018). Ferritin is present as cytosolic protein in most tissues, but in limited quantities, it is released into the serum, where it works as an iron carrier. Plasma ferritin also indirectly represents the total amount of iron contained in the body and is also used as an iron deficiency anaemia diagnostic test (Pandolfi et al., 2019). It consists of 24 protéin subunits forming nanocages with numerous metal-protein interactions. Ferritin is a globular protein complex. In prokaryotic and eucaryotic it is the main intracellular iron-storing protein and maintains iron in a soluble and non-toxic way. Ferritin not mixed with iron is referred to as apoferritin (Puligundla et al., 2017).
changes in flavour and colour fortified foodstuffs (Gozzellino et al., 2016). In addition, experiments in vitro and in vivo revealed that iron NPs are healthy. The fortification of animal foods also included nanoformulations. Well-absorbed ferritin is made of an iron oxide nanocore and has been recently presented as a possible side-effect-free source of inexpensive, supplementary iron. The nanoparticulate mimic of the ferritin core is also presented (Cappellini et al., 2015). Iron nanoparticulate can follow another pathway to enterocyte cytoplasm. Endocytosis is the canonical mechanism used by NPs, but it may not be the only one (Izquierdo et al., 2016). When applied to the polymer matrix, nanoparticles can quickly be aggregated and agglomerated. During the manufacturing, process nanoparticles may be aggregated and/or incorporated into polymers (Zappalorto et al., 2015). Aggregation, as well as agglomeration, are clusters of nanoparticles with aggregations referred to as solid and compact particle collectives. Agglomeration also occurs when particles are loosely combined and can be broken down by mechanical forces (Jin et al., 2015). The agglomeration prevents improved properties from being achieved and, thus, various applications are achieved with nanostructured materials. The agglomeration is a direct reciprocal attraction between nanoparticle forces or chemical links through the van der Waals. The methods to prevent aggregation are primarily due to capping, coupling or compatibility of the particles and loading the surface of the filler to isolate the filler using an electrostatic spillage (Fasih et al., 2016). Furthermore, optimal output parameters will result in a successful aggregate breakdown. For example, in extruder melting, an ideal velocity and feeding rate are highly stressful for melting materials that disturb the aggregates of the particles (Zare et al., 2017).

5. Ferritin nanoparticles structure
Structure Ferritin nanoparticles ubiquitously found in nature contain a hollow core of inner and outer diameters of 8 and 12 nm, respectively, that can internalize up to 4500 iron atoms in the form of ferric oxyhydroxide, with variable amounts of phosphate (Zeth et al., 2016) [50]. The ferritin structure of mammals, amphibians, plants, and bacteria has been reviewed elsewhere (Zhen et al., 2013). Although there are considerable variations in the amino acid sequence (up to 80%) and the presence of haem moiety in some bacterial ferritins, their tertiary structure is quite similar and some subdomains such as the iron entry/exit channels contain highly conserved sequences across different species (Tian et al., 2016). Ferritin particles isolated from vertebrates are composed of two types of subunits, H-chain (heavy, 21 kDa) and L-chain (light, 19 kDa), whereas those found in plants and bacteria contain only one type resembling the H-chain of vertebrates (Kitagawa et al., 2012). Each ferritin particle is made up of 24 identical or homologous subunits that self-assemble in octahedral (432) symmetry such that small channels are formed at the 4-fold and 3-fold symmetry axes. These channels allow the passage of iron and other ions or small molecules, with iron being guided via the 3-fold channels (Falvo et al., 2013). Each monomer is composed of a four-α-helix bundle (A, B, C, and D helices) with a short fifth E-α-helix at the C-terminus that runs from the outside to the inside, making the C-terminal end of the ferritin chain to be inside the assembled nanoparticle. Additionally, a long loop (L) of about nineteen residues connects the C-terminal of
the B-helix to the N-terminal of the C-helix. The N-terminal, L loop, and A- and C-helices are solvent-accessible, while the C-terminal, and B- and D-helices face the inner side of the ferritin nanocage (Mamo and Poland., 2012).

5.1 Stabilization of iron nanoparticles
In many manufacturing technologies and industrial goods, stabilization of nanoparticles in condensed aqueous suspensions is essential. The adsorption of a dispersant coating across the surface of the particles typically stabilizes nanoparticles. For the stabilization of suspensions containing high nanoparticle concentrations, the formation of the required thickness dispersants (adlayer) is essential (Purcar et al., 2017). Thick adlayers contribute to excessive excluded volume, while thin adlayers cause agglomeration of the particles. The maximum suspension nanoparticle concentration is reduced in both effects however, traditional dispersants cannot systematically track the thickness of the adlayer on the surface of the particles (Caprarescu et al., 2015). In many current and future technologies for device manufacturing, suspensions with high contents of nanoparticles (>40 vol%) may be very beneficial, if not the main requirement. Several changes have been made to the surface and stabilization methods utilizing different kinds of add-ons such as surfactants, polymers, water- soluble starch, carboxymethyl cellulose, cellulose acetate, polycrylic acid, etc to resolve these constraints (Ahmad et al., 2015). These additives effectively regulate the form and size of nanoparticles, improve the stability and mobility of nanoparticles, and thus improve the efficiency of nanoparticles (Podporska et al., 2017).

6. Characterization
6.1 Zeta potential
Dynamic light dispersion is the technique used to determine the size distribution profile for silver nanoparticles dispersed in deionized water in material physics. The size distribution profile of the nanoparticles in the final solution is calculated after ultracentrifuge using light dispersion techniques. Research has found that the average NPS particle size is hydrodynamic (Lowry et al., 2015).

6.2 UV-visible spectroscopy
UV-Vis spectroscopy in the spectral area of ultra-violet and visible spectra can be understood as absorption spectroscopy. It usually uses visible and almost UV light. Ultraviolet and visible light is powerful enough to increase external electrons and the spectroscopy of UV-Vis is normally applied to solvent molecules (Cahyana et al., 2017). The UV-Vis spectrum has broad functions, which are restricted in sample identification but are very helpful for quantitative measurements. By measuring absorption at a particular wavelength and by applying the BeerLambert Act the concentration of analytes in the solution can be calculated (Gemede et al., 2018). As the UV-Vis range covers approximately 400-750 nm of human visual acuity, UV-Vis spectroscopy serves as a characteristic for the absorption, transmission and reflection of a range of technologically important materials, such as pigments, coatings etc. The mucilage nanoparticles will be scattered in a 2 mg/ml dilute suspension using a 30-minute bath sonicator into MilliQ water. The absorption strength of the particles will be calculated using the visible UV spectrophotometer when fully dispersed in water (Zhang et al., 2016).

6.3 Differential scanning colourimetry
To investigate the heat-effectiveness of the sample under argon atmosphere and DSC analysis at a rate of 10 °C/min under argon atmosphere from 25 °C and a differential scanning calorimetry (DSC 302 BUHR, Germany) will be performed at a heating speed of 25 °C/min (Zhang et al., 2016).

7. Food fortification and application
Fortification is defined as the addition of one or more essential elements to a food article, whether it has previously been added to the food, to prevent or correct nutrient deficiency in the general population or a specific population group. Food fortification with minerals and vitamins aids in food fortification with iron to prevent iron deficiency and anaemia and vitamin A deficiency (Yao et al., 2015). For more than 50 years, flour fortification with iron to prevent iron deficiency and anaemia has been used successfully in the United States and Canada, and more recently in some African and South American countries. The results indicate that food fortification has had a positive impact on health in the communities where it has been implemented (Ani and Abel., 2018).

8. Conclusion
Although iron supplementation has a greater impact on health than fortification, iron fortification is less expensive and has the major advantage of aligning with the human body's functioning and physiology. As a result, fortification remains the most secure intervention to address the issue of iron deficiency. For long-term applicability, various technical opportunities, such as the safety and efficacy of nanotechnology in food fortification, must be investigated. There is a need for a better understanding of nutrient bioavailability as well as solutions to organoleptic and degradation issues associated with fortifiers. Most efforts to combat iron deficiency through fortification strategies have thus far focused on overcoming technical issues such as discolouration, off-flavour development, and fatty acid oxidation, often overlooking other practical issues such as large-scale production, marketing, and quality control, which are critical for successful implementation. There is still a need for novel food carrier systems that allow for correlation with food processing techniques. To do so, a better understanding of dietary components, processing methods, and physiological factors is required. This must then be linked to the chemodynamics of iron during food processing and after
ingestion, as this determines the mineral’s fate during processing and digestion. Individual applications must also address issues such as iron compound stability, powder/product characteristics, toxicity, and sustainability.

9. References
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