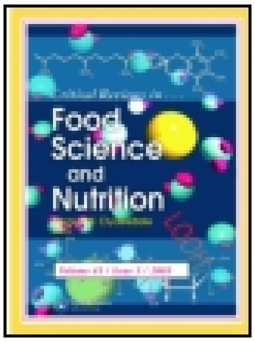

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REVIEW

Iron supplementation and iron-fortified foods: a review

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ABSTRACT
About one-third of the world population is suffering from iron deficiency. Delivery of iron through diet is a practical, economical, and sustainable approach. Clinical studies have shown that the consumption of iron-fortified foods is one of the most effective methods for the prevention of iron deficiency. However, supplementing iron through diet can cause undesirable side-effects. Thus, it is essential to develop new iron-rich ingredients, iron-fortified products with high bioavailability, better stability, and lower cost. It is also essential to develop newer processing technologies for more effective fortification. This review compared the iron supplementation strategies used to treat the highly iron-deficient population and the general public. We also reviewed the efficacy of functional (iron-rich) ingredients that can be incorporated into food materials to produce iron-fortified foods. The most commonly available foods, such as cereals, bakery products, dairy products, beverages, and condiments are still the best vehicles for iron fortification and delivery.
Scope of review
The manuscript aims at providing a comprehensive review of the latest publications that cover three aspects: administration routes for iron supplementation, iron-rich ingredients used for iron supplementation, and iron-fortified foods.

KEYWORDS
Administration route; iron deficiency; iron-fortified foods; iron-rich ingredients; iron supplementation

Introduction

Iron deficiency is one of the most commonly observed nutritional deficiencies (Zimmermann and Hurrell 2007; Fu et al. 2018). According to the Rome declaration on nutrition (2014), two billion individuals suffer from iron deficiency every year, making it a leading cause of anemia (Jia et al. 2016; Anderson and Frazer 2017).

The Global Health Observatory (GHO) reported that the prevalence of anemia among women of childbearing age in the world was 33% in 2016 (Figure 1) (Xing et al. 2013). The prevalence rate of anemia in Asia and Africa is above the world average (exceeding 35%), and it has increased in Asia from 33 to 37% in the last ten years (Xing et al. 2013). The prevalence in Latin America and the Caribbean countries has declined from 25 to 22% in the same period. Although the prevalence rate of anemia has increased in North America and Europe, and Oceania, it is still less than 20% (Xing et al. 2013). In fact, iron deficiency is more widespread than it is captured in scientific reports. This is because studies generally do not indicate the states of depletion of iron deposits (first stage) and few include states of deficiency (Clark 2008; Camaschella 2015). To reduce the probability of anemia and iron deficiency, WHO has published the recommended dietary allowance: 2 mg/kg body weight daily in kids under 5 years old; 30 mg/kg body weight daily in children from 5 to 12 years old; and 60 mg/kg body weight daily in the female of childbearing age (WHO 2011; Lopez et al. 2016).

Diversification of diet is the first-rank approach for the prevention of iron deficiency as it can be easily implemented and accepted. Dietary diversification involves creating balance recipes to meet the iron requirements. Notwithstanding, consumption of diversified or balanced foods is limited by the economic, social, and cultural environments (Akhtar et al. 2013). For example, intake of more heme iron from animal foods could significantly reduce the risk of anemia. At the same time, consuming excess animal food could trigger hypertension, type 2 diabetes, chronic diseases, and gastrointestinal cancers (Ma et al. 2016; Kruger and Zhou 2018; de La Pomélie et al. 2019). Therefore, special attention needs to be paid to iron supplementation.

Conventional iron supplements have the potential of causing some degree of adverse reactions in the human body. Thus, it is important to explore and develop novel products with high iron bioavailability, better stability, and affordable cost. For this purpose, emphasis in research has to be placed on using natural functional ingredients (e.g., plant ferritin, lactoferrin (LF), and heme iron). Care must be taken while incorporating these iron-rich ingredients in food products to avoid side effects, such as weakening the bone metabolism and probability of infection that can be resulted due to excess iron intake (Chen et al. 2019). This is

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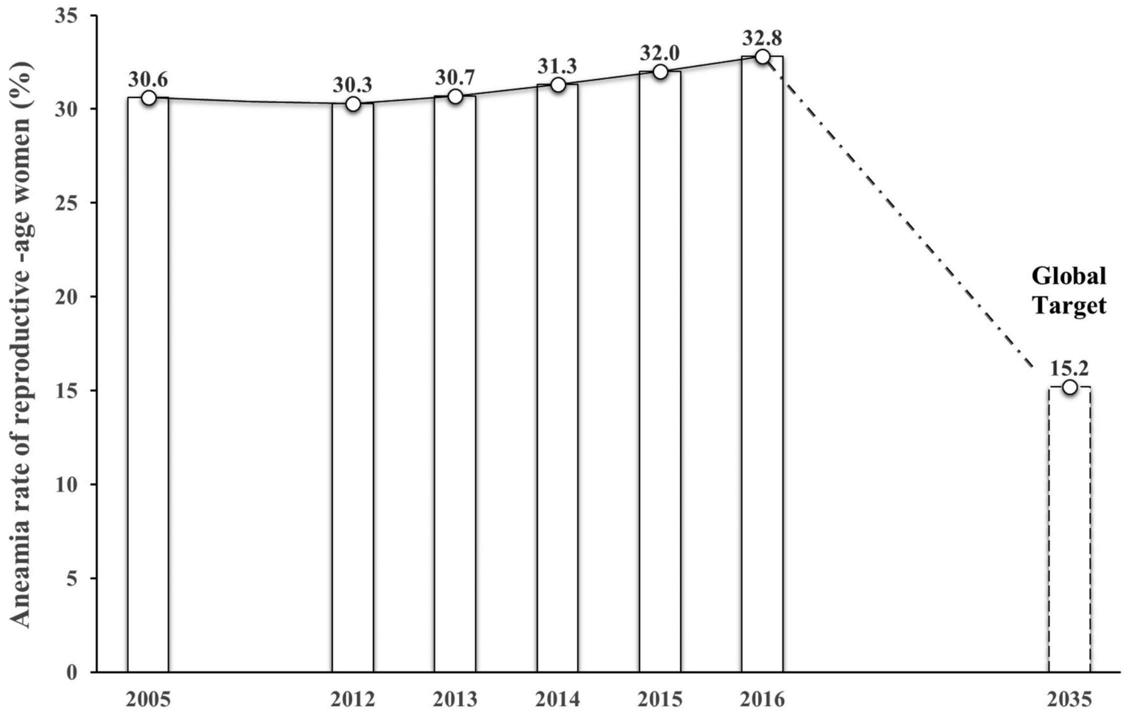

Figure 1. Anemia rate of reproductive-age women (%). Source: Egal (2019); FAO (2019)

the reason why many iron-fortified foods do not oversupply the iron dosage.

Iron-fortified foods are the most secure and cost-effective iron supplements. These foods (e.g., cereal, dairy products, and condiments) can carry either iron or iron-carrying functional ingredients that deliver and facilitate iron absorption. Depending on the targeted population, iron-fortified foods are divided into two categories: 1) aimed at the patient and in-risk population and 2) aimed at the general population. Infants are a group of people that belong to category 1, as they are at high risk of suffering from iron deficiency. Infants under six months of age have their iron reserves and the need for iron gradually increases in the transition period of breastfeeding and supplementary feeding. Supplementary foods, such as iron-rich infant formula products are important as the infants grow (Burke, Leon, and Suchdev 2014; Gandhi et al. 2019). Cereals products, such as wheat and maize flours are also frequently used to fortify with iron (de Oliveira e Silva, de Castro, and de Andrade 2018). Considering affordability, widespread availability, and convenience, various types of bread (e.g., French bread and gluten-free bread) are utilized as the vehicle for iron fortification as well. These iron-fortified foods are further explained and discussed in iron-fortified foods section.

The limitation of iron-fortified foods is the potential reactivity of iron with other components, which triggers undesirable changes in color, and flavor. In order to overcome these difficulties, iron and/or iron carrying components are delivered as microcapsules using food vehicles (Ilyasoglu Buyukkestelli and El 2019). In the encapsulated form, the iron-carrying compounds are protected and/or prevented from reacting with other food components, better preserve their bioavailability and only minimally affect the organoleptic properties of the encapsulated foods.

Metabolic iron and dietary iron

Iron is a fundamental micronutrient and is essential for metabolic processes including oxygen transport and storage, replication of Deoxyribonucleic acid (DNA) and Ribonucleic acid (RNA), and protein and electron transport. Approximately, 65% of the iron in the human body exists as hemoglobin circulating as erythrocytes (Sackmann et al. 2007; Lopez et al. 2016). The remaining iron is mostly located in the liver and spleen in the form of ferritin and heme (Hentze, Muckenthaler, and Andrews 2004). Only a small amount (<1%) of iron in the human body is found in various enzyme systems (Sackmann et al. 2007). The major carriers of iron in the human body are iron-containing proteins including hemoproteins, iron-sulfur proteins, and other iron-containing proteins (e.g., non-heme iron enzymes) (Lynch et al. 2018). Due to the iron carrying efficacy of these vehicles and the well-functioned metabolic system, the absorption and release of the iron in the human body are generally in a state of equilibrium (Figure 2). Nonetheless, a large population is suffering from iron deficiency caused by inadequate dietary iron intake, blood loss, and anomaly iron absorption (Lu 2016). The principal cause of iron deficiency is inadequate dietary iron intake.

There are two forms of dietary iron: heme iron and non-heme iron. Animal foods are rich in heme iron whereas plant foods are rich in non-heme one. Interestingly, plant foods (e.g., fruits, vegetables, and cereals) also account for a big proportion of dietary iron that people dine (Salim-Ur-Rehman et al. 2010).

Literature indicates that there are two pathways (Figures 2 and 3) through which dietary iron absorbs and metabolizes in the human body (Abbaspour, Hurrell, and Kelishadi, 2014). In the case of heme iron, the ingested food firstly

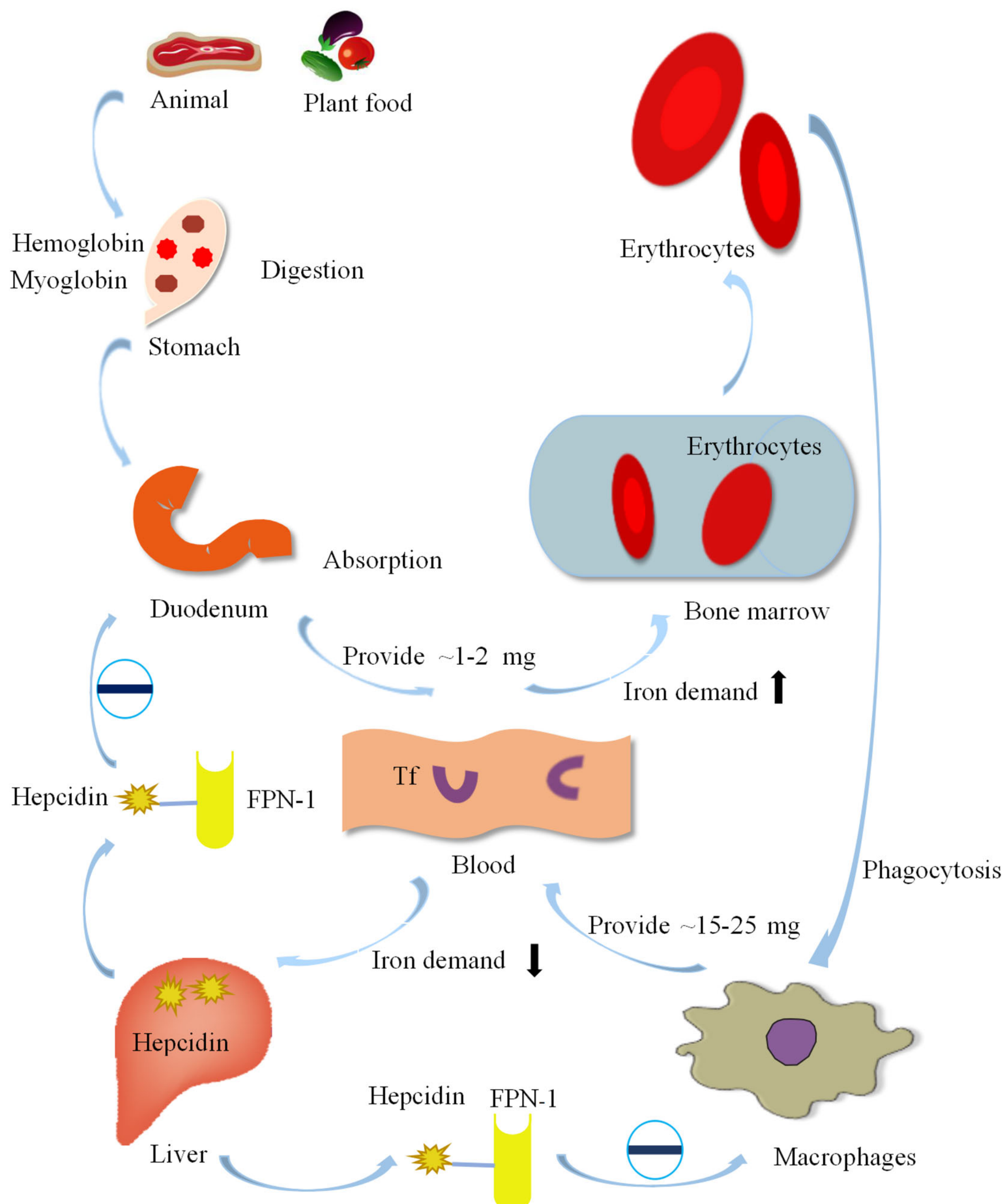

Figure 2. Schematic diagram iron absorption and regulation of iron in the human body.

enters the stomach and releases the hemoglobin and myoglobin. This process is induced by hydrolysis of food matrix that carries heme by pepsin. The heme carrier protein-1 (HCP-1) located in the brush border membrane of intestinal epithelial cells absorbs heme iron. HCP-1 is also a proton-coupled folate transporter (PCFT) (Shayeghi et al. 2005; Shin et al. 2011). Then, heme oxygenase-1 (HO-1) catalyzes the reaction and release free ferrous iron into the labile iron pool (LIP) (Kakhlon and Cabantchik 2002). Another pathway is that hemoglobin is absorbed into the circulation system via exporting protein, breast cancer resistant protein (BCRP), and feline leukemia virus subgroup C (FLVCR) (Krishnamurthy et al. 2004; Philip et al. 2015), on the basolateral membrane of intestinal epithelial cells. Unlike the absorption mechanism of heme iron, non-heme iron is firstly reduced from Fe^{3+} to Fe^{2+} (Figure 3). Ascorbic acid (AA) in food facilitates this process. Iron absorption of non-heme iron occurs mainly in the duodenum and proximal jejunum (De Domenico, McVey Ward, and Kaplan 2008). Duodenal cytochrome b (Dcytb) is an iron reductase, which accepts the electrons produced by the oxidative dehydrogenation of AA to catalyze the reduction of Fe^{3+} (Lane et al. 2015). Divalent metal transporter-1 (DMT-1) transports ferrous iron to the duodenal epithelial cells (Garrick et al. 2003). At this time, the free Fe^{2+} with high reactivity can chelate with organic acids, amino acids, proteins, etc., then enters LIP. The route taken for the uptake of ferrous iron depends on the body's demand for it. When the demand is low, the absorbed iron is stored in the intestinal cells in the form of ferritin. In contrast, when the demand is high, ferroportin-1 (FPN-1), ferrous export protein enables Fe^{2+} to pass through the basolateral membrane into the blood (Van

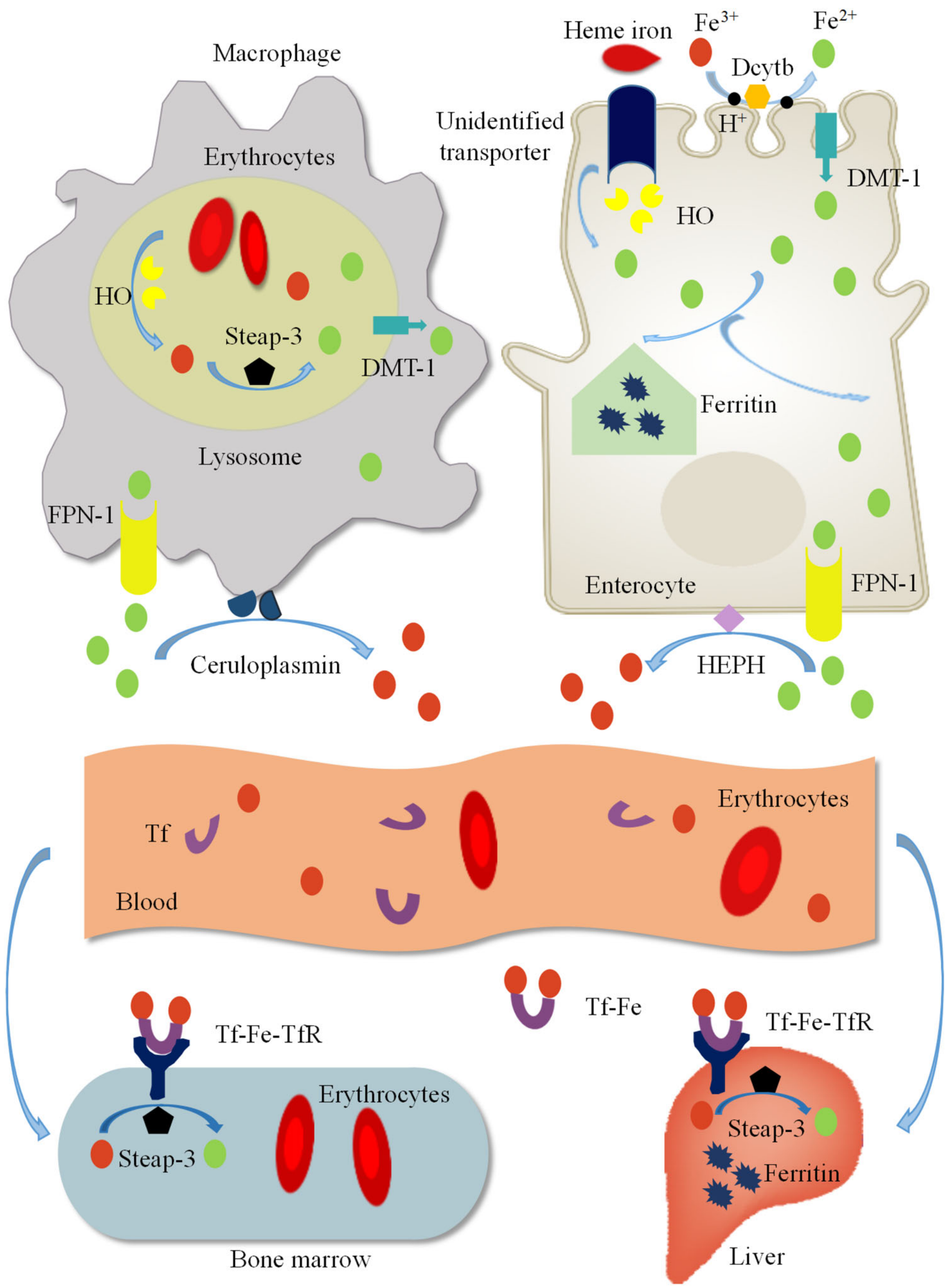

Figure 3. Schematic diagram of pathways through which iron metabolizes.

Zandt et al. 2008). FPN-1 regulates the amount of iron that enters the circulation system to be used by the body. Expression of FPN-1 is strictly regulated by hepcidin (Young-Hee et al. 2007). Hephaestin (HEPH) is an oxidase that is coupled to FPN-1 on the basolateral membrane of intestinal epithelial cells and catalyzes the oxidation of Fe^{2+} to Fe^{3+} (Chen et al. 2004). The daily iron obtained through the diet is 1–2 mg, hence the main source is macrophages, 15–25 mg (Ganz 2013). The senescent red blood cells are engulfed by macrophages, lysed in the lysosome. Through the hemoglobin oxidase, Fe^{3+} is obtained. Metalloreductase steap-3 reduces Fe^{3+} to Fe^{2+} (Dong et al. 2008a, 2008b). DMT-1 transports ferrous iron to the cytoplasm (Zhang et al. 2011). FPN-1 transports it out of macrophages and ceruloplasmin oxidizes Fe^{2+} to Fe^{3+} (Ayton et al. 2013). After that, Fe^{3+} is transported by the blood circulatory system throughout the body through transferrin (Tf) (Frazer and Anderson 2005; Gkouvatsos, Papanikolaou, and Pantopoulos 2012). Tf (~30%) binds to iron and attains its iron saturation stage. Tf mainly transports Fe^{3+} to the bone marrow for hematopoiesis, which is the synthesis of red blood cells. Senescent red blood cells are engulfed by macrophages and circulate continuously (Grant and Donaldson 2009). Primarily the liver acts as a reservoir of iron for ferritin (Meynard, Babitt, and Lin, 2014). Transferrin receptors (TfR) can bind to Tf-Fe^{3+} and ultimately transport iron to various organs (Rouault 2006). FPN-1 and HEPH can prevent the sudden accumulation of iron that is not bound to Tf. Interestingly, hepcidin is a negative regulatory hormone secreted by the liver (Nicolas et al. 2002). Inflammation has a profound effect on the normal metabolism of iron. When infected or inflamed, the synthesis of hepcidin increases, which results in the absorption reduction of iron in the small intestine. Increased synthesis of hepcidin reduces the iron efflux from macrophages and ultimately reduces the iron content in the blood (McClung and Karl 2009; Nemeth et al. 2003; Ganz 2003). Ferroportin is an iron efflux channel in the small intestine and macrophage. Hepcidin can be combined with amalgam in to degrade endocytosis and eventually remove it from the cell membrane (Nemeth et al. 2004; Ganz 2011). In this way, iron is retained in the intestinal epithelial cells without being absorbed into the blood to circulate. The accumulated iron gets discharged as the epithelial cells fall off. Similarly, iron enters macrophages through the erythrocyte, trapped inside the cells. Under physiological conditions, hepcidin expression is strictly regulated to maintain the normal iron levels in the body (Lim et al. 2018).

In general, the non-heme iron in plant foods exists in the chelated state with tannin, phytate, and polyphenol; hence its bioavailability is relatively lower than that of heme iron (Bechaux et al. 2018). Some herbs and spices can also exhibit adverse effects on iron absorption in the body. The main reason for this adverse effect is that polyphenols and phytate can form an insoluble complex with iron and reduces its bioavailability (Tuntipopipat et al. 2009; Al Hasan et al. 2016). There are some suggestions that the inhibition of iron intake by polyphenols is closely related to their type and concentration. It was reported that polyphenol-rich turmeric meal had no effect on iron absorption (Ma et al. 2011; Tuntipopipat et al. 2006). Commonly consumed nonalcoholic drinks, such as tea, and coffee as well as alcoholic drinks, such as red wines are rich in polyphenols (Ma et al. 2011; Tuntipopipat et al. 2006); while commonly consumed grains and beans contain phytic acid (Gibson, Raboy, and King 2018), which can impair iron absorption. In contrast, AA, citric acid, and some other organic acid also enhance the absorption rate of non-heme iron (Beck et al. 2014). AA improves the iron solubility and forms a soluble complex with iron both of which favor the reduction of ferric iron (Teucher, Olivares, and Cori 2004; Saunders et al. 2012).

The vegetarian group includes semi-vegetarian, pesco-vegetarian, lacto-vegetarian, ovo-vegetarian, lacto-ovo-vegetarian, and vegan (Pawlak and Bell 2017; Dinu et al. 2017). Heme iron, which is richly found in meats, poultry, and seafood, facilitates iron absorption via the gastrointestinal tract in the form of ferrous iron (Fe^{2+}). Thus, iron deficiency arising from consumption of same type of vegetarian diet for a long time is principally a result of excessive intake of non-heme iron (which has much lower bioavailability compared to heme iron). The continuous consumption of a vegetarian diet causes excess absorption of iron in the ferric form (Fe^{3+}) (Martínez-Navarrete et al. 2002; Turhan, Ustun, and Altunkaynak 2004). Considering that the iron requirement of vegetarians is about 1.8 times higher than that of non-vegetarians, it may be difficult to obtain sufficient iron from non-heme iron sources (Pawlak and Bell 2017). Substitution of meat by plant products is regarded as an emerging strategy to reduce meat consumption and meet the body's nutritional needs for vegetarians. Plant-based meat substitutes are typically designed to have a fairly similar look, feel, taste, and shelf-life, which include plant-based milk, burgers, sausages, mince, chicken, seafood, etc. An Australian study showed that about a quarter of plant-based meat substitutes are fortified with Vitamin B12 and iron-, and zinc-fortification account for almost the same proportion, i.e., less than 20% (Curtain and Grafenauer 2019; Cofnas 2019).

Evidently, the majority of iron deficiency is due to regular consumption of a diet that is not balanced with the right type of iron; thus, dietary iron supplements can redress this imbalance. Thus, consumption of iron-fortified foods can promote health and wellbeing.

Administration routes for iron supplementation

Iron supplementation includes oral administration and intravenous administration. Oral administration of iron supplement is a cost-effective intervention to reduce iron deficiency. By contrast, intravenous administration of iron supplement is adopted when oral iron administration is ineffective or poorly tolerated.

Oral administration

Oral administration of iron supplement is affordable, convenient, and unrestricted by external conditions, making it a popular method for iron delivery (Niehaus et al. 2015). The orally delivered iron supplement consists of divalent or trivalent iron. It is almost universally observed that iron-deficient patients choose ferrous salts as iron supplements due to the higher absorption rates. The dosage forms of iron supplements are quite diverse. For instance, sustained-release tablets, effervescent tablets, capsules, and granules are clinically used in iron supplement therapy. The prototypical example of orally administered iron is ferrous sulfate ($FeSO_4$) tablets, which are also considered to be the first-generation iron supplement (Mani Tiwari et al. 2011). $FeSO_4$ tablets are easy to handle and inexpensive. However, $FeSO_4$ and other inorganic iron are capable of combining with sulfide and polyphenol, causing food discoloration, and deterioration, causing some degree of negative impact on the gastrointestinal tract, all of which lead to poor absorption. Patients administered $FeSO_4$ and other inorganic iron supplements can also experience nausea, vomit, and diarrhea, triggering treatment delay (Mimura et al. 2008; Kadota et al. 2002). The second-generation iron supplements include ferrous citrate, ferrous gluconate, ferrous fumarate, and ferrous lactate, which are organic acid iron salt chelated with a small molecule. In this form, the ion and organic acid radicals interact with each other. Consequently, the iron in the acidic gastric stage releases slowly, avoiding rapid surges and subsequent decreasing stimulation. For example, ferrous succinate contains twice as much iron as $FeSO_4$ and succinic acid can promote the absorption of ferrous ions.

Table 1. Chemicals used for intravenous administration and their iron supplementation characteristics

Compounds	Iron content (mg/mL)	Recommended maximal dose	Iron desorption in 10 h (%)	Serious adverse reaction rates (%)	References
Ferric gluconate	12.5	125 mg	100	0.44	Auerbach and
Iron sucrose	20	200 mg	72	0.03–0.04	Macdougall (2017)
Ferric carboxymaltose	50	1000 mg (15 mg/kg)	50	3	Ponikowski et al. (2015)
Iron isomaltoside-1000	100	1000 mg (20 mg/kg)	24	–	Jahn et al. (2011)
Ferumoxytol	30	510 mg	36	–	Lopez et al. (2016)
Iron dextran with low molecular weight	50	20 mg/kg	20	0.44	Okam et al. (2012)

Compared with the first-generation iron supplements, the absorption of iron from the second-generation products has been significantly improved. However, these second-generation iron supplements still cause adverse gastrointestinal reactions (Cao et al. 2011; Muñoz et al. 2017).

Most of the traditional oral iron supplements can trigger various deleterious side effects. In order to solve this problem, chelated and encapsulated iron has been developed. Chelated iron is an iron-bound to an amino acid by forming a complex through coordination and ionic bonds, in which the molar ratio of an iron ion (in a soluble salt) to amino acid ranges from 1:1 to 1:3 (Hertrampf and Olivares 2004). In the iron chelate with amino acids, a ligand has at least two coordination atoms bonded to the central ion (Fe^{2+}) at the same time, forming a ring structure. This particular structure gives the amino acid iron chelate a suitable stability constant ($K = 4$–15). This not only facilitates the absorption and transport of chelates but also allows iron to be rapidly separated from the ligand. The K value of the EDTA-Fe^{2+} complex is about 14.3. Therefore, it is reasonable to utilize as a high-efficient iron supplement (Bao and Yu 1987; Türkel 2015; Miao et al. 2018). The chelated form effectively improves the stability of iron ions in the intestinal tract (Berryman, Baker, and Boyd 2014). There are two iron ion absorption pathways: the ionic pathway and the chelated pathway. The inorganic/organic iron salts are absorbed by ionic mode, while the amino acid chelated iron enters intestinal cells through the absorption pathway of amino acids. The absorption pathway of chelated iron is characterized by faster absorption speed and encounters less interference (Ashmead 2001). Hence, chelates integrated with macromolecular compounds, such as heme iron, ferric citrate, ferric maltol, NaFeEDTA, iron amino acid chelate, and polysaccharide iron are more suitable for oral iron supplementation (Pergola, Fishbane, and Ganz 2019). Another advantage of the chelated iron is that it can carry more payload compared to the iron salts. However, the most critical limitation of amino acid chelated iron is that once the chelated structure is destroyed, its bioavailability will be reduced. Because of this reason, it is necessary to protect the chelated iron in the acidic gastric environment (Allen 2002). Another approach to improve the efficacy of oral iron supplements is to microencapsulate them. Microencapsulation technology uses a polymer film-forming material (wall material) to encapsulate a sensitive core material. Microencapsulation enables the control and targeted releases of the embedded substance (Zimmermann et al. 2004; Lu et al. 2008). The choice of wall material profoundly affects the embedding and releasing rates and stability of the microcapsules. Wall materials, commonly used for microencapsulation, include polysaccharides, such as starch, dextrin, sodium alginate, dextran, and proteins such as whey protein, zein, gelatin, etc. Lipids, such as fatty acids, fatty alcohols, glycerides, and phospholipids are also used as part of shell materials (Dueik and Diosady 2017). Sensitive compounds, such as vitamins, minerals, active peptides, iron, and probiotics are commonly microencapsulated (Ilyasoglu Buyukkestelli and El 2019; Zheng et al. 2009). Nanoparticle-based iron microcapsules have now emerged as novel oral iron supplements and demonstrated favorable bioavailability and safety. These microcapsules show advantages over the chelated iron in terms of lower side effects (e.g., constipation, abdominal colic, vomiting, and diarrhea) (Abdel Moety et al. 2017). Liposomes, as a nanometric delivery system, separate the core material from the external environment and improve its stability. In addition, the most prominent feature of liposomes is their ability to target drug delivery, which improves the efficacy and reduces the side-effects (Torchilin 2005; Malam, Loizidou, and Seifalian 2009). Alternatively, encapsulation of $FeSO_4$ by solid lipid nanoparticles (SLNs) is effective for iron supplementation. Hatefi and Farhadian prepared a SLN coated $FeSO_4$ tablet. They found the lipid coating improved the drug release properties in the phosphate buffer saline at pH = 7.4 with a higher and sustained drug release from SLN, which is nearly twice that of the free drug (Hatefi and Farhadian 2020).

Oral administration of iron usually results in poor bioavailability and low iron supplementation efficiency. This mode of oral therapy can induce side-effect to gastrointestinal function, which can then lead to intolerance to patients up to 50% (Boone et al. 2019). Recent studies revealed that 80–90% of oral iron supplements (e.g., $FeSO_4$ tablets) were left in the gut lumen that caused acute iron poisoning and oxidative stress to the intestinal lumen (Schümann et al. 2007). Besides, oral iron therapy is a time-consuming treatment. According to recent clinical research, more than three months are required to replenish the iron level in the human body (Tiwari, Mahdi, and Mishra 2018). In order to shorten the treatment time, researchers have developed novel edible matrices based on alginate and whey iron vehicles via ionic gelation technology (Durán et al. 2020). SLNs are also utilized as delivery systems (Kumar et al. 2012). Continued implementation of these new technologies might help to improve the efficiency of oral administration of iron and minimize its side effects.

Intravenous administration

Intravenous iron delivery is a practical way of treating iron deficiency in patients who are recalcitrant to oral treatment or have low tolerability. This mode of iron delivery is effective in patients with severe anemia, inflammatory bowel disease, and chronic kidney disease (Sultan et al. 2019). Different types of intravenous iron are used in clinical trials: ferric gluconate (FG), iron sucrose (IS), ferric carboxymaltose (FCM), iron isomaltoside-1000 (ISM), ferumoxytol (FXT), and iron dextran with low molecular weight (LMWID) (Table 1) (Lopez et al. 2016). Akin to a double-edged sword effect, intravenous iron is also accompanied by nausea, hypotension, injury due to oxidative stress, easy iron overload, and iron intoxication (Rostoker and Vaziri 2019). FCM was perhaps the first batch of new reagents with high efficiency and dose supplementation of iron. It is known to be stable and has shown a low incidence of allergic reactions. After intravenous injection, the therapeutic efficiency and safety of FCM were assessed through many clinical trials (Moore et al. 2011; Barish et al. 2012; Bregman and Goodnough 2014). It was reported that compared to oral administration, the incidence of nausea, headache, hypertension, dizziness, and dysgeusia was higher; while the incidence of constipation, vomiting, and diarrhea was lower (Tomer et al. 2015; Wang et al. 2015). Interestingly, decreased blood phosphorus, the reaction on the spot of injection (discoloration, extravasation, etc.), flushing, and hypotension only observed in the case of the FCM group, compared with oral iron (Friedrisch and Cançado 2015). A recent study showed that the efficacy of intravenous iron supplementation using IS and oral supplementation using $FeSO_4$ during iron prophylaxis in pregnancy showed no significant difference (Bencaiova, von Mandach, and Zimmermann 2009).

Overall, oral iron therapy is recommended for patients with mild or moderate iron-deficiency anemia (IDA); intravenous injection suits the patients with severe IDA or those requiring to increase the iron level operation. After intravenous injection, the hemoglobin and the reticulocyte content are generally increased within a few days (Muñoz et al. 2017; Estadella et al. 2018). Regarding the hemoglobin increment (target of 11 g/dL), it has been shown that the level of iron by intravenous administration can be 2–4 times higher than that by administered orally (Al et al. 2005). The major barrier of iron delivery by oral as well as intravenous iron therapy is potential undesirable reactions. By contrast, supplementation of iron as part of food is a normal part of human life, which is more acceptable to iron-deficient population as they prefer non-drug forms of iron supplementation.

Discovery and development of iron supplementing ingredients

Innovation and new findings on functional properties enable the development of newer and more effective iron supplementation methods. The functional properties of iron supplements are used to tailor tablets, capsules, pills, and sirups. In addition, it is practical to use food as the vehicle by adding iron-rich ingredients, eventually producing iron-fortified foods. The iron-rich ingredients used to deliver iron (in iron-fortified food) can be classified into two types: (1) the synthetic substances (e.g., obtained from chemical synthesis) and; (2) the natural substances (e.g., plant ferritin, LF, and heme iron). To date, there is no consensus on whether synthetic or natural ingredients are more suitable for iron supplementation.

Synthetic iron supplementation factors

The efficacious enhancers improving iron absorbance include AA, sodium hexametaphosphate (SHMP), and disodium ethylenediaminetetraacetic acid (NaEDTA) (Nayak and Nair 2003). The function of these enhancers is affected by many other factors. Infante et al. (2017) incorporated carotenoids into sorghum cookies, which were found to have similar iron bioavailability, compared to those with $FeSO_4$ added cookies. The customer acceptance of the natural iron-fortified cookies was higher in terms of color, flavor, and texture. On the contrary, phytates (especially inositol hexaphosphate and inositol pentaphosphate), and polyphenols exerted a negative influence on iron bioavailability (Blanco-Rojo and Vaquero 2019). The effect of calcium on iron bioavailability is still a matter of debate. A review by Lynch (2000) pointed out that calcium improves the absorption of iron through a single meal. In contrast, Thompson et al. (2010) proposed a mechanism explaining that the presence of calcium inhibited the absorption of non-heme iron. According to these authors, calcium could decrease the expression of DMT-1 on the apical membrane of intestinal cells, thereby reducing iron absorption. Other researches indicate that the absorption of iron is closely related to the calcium dose. The dose-response of non-heme to calcium iron (5 mg) is 1000 mg and heme iron (5 mg) is 800 mg. It is shown that when the concentration of calcium exceeds the dose-response value, the rate of iron absorption can be reduced by 49.6% for non-heme iron and 37.7% for heme iron (Gaitán et al. 2011).

$FeSO_4$ is the most frequently used inorganic iron salt to treat patients with iron deficiency due to its overall efficacy in terms of tolerance, efficiency, and cost (Zariwala et al. 2013; Santiago 2012). Fortification of $FeSO_4$ into wheat flour is one of the most common approaches to compensate iron (Pachón, Stoltzfus, and Glahn 2008). However, the rusty small of $FeSO_4$ makes it unappealing to the patient (Diosady et al. 2002).

Ferrous citrate, gluconate, lactate, fumarate, and ferric pyrophosphate are representative organic iron salts that have a lower negative effect on gastrointestinal organs. Therefore, organic iron salts have been increasingly used to treat iron deficiency. Synthetic inorganic and organic iron have their sophisticated synergistic and antagonism action with dietary compounds. The food macromolecules can react with the supplemented iron and form iron-chelating peptides (e.g., barley proteins), polysaccharide iron, poly-maltose iron, and

Table 2. Characteristics of conventional iron supplementation ingredients

Compounds	Supplementation	Iron content (%)	Relative bioavailability (RBV) (%)	Gastrointestinal disturbances (%)	References
Ferrous sulfate	Sustained-release tablets、Granules、Drops	20	100	3.7 (sustained-release tablets) 31.6～32.3 (other forms)	Ludwig et al. (2015), Jafarbegloo, Tehran, and Tehrani (2015)
Ferrous lactate	Drops、Tablets、Capsules	18.9～19.5	106	11.4	Santiago (2012)
Ferrous gluconate	Tablets、Sirups、Drops、Powder	12	85～95	30	Cancelo-Hidalgo et al. (2013)
Ferrous fumarate	Capsules、Granules、Sprinkles、Tablets	27～33	100	43.4	Liyanage and Zlotkin (2002), Hartman-Craven et al. (2009)
Ferric pyrophosphate (micronized、dispersible)	Powder	25	82～92	–	Fidler et al. (2004), Hartman-Craven et al. (2009)
Ferrous citrate	Capsules、Pills	14～17	51	–	Blanco-Rojo and Vaquero (2019)
Ferrous glycinate	Granules、Powder、Capsules、Drops	20～28	125	18.5	Bovell-Benjamin, Viteri, and Allen (2000)
NaFeEDTA	Tablets、Drops	13	>100	–	Bothwell and MacPhail (2004)
Iron polymaltose complex	Tablets	～32	～100	18	Santiago (2012)
Iron-protein succinylate	Drops	35	>100	7	Cancelo-Hidalgo et al. (2013)
Electrolytic iron	Powder	97	75	–	Blanco-Rojo and Vaquero (2019)

Note: Gastrointestinal disturbances: nausea, vomiting, heartburn, pain, constipation, and diarrhea, etc.

dextrin iron (Eckert et al. 2016). These iron supplementing materials and their characteristics are presented in Table 2.

Natural iron supplementing ingredients

Natural resources provide a vast pool of resources for developing iron supplements. Herein we focus on three natural iron supplementing ingredients, i.e., ferritin (plant and animal ferritin), LF, and heme iron. Ferritin exists abundantly in leguminous crops, storing a large amount of mineralized iron in a soluble, benign, and bioavailable form (Liao, Yun, and Zhao 2014; Donf et al. 2008). LF derived from human and bovine milk is proven to be a high-value iron source for food and medicinal application. It is also the second abundant protein in breast milk (Ballard and Morrow 2013; Steijns 2001). Heme iron is the biological iron that does not cause gastrointestinal irritation and is readily absorbed by the intestinal mucous membrane cells. Heme iron can be utilized not only as part of iron supplements such as tablets, capsules, and granules, but also as an enhancer of food nutrition (Tang, Chen, and Zhuang 2014; Park et al. 2010; Tang, Zhu, and Zhuang 2015).

Ferritin

Ferritin extensively exists on plants, animals, and microorganisms and has the dual functions of regulating iron metabolic balance and eliminating ferrous toxicity by converting ferrous ion into ferric one (Liu et al. 2019). Ferritin exhibits many useful functional properties (Wang et al. 2016). It is suggested that with the nano-spatial structure of apoferritin, food bioactive molecules can be encapsulated in its inner cavity and improve the solubility of the embedded compound in water. Moreover, ferritin nanocapsules are increasingly used for delivering important medicinal compounds (Zhang et al. 2014).

Plant ferritin presents in almost all plant somatic cells, which can store a large amount of mineralized iron in a soluble, benign, and bioavailable form. Animal ferritin exists on the spleen, liver, and bone marrow and in serum, and blood cells from other tissues. Approximately 4500 iron atoms can be stockpiled in the core of single ferritin (Yang et al. 2015; Lv, Zhao, and Lönnerdal 2015). At present, ferritin has been mostly extracted from soybean seeds, garbanzo, and pea seeds (Briat et al. 2010). Plant ferritin is known to have satisfactory iron supplement efficacy without reported side effects. Compared with synthetic iron supplements, plant ferritin is natural and is easily absorbed than $FeSO_4$.

Lactoferrin

LF is typical animal ferritin that has been applied in iron supplementation. It is an important non-heme iron-binding glycoprotein with many useful physiological functions. In theory, one LF molecule can bind two trivalent iron (Fe^{3+}); thus, one gram of apo-LF (zero iron saturation) could carry ~1.4 mg Fe^{3+} (Karav et al. 2017; Leonsicairos et al. 2006). In the human body, LF exerts important functions including strengthening absorption of iron, avoiding the direct stimulation of free iron on the intestinal tract, anti-diabetic, anti-inflammatory functions (Cutone et al. 2020; Zhang et al. 2019; Rosa et al. 2017; Karav et al. 2017). LF contents in human colostrum are the highest, followed by bovine milk; the LF concentration in the former is 5–7 g/L, while that in the latter is 1–3 g/L (Lönnerdal 2003; Van Berkel et al. 2002). It has been reported that human LF receptors are located on the surface of the mammal intestinal mucous membrane cells and express the highest level, immediately after giving birth to the body. Human LF is expected to exhibit a high iron absorption rate due to the iron need of the infant. In comparison, bovine milk contains less LF with only ~0.8 g/L in colostrum and 0.1–0.4 g/L in mature milk (Telang 2018). Furthermore, the capacity of bovine LF to inhibit bacterial proliferation is lower than that of human LF (Woodman et al. 2018). Although the absorption of human LF is high, due to various reasons, infants still need supplementation of iron. To meet the need for iron in the infant and adult population, LF is isolated and extracted from bovine milk, especially from colostrum and whey (Pammi and Suresh 2017).

The oral delivery of bovine LF shows higher iron bioavailability and lower side-effect on the gastrointestinal tract than the $FeSO_4$ dose (Paesano et al. 2010; Macciò et al. 2010). Because of this reason, infant formula products are fortified with bovine LF. Clinical trials have been conducted by Ke et al. (2015) to determine the iron absorption metabolism of infants at 4–6 years of age. The infant formula fortified with bovine LF (38 mg/100 g milk) showed many beneficial effects including increased stature (6.3%), enhanced hemoglobin (11.7%), serum ferritin (76%), and total body iron content (28.8%). It also reduced the incidence of iron deficiency (54%), IDA (81.8%), and anemia (58%).

Heme iron

Heme iron is from animal blood that contains >40 mg iron/100 g (Dailey et al. 2017). Heme iron (porphyrin iron) is also found in many animal foods including lean meat, liver, blood curd, shellfish, and flesh fish, all of which can be combined with other components in the diet for iron intake (Taniguchi, Dobbs, and Dunn 2017). After cooking, the heme iron in beef remains the highest (1.06–2.63 mg/100 g), followed by pork (0.30–0.61 mg/100 g), fish (~0.46 mg/100 g), and chicken (0.17–0.49 mg/100 g). Generally, the bioavailability of meat derived heme iron is in the range of 15–35% (Schönfeldt and Hall 2011; de La Pomélie, Santé-Lhoutellier, and Gatellier 2018; Hurrell and Egli, 2010).

The advantage of heme iron is that it barely induces gastrointestinal irritation symptoms, which means it is directly absorbed by intestinal mucous membrane cells and readily utilizable by the body (Pizarro et al. 2016). Food hemoglobin and myoglobin are digested in the stomach, where free heme is released. The free heme in the intestine is attached to the intestinal mucosal epithelial cells. Then, it moves across the cytoplasm and finally across the basal cell membrane of the absorbing cell into the blood circulation (Han 2011). Despite the above-mentioned facts, the absorption mechanism of heme iron still remains unclear. The first hypothesis explaining the absorption of heme iron is the receptor pathway. According to this pathway, heme iron is ingested by cells through receptor-mediated endocytosis, a protein that has not yet been identified (Gräsbeck et al. 1979; Tenhunen et al. 1980). The second hypothesis is the HCP-1 (Heme Carrier Protein-1) transporter pathway (Nakai et al. 2007; Laftah et al. 2008), which explains that HCP-1 is expressed at a high level in the duodenum. After binding to heme iron, the complex enters the absorbing cells through endocytosis. Then, it is decomposed under the action of HO-1 (Camara and Soares 2005; Araujo, Zhang, and Yin, 2012). Researches have shown that the affinity of HCP-1 to folic acid is higher than that of heme iron and it works as an effective transporter of folic acid; but heme is a low-affinity transporter (Hoppe et al. 2013; West and Oates 2008). The third hypothesis is the synergy between the receptor and HCP-1, in which the endocytosis of heme and its receptor (HCP-1) is also internalized. Subsequently, heme that combined with HCP-1, is transported into the cytoplasm (Oates and West 2006). In the absorption study of heme in *Caenorhabditis elegans*, Rajagopal et al. (2008) found that the heme-responsive gene (HRG) (transmembrane protein) played an important role in the heme iron homeostasis of worms and vertebrates. The loss of HRG-1 or HRG-4 could cause abnormal heme sensing in the body. Worms had four HRG analogs, while humans have only HRG-1. Therefore, through the heme transport mechanism of *C. elegans*, they indicated that HRG-1 was the heme iron transporter (Rajagopal et al. 2008).

Another beneficial aspect of heme iron is its good bioavailability. Due to this reason, heme iron supplements (e.g., tablets, capsules, and granules), are much effective than traditional iron replenishes (Hurrell and Egli 2010). Furthermore, the incorporation of heme iron in food does not drastically affect the quality of the food, in which it is incorporated. Neither the organoleptic properties (tincture, flavor, and mouthfeel) nor the original nutrients were affected by the addition of heme iron in bakery products (Alemán et al. 2016; Martínez-Navarrete et al. 2002). The most common foods, used as vehicles for heme iron are dairy products, biscuits, bread, confections, pastries, and noodles.

Chocolate and heme iron shared a similar color. Therefore, sandwich-type cookies filled with heme iron-fortified chocolate creams (0.31 mg iron/1 g cream or 0.11 mg iron/1 g cookie) had a high level of acceptability and popularity among consumers (Alemán et al. 2016). The color of the iron-fortified cream was close to that of the chocolate bar, making it a feasible way to incorporate iron (Alemán et al. 2016). These researchers tested the efficiency of these heme fortified chocolate bars, using pubertal Mexican girls between the ages of 11–16 as the subjects. They divided the subjects into three groups: The first group (control) was provided with unfortified biscuits (0.2 mg iron per biscuit); the second group was provided with fortified biscuits with iron sulfate (average 1.71 mg iron per biscuit); the third group was provided with fortified biscuits with heme iron (ditto). At the end of the experiment, hemoglobin between the control group and the enhanced groups (iron sulfate fortification and heme iron fortification) was increased by 3.7% and 2.9%, respectively. The results also showed that the iron bioavailability of the heme iron-fortified biscuits was ~27% higher, compared to that of sulfate fortified ones (González-Rosendo et al. 2010). Churio and Valenzuela (2018) selected low cost and good compatibility maltodextrin as the wall material to embed the atomized bovine erythrocytes (heme iron source). They found that the concentration of maltodextrin with the best encapsulation effect was 40% w/v by spray-drying. In the future, combining microcapsule technology with heme iron-fortified foods is an effective way to supplement iron with food.

Iron-fortified foods

Production of iron-fortified foods is an economic, sustainable, and long-term strategy to prevent iron deficiency (Berendsen et al. 2016). A prerequisite for the formulation of iron-fortified foods is that they deliver adequate iron content within the recommended dietary standard. The panacea of iron deficiency through iron-fortified foods is ensuring high bioavailability, avoiding negative effects on physicochemical and sensory properties of food vehicles, and ensuring ready absorption of iron by the human body. From the industrial production perspective, the food matrix used as the vehicle of iron should have three important characteristics: (1) mainstream food product commonly used by consumers; (2) maintains excellent organoleptic properties after iron fortification; (3) affordable (Bovell-Benjamin and Guinard 2003). Ideally, the iron-fortified foods should also have the following two functional characteristics: (1) high bioavailability; (2) readily available or secure source.

As described before, iron-fortified foods can be divided into two categories, i.e., iron-fortified food for the target population and the public. The iron-fortified foods falling under the first category are aimed at the target population (having specific iron absorption, storage, and recycling needs) that include pregnant women, menstrual adolescents, women of childbearing age, children, newborns, infants, elderly, and athletes (Moreira-Araújo, Araújo, and Arêas 2008; Zoller and Vogel 2004; Wawer, Jennings, and Fairweather-Tait 2018; Iglesias, Canals, and Arija 2018). Supplementation of docosahexaenoic acid (DHA) together with iron was shown to improve iron homeostasis. For example, DHA was found to improve iron stores in new-born babies (Diaz-castro et al. 2015). Thus, iron and DHA co-fortified food products are produced by the food industry including reinforced infant formula, and iron-fortified biscuits. The second category of iron-fortified foods is targeted for reducing the risk of iron deficiency in the general public. For this purpose, iron content in staple foods, such as rice, flour, salt, and soy sauce, is increased by adding iron-rich ingredients.

As mentioned in the earlier section, the common iron-rich ingredients incorporated into iron-fortified foods are $FeSO_4$, ferrous fumarate, amino acid iron chelate, ferric pyrophosphate, NaFeEDTA, heme iron, etc. The common food vehicles used to carry these ingredients are cereals, bakery products, dairy products, beverages, condiments, etc. Table 3 lists the characteristics of iron-fortified foods and iron supplementing (iron-rich) ingredients. Table 4 lists the commercial iron-fortified products. Flour, cereal, and bread made from flour and cereal are effective and sustainable vehicles for iron fortification as they are regularly consumed by a large population (Diego Quintaes, Barberá, and Cilla 2017). Mandatory fortification of wheat and corn flours was implemented in Brazil in 2004 and it was shown that average iron intake through fortified foods (e.g., French bread, cream crackers, sweet biscuits, and couscous) was higher than through general diets (Grande et al. 2019; Hurrell 1997). However, it is commonly noted that iron-fortified diets containing a high level of iron are not that satisfactory for consumers because it changes color and introduces unpleasant odor and flavor (Chunling and Yu 2013). In order to overcome this problem, new technologies have been developed for iron supplementation and these technologies are specific to the food material used. For example, Nestel et al. (2006) produced iron-fortified beverages and fruit powders by encapsulating iron-rich ingredients and also using a chelating approach.

The regulation applied to iron-fortified foods is different in different countries. In China, the maximum dosage of $FeSO_4$ permitted to incorporate into cocoa powder, infant food, and salt is $11\sim12$ mg/kg, $300\sim500$ mg/kg, and $3000\sim6000$ mg/kg, respectively. Similarly, the maximum permitted dosage of gluconate in salt in China is $4800\sim6000$ mg/kg. In Japan, the maximum dosage of ferrous gluconate that can be added to edible olive oil is $\sim$150 mg/kg (Ruíz 2015). Thus, it is important to follow the food standards of the countries in which the iron-fortified foods are produced and marketed.

Cereals

Consumption of iron-fortified staple foods is one of the most effective ways of treating iron deficiency. The main obstacle for increased consumption of this type of iron-fortified food is the presence of phytic acid that inhibits iron absorption (Huma et al. 2007).

Rice, one of the most widely available staple foods, is a suitable food vehicle to carry iron and alleviate insufficient iron intake. Compared to un-parboiled and parboiled rice, the iron content and its bioavailability in ferritin-fortified parboiled rice (I-rice) was much higher (Prom-u-thai et al. 2009). Further research indicated that continuous intake of I-rice (18 mg $FeSO_4$ per 100 g rice) was able to enhance hemoglobin and hematocrit content in women with IDA (Losso et al. 2017). It is expected that the gender, consumers' age, level of education, and the ability to buy I-rice kernels would greatly affect the efficacy of this approach. A survey in the Philippines indicated that iron-fortified rice and mingling iron rice premixed with the ordinary rice at a ratio of 1:250 was able to supplement iron at a moderate acceptance rate (Juan et al. 2011; Dalbhagat and Mishra 2019).

Wheat flour is widely used in noodles, steamed buns, and dumplings, as well as in the production of bread and cake. Huang et al. (2009) explored the effect of fortification by adding different iron-rich ingredients in wheat flour. These authors incorporated NaFeEDTA (20 mg of iron per 1 kg), $FeSO_4$ (30 mg of iron per 1 kg), and electrolytic iron (60 mg of iron per 1 kg) into wheat flour. After 6 months of feeding, NaFeEDTA-fortified flour achieved the highest body iron store, followed by $FeSO_4$ and electrolytic iron-flours. Another work that provided iron-fortified whole maize flour to children indicated that the addition of NaFeEDTA was associated with decreasing the prevalence of iron deficiency (Andang'o et al. 2007). Tripathi and Platel (2011) fortified finger millet with iron and showed that synergistic interaction between EDTA and ferrous fumarate or ferric pyrophosphate could greatly improve the bio-accessibility of iron and zinc. The bioaccessible iron content in ferrous fumarate fortified sorghum flour (6 mg iron per 100 g flour) was substantially high in the presence of EDTA (iron: EDTA = 1:1). The bioavailability of iron in the mixture of ferrous fumarate and EDTA was 4–5 times higher than that in individual ferrous fumarate and folic acid group and 6 times higher than that in unfortified control. However, such synergistic or enhancing effect was found to decrease with storage time (Tripathi and Plate 2013).

Bakery products

Biscuits have a long storage shelf life and a high acceptance rate among the populace all over the world. Iron-fortified biscuits can be divided into two categories: (1) biscuits baked from fortified flour and (2) sandwich biscuits that add iron-supplementing ingredients in the cream. A survey in Brazil showed that iron intake via biscuits (produced from iron-fortified flour) accounted for 20–30% of the RDI iron for children, 9.5–14% for adults, and 5–7.2% for pregnant women (Rebellato et al. 2015). Biscuits containing bovine liver (rich in heme iron) were also used to reduce the prevalence of IDA in preschool children (Oliveira et al. 2013).

Bread produced using whole meal rye contains relatively low phytate content. It was shown that when women (20–38 years old) regularly consumed iron-fortified whole meal rye bread, the iron content in their body became stable (Hansen et al. 2005). A study conducted using French bread (produced by refined wheat flour) found that the iron supplementing effects of different iron-rich (supplementing) ingredients such as iron sulfate monohydrate, ferrous fumarate, reduced iron, and NaFeEDTA was quite different. The NaFeEDTA incorporated French bread showed the best iron supplementing efficacy (Rebellato et al. 2017). Furthermore, the sensory properties of NaFeEDTA incorporated bread are similar to those of unincorporated bread (El Ouyoun Najm et al. 2010). The quality of iron-fortified bread can be further improved when microencapsulated ingredients with iron at the core are used. It has been shown that the iron content and its bio-accessibility in the gastrointestinal tract were higher in products that used microencapsulated iron (Gupta et al. 2015; Dueik and Diosady 2017). When microencapsulated $FeSO_4$ and ferrous lactate were used to produce fortified bread, their bio-accessibility of iron was increased by 80% and 84%, respectively (Bryszewska et al. 2019).

Margarine has a bright yellow appearance, uniform texture, delicate, satisfying flavor, and thus, it is widely used to produce ice cream, biscuits, cakes, desserts, and pastries. Andersson et al. (2010) produced iron-fortified margarine (14 g iron per 1 kg margarine) adding ferric pyrophosphate or NaFeEDTA. The authors reported that the body iron reserve rate of NaFeEDTA fortified margarine was 2–3 times higher than that of the ferric pyrophosphate fortified ones.

Dairy products

Dairy products are the primary source of protein, calcium, phosphorus, and vitamins; however, they contain insufficient iron content for supplementation (Lopez et al. 2016).

Through in vitro digestion and the Caco-2 cell model, it is shown that both cow milk and goat milk are suitable for iron fortification (Bosscher et al. 2001; Glahn et al. 1998). The iron bioavailability in dairy products can be increased by adding a moderate amount of AA (Stewart et al. 2018). Iron-fortified cow milk (10 mg/L) was found to effectively supplement iron to infants up to 18 months (Torrejón et al. 2004). By contrast, milk containing zinc (5 mg/L) did not exhibit the same supplementation effect as iron (Torrejón et al. 2004). Iron-fortified chocolate milk was also found to be an effective product to replenish iron in children due to its rich aroma and attractive color (Douglas et al. 1981).

Considering the low iron content in breast milk (0.25–0.35 mg/d), it is prudent to develop iron-fortified infant formula products (Breymann et al. 2007). Infant milk powders (IMF) are formulated and manufactured according to the growing needs of infants at different growth stages and contain a good balance of proteins, fats, carbohydrates, minerals, and vitamins. An iron-fortified IMF powder should retain the organoleptic characteristics of a standard unfortified IMF powder. Similar to the unfortified-IMF, the iron fortified-IMF should easily dissolve in water. The most important challenge to overcome in iron-fortified formula products is the likelihood of diarrhea. There always is a risk of diarrhea in iron-fortified-IMF products. Generally, the minimum dose of iron supplementation (2.5 mg/d) is the safe dose. However, 12.5–15 mg/d is recommended for replenishing iron (Hyder et al. 2002; Olsen et al. 2004; Thompson et al. 2005). The replenishing iron dose has shown to have a negative impact on gut microbiota and iron absorption, both of which may lead to diarrhea and intestinal inflammation (Paganini, Uyoga, and Zimmermann 2016). Studies on 2-week-old infants by Johnston et al. (2015) suggested that the infants had good tolerance to the iron-fortified formula with bovine LF at 0.6 g/L.

Fermented dairy products such as yogurt are helpful to inhibit the growth and proliferation of spoilage bacteria in the intestinal tract (Aryana and Olson 2017). A study in Bangladesh on school-age children suggested that iron-fortified yogurt was able to supply three-tenths of the recommended daily iron allowance (Sazawal et al. 2013). Yogurt is also a suitable medium to supplement iron for lactose intolerant patients as it promotes gastrointestinal peristalsis, and facilitates digestion (Hashemi Gahruie et al. 2015). A limitation associate with iron-fortified yogurt is the likely reaction between some components of yogurt with iron-carrying (fortifying) ingredient. The emergence of nanomaterials and encapsulation technology provides a pathway to

Table 3. List of iron-fortified foods

Vehicles	Target population	Iron content (mg/100 g)	Functional ingredients	Effectiveness	References
Rice	The public	4.23	$FeSO_4$	Hemoglobin ↑ Hematocrit ↑	Losso et al. (2017)
Wheat flour	The public	5.37	NaFeEDTA $FeSO_4$	Hemoglobin↑ Serum ferritin↑ Transferrin receptor↑ Body iron store↑	Huang et al. (2009)
Chocolate biscuit	The public	0.06	Heme iron	Hemoglobin↑ Iron bioavailability↑	González-Rosendo et al. (2010)
Bread	The public	2	Encapsulated ferrous sulfate	Bioaccessibility↑ Iron content in the digestate↑	Bryszewska et al. (2019)
			Encapsulated ferrous lactate	Bioaccessibility↑ Iron content in the digestate↑	
Pocket-type bread	The public		$FeSO_4$ NaFeEDTA	Good sensory properties	El Ouyoun Najm et al. (2010)
Blood-based crisp bread	Women of reproductive age		Heme iron	Ferritin ↑ Body iron ↑	Hoppe, Brün, Larsson, Moraeus, and Hulthén (2013)
Margarine	The public	1	Micronized ground ferric pyrophosphate NaFeEDTA	Body iron stores ↑ Prevalence of anemia↓ Prevalence of ID↓	Andersson et al. (20100
Milk	Infants, toddler young children	0.3	Ferrous gluconate	Prevalence of anemia↓ Prevalence of ID↓	Rivera et al. (2010)
			Ferrous lactate	Serum ferritin↑	Virtanen et al. (2001)
Infant formula	Infants	4	Lactoferrin	Hemoglobin↑ Serum ferritin↑ Serum transferring receptor↑ Iron absorption in the intestine↑ Prevalence of anemia↓ Prevalence of IDA↓ Prevalence of ID↓	Ke et al. (2015)
Yogurt	Women and children	0.4	Microencapsulated $FeNH_4(SO_4)_2\ 4H_2O$	Good sensory property Reduction of oxidized flavor	Kim et al. (2003)
			Casein-chelated iron (56 mg Fe/g)		Hekmat and Mcmahon (1997)
Fruit beverage	Children		Whey protein-chelated iron (137 mg Fe/g)	Improvement in iron statue	Solon et al. (2003)
Orange juice	The public	0.2	$FeSO_4{\cdot}7H_2O$	Hemoglobin↑	De Almeida et al. (2003)
Coffee	The public	0.1	$(Fe_4(P_2O_7)_3.9\,H_2O$	Prevalence of anemia↓	Wilson et al. (1977)
Salt	The public	0.3	$FeSO_4{\cdot}7H_2O$	Prevalence of anemia↓	Sivakumar et al. (2001)
Soy sauce	The public	8.6	NaFeEDTA	Hemoglobin↑ Prevalence of anemia↓ Prevalence of IDA ↓	Scrimshaw and Gleason (2005)
Sugar	Preschool children Women of reproductive age	3.4	Iron tris-glycinate chelate NaFeEDTA	Hemoglobin↑ Serum ferritin↑ Iron store↑(significantly)	Viteri et al. (1995)
Jelly	Adolescent girls	0.2	Snake fruit seed flour		Nugraheni, Indarto, and Pamungkasari (2019)
Pumpkin	The public	0.4	$FeSO_4{\cdot}7H_2O$	~50% bioaccessibility	Genevois, de Escalada Pla, and Flores (2017)

overcoming this problem. Compared to traditional iron-fortified yogurt, the yogurt enriched with iron oxide nanoparticles (encapsulated in inulin) was shown to have better acidity, density, and color (Santillán-Urquiza, Méndez-Rojas, and Vélez-Ruiz 2017). Similarly, a new type of yogurt containing iron encapsulated in niosomes also showed desirable iron supplementing efficacy (Gutiérrez et al. 2016).

Beverages

The prevalence of IDA in Tanzanian was lowered by 56% using a specifically formulated micronutrient-fortified beverage. The micronutrients in this fortified beverage were: iron (10.8 mg), Vitamin A (1050 μg, retinol equivalents), iodine (90 μg), zine (10.5 mg), AA (144 mg), riboflavin (1.2 mg), folic acid (280 μg), VB_{12} (6 μg), VB_6 (1.4 mg), niacin (10 mg, niacin equivalents), and VE (21 mg, alpha-tocopherol equivalents) (Makola et al. 2003). In addition, the iron-fortified beverage was also popular among school-age children. A study in Philippines showed that a fortified fruit powder beverage (4.8 mg iron and 48 μg iodine per 25 g beverage powder) was beneficial to school-age children (1–6 grades), who suffered from iron and iodine deficiency. After drinking 200 mL of this beverage twice a day, the subjects showed improvements in iron storage, iodine status, cognitive performance, and physical fitness (Solon et al. 2003). Similarly,

Table 4. Commercial iron-fortified products

Name of the product	Place of origin	Industry	Target population	Recommendations for use	Iron content per edible portion	References/ official website
Floradix Eisen Folsaure Dragees (tablets)	Germany	Salus Pharma GmbH (health products)	Infants over 1 year, pregnant women, adults	1–12 years, 1 tablet a day; > 12 years, 2 tablets a day	7 mg Fe/tablet	https://www.salus-haus.com
Floradix mit Eisen (oral liquid)	Germany	Salus Pharma GmbH (health products)	Children over 6 years and adults	6–10 years, twice a day, 15 mL each time; > 10 years, three times a day, 15 mL each time	81.75 mg Fe/100 mL	https://www.salus-haus.com
Orthomol Eisen Plus (capsule)	Germany	Orthomol pharmazeutische Vertriebs GmbH (health products)	Reproductive woman	1 capsule per day	18 mg Fe/capsule	https://www.orthomol.com
Eric Favre Prenatal (oral liquid)	France	Eric Favre (health products)	Babies over 6 months	6 months – 5 years, 5 mL; > 5 years, 10 mL	14 mg Fe/10 mL	https://www.ericfavre.com
Soria Natural IroNat (oral liquid)	Spain	Soria Natural SA (health products)	Babies over 1 year and adults	1–4 years, 7 mL a day; 4–10 years, 10 mL a day; > 10 years, 15 mL a day	14 mg Fe/15 mL	https://www.sorianatural.com
Little Freddie Baby rice	United Kingdom	Little Freddie (food)	Babies over 6 month	Twice a day, 5–25 g each time	5.75 mg Fe/100 g	https://littlefreddie.com
Ferrolip (instant powder)	Italy	U.G.A. Nutraceuticals S.r.l. (health products)	Public	< 10 years, half a pack a day; > 10 years, 1 pack a day	30 mg Fe/pack	https://www.uganutraceuticals.com
Eisenvida (capsule)	Switzerland	Kingnature AG (health products)	Adults	1–2 capsules a day	14 mg Fe/capsule	https://www.kingnature.co.uk
MeadJohnson Enfinitas	Netherlands	Mead Johnson B.V (formula)	Babies of 1–3 years	Three times a day, 40 g each time	330 mg lactoferrin/100 g	https://www.meadjohnson.com
NURIZ Lactoferrin formula powder	New Zealand	Naturies Health Products Ltd (formula)	Infants	1 pack a day (1 g/pack)	1200 mg lactoferrin/100 g	http://www.nuriz.com.cn
ICREO	Japan	ICREO Co. Ltd (formula)	Babies of 1–3 years	Twice a day, 13 g each time	8.3 mg Fe/100 g	https://www.icreo.jp
HABA iron-fortified gummy	Japan	HABA (food)	Children, adults	15 g a day	2.7 mg Fe/15 g	https://www.japankt.com
Kirkland omega + infant formula	American	Kirkland Signature (formula)	Infant under 1 year	1 tablespoon milk powder in 60 mL water	9.3 mg Fe/100 g	https://www.costco.com
President's Choice	Canada	President's Choice (formula)	Infant under 1 year	1 tablespoon milk powder (8.6 g) in 60 mL water	9.3 mg Fe/100 g	https://www.presidentschoice.ca
Goldroast instant nutritious cereal	China	Shantou Jinwei Food Industry Co. Ltd (food)	Quinquagenarian	2 packs a day (23 g/pack)	3.5 mg Fe/100 g	http://www.jinweimaipian.com
Iron-fortified gummy	China	Guangdong Yichao Biological Technology Co. Ltd (food)	People over 3 years	10 g a day	100 mg Fe/100 g	http://www.yichaobio.com
Iron-fortified mushroom soy sauce	China	Foshan Haitian Flavoring Food Co. Ltd (food)	Public	Add to the dish in moderation	3.6 mg Fe/15 mL	http://www.haitian-food.com
Fortified iron solid beverage	China	Zhuhai Yuanfu Technology Development Co. Ltd (food)	Public	1–2 packs a day (25 g/pack)	16 mg Fe/100 g	http://www.yfbao.com.cn

iron-fortified orange juice was successfully used to replenish iron in preschool children in Brazil (De Almeida et al. 2003), and coffee which was first appeared in 1977 in America (Wilson et al. 1977).

Condiments

Table salt can be readily fortified with iron and iodine (Banerjee, Barnhardt, and Duflo 2018). Salt iodization programs have made it possible to control and eliminate iodine deficiency at a low cost (Diosady, Alberti, and Venkatesh Mannar 2002). Iron-iodine double fortified salts can be easily formulated. Using salt as the carrier, it has become feasible to supplement iron in remote and poor areas (Horton, Wesley, and Venkatesh Mannar 2011). A most plausible approach is to incorporate microencapsulated ferrous fumarate and iodine into common salt. This approach avoids the interaction between iron and iodine. It also improves the bioavailability and increases the storage period (Li, Diosady, and Wesley 2010).

Soy sauce is also a suitable vehicle for iron fortification, which enables high bioavailability of iron. It has been shown that NaFeEDTA fortified soy sauce could protect consumers against IDA (Huo et al. 2015). The consumption of iron-fortified soy sauce and similar products also depends on the education level of the consumers and nutritionally aware consumers have a greater tendency to buy iron-fortified products including soy sauce (Wei et al. 2016).

Monosodium glutamate (MSG) is a fresh seasoning product that enhances the natural taste of food, especially that of meat and vegetables. Shi et al. (2012), found that the intake of MSG could increase the level of hemoglobin in adults. Therefore, fortification of MSG with iron can may synergistically enhance the efficacy of iron.

Snacks

As early as the 1970s, sugar was used in the processing of iron-fortified food. Disler et al. (1975) added 1 g $FeSO_4$ and 10 g AA into 1 kg sugar. The authors reported that the corn porridge cooked with this fortified sugar could double the absorption of iron, compared to the one cooked with unfortified sugar. Furthermore, the rate of iron absorption was increased by at least three times when AA was added to the formulation (Disler et al. 1975). The efficacy of double-blind sugar, in which 15 mg Vitamin A (15 mg retinol per 1 kg sugar) and 130 mg iron (1 g NaFeEDTA per 1 kg sugar) as iron enhancer was studied. Although the color of sugar fortified with NaFeEDTA was yellow, it is still acceptable to the consumers and was effective in reducing the prevalence and incidence of anemia (Viteri et al. 1995). The sweet taste, attractive shapes, and affordable cost make candy as one of children's most favorite snacks. Sari et al. 2001 provided 4–6-year-old children ten candies (3 mg iron per candy) per person per week for around 3 months and reported that the prevalence of anemia fell by ~82% (Sari et al. 2001).

Jellies come with an appealing appearance, bright color, soft, and smooth taste. As a semi-solid dessert, it is particularly favored by children and teenagers. In Indonesia, a 2.5-month study was conducted to determine the efficacy of delivering iron to adolescent girls with moderate anemia through jelly. The jelly was formulated from iron-fortified snake fruit seeds flour and agar flour. This fortified jelly was found to be suitable for delivering iron as well as other micronutrients such as iron, zinc, and AA (Nugraheni, Indarto, and Pamungkasari 2019).

Other vehicles of iron fortifying

Besides the above-listed food materials, there are many others that are suitable for iron fortification; however, they may need further functionalization. For instance, the bio-accessibility of iron and sensory properties of the iron-fortified pumpkin could be significantly increased (~3–4 times) when iron and probiotic bacteria are incorporated together (*Lactobacillus casei*) (Genevois, de Escalada Pla, and Flores 2017).

Egg white and egg yolk can be a good choice for iron fortification. The nutritional value of eggs could be enhanced by fortifying the hen's feed, which increases the iron content in egg white and the yolk (Chambers et al. 2017; Browning and Cowieson 2014). It was reported that the hatchability and iron content in egg yolk was substantially improved by adding iron supplements (iron soy protein chelates) to hen feed (Sujatha et al. 2014).

Meat products can also be used as a vehicle for iron fortification. The heme iron content in meat products varies from species to species; however, it is scarcely affected by the cooking methods used (Cross et al. 2012). Navas-Carretero et al. (2009) studied iron absorption in cans from meat pâté (15 mg iron from enhancer) containing $FeSO_4$, and ferric pyrophosphate encapsulated in liposomes. Meat pâté was placed between two slices of bread similar to a hamburger. The authors reported that the meat pâté fortified with ferric pyrophosphate encapsulated in liposomes was highly effective in delivering iron. Similarly, sausages, especially those double fortified with iron and calcium can be suitable vehicles for iron delivery.

Concluding remarks

Iron deficiency is a problem of global dimension. Compared with clinical iron supplementation (e.g., oral and intravenous treatment), dietary supplementation through iron-fortified foods is more practical and acceptable to the general public. Insufficient or excess iron supplementation should be avoided while delivering iron through iron-fortified foods. It is important to continuously innovate the processing technologies and novel ingredients for iron fortification. Biological iron-rich ingredients such as ferritin, LF, and heme iron can be highly effective in supplementing iron, compared to the inorganic iron salts due to their high absorption rate. Advances in structure-activity relationships of iron-rich compounds and processing technologies (e.g., microencapsulation) to incorporate them in various food vehicles have led to the manufacturing of a wide spectrum of iron-fortified foods including cereals, meats, bakery products, dairy products, beverages, condiments, and snacks. Increased consumption of these iron-fortified products has shown impressive benefits of reducing or preventing iron deficiency. Prevention of iron-deficiency through the widespread consumption of iron-fortified foods requires continuous innovation in products and processes and also requires a high level of public awareness. Micro-nano encapsulation and chelating of iron play an important role in enhancing the bio-accessibility and absorption rate of iron. It also helps to avoid undesirable changes in the organoleptic properties of the final products. Overall, consumption of iron-fortified foods by iron-deficient people will significantly improve their health and well-being.

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