Food fortification strategies to deliver nutrients for the management of iron deficiency anaemia

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ARTICLE INFO

Keywords: Iron deficiency anaemia
Conventional fortification
Iron compounds
Food-to-food fortification
Iron rich foods
Underutilised crops

ABSTRACT

A rising trend in the global prevalence of anaemia is still prevailing. To combat micronutrient deficiencies, World Health Organisation/Food Agriculture Organisation (2006) guidelines recommended four chief strategies – supplementation, fortification, nutrition education and dietary diversity. Of the four strategies, food fortification has been considered as the most efficacious and economical approach. However, it is the directives themselves that highlight two major bottlenecks associated with conventional fortification - uniform dissemination of the fortifier in food vehicle that mostly include staple foods, and internal and external compliance evaluation of fortification regulations and standards by the producers. As a result, researchers envisaged a new strategy - Food-to-food fortification that complements conventional fortification. This strategy involves fortification of food vehicles with nutrient-rich food-based fortifiers. The major advantage of utilising food-based fortifiers is that they hold the potential of enhancing the bioavailability of the fortified food and providing additional nutrients and thus, resulting in dietary diversification. It also facilitates the utilisation of underutilised crops as food-based fortifiers. Underutilised crops have been recognised as potential beneficial food source accounting to their nutritional, ecological, and fiscal benefits. This review paper delves into the strengths and shortcomings of conventional iron fortification. It delineates the concept of food-to-food fortification, while precisely discussing about the best practices to be followed to address the possible challenges associated with this strategy. It also promotes the utilisation of underutilised iron rich foods to develop fortified foods and avert global food insecurity. Furthermore, it provides a summary of the studies conducted around the world to develop fortified foods using iron compounds and iron-rich foods, and to investigate their efficacy in managing iron deficiency anaemia.

1. Introduction

Anaemia is a condition diagnosed by reduced levels and atypical morphological characteristics of erythrocytes, or by insufficient blood haemoglobin (Hb) levels in the human body. The reduced Hb levels have been recognised as a causal factor for an inadequate oxygen supply in the human body. This has been ascribed to suboptimal production of erythrocytes (erythropoiesis), amplified erythrocyte annihilation, loss of blood, or due to combination of all these aspects (da Silva Lopes et al., 2018). World Health Organisation (WHO) defines anaemia as Hb levels less than 13.0 g/dl in men and less than 12.0 g/dl in women of reproductive age (WRA) (World Health Organization, 1972). The global burden of anaemia among all age groups was reported to have dropped by 4.2 percentage points, i.e., from 27% in 1990 to 22.8% in 2019 (Gardner and Kassebaum, 2020). Although, the global prevalence has declined over nearly three decades, a rise in the total number of anaemia cases by 0.32 billion, that is from 1.42 billion cases (1990) to 1.74 billion cases (2019) was reported. In 2019, the maximum burden of anaemia was reported in children below the age of 5 years (39.7%). The global age-standardised point prevalence of mild, moderate, and severe anaemia was reported as 54.1%, 42.5% and 3.4% cases, respectively. Furthermore, global anaemia was accounted for 58.6 million Disability Adjusted Life Years in 2019. Reportedly, the maximum age-standardised point prevalence of anaemia was found in Western [40977.0 (95% UI: 39,789.3–42,154.8)] and Central [36861.4 (95% UI: 35,218.3–38,434.2)] Sub-Saharan Africa as well as South Asia [41646.1 (95% UI: 41,034.3–42,208.3)] (Gardner and Kassebaum, 2020). Based on National Family Health Survey (NFHS) – 4 (2015–16), anaemia affected 53% WRA (15–49 years), 23% men and 50% pregnant women in India. During the same period, Government of India committed to Global
The drivers of anaemia include nutritional deficiencies, disease conditions, or genetic ailments. Iron deficiency (ID) has been recognised as the chief cause of anaemia, which has been approximated to account for nearly 50% of gross anaemia cases (Stevens et al., 2013; Petry et al., 2016). Primarily, insufficient dietary iron intake has been considered as the leading cause of poor erythropoiesis and Hb production. Reportedly, diets in various low- and middle-income nations are micronutrient deficient. Lack dietary diversity and possess high levels of antinutrient factors (ANFs) like phytates, tannins, which compromise iron absorption in the body (World Health Organization, 2017).

There exist a variety of “food-based strategies” to alleviate anaemia which focus on enhancing the accessibility as well as consumption of a diverse and micronutrient rich diet (World Health Organization, 2017). Additionally, these strategies aim at augmenting bioavailability of nutrients present in the diet by incorporating constituents which promote nutrient absorption or by employing food processing or storage strategies that minimise the adverse effects caused by ANFs. Food-based strategies including fortification and bio-fortification also focus on increasing the reachability of micronutrient rich foods, specifically for those at higher risk of anaemia (World Health Organisation and Food and Agricultural Organisation (FAO), 2006). Based on recommendations provided by World Health Organisation and Food and Agricultural Organisation, 2006, there are four approaches that aim at alleviating micronutrient deficiencies – dietary diversification, supplementation, food fortification and nutrition education. Although, of all the approaches, food fortification has been recognised as the most efficacious and economical approach, there are two chief challenges associated with conventional fortification that have been highlighted in the World Health Organisation and Food and Agricultural Organisation (2006) guidelines. These include - uniform dissemination of the fortifier in targeted foods, mostly staple foods such as cereals, oils, dairy products, beverages and condiments (salt and soy sauce); and internal (done by the producers themselves) and external (done by government authorities) evaluation of compliance of fortification regulations and standards by the producers, particularly in areas where staple food production is carried out by certain locally established small enterprises rather than large industrial enterprises (World Health Organisation and Food and Agricultural Organisation, 2006).

Recently, scientists have worked out a newer food-based strategy termed as Food-to-food fortification (FtFF). This strategy involves fortification of staple food vehicles with food-based fortifiers that are economical and locally available to the target population. With respect to iron rich food-based fortifiers, some of the underutilised foods include amaranth grains, sesame seeds, moringa oleifera, and finger millet (Orsango et al., 2020; Riziki, 2020; Boateng et al., 2019; Singh and Baruah, 2020). For instance, a growing inclination towards the utilisation and promotion of underutilised crops has been observed owing to their nutritional richness (Deedi Sogbohossou et al., 2020). As defined by Global Facilitation Unit for underutilised species, underutilised crops are those plant crops that have remained un tapped to promote food security and alleviate poverty. Most underutilised crops are nutrient rich; possess several potential health and nutritional benefits; and hold the ability to reduce malnutrition (Singh and Premavalli, 2020; Has and Arestingsih, 2020; Orsango et al., 2020; Singh and Baruah, 2020). Although, these promising crops are locally available and withhold various other nutritional, ecological, and fiscal benefits, their utilisation in daily diet across the world has remained a challenge ascribing to lack of awareness about their nutritive and fiscal benefits among the population; and overemphasis given to high yielding but less nutritious staple crops like rice, maize, and cassava (Teye et al., 2020; Padulosi et al., 2013). FtFF holds the potential of amplifying the knowledge about the nutritive value of such crops and interactions between different compounds which impact the bioavailability of nutrients enabling a safe as well as efficacious implementation of this strategy at a commercial scale (Kruger et al., 2020).

This review paper discusses in detail the concept of conventional iron fortification and sheds light on the limitations associated with this approach. It emphasises on the importance of focusing on FtFF, an emerging fortification technique and aims at promoting the utilisation of underutilised iron rich foods for the development of low-cost and nutrient-dense fortified foods that are accessible to wide population, especially those at higher risk but, belonging to low-income group.

To ensure a high-quality review of literature published on recent studies conducted to develop fortified food using iron fortifiers and iron rich plant-based food fortifiers, the methodology involved comprehensive and exhaustive search of peer-reviewed journals, reports, conference papers and proceedings. A variety of databases including Google Scholar, PubMed, Web of Science, and Scopus were surveyed for the selection of studies. The studies were selected if they were conducted to develop fortified foods using iron fortifiers and iron rich food-based fortifiers and if they investigated the effect of the developed foods on the iron status (Hb levels, serum ferritin levels, and other indices of blood profile), and anaemia prevalence of the target population (only human studies).

2. Strategies to combat iron deficiency anaemia

Iron, an indispensable micronutrient for human body serves various metabolic functions including carrying oxygen, synthesis of enzymes as well as DNA, erythropoiesis, and immune response (World Health Organization, 2017). Deficient iron reservoir in human body may cause iron deficiency anaemia (IDA); and may also contribute in compromised physical, cognitive, and immune development as well as functions (Patricia and Drakemith, 2016). Furthermore, ID in the absence of IDA has also been correlated with adverse outcomes in adults, which includes compromised immune system, lassitude, poor concentration (Musallam and Taher, 2018).

Dietary iron can be classified into - haeme iron (HI) and non-haeme iron (NHI), of which HI is more efficaciously absorbed in the human body. This is attributable to presence of certain haeme transporters which permit the permeation of HI across cell membranes and into the blood vessels. Contrariwise, NHI does not possess the ability to employ haeme transporters, instead, necessitating ferric iron reduction to ferrous iron prior to absorption (Dasa and Abara, 2018). The chief dietary contributors of HI include meat, fish, and poultry, which comprise nearly 55%-70% of the total dietary iron. On the other hand, NHI include cereals, pulses/legumes as well as elemental iron utilised in supplementation and food fortification (Park, 2019). HI constitutes only 10%–15% of dietary intake of iron in an omnivorous diet, it promotes at least 40% to the gross iron absorption in the body (Dasa and Abara, 2018). The constitution of HI and NHI in an individual’s diet is primarily contingent on the kind of diet and the proportion of animal source foods consumed.

The form of dietary iron, whether haeme or non-haeme is a critical determinant of iron status in comparison to the total intake of dietary iron (Dasa and Abara, 2018). The inclusion of “iron absorption enhancers” in the diet, which are foods rich in citric (such as citrus fruits, guava, germinated pulses), ascorbic, or malic acid and have been reported to enhance iron absorption from foods rich in NHI (Nair and Augustine, 2018). Besides, various food processing strategies have also
been studied over the past decades which aid in augmenting iron bioavailability of foods. These include germination, soaking, fermentation, and thermal or mechanical processing (Suma and Urooj, 2014; Gupta et al., 2015; Samitiy et al., 2021). Furthermore, the consumption of “iron inhibitors” like foods rich in polyphenols (red wine, tea, cocoa or coffee) along with meals, may also reduce iron absorption in the body (Piskin et al., 2022).

It has also been recommended that all the approaches recommended by World Health Organisation and Food and Agricultural Organisation (2006) should be considered complementary and may be employed individually or in combination with other approaches depending upon the specific necessities of the target population. Oftentimes, among the three approaches directed towards enhanced micronutrient intake, micronutrient supplementation programs result in rapid improvement in the micronutrient status of targeted populations, while food fortification results in less expeditious, but a more sizeable and persistent effect. Dietary diversity, another food-based approach is considered as the most valuable and viable choice, however, its implementation requires longer duration (World Health Organisation and Food and Agricultural Organisation, 2006).

3. Food fortification

Food fortification involves adding at least one vitamin or mineral to foods which forms a part of a daily diet. It has been identified as cost-effective food-based approach which aids in combating micronutrient deficiencies by enhancing the nutritive value of the food supplied to the population (Bhatta et al., 2013). Evidently, food fortification has contributed to a significant surge in enhancing the availability of certain vital nutrients, like iron, vitamin A, iodine, and folate (Beal et al., 2017). Regular consumption of fortified staple foods aids in the consistent supply of nutrients without impediments caused from seasonal availability of foods. Veritably, widely consumed foods like wheat, rice, salt, and maize when employed as a vehicle for fortification can potentially augment the nutritional status of a huge population in a simple, efficacious, and economical way. This is known as “mass” or “universal fortification” (World Health Organization, 2017). Mass/universal fortification is particularly effectuated, ordained, and monitored by the government authorities World Health Organisation and Food and Agricultural Organisation (2006). Recently, a systematic review and meta-analysis conducted on large-scale food fortification programs validated the positive influence of fortification on nutritional as well as functional consequences (Keats et al., 2019). This was evident, especially with respect to a decline in the burden of vitamin A, iron, and iodine deficiency as well as anaemia among children and women. A substantial retardation in goitre and neural tube defects (NTDs) among children; and enhanced serum folate levels among WRA was also observed. Reportedly, a significant reduction in the odds of anaemia (34%), goitre (74%) and NTDs (41%) has been ascribed to the implementation of population-wide fortification programs (Keats et al., 2019).

There exist different methods of food fortifications, namely - mass fortification, targeted fortification, “point-of-use fortification” or home fortification, and biofortification. Generally, mass fortification isadopted in cases where a sizeable population suffers from a micronutrient deficiency or is at-risk of becoming micronutrient deficient (World Health Organisation and Food and Agricultural Organisation, 2006). Contrariwise, targeted fortification aims at augmenting the micronutrient intake of a target group by fortifying food vehicles while ensuring that the entire population remains unaffected. This method of fortification is very helpful in cases where specific micronutrient needs of a target group cannot be met via mass fortification alone. The examples for this method include fortified complementary foods, fortified foods for emergency/school feeding or to feed refugees (World Health Organisation, 2001). “Point-of-use” or “home” fortification, another fortification technique involves immediate addition of fortifiers in either powdered or lipid-based form to the food before consuming it, hence, it derives its name “point-of-use”. This technique is mostly adopted in home, school, and institutional settings during the meal preparation at site. The powdered fortifiers employed in this technique are single-dose sachets comprising powdered vitamins and minerals which are sprinkled upon foods consumed at any settings – home, school, or any other site (Zlotkin et al., 2005; World Health Organization, 2016). The fortifiers present in lipid-based form, known as lipid-based nutrient supplements (LNS) are composed of a variety of vitamins and minerals in combination with energy, protein, and essential fatty acids. Although, a major portion of energy in LNS is derived from fat, the total calories provided by LNS utilised for the purpose of home-fortification is nearly 120 kcal from a 20 g “dose”. Reportedly, point-of-use fortification using multiple micronutrient powders is an efficacious technique to alleviate anaemia and enhancing iron stores among children below 2 years and between 2 and 12 years (De-regil et al., 2011; De-Regil et al., 2017). Additionally, this technique reduces the challenges associated with shelf stability and sensorial modifications such as rancidity or modifications in taste or appearance (World Health Organization, 2017). Another fortification technique is biofortification which involves enhancing the nutritional quality of crops by indirectly adding nutrients by means of modern biotechnology or conventional plant-breeding or agronomic practices. Furthermore, biofortifications help in targeting the LIG that consume a crop as a staple food. Biofortification also entails low recurrent expenses once the crop seeds are developed. Despite significant expense of fertilisation incurring every year, biofortified crops have been considered as sustainable crops as these can be cultivated every year even when funding from government or international agencies declines. In the past few years, crops have been biofortified with iron, zinc, carotenoids, as well as proteins (World Health Organization, 2017).

In 1980, the Food and drug administration established Food Fortification Policy which was guided by six fundamental principles - (i) in the absence of fortification the nutrient intake is lower than the desirable content for a considerable fraction of the population, (ii) the fortified food should be consumed in amount which contributes substantially in the nutrient intake of the population, (iii) the intake of supplementary nutrients from fortified foods should not create disequilibrium of vital nutrients in the body, (iv) the fortifiers to be added in a food should remain stable under storage as well as usage conditions, (v) the nutrients added to the food should be biologically available, and (vi) the fortifiers added to a food should not cause potential toxicity in the human body (Food and Agriculture Organization of the United Nations/World Health Organization, 1987). Additionally, the primary prerequisite for the achievement of any fortification program is an exemplified requirement to augment the intake of a vital nutrient in population groups. This requirement may be explained with biochemical/chemical data providing information about nutritional status, data on dietary patterns, exhaustive data on dietary intakes of micronutrients of interest (World Health Organisation and Food and Agricultural Organisation, 2006).

The process of food fortification involves identification of foods commonly consumed by a population which can be employed as food vehicles for one or more essential nutrients. World Health Organisation and Food and Agricultural Organisation (2006) has recommended to undertake dietary surveys in population groups to identify the intake of micronutrients and staple foods that can serve as potential food vehicles to supply healthy levels of nutrients to regular consumption of fortified food vehicles. It is also critical to consider variation in consumption of foods to ensure food safety of individuals at higher and lower end of the scale. Various factors such as nutritional requirements and deficiencies among the population; consumption profile of the potential food vehicle; bioavailability, cost, sensory acceptability as well as storage stability of the fortifier, must be taken into account to develop a suitable combination of nutrient and food vehicle (World Health Organization, 2009). The examples of commonly used food vehicles are wheat, rice, maize.
Iron compounds as fortifiers

Iron fortification involves the addition of iron into different food matrices to enhance the nutritive value of food and to potentially increase iron intake of the population (WHO, 2011). Although, fortification is an easy, cost-effective, and viable technique, fortifying foods with iron is a challenging task. This can be ascribed to the highly reactive and oxidative nature of iron which is contingent on temperature as well as air which leads to undesirable sensory modifications and reduce the quality and shelf life the food (Kumari and Chauban, 2022). Therefore, to identify a form of iron with sufficient bioavailability which when supplemented in appropriate quantity in food is not rejected as a result of unacceptable sensory modifications or antagonistic gastrointestinal response (Hurrell et al., 2004). Nevertheless, like any other micronutrient fortification, the effectuality of iron fortification strategy is contingent on three vital factors - burden of nutritional deficiency, selection of food vehicle, and iron compound to be selected as a fortifier. In addition, consumption of nutritional and antinutritional components present in diet also substantially contribute to enhancing or inhibiting absorption of iron in the body, respectively. Even though, there exist several iron compounds that are suitable fortifiers, the chief challenge faced during iron fortification is to locate the one with superior bioavailability, solubility, and minimum impact on the organoleptic properties of the food vehicle (Kumar et al., 2020). The proportion of iron fortifier to be added in the food is another essential factor to be determined to ensure food safety and efficacious outcomes of iron fortification (World Health Organization, 2009).

Barkley et al. (2015) utilised the existing national-level data of several countries to observe the decline in the anaemia prevalence among non-pregnant women post-implementation of fortification programmes involving fortification of flour with iron. The criteria for selection of the countries included – countries with at least one anaemia survey available before implementation of the programme and at least one survey available after at least two years of programme implementation. Table 1 provides the data from various countries where fortification programmes providing flour fortified with iron exhibited a substantial decline in the burden of anaemia among non-pregnant women (Barkley et al., 2015).

5. Iron compounds as fortifiers

Iron compounds employed for fortification of foods are inorganic salts that are broadly categorised into – water soluble and water insoluble based on their ability to dissolve in water. Generally, iron compounds with high water solubility possess highest bioavailability,
et al. (2003), and World Health Organisation and Food and Agricultural Organisation (2006). The negative synergy occurring between iron compounds and food interactions between iron and food constituents, and to further decline fortification of cereal flours, dry food products like pasta and milk powder-based infant foods. Another form of iron phosphate is available as several hydrates—anhydrous (33% iron), mono-, di-, and trihydrates (Sodium ferredetate-Na Fe EDTA). Hence, it is essential to evaluate its feasibility as a fortifier prior to its utilisation (World Health Organisation and Food and Agricultural Organisation, 2006). The wide variance in the bioavailability of different iron compounds results in major heterogeneity in the levels of fortification. Generally, bioavailability of iron fortifiers is estimated against ferrous sulphate (Relative Bioavailability (RBV) = 100) (Hurrell, 2021).

Evidently, absorption of iron from water soluble and other iron fortifiers that are entirely soluble in the gastric juice produced during digestion, is correspondent to dietary iron absorption, necessary to fulfil the requirements. This iron requirement can be met with equal amounts of ferrous sulphate, ferrous gluconate, or ferrous fumarate. However, the fortification level of ferric pyrophosphate (FPP) and electrolytic iron should be twice than that required for ferrous sulphate as a result of their lower RBV (ca. 50), while for ferric sodium ethylenediaminetetraacetate (NaFeEDTA) and ferrous bisglycinate (FBG) the fortification level should be lower than that for ferrous sulphate due to their higher RBV (Hurrell, 2018). In comparison to ferrous sulphate, iron absorption from iron fortifiers insoluble in water varies from nearly 20% to 75%.

Table 2
Key characteristics of iron compounds commonly used for food fortification: solubility, bioavailability and cost adapted from Hurrell et al. (2002), Swain et al. (2003), and World Health Organisation and Food and Agricultural Organisation (2006).

| Compound | Iron Content (%) | RBV<sup>a</sup> | Relative cost (per mg iron)<sup>b</sup> |
|----------|----------------|---------------|-------------------------------------|
| Water soluble | | | |
| Ferrous sulphate, 7H₂O | 20 | 100 | 1.0 |
| Ferrous sulphate, dried | 33 | 100 | 1.0 |
| Ferrous bisglycinate | 20 | >100<sup>c</sup> | 17.6 |
| NaFeEDTA | 13 | >100<sup>c</sup> | 16.7 |
| Water insoluble, poorly soluble in dilute acid | | | |
| Ferrous fumarate | 33 | 100 | 2.2 |
| Water insoluble, soluble in dilute acid | | | |
| Ferric pyrophosphate | 25 | 21–74 | 4.7 |

<sup>a</sup> In comparison with hydrated ferrous sulphate, among adult. Values in parenthesis obtained with reference from studies conducted on rats.

<sup>b</sup> In comparison with dried ferrous sulphate. Per mg of iron, the cost of hydrated and dry ferrous sulphate is similar.

<sup>c</sup> Absorption is 2–3 folds efficient in comparison to ferrous sulphate in food vehicles with high phytic acid content.

Table 3
Levels of iron to consider for adding to fortified maize flour/corn meal and wheat flour adapted from World Health Organization (2009) and World Health Organization (2018).

| Food | Flour-extraction rate | Iron compound | Nutrient concentration to be added by estimated availability/consumption (mg nutrient/kg flour) |
|------|----------------------|---------------|--------------------------------------------------------------------------------------------------|
|      |                      |               | <75 g/day | 75–149 g/day | 150–300 g/day | >300 g/day |
| Maize flour and corn meal | Low | NaFeEDTA | 40 | 40 | 20 | – |
|                           |     | Ferrous sulphate | 60 | 60 | 30 | – |
|                           | High | NaFeEDTA | 40 | 40 | 40 | – |
|                           |     | Ferrous fumarate | 60 | 60 | 60 | – |
| Wheat flour               | Low  | NaFeEDTA | 40 | 40 | 20 | 15 |
|                           |     | Ferrous sulphate | 60 | 60 | 30 | 20 |
|                           | High | NaFeEDTA | 40 | 40 | 20 | 15 |

Note: <sup>a</sup> added at a higher level to account for less bioavailability.

However, they are also extremely reactive with food (Henare et al., 2019). Usually, the water-soluble iron compounds are employed for the fortification of cereal flours, dry food products like pasta and milk powder, and milk powder-based infant foods. Another form of iron compounds are encapsulated forms, which are coated to prevent the interactions between iron and food constituents, and to further decline or completely avoid any organoleptic alterations in the fortified foods. The negative synergy occurring between iron compounds and food macronutrients lead to oxidative reactions which results in sensory alterations, specifically off-flavours. Additionally, the interactions between iron and minor food constituents like phenolic elements in tea, and coffee result in colour modifications in foods (World Health Organisation and Food and Agricultural Organisation, 2006).

By far, a variety of iron fortifiers, ferrous sulphate has been the most used water-soluble iron fortifier, attributing to its low-cost. Mostly, it has been employed in fortification of a variety of flours. Ferrous sulphate is available as several hydrates -anhydrous (33% iron), mono-, di-, and hepta-hydrates (20% iron). The former is readily dissolvable in water while, the latter dissolves steadily in water and results in minimum sensory alterations. Ferrous sulphate has been recommended as an iron fortifier to fortify low extraction wheat and maize flour (World Health Organization, 2009). An enhancement in iron status of women and adolescents fed with wheat flour products fortified with ferrous sulphate for almost 69 months was reported by efficacy studies conducted in countries like China, Thailand, Kuwait, and Morocco (Hurrell, 2010; Bouhouch et al., 2016). A study also reported a decline in ID and IDA (38%–5% and 14%-3%, respectively) among Moroccan school children that were fed with wheat flour biscuits fortified with ferrous sulphate (8 mg Fe/day) for 28 weeks (Bouhouch et al., 2016). Nevertheless, ferrous sulphate can result in rancidity ascribing to its physical properties, climatic conditions, and the level of fat in the flour (food vehicle). Hence, it is essential to evaluate its feasibility as a fortifier prior to its utilisation (World Health Organisation and Food and Agricultural Organisation, 2006).
Table 5
Summary of studies conducted to evaluate the efficacy of food products fortified using iron compounds as fortifier (2017–2020).

| Study setting          | Food vehicle and fortifier | Study design and respondents | Outcomes                                                                                                                                                                                                 | Reference |
|------------------------|----------------------------|------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| East Cameroon, Africa  | **Food vehicle:** Wheat-based infant cereal (IC) | **Respondents:** Children (18–59 months) | - Duration: 6 months  
- Participants divided into Intervention (IG) and control groups (CG)  
- Both the groups received usual diet (50g servings/day).  
- IG received two servings of micronutrient-fortified IC (providing 3.75 mg iron/serving)  
- CG received the same IC without iron fortification.  
- IG was divided into 2 groups (IF and HIF)  
| - Baseline adjusted mean Hb: higher in IG (10.0 g/dl) than CG (9.7 g/dl) (p = 0.023).  
- Ferritin adjusted for CRP: higher in IG (16.1 μg/L) than CG (9.5 μg/L) (p < 0.001).  
- Serum iron: Higher in IG (14.5 μg/dl) than CG (11.2 μg/dl) (p = 0.001).  
- Transferrin saturation at 6 months: Higher in IG (19.0) than CG (10.7) (p < 0.001).  
- The prevalence of anaemia, iron deficiency, and IDA at 6 months: significant reduction in IG than CG (all p < 0.01).  
- Weight-for-age z-scores at 6 months: Higher in IG (p = 0.016) than CG.  
- Improved dietary iron intake in IG than CG (p = 0.024).  
- 20% reduction in anaemia prevalence in IG by 4.8% (39%-34%).  
- A significant reduction (p = 0.035) in anaemia after 12 months of FFR consumption.  
- DID in mean Hb level after 12 months of FFR consumption was significant (p = 0.002).  
- Hb: increase greater among boys (0.72 g/dL) than girls (0.38 g/dL).  
- Haematocrit: Increase in IF group (1.83%) (p = 0.0248). | Elloe et al. (2020) |
| Bangladesh             | **Food vehicle:** Rice | **Respondents:** Women (15–49 years) | - Duration: 12 months  
- Participants divided into Intervention (IG) and control groups (CG)  
- IG received 30 kg Fortified rice (FRR)  
- CG received 30 kg non-FR for every month for a year.  
- IF rice was rinsed and cooked (RC), fried and cooked (FC), or soaked and cooked with extra water (SCW), cooked in a lab (C-Uganda) and households using traditional cooking method (TC-Uganda) for iron retention evaluation  
| - Duration: 6 months  
- Respondents divided into IG and CG - Soluble transferrin receptor: Lower in IG (1.70 μg/l) than CG (2.07 μg/l) (p = 0.014). - Iron retention, from highest to lowest, was (C), (RC), (FC), (C-Uganda), (CW), (SCW) and (TC-Uganda). | Ara et al. (2019) |
| Los Angeles and Uganda | **Food vehicle:** Rice | **Respondents:** Women with IDA (18–50 years) (n = 17) | - Duration: 2 weeks  
- Fortified rice contained 18 mg/d IF or 0.5 mg/d iron  
- 9 women received 100 g/d of rice (2 cooked 0.75 cup servings) for 2 weeks containing 8 mg/d (IF)  
- 6 women received 100 g/d of rice (2 cooked 0.75 cup servings) for 2 weeks containing 0.5 mg/d iron (non-IF)  
- IF rice was rinsed and cooked (RC), fried and cooked (FC), or soaked and cooked with extra water (SCW), cooked in a lab (C-Uganda) and households using traditional cooking method (TC-Uganda) for iron retention evaluation  
| - Average Hb level increased by 0.136 g/dl ( Kr 0.980) higher in IG than CG (P < 0.003).  
- Mean Hb: higher in IG (118.1 g/l) than CG (109.5 g/l) at age 12 months.  
- Hematocrit: Increase in IF group (1.83%) (p = 0.0248).  
- 20% reduction in anaemia prevalence (80%–60%), no differences between groups.  
- Hb: increased by 0.55 g/dL in IG than CG.  
- Han: increase greater among boys (0.72 g/dL) than girls (0.38 g/dL).  
- Haematocrit: Increase in IF group (1.83%) (p = 0.0248). | Losso et al. (2017) |
| Senegal                | **Food vehicle:** Yoghurt | **Respondents:** Children (24–59 months) (n = 449) | - Duration: 12 months  
- Fortified yoghurt, and Behaviour change communication (BCC) campaign focusing on anaemia prevention.  
- CG only receiving BCC only) after 1 year  
- Mean Hb: higher in IG (118.1 g/l) than CG (109.5 g/l) at age 12 months.  
- Hematocrit: Increase in IF group (1.83%) (p = 0.0248).  
- 20% reduction in anaemia prevalence (80%–60%), no differences between groups.  
- Hb: increased by 0.55 g/dL in IG than CG.  
- Han: increase greater among boys (0.72 g/dL) than girls (0.38 g/dL).  
- Haematocrit: Increase in IF group (1.83%) (p = 0.0248). | Le Port et al. (2017) |
| National Studies      | **Food vehicle:** Rice-based cereal | **Respondents:** Infants (6 months and 12 months old) (n = 160) | - Duration: 12 months  
- Respondents divided into IG and CG  
- IG received 50 g/d of rice-based cereal providing 3.75 mg iron/day ferrous fumarate for 6 months  
- CG did not receive any treatment  
- Mean Hb: higher in IG (118.1 g/l) than CG (109.5 g/l) at age 12 months.  
- Geometric mean serum ferritin: Higher in IG (27.0 ng/ml) than CG (20.3 ng/ml) (p = 0.085).  
- Soluble transferrin receptor: Lower in IG (1.70 mg/l) than CG (2.07 mg/l) (p = 0.014).  
- Anaemia and ID were lower in the IG (23% and 17%, respectively) than CG (40% and 45%, respectively) (p = 0.003 and p = 0.007).  
- Bayley-III scores for language (P = 0.003), motor development (P = 0.018), social-emotional (P = 0.004), and adaptive behaviour (P < 0.001), not cognitive development (P = 0.980) higher in IG than CG.  
- Mean Hb: higher in IG (118.1 g/l) than CG (109.5 g/l) at age 12 months.  
| Awashti et al. (2020) |
| Lucknow, Hyderabad, and Kolkata | **Food vehicle:** Salt | **Respondents:** School children (age 7 years) (n = 108) | - Duration: 12 months  
- Respondents divided into IG and CG  
- IG provided with double fortified salt (DFS)  
- CG did not receive any treatment and continued to use the conventional iodized salt  
- Mean Hb: higher in IG (118.1 g/l) than CG (109.5 g/l) at age 12 months.  
| - Average Hb level increased by 0.136 g/dl (Kr 0.980).  
- 20% reduction in anaemia prevalence in IG than CG.  
- The likelihood of a child to suffer from mild anaemia (Hb ≥ 11 & < 11.5 g/dl) reduced by 6.0% on average (equivalent to a reduction mild anaemia burden by nearly 30%).  
- Improved dietary iron intake in IG than CG (p < 0.001). | (continued on next page) |
| Bihar                  | **Food vehicle:** Salt | **Respondents:** Encapsulated ferrous fumarate | - Duration: 12 months  
- Respondents divided into IG and CG  
- IG provided with double fortified salt (DFS)  
- CG did not receive any treatment and continued to use the conventional iodized salt  
| - Average Hb level increased by 0.136 g/dl (Kr 0.980).  
- 20% reduction in anaemia prevalence in IG than CG.  
- The likelihood of a child to suffer from mild anaemia (Hb ≥ 11 & < 11.5 g/dl) reduced by 6.0% on average (equivalent to a reduction mild anaemia burden by nearly 30%).  
- Improved dietary iron intake in IG than CG (p < 0.001). | (continued on next page) |
| West Bengal            | **Food vehicle:** Salt | **Respondents:** Women (18–55 years); Not pregnant/lactating, not severely anaemic (Hb < 8.0 g/dL) (n = 245) | - Duration: 7.5–9 months  
- Respondents divided into IG and CG  
| - No other dietary or anthropometric differences could be attributed to treatment. | Venkatramanan et al. (2017) |
less impact on the organoleptic characteristics of food vehicles, at the levels currently used. Despite that, they are still considered as a fallback, particularly in regions where the target population’s diet is rich in iron absorption inhibitors. To utilise a water-insoluble iron fortifier, it is vital to choose a fortifier with absorption equivalent to at least 50% to that of ferrous sulphate, and two folds higher than required to compensate for the reduced absorption rate (World Health Organisation and Food and Agricultural Organisation, 2006). Table 2 provides key characteristics (solubility, bioavailability, and cost) of certain commonly used iron compounds to produce fortified foods.

### Table 6

**Summary: Food fortification.**

| Study setting | Food vehicle and fortifier | Study design and respondents | Outcomes | Reference |
|---------------|---------------------------|-----------------------------|----------|-----------|
| Darjeeling    | **Food vehicle:** Salt    | **Fortifier:** Potassium iodate and micro-encapsulated ferrous fumarate | **Respondents:** Women (18–55 years); Not pregnant/lactating, 66% iron deficient and 49% anaemic (n = 126) | - Significant improvement in iron status and perceptual, attentional, and mnemonic function in IG than CG (percentage of variance: 16.5%); - The amount of change in perceptual and cognitive performance significantly (P < 0.05) related to the amount of change in blood iron markers (mean percentage of variance: 16.0%) and baseline concentrations of blood iron markers (mean percentage of variance: 25.0%) | Wenger et al. (2017) |

WHO has issued guidelines recommending levels of iron compounds to be construed when utilising them for the fortification of worldwide common staple foods -maize flour/corn meal (World Health Organization, 2009; World Health Organization, 2016) and wheat flour (World Health Organization, 2009). These levels were based on extraction rate, chemical form and estimated per capita consumption of flours. Based on WHO guidelines, Table 3 provides the levels of iron fortifiers for flour fortification, which should be referred for guidance and levels of nutrients should be adapted based on the needs of a country’s population. The estimated levels depicted in the table consider only maize flour/-corn meal and wheat flour as the chief food vehicle for any public health program. However, in fortification programs where other food vehicles and micronutrient interventions are being implemented jointly and efficaciously, the iron levels for fortification suggested in the table must be modified as required. Different countries have their own standards for the iron fortification of different foods. In India, for instance, Food Safety and Standards Authority of India (FSSAI) issued a regulation titled ‘Food Safety and Standards (Fortification of Foods) Regulations, 2016 to which all Food Business Operator must comply (FSSAI, 2016). Table 4 provides iron fortification standards provided by FSSAI to fortify foods like salt, atta/maida, rice, cereal-based products (breakfast cereals, pasta, and noodles) and bakery products (bread, biscuits, rusk, and buns).

### 5.1. Ferric pyrophosphate (FPP)

FPP has been considered as a feasible iron fortifier ascribing to its minimal effect on the organoleptic properties of the food vehicle. It has been widely used in the fortification of rice grains by employing the “kernel-premix technique” which involves coating (one of three methods for fortifying rice kernels) of kernel/grain with fortifier, salt and margarine (Moretti et al., 2005; Zimmermann, 2004; Andersson et al., 2010). Nevertheless, it is a water-insoluble compound and is relatively costlier than ferrous sulphate and ferrous fumarate. Furthermore, attributing to its poor solvability in gastric juice, only 50% of it is absorbed in the body. It is mostly utilised in the fortification of foods sensitive to colour modifications like bouillon cubes, drinking chocolate powders, as well as plant-based complementary foods (Hurrell, 2018).

- **Key characteristics**
  - Food fortification involves the addition of one or more micronutrient to a staple food like wheat, rice, and maize
  - It is a cost-effective, simple, and efficacious strategy to augment nutritional status of a population
  - It ensures consistent nutrient supply without obstructions caused due to seasonal food availability
  - Different methods of food fortification include - mass fortification, targeted fortification, “point-of-use fortification” or home fortification, and biofortification

### 5.2. Ferric sodium ethylenediaminetetraacetate (NaFeEDTA)

NaFeEDTA has been recognised as a suitable iron fortifier for food vehicles (cereals and legumes) comprising phytic acid (World Health Organisation and Food and Agricultural Organisation, 2006; World Health Organization, 2009)). In such foods, fortification using NaFeEDTA results in two-to-four-fold higher iron absorption as compared to ferrous sulphate (World Health Organisation and Food and Agricultural Organisation, 2006). Additionally, EDTA also helps in enhancing the absorption of dietary iron. Although, it may lead to colour modification in certain food vehicles, it does not stimulate fat oxidation in flours derived from cereals. Besides fortification of cereal-based products, NaFeEDTA...
Table 8  
Summary of studies conducted to evaluate the efficacy of food products fortified using iron rich food-based fortifier (2017–20).

| Study setting | Food vehicle and fortifier | Study design and respondents | Outcomes | Reference |
|---------------|----------------------------|------------------------------|----------|-----------|
| **International Studies** | | | | |
| Ethiopia | **Food vehicle**: Bread | **Respondents**: Children (2–5 years); with Hb < 110 g/L (n = 100) | - Anemia prevalence significantly lower in AG (32%) than MG (56%) | Orsango et al. (2020) |
|                      | **Fortifier**: Amaranth and maize | **Duration**: Six months | - HB concentration estimate of beta coefficient was significantly higher in AG than MG (p < 0.01). | |
|                      | | - Respondents divided into amaranth (AG) and maize group (MG). | - No significant difference between groups in ID | |
|                      | | - AG received bread with 70% amaranth grain and 30% mashed chick peas. | | |
|                      | | - MG received bread with 100% maize | | |
| Kenya | **Food vehicle**: Vegetable mix | **Respondents**: Adolescent girls (Hb < 11.9 mg/dl) (n = 32) | - Mean baseline HB: Lower in IG (10.5 g/dl) than CG (11.2 g/dl) (difference not significant (p = 0.052) | Riziki (2020) |
|                      | **Fortifier**: Bubub | **Duration**: 1 month | - Post 30 days feeding trial 14 girls representing 45.2% of the adolescent girls achieved normal HB (≥11.9 g/dl). | |
|                      | | - Respondents divided into IG and CG. | - Mean final HB: IG (11.6 g/dl) and CG (11.8 g/dl) with a mean change of 1.1 g/dl and 0.6 g/dl respectively significant at (p = 0.045) | |
| Malawi | **Food vehicle**: Ready-to-use therapeutic food (RUTF) | **Respondents**: Children (6–59 months old), severely acute malnutrition (n = 389) | - ANAemia prevalence (at discharge): Least for MSMS-RUTF (12.0%), FSMS-RUTF (18.2% MSMS-RUTF) and P-RUTF (24.5%) (p = 0.023) | Akomo et al. (2019) |
|                      | **Fortifier**: Soybean, maize, and sorghum | **Duration**: 21 days | - IDA prevalence (at discharge): Least for FSMS-RUTF (7.9%), MSMS-RUTF (10.9%) and P-RUTF (20.5%) (p = 0.028) | |
|                      | | - IG received mixed vegetables enriched with 10g soybean powder/225g serving | - SMS-RUTF displayed increase in body iron stores among the iron deplete at admission (6.2, 3.2, 2.2 for the same arms; p = 0.045) | |
|                      | | - CG received vegetables with soybean powder | | |
| Ghana | **Food vehicle**: Complementary food | **Respondents**: Infants (age 0–12 months), (n = 363) | - Anemia prevalence significantly lower in AG (32%) | Boateng et al. (2019) |
|                      | **Fortifier**: Moringa | **Duration**: 4 months | compared to P-RUTF, FSMS-RUTF had the highest adjusted recovery rate [OR (95%CI) = 0.3 (0.2–0.5) with p < 0.001 for FSMS-RUTF and 0.6 (0.3–1.0) with p < 0.068 for MSMS-RUTF]. | |
|                      | | - Responds divided into three arms | - HB: Highest increase in CF-35g group followed by the MS-5g | |
|                      | | - First arm received FSMS-RUTF with extruded soya, maize, and sorghum, and containing no milk | - MCL-35g group had the least increase in HB levels | |
|                      | | - Second group received MSMS-RUTF with extruded soya, maize, and sorghum, and 9% milk | | |
|                      | | - Third group received standard PM-RUTF with peanuts and dried skim milk and 28% milk | | |
| National Studies | Odisha | **Food vehicle**: Ladoo | **Respondents**: Children (7–9 years of age) (underweight-35.0%–30.0%, Grade-I and 5.0% Grade-II; 26.67% stunted; 58.33% wasted-46.67% mild and 11.67% moderate; 60.0% anaemic-50.0% mild and 10.0% moderate anaemic), (n = 60) | - Height: Significant improvement in EG (from 123.52 cm to 124.8 cm), | Singh & Baruah (2020) |
|                      | **Fortifier**: Bengal gram flour, rice flakes, ground nuts, and angingelly seeds | **Duration**: 6 months | - Mean final Hb: IG (11.6 g/dl) and CG (11.8 g/dl) | |
|                      | | - Respondents were divided into experimental (EG) and control (CF) groups | - Mean final Hb: IG (11.6 g/dl) and CG (11.8 g/dl) | |
|                      | | - EG received laddo for 6-month, CG did not receive any treatment | - HB level: Significant increase in EG (from 11.38 g/dl to 12.57 g/dl) | |
| Udupi | **Food vehicle**: Porridge | **Respondents**: Adolescent girls, (n = 60) | - HB: Significant increase in IG after 90 days (11.3 g/dl to 12.54 g/dl) (p < 0.0001) | Karkada et al. (2019) |
|                      | **Fortifier**: Ragi | **Duration**: 90 days | - No statistically significant differences between IG and CG for mean corpuscular Hb, mean corpuscular Hb concentration, mean corpuscular volume, red cell distribution width, BMI, and scholastic performance. | Dhore (2018) |
|                      | | - Respondents were divided into IG (HB-12 to 12.5 g %) and CG (HB-10 to 11.9g%) | - Mean HB level of IG: initially –9.15 g/dl and at the end of study –9.81 g/dl (difference = 0.66 g/dl, significant at 1%) | |
|                      | | - IG received ragi porridge for 90 days | - Mean HB level of CG: initially –9.19 g/dl and at the end of study -9.20 g/dl (difference = 0.01 g/dl, mean difference of HB level was non-significant) | |
| Akola | **Food vehicle**: Ladoo | **Respondents**: Adolescent girls (16–18 years; moderate anaemia) (n = 60) | - Height: Significant improvement in EG (from 22.39 kg to 23.63 kg) | Jain et al. (2017) |
|                      | **Fortifier**: Rice flakes, soybean, wheat, Bengal gram, ginja, seeds, garden cress seeds, and jaggery | **Duration**: 90 days | - Height: Significant improvement in EG (from 22.39 kg to 23.63 kg) | |
|                      | | - Respondents were divided into IG and CG | - Height: Significant improvement in EG (from 22.39 kg to 23.63 kg) | |
|                      | | - IG were fed two laados daily (80 g) for 90 days | - Height: Significant improvement in EG (from 22.39 kg to 23.63 kg) | |
| Ludhiana | **Food vehicle**: Biscuits | **Respondents**: Children (7–9 years of age; underweight and anemia, according to WHO) (n = 60) | - Steep increase (p ≤ 0.05) observed in cereal, fat, and sugar post supplementation | Jain et al. (2017) |
|                      | **Fortifier**: Garden cress | **Duration**: 3 months | - 3.56 and 0.87% gain in weight and height (p ≤ 0.05) respectively | |
|                      | | - IG received biscuits (60 g) developed using roasted garden cress seeds for 3 months | - HB levels increased from 10.6 to 11 g/dl | |
|                      | | - CG received biscuits without garden cress seeds for 3 months | - Little improvement (p ≤ 0.05) in proteins, albumin, and other indices of blood profile and 9 subjects fell in non-anaemic category | |
has also been utilised in the fortification of soy and fish sauces where it has been observed that, in contrast to other water-soluble iron fortifiers, NaFeEDTA does not cause precipitation of the peptides. A meta-analysis study conducted on 16 Chinese studies to investigate the efficacy of NaFeEDTA-fortified soy sauce reported a positive impact of NaFeEDTA fortification on anaemia control in at-risk populations (Huo et al., 2015).

5.3. Ferrous fumarate

Ferrous fumarate, a dark red brown coloured iron compound is widely employed in the fortification of cereal-based complementary foods. Occasionally, it is also utilised to fortify cereal flours and chocolate drink powders. The poor solubility of ferrous fumarate in water results in minimum modifications in sensory characteristics of food vehicles. In most age groups except children with poor iron reservoir in body, the iron absorption from this compound is comparable to ferrous sulphate as it is soluble in gastric juice (Andersson et al., 2010; Harrington et al., 2011). Studies conducted in Mexico and Bangladesh on infants with low iron status reported 30%-35% iron absorption from ferrous fumarate (incorporated in test meals) in comparison to ferrous sulphate. These findings have been attributed to lower iron status among children which resulted in higher absorption of iron by increasing the cell response; reduction in the secretion of gastric acid secretion which led to retardation in ferrous fumarate dissolution; or effect of ascorbic acid addition on relative bioavailability (Sarker et al., 2004; Perez-Exposito et al., 2005).

5.4. Ferrous bisglycinate (FBG)

FBG is a ring-shaped compound comprising iron and two glycine molecules. It has been commonly utilised in Latin America to fortify dairy products like milk, and curd. In 2006, WHO recommended its utilisation to fortify beverages like milk and fruit juice (World Health Organisation and Food and Agricultural Organisation, 2006). It has been patented and manufactured by Albion Laboratories (Clearfield, UT, USA), and is nearly twenty-times costlier than ferrous sulphate per unit of iron (Hertrampf and Olivares, 2004). Since FBG is chiefly used as a fortifier in dairy foods targeted at children, its fortification level should essentially be derived in accordance with Estimated Average Requirement (EAR) of children to compensate the iron content lacking in their diet. In Costa Rica, a national fortification program supplied nearly 20% of the young child’s EAR for iron in the form of FBG through powdered and liquid milk, as well as maize flour, and additional 20% EAR in the form of ferrous fumarate through wheat flour. After six to seven years post its implementation, the program was reported to have resulted in 20 percentage points (27%-7%) decline in ID, and 15 percentage points (19%-4%) decline in anaemia among 17-year-old children (Martorell et al., 2015).

6. Recent research investigating efficacy of foods fortified with iron fortifiers in managing iron deficiency anaemia

Table 5 provides a summary of eight human studies (2017–20) conducted across the world that studied the efficacy of different types of iron compounds as fortifiers in varying food vehicles. The studies reported that intervention reported in significant improvement in mean Hb (Ekoe et al., 2020; Ara et al., 2019; Losso et al., 2017; Le Port et al., 2017; Awasthi et al., 2020; Kramer et al., 2018) serum ferritin (Ekoe et al., 2020; Awasthi et al., 2020), serum iron (Ekoe et al., 2020), haematoctrit (Losso et al., 2017), and soluble transferrin receptor (Awasthi et al., 2020). Additionally, they also reported a reduction in anaemia burden among intervention groups (IG) (Ekoe et al., 2020; Kramer et al., 2018) with higher reduction among boys than girls (Kramer et al., 2018). Only one study reported no significant difference in the reduction of anaemia prevalence among control group (CG) and intervention group (IG) (Le Port et al., 2017). Besides, interventions were also reported to be efficacious in improving dietary iron intake among children (Kramer et al., 2018), reducing the likelihood of childhood anaemia (Kramer et al., 2018), improving weight-for-age z scores (Ekoe et al., 2020); Bayley scores for language, motor development, socio-emotional and adaptive behaviour (Awasthi et al., 2020); and perpetual as well as cognitive development (Wenger et al., 2017) among children.

7. Challenges associated with conventional fortification

The iron status in the human body is regulated by a complex mechanism that maintains an equilibrium between iron absorption in the duodenum, iron salvaging by macrophages and iron storage, chiefly in the liver (Rybinka and Cairo, 2017). Currently, there exists no established biological mechanism to eliminate iron from the human body, and the presence of high levels of iron in the blood may result in toxicity. However, hepcidin, a hormone produced by hepatocytes has been reported to play a pivotal role in regulating the uptake and release of iron in tissues (Agarwal and Yee, 2019; Ganz and Nemeth, 2012). Hepcidin production is contingent on iron load, erythropoietic requisites, as well as inflammatory status (Agarwal and Yee, 2019). Hepcidin hormone inhibits absorption and mobilisation of iron from tissues and negatively regulates iron homeostasis (Ganz and Nemeth, 2012). This hormone is known to bind with an exporter transmembrane protein known as ferroportin which results to the protein degradation which further leads to obstructed iron release from target cells such as hepatocytes, macrophages as well as enterocytes (Ganz and Nemeth, 2012). Furthermore, recent research has also demonstrated the potential role of hepcidin in regulating body iron uptake by reduced expression of the genes responsible for iron absorption (Bergamaschi et al., 2017). Therefore, even though, iron fortification of staple foods as well as certain condiments has been recognised as a promising strategy to combat ID, concerns associated with the overdosage of iron have been raised by various researchers, which are required to be addressed vigilantly (Kumar et al., 2020). Serum ferritin levels greater than 20 μg/L in human beings has been correlated with suboptimal HI and NHI absorption. High iron levels in human body have also been regarded as a causal factor for severe epidemic malaria as it creates suitable conditions for the growth of pathogens. Furthermore, high iron content in body has been considered as a driver for metabolic diseases like diabetes mellitus, cardiovascular disease, as well as cancer (Basuli et al., 2014).

Reportedly, increase in iron levels resulting from in-home iron fortification (with high iron dose delivered through MNPs, which is comparable on a mg iron/kg body weight to the supplemental doses (2 mg/kg) that is given to older children) may aggravate the risk of elevated colonic iron levels among infants, and adversely affect the equilibrium of the gut microbiota and promote the growth of pathogenic microbes instead of potentially beneficial gut microbiota. Based on the results obtained from various research, the adverse impact associated with iron fortification on the gut microorganisms of infants can be effectively reduced by supplementing the infant formulas with prebiotic galacto-oligosaccharides (Paganini et al., 2016). In young children, multiple micronutrient supplementation has been reported to result in fever and diarrhoea. Iron fortification of food has also been associated with iron overload in individuals suffering from haemochromatosis (Kumar et al., 2020). The adverse effects of iron load can be minimised using dietary sources of iron chelators like milk, black tea, turmeric, and non-citrus fruits. Therefore, it is critical to maintain an equilibrium in iron uptake and utilisation with the help of effective implementation and regulation, and persistent monitoring. Additionally, monitoring the additional iron intake by non-targeted groups is a critical component for any intervention.

Mandatory fortification has been associated with positive outcomes in various developed nations. For instance, a study conducted in Australia on Aboriginal and non-aboriginal population reported 68% and 15% reduction in NTD prevalence, respectively, resulting from mandatory fortification (2010–2014) (D’Antoine and Bower, 2019).
Originally, one of the chief limitations of conventional fortification reported was the inflated cost of the fortified foods, which affected the food security and livelihoods of the lower-income populations who could not afford expensive foods, especially in developing nations which also lacked industrial concentration (Temple and Steyn, 2011; Bhugwat et al., 2014). However, recent studies across the globe including those conducted in India and Africa have reported an insignificant increase in the cost of foods (flour, milk, and salt) resulting from fortification (Fiedler et al., 2013; Tripathi and Mishra, 2020). Additionally, some countries have chosen to subsidise fortified foods fully or partly, for example, during 2008–2012, the Indian government executed a 4-year food-based safety net programme to supply fortified wheat flour via public distribution system (Fiedler et al., 2012; Chakrabarti et al., 2019). Yet another limitation associated with conventional fortification is the cost related to specific fortification strategy which would also vary. For example, the expenses of fortification done by employing encapsulation techniques may result in price hike of the commodity by 2–5% (Kumar et al., 2020).

There exist certain technical challenges associated with conventional fortification, which include - nutrient losses; exposure of fortified foods to sunlight during retail; irregular internal and external monitoring; as well as substandard quality control protocols followed by companies. Ensuring a regulatory monitoring system which intends to meet national fortification standards for developing fortified foods is another imperative challenge faced during conventional fortification (Method and Tulchinsky, 2015). This challenge is particularly faced in developing countries, which may not possess the resources for an effective monitoring of compliance of fortification regulations and standards by the producers, specifically in the presence of several operational small processing companies. It has been reported that the flow of funds required to conduct monitoring has a significant proportional impact on the efficacy of detecting and enforcement of noncompliant and under fortified products (Lutbringer et al., 2015). Challenges associated with conventional fortification like selection of suitable food vehicles, reaching the target populations, preventing overconsumption of fortified foods among non-target groups, and monitoring the nutritional status of the target populations are faced by all nations, where an attempt to fortify food is made to enhance nutrient consumption and nutritional level of the population (Dwyer et al., 2015). Table 6 provides a summary of key characteristics and best practices to address the challenges associated with food fortification.

8. Food-to-food fortification (FtFF)

To attain desirable food fortification, effective measures should be taken in food processing by employing advanced techniques; efficacious monitoring as well as quality control mechanism; quality disbursement facilities; supervisory sustenance; as well as by managing the market dynamics by enabling accessibility to food for lower-income population. Reportedly, both urban poor (Anand et al., 2019; Joshi et al., 2019) and rural poor (Pandey and Bardsley, 2019; Sani and Kemaw, 2017) populations in developing nations are exposed to the risk of food insecurity and limited access to fortified foods (Osendarp et al., 2018). This lack of access to nutritional diets and fortified foods has been correlated to the greater risk of developing micronutrient deficiencies (World Health Organisation and Food and Agricultural Organisation, 2006; Wimalawansa, 2013). Therefore, it is of paramount importance to discover a strategy which employs a fortifier that is financially as well as physically procurable and is utilised by the target population (Dwyer et al., 2015). Constant efforts are being made by the researchers to develop nutrient-rich, economical foods by employing FtFF strategy. Although, both conventional fortification and FtFF aim to enhance the nutritive value of the fortified foods, the chief difference between the two approaches is that FtFF aims to enhance nutrient content as well as bioavailability in foods by adding or replacing food ingredients (Teye et al., 2020).

8.1. Working definition of food-to-food fortification

FtFF is an emerging fortification technique which involves the enhancement in the content of the micronutrient of interest of a particular food by utilising nutrient rich, low-cost, and locally available foods (plant or animal) as a fortifier. Furthermore, it supplies additional nutrients present in the food-based fortifier, which helps in dietary diversification of the food (Teye et al., 2020; Uvere et al., 2010). Currently, there does not exist a scientific definition for FtFF given by WHO/FAO, and between two decades from the first to the most recent definitions, there have been a variety and at times discrepant definitions and uses of this term (Kruger et al., 2020). The most recently published working definitions of FtFF were provided by Chadare et al. (2019) as a technique that employs the use of a micronutrient rich, locally available and locally accessible plant or animal resource for fortification of other foods; and by Kruger et al., 2020 as an approach for the production of staple food products enriched with nutrients using micronutrient-rich fruit and vegetables. Therefore, FtFF, an incipient food-based strategy can be described as the incorporation of micronutrient-rich food/s to food formulations (at household or industrial level), or the substitution of foods that lack micronutrient/s or are rich in ANFs, for a significant enhancement in micronutrient/s bioavailability (Kruger et al., 2020).

8.2. Best practices to select food-based fortifier

The primary objective of FtFF is the elevation in micronutrient status of populations, particularly those with inadequate dietary micronutrient intake (Orsango et al., 2020; Riziki, 2020; Singh and Barua, 2020; Singh and Premavalli, 2020; Has and Aniestiningsih, 2020). Generally, to accomplish this goal, food-based fortifiers to be utilised should be considerably rich in the desired nutrient/s, possess micronutrient bioavailability enhancers, and/or minimal levels of antinutrients (Chadare et al., 2019; Kruger et al., 2020). The proportion of micronutrient-rich food to be added in a food vehicle to obtain significant increase in micronutrient level using this approach ranges from 1% to 50% and is contingent on the food vehicle and fortifier compatibility (Chadare et al., 2019). For example, 2% and 3% of dry Moringa oleifera leaves (DLMO) was found to be sufficient for augmenting the nutrient content of Labneh cheese and buttermilk, respectively, despite their lower proportion. However, reduction in the sensory attributes (flavour, body, texture, appearance, and overall sensory score) was reported with increasing proportion of DLMO (Saleem et al., 2013). Similarly, various studies have reported a desirable change in the organoleptic properties of the foods fortified by incorporating food-based fortifiers to a certain level (Nurjanah et al., 2021; Nurhanan et al., 2021; Bhuvaneshwari and Nazni, 2020).

To employ FtFF technique for the development of nutrient rich fortified foods, it is critical to make certain considerations of best practices to utilise food-based fortifier, especially plant-based fortifiers. As outlined by European Food Safety Authority and Food and Drug Administration, a plant-based fortifier should meet the criteria of “generally recognised as safe”. To ensure the quality and to eliminate risk associated with contamination or adulteration of a potential plant-based fortifier, the taxonomic identification of the plant including - identification (family, genus, and species of plant); portion of the plant to be utilised; its geographic origin and climatic conditions for its growth; cultivation practice employed; phytosanitary measures involved, i.e. use of pesticides and their levels; and postharvest handling must be noted (Kroes and Walker, 2004). Additionally, certain plant-based fortifiers possess considerable amount of ANFs that may inhibit the absorption of certain micronutrients. Therefore, during the selection of plant-based fortifier, a careful evaluation of the relative levels of micronutrients and ANFs present in fortifier and food vehicle is required (Kruger et al., 2020). Furthermore, since certain plant-based fortifiers also comprise a substantial levels of micronutrient bioavailability enhancers, such as...
ascorbic acid, a scrupulous investigation of levels of bioavailability enhancers to micronutrients is of utmost importance (Kruger et al., 2020). In addition, it is vital to ensure that the food being considered as a fortifier in a relatively cheaper staple food should be inexpensive and readily procurable to avoid unaffordability of the population to procure the fortified food (Kruger et al., 2020).

8.3. Utilisation of underutilised crops as food-based fortifier

Over the recent years, utilisation of underutilised plant species as a food-based fortifier has been recognised and much appreciated by the researchers. Underutilised crops are not only rich in nutrients but are also acclimatised to harsh and arid conditions and necessitate minimum agricultural inputs such as irrigation (IPGRI, 2002). The potential advantages of employing underutilised crops as a fortifier goes beyond the nutritional enhancement of the formulated food and maintaining dietary diversity. For instance, such crops require lower agricultural input i.e., they do not necessitate substantial employment of fertilisers, herbicides, pesticides, and other agricultural inputs (Aworh, 2018; Kasolo et al., 2018; Padulosi et al., 2013). They also require simple technology which is available even at rural or lower-income household (Ruel and Levin, 2000). Additionally, these crops hold the potential of alleviating food insecurity resulting from change in climatic conditions (Chandra et al., 2020). Underutilised crops are capable of growing on marginal lands and under abiotic stresses, unlike major crops like wheat and rice (IPGRI, 2002; Chandra et al., 2020) and hence, require environment-friendly ways to intensify agricultural produce (Mayes et al., 2012; Padulosi et al., 2013; Aworh, 2018), particularly during water scarcity (Baldermann et al., 2016; Mabhaudhi et al., 2019). Furthermore, the enhanced consumption of underutilised crops would also aid in the generation of income and prevention of their post-harvest losses (Teye et al., 2020; Chandra et al., 2020). Table 7 provides a summary of key characteristics and best practices to address the challenges associated with FtFF.

9. Recent research investigating efficacy of foods fortified with iron rich food-based fortifiers in managing iron deficiency anaemia

Table 8 provides a summary of eight studies (2017–21) conducted in Indian cities and countries across the world that studied the efficacy of different types of iron rich foods as fortifiers in varying food vehicles. The studies reported that intervention resulted in significant improvement in mean Hb (Orsango et al., 2020; Riziki, 2020; Boateng et al., 2019; Karkada et al., 2019; Jain et al., 2017), body iron store levels (Akomo et al., 2019), protein (Jain et al., 2017), albumin (Jain et al., 2017), and other blood profile indices (Jain et al., 2017). Additionally, they reported a reduction in anaemia burden among Ig's (Orsango et al., 2020; Akomo et al., 2019). Only one study reported no significant difference in the reduction of anaemia prevalence among CG and IG (Dhore, 2018). Besides, interventions were also reported to be efficacious in improving weight-for-age z scores among children (Jain et al., 2017; Singh and Baruah, 2020). However, the studies reported no significant improvement in reduction of ID (Orsango et al., 2020) and mean corpuscular Hb, mean corpuscular Hb concentration, red cell distribution, body mass index (BMI), and scholastic performance (Karkada et al., 2019).

The positive impact of FtFF on anaemia was also reported by an animal study conducted on four weeks old albino rats that were divided into three groups. Control and anaemia (An+) groups were fed with standard diet, and anaemic group were fed with 90% standard-diet and 10% biscuit with 15% beetroot pomace (AnB). Anaemia was induced by injecting rats with phenylhydrazine (40 mg/kg) for two consecutive days. The study reported an enhancement in protein, fibre, calcium, phosphorus, and iron in the biscuit with an increase in the proportion of pomace. Consuming biscuits containing 15% pomace increased Hb, RBCs, and antioxidant enzymes in (AnB) rats after 28 days (p ≤ 0.05) (Abdo et al., 2021).

10. Conclusion

Iron deficiency anaemia is a global public health concern which demands for immediate, efficacious, yet cost-effective measures for its mitigation. Although, various food-based strategies have been in place, both nationally and internationally, global anaemia cases are still rising rapidly. Food fortification is one such food-based strategies that has been adopted by over 140 countries across the world. The conventional food fortification holds the potential of economically alleviating IDA at mass-scale. However, as a result of the challenges associated with conventional fortification including suboptimal internal and external evaluation of compliance to regulations by the producers, concerns associated with iron overdosage, risk of cost inflation of fortified foods, expensive fortification technique, nutrient losses, and exposure of fortified foods to sunlight during retail, food scientists have identified FtFF as a recent food-based strategy to complement conventional fortification. This emerging strategy involves the incorporation of nutrient-dense food as a fortifier in a staple food vehicle to enhance its micro-nutrient content. Additionally, FtFF leverages the utilisation of crops that have been marginalised due to overproduction of staple crops; and to develop local value-added food enterprises which may potentially promote the fiscal development of community besides providing health and nutritional benefits. Although, there exist a wide variety of food-based fortifiers that hold the potential of mitigating IDA, limited research has been conducted to develop fortified foods using FtFF and to evaluate the efficacy of foods developed from FtFF against IDA. Considering the strengths and limitations of FtFF and conventional fortification, these two techniques can be employed in combinations to efficiently alleviate IDA. Hence, it is paramount importance to study this emerging food-based strategy, utilise underutilised crops for the development of fortified foods, evaluate the efficacy of these products in the reduction of IDA, and to promote them at both commercial as well as public sector. Concurrently, it is imperative to sensitise and educate the smallholder farmers that have moved away from producing traditional crops that could be employed in FtFF due to productivity and economic reasons, about the need and significance of crop domestication, crop diversification and production of traditional and other crops useful in FtFF.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Naman Kaur: drafted the manuscript. Aparna Agarwal: and. Manisha Sabharwal: conceived the study, reviewed the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Acknowledgements

This review paper has been developed with the constant support from the faculty of Lady Irwin College, University of Delhi.
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