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Effect of Biofortified Staple Food Crops on Iron Status- A Review

Review Article

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Abstract

Background: Iron deficiency is the most common micronutrient deficiency globally and represents a major threat to public health. Food-based strategies alone have not been universally successful to reduce nutritional iron deficiency. Biofortification has the potential to become a sustainable, inexpensive, and effective solution, particularly in resource-limited settings.

Objective: To determine the efficacy of iron-biofortified staple food crops such as rice, beans, pearl millets to improve the iron status of the individuals.

Methods: A systematic literature search of randomized and non-randomized trials was done by two authors in scientific databases such as PubMed, Google scholar, IndMed, Cochrane library published till June 2019. The search strategy comprised of using keywords like 'Biofortification and iron status', 'Biofortification and anemia', and 'Biofortification of staplefoods.

Results: The total number of studies included in the final review is eight. Serum ferritin (SF), Total body iron (TBI), quantity of iron absorbed, C-reactive protein (CRP), Alpha-1-glycoprotein (AGP), haemoglobin level, soluble transferrin receptor (sTfR) was measured to assess the iron status. Four studies reported a significant increase in SF level after the intervention with certain iron-biofortified food such as rice, beans, pearl millets. On average, a significant increase in SF or Hb level was recorded after consumption of beans and rice. Three studies reported an increase in iron absorption in the body by consuming biofortified crops as compared to non-biofortified crops.

Conclusion: Iron Biofortification of staple food crops such as rice, beans, and pearl millets can improve iron status in individuals by improving the blood haemoglobin levels or SF, or TBI. Further research is required on the efficacy and effectiveness of the intervention strategy.

Keywords: Biofortification; Iron; Anemia; Staple food; Sustainable; Haemoglobin

Introduction

Among various global issues, micronutrient malnutrition is a primary concern that requires urgent and concerted attention. In India, malnutrition is particularly prevalent among women, children, and adolescents, with about 35.8% of children under-5 years of age being reported to be underweight and around 38.4% being reported to be stunted [1].Worldwide, the most common micronutrient deficiency is iron deficiency and disproportionately affects the poorest and most vulnerable populations in resource-limited settings. Among the micronutrient deficiencies, iron deficiency anaemia (IDA) is the most serious public health problem affecting over two billion people (or about one-third of the world's population) [2]. The WHO mortality data reports that around 0.8 million deaths (1.5% of the total) are attributable to iron deficiency each year. Estimated prevalence of IDA among women (particularly pregnant women) and children varies between 50-70% [3]. Iron deficiency is associated with adverse health outcomes, and even mild iron deficiency can lead to cognitive dysfunction or impairment in children, and reduced physical work capacity in adults and if this deficiency is present at the time of pregnancy, it may be associated with low birth weight and increased risk of maternal and fetal mortality [4,5].

In India, the Ministry of Family and Health Welfare (MoHFW), Government of India launched National Iron Plus Initiative (NIPI) in 2013 in order to combat the public health issue of iron deficiency anemia which is prevalent among all age groups. The program focuses on providing Iron Folic Acid (IFA) supplementation and deworming for improving the haemoglobin status for all the age groups, i.e., children aged 6-59 months, children aged 5-10 years, adolescent boys and girls aged 11-19 years, pregnant and lactating women and reproductive-age women (20-49 years) [6]. In 2018, MoHFW has launched 'AnemiaMukt Bharat', an intensive national iron plus initiative strategy to accelerate the anemia control activities in India and to combat the problems of anemia. One of the interventions under AnemiaMukt Bharat is the mandatory provision of iron and folic acid fortified foods in public health programs [7]. Therefore, it creates a further need for in-depth research in biofortification and food fortification to be scaled up as a future public health preventive strategy for micronutrient deficiencies.

Among various strategies adopted globally, food-based approaches including food production, dietary diversification, food fortification, and biofortification are considered to be sustainable strategies for improving the micronutrient status of populations and raising the nutritional levels [8]. However, in a country like India, the majority of the poor especially the agricultural community are dependent on their own to produce food, and the reach of commercially processed foods through fortification is minimal. Dietary diversity is also often limited by crop seasonality and low bioavailability of specific micronutrients. Therefore, emphasis should be given to formulate methods to apply fertilizers or use plant breeding strategies to increase the bioavailability of edible portions of crop plants. Biofortification is termed as a process of increasing the amount and bioavailability of essential vitamins or minerals in staple crops, through plant breeding or agronomic practices, to improve nutritional status [9]. In 2013, Lancet published a study on maternal and child malnutrition identifying biofortification as one of the key interventions to reduce micronutrient deficiencies in low- and middle-income countries [10].

Biofortification is a promising and sustainable strategy to target iron deficiency, particularly in high-risk populations in resource-limited settings. The Biofortification approach complements other interventions and is a viable means to provide micronutrients to the most vulnerable sections of the population in a comparatively inexpensive and cost-effective way, using sustainable agricultural interventions [11].

Around the globe, iron, zinc, selenium, and vitamin A are the focus of biofortification programs and aim to complement and in some cases replace chemical fortification or food supplementation [12]. Many nutrition intervention studies concluded that iron-biofortified crops can indeed increase the iron status of target groups [13].

In this review, the findings from the eight randomized efficacy trials have been summarized that depict the effects and efficacy of iron- biofortified staple food crops on iron status in populations. This may help to inform public health programs to incorporate biofortification as an intervention strategy to target iron deficiency in diverse population groups.

Methodology

A systematic literature search of randomized and non-randomized trials was done by two authors in scientific databases such as PubMed, Google scholar, IndMed, Cochrane library published till June 2019. No date restrictions were applied because of limited availability of articles. The search strategy comprised of using keywords like 'Biofortification and iron status', 'Biofortification and anemia', 'Biofortification of staple foods' and also using Medical Subject Headings (MeSH) terms that are used for indexing articles like 'Biofortification', 'Staple food', 'Anemia', also using Boolean operators AND, OR like 'Biofortification' AND 'Anemia', 'Biofortification' AND 'Iron', 'Biofortification' AND 'prevention of iron deficiency'. Various combinations of keywords (MeSH and Title/ Abstract [tiab]) were used for literature search. The reference lists of all included articles were searched and related reference searches were also carried out.

Inclusion Criteria

Original articles that were available full text in English language and studies with Randomised controlled trials (RCTs) with randomisation at either the individual or cluster level, including cross-over trials were included. Also following attributes in the studies were considered-

- Effect of biofortified crops on iron status or iron status indicators.
- Influence of biofortified crops on iron bioavailability.
- Effect of phytic acid on iron absorption in biofortified crops.
- Comparison of iron absorption in biofortified and non-biofortified crops.
- The studies that examined the effects of Biofortification of staple food crops with iron alone, or in combination with other micronutrients compared with the same non-biofortified food crop

Exclusion Criteria: Animal studies, review articles, conference proceedings, nutrition bulletins, ex-ante research, studies stating feasibility or acceptance of biofortification were excluded.

Two authors independently screened the title and abstract for relevancy and the full text of relevant articles was further evaluated for eligibility in accordance with the inclusion and exclusion criteria.

Types of participants: All age groups (including young children) from any country on which articles were available were included.

All the studies that assessed any of the following as primary or secondary outcomes were included:

- In humans, the haemoglobin level was taken as the outcome measure to assess the effect of Biofortification. The results on

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other haematological parameters and iron status indicators like CRP, AGP, sTfR, PF, SF,TBI, were also taken into account if they were reported in the studies.

- In laboratory studies, the iron content of the biofortified cooked meals was assessed.

Result

The literature search identified 93 studies from electronic databases. Out of 93 articles, 78 articles were removed due to duplication and not fulfilling objectives, hence were removed (Figure 1). Full text of the articles (15) was accessed for eligibility. Animal studies and articles which were not available in full text were excluded. 85 studies were excluded due to the following reasons: intervention did not meet inclusion criteria, Biofortification with micronutrients other than iron, and outcomes measured were not specific to iron (Table 1). 8 studies were included in the final review. Study participants were mainly comprised of young children aged 6-24 months, 22-35 months, school-aged children aged 5-12 years and 12-16 years, non-pregnant and non-lactating (NPNL) women aged 17- 35 years, 18-30 years, 18-45 years and 18- 27 years.

Two studies were reported from India, two from Rwanda, and one each from Mexico, Benin, the Philippines, and Brazil. Three types of biofortified staple food crops were used as interventions that can be broadly categorized into iron biofortified pearl millets, beans, and rice. The sample size ranged from 22 to 574 in all eight studies.

Outcomes Measured: Serum ferritin (SF), Total body iron (TBI), quantity of iron absorbed, C-reactive protein (CRP), Alpha-1-glycoprotein (AGP), haemoglobin level, soluble transferrin receptor (sTfR) were measured to assess the iron status.

Effect on Serum Ferritin (SF) and total body iron levels: Four studies reported a significant increase in SF level. A study conducted by [14] reported an increase of 2.1 mg/L in SF that is 8.9 mg/L at the baseline to 11.0 mg/L at the endline in the intervention group consuming iron-fortified beans [14]. Also, significant changes were observed in Hb and TBI. The mean change of 3.0 g/L was observed in the Hb in the Fe-Beans group whereas a reduction in Hb levels and a change of −1.2 g/L was observed in the control-beans group. A study done by [15] reported a significant difference in the median change in SF in the first 4 months of the study which was higher in the Fe-Pearl millet group (5.7 mg/L) as compared to the control-Pearl Millet group (1.2 mg/L) [15]. However, no significant difference was observed in TBI of the two groups at the end of the trial.

In a study by [16], a significant positive correlation was seen between intake of iron-fortified rice and change in SF [16]**.** Among non-anemic women, the treatment group showed a significantly greater SF levels (3.28 ± 0.07 µg/L) as compared to the control group (3.06 ± 0.07 µg/L) for the non-anemic women (t = 2.41, P = 0.02). Non- anemic women had significantly higher body iron (93.5 ± 7.1 µmol/kg) than the control group (77.6 ±7.1 µmol/kg) whereas no effect was seen in anemic subjects. A study by [17] reported a significant increase in hemoglobin (3.8 g/L), log SF (0.1 log µg/L), and BI (0.5 mg/kg) in the Fe-Beans group than did controls after 128 days (at the end of the trial) [17]. In a study by Beinner et al. (2009), Micronized ferric pyrophosphate or MPF-fortified rice (MFP is a white, poorly water-soluble iron compound reported to cause few sensory problems that are particularly useful in fortifying white foods and it is less costly than many other iron compounds) increased iron stores and reduced anemia in a group of mildly anemic children of age 6–24 months. SF and Hb levels increased significantly after the consumption of fortified rice in these children. A mean difference of 4.3±0.63 µg/L in the SF from the baseline was observed in the treatment group as compared to mean difference of 3.5±0.67 µg/L in the control group [18].

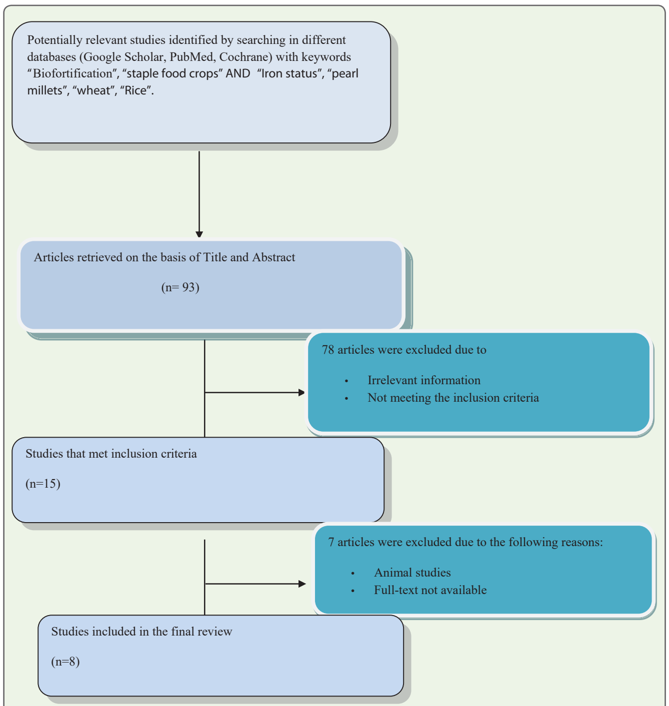
Effect on iron absorption: Three studies reported an increase in iron absorption in the body by consuming biofortified crops as compared to controls. The quantity of iron absorbed from the iron- and zinc-biofortified pearl millet test meals fed three times per day was significantly greater (0.7 ± 0.5mg/day) than that from the control (0.2 ± 0.2mg/day) [19].

In a study by [20], total iron absorbed from the iron biofortified pearl millet meals (1.13mg/d) was double as compared to that from the control (0.53mg/d) [20].

In a study by [14], the mean Plasma Ferritin concentration increased to 11.0 µg/L at the end of the 12-wk study period from a baseline of 8.9 µg/L and dephytinization (reduction of phytic acid concentration) had a proportionally greater impact on iron absorption from the biofortified bean meals [14].

Discussion

This review includes eight randomized controlled studies in total to determine the efficacy of iron- biofortified staple food crops such as rice, beans, pearl millets to improve the iron status of the individuals.



Flow chart: Literature Search Strategy.

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Table 1: Summarized Table of the Studies Reviewed**.**

Author and publication year	Study design and study site	Sample size and study participant	Intervention and feeding time	Assessment	Key findings
			PEARL MILLET		
Finkelstein et al. 2015 [15]	double-blind, randomized efficacy trial, Maharashtra	220, with 109 children in the Fe-PM group and 111 in the Control-PM group school-aged children (12–16 y)	Iron-biofortified pearl millet	1. At baseline: Anthropometric, dietary and clinical assessment. 2.Laboratory methods: CBC, SF, sTfR, CRP, sTfR, and AGP	1.Significant difference in SF:Fe-PM group= 5.7 mg/L Control-PM group= 1.2 mg/L 2. Fe-PM group= 64% iron repleted vs. control-PM group= 40% iron repleted by 6 months.
Kodkany et al. 2013 [19]	double-blinded, randomized control, Karnataka	40, Age:22- 35 months	Sweetened/savoury porridge, or flat breads made of biofortified pearl millet	1. Total zinc and iron 2.Fractional absorption of iron determined	Significantly >iron absorbed from the biofortified pearl millet fed in 1 d (0.7 ± 0.5mg/day) as compared to control (0.2 ± 0.2mg/day)
Cercamondi et al. 2013 [20]	Randomized cross-over design, Benin	22, healthy NPNL women 17 and 35 y	Iron-biofortified, iron-fortified pearl millet	Baseline measurements: Body weight and height, Hb, PF, CRP and malaria parasitaemia Endpoint measurements: stable isotope technique	1. Doubling of total iron absorbed from the iron biofortified meals (1.13mg/d) v/s regular meal (0.53mg/d) 2. >40% mean fractional absorption in post-harvest iron-fortified millet meals than in iron-biofortified millet meals and the regular-iron millet meals.
			BEANS		
Finkelstein et al.2019	double-blind, cluster-randomized controlled trial, Mexico	574; school-aged children (5–12 years)	Iron-biofortified black beans	At Baseline: dietary iron intake, blood parameters, anthropometry and morbidity status. Endpoint measurements: SF, sTfR, CRP and AGP	1. No significant improvement in iron biomarkers 2. <(sTfR) values in Fe-Bean group compared to Control-Beans at the endline.
Petry et al. 2014 [14]	Randomized crossover design, Rwanda	25, healthy, NPNL women aged between 18 and 30 years.	Iron fortified beans	At Baseline: Body weight and height, iron status and inflammation. Food Analysis: Plasma Albumin concentration in bean seeds Isotope analysis: Iron absorption	1. >Mean PF concentration from baseline of 8.9 mg/L to 11.0 mg/L 2. Partial increased amount of iron absorbed from the biofortified bean meals by 47% and 84% respectively
Haas et al. 2016 [17]	Double-blind randomized efficacy trial, Rwandan	195 non- pregnant women aged 18–27 years	Iron- biofortified Beans	Baseline assessment: Hb, SF, sTfR, and BI; Serum CRP and serum AGP, Anthropometric measurements, 24-hr diet Recall Endline measurements: Anthropometric measurements and Plate waste	1. The daily amount of absorbed iron from Fe-beans and control beans was 1.06 mg/d and 0.79 mg/d, respectively 3. The Fe-Beans group had significantly greater increase in hemoglobin (3.8 g/L), log SF (0.1 log μg/L), and BI (0.5 mg/kg) than did controls after 128 days of trial.
			RICE		
Haas et al. 2005 [16]	Prospective, randomized, controlled, double-blind, longitudinal, intervention trial, Philippines	192, age group of 18-45 years.	Iron-biofortified rice	At Baseline: Anthropometric data Laboratory methods: Hb, Hematocrit, plasma iron, total iron - binding capacity, SF, sTfR, AGP, serum folate and vitamin B-12, Serum retinol and serum zinc.	1. In non-anemic women, significantly greater final Ferritin in the treatment group 2. Non- anemic women had significantly higher body iron (93.5 ± 7.1 μmol/kg) than the control group (77.6 ±7.1μmol/kg) 3. For women with low initial body iron, the effect of iron treatment was 43% greater in the treatment group compared to the controls for the same value of baseline body iron.
Beinner et al. 2010 [18]	Randomized, double-blinded efficacy trial, Brazil.	175, 6- to 24 months old children	Rice fortified with MFP and iron-free placebo solution	At baseline, height and weight SF and CRP Single 24-hr dietary intake assessment	1. SF and Hb levels showed higher increase in the fortified rice group. 2.Prevalence of ID decrease was more prominent in treatment group (from 69.1 to 25%) than the control group (from 76.9 to 52.7%).

CRP: C-reactive protein; AGP: a-1-glycoprotein; SF: Serum Ferritin; sTfR: Soluble Transferrin Receptor; Hb:Hemoglobin ; PF: Plasma Ferritin; BI:Body Iron ; NPNL: Non Pregnant Non- Lactating

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This review documents an increase in haemoglobin level and/or SF or TBI in different age groups using biofortified staple food crops such as pearl millets, rice, and beans.

The effect of biofortified staple food crops on iron status varied across the studies. Some of the studies showed a major change in haemoglobin as well as SF levels while others showed a non-significant change.

A study by [15] showed a significant increase in SF and TBI after 6 months of intervention. A clear reduction in iron deficiency status associated with the iron- biofortified pearl millet group was documented [15]. A randomized controlled trial by [19] showed that the absorption of iron from the biofortified pearl millets was higher than the physiological requirement of young children of age between 22- 35 months. Though, no effect was seen in C-reactive protein (CRP) and a-1-glycoprotein (AGP) and Hb levels. The study suggests that the increased concentrations of iron in pearl millet when consumed as a staple food, has higher bioavailability and meets the physiological requirements of iron in young children [19].

It was also observed that the quantity of iron absorbed from the biofortified bean meals was 19% higher than from the control bean meals and dephytinization can increase the amount of iron absorbed from the biofortified bean meals. Additionally, the amount of beans consumed significantly correlated with change in body weight [14].

A study by [17] documented that for every 1 g of iron consumed from beans, there was a significant increase in haemoglobin (4.2 g/L). There was also a significant increase in log SF, SF, and Body Iron for each gram of iron consumed from beans. The consumption of iron-biofortified beans significantly improved the iron status of non-pregnant and non-lactating (NPNL) women [17].

Iron- biofortified rice increased SF, Hb, iron stores and reduced anemia in a group of mildly anemic children of age 6–24 months. A clear reduction in the prevalence of iron deficiency was also seen from 69.1% to 25% in the iron- biofortified rice groups. Most of the studies did not report a direct link between biofortified staple food crops and reduction in iron deficiency anemia. Only one study by Beinner et al. (2009) showed significant changes in the prevalence of iron deficiency anemia [18].

Through All Indian Coordinated Research Projects (AICRPs), The National Agricultural Research System (NARS), has released a series of biofortified crops that takes into account not only the process of yield enhancement but also the nutritional quality. The baseline level of iron in the targeted crops such as wheat and pearl millet is 28.0-32.0 ppm and 45.0-50.0 ppm respectively whereas the levels achieved through biofortification in these crops are >38.0 ppm and >70.0 ppm respectively [21].

The review has few limitations. The major limitation in this study is the unavailability of a sufficient number of studies to determine the efficacy of iron-biofortified staple food crops such as rice, beans, pearl millets to improve the iron status of the individuals or reduce the prevalence of iron- deficiency anemia. Also, the low sample size and diversity of the populations is a potential limitation, and therefore on its basis, an inference cannot be drawn.

There is a need for more research or randomized control trials to be conducted in the future to determine the efficacy of iron-biofortified staple food crops such as rice, beans, pearl millets to improve the iron status of the individuals or reduce the prevalence of iron- deficiency anemia.

Conclusion

Findings from the eight randomized trials suggest that iron-biofortified crops are an effective intervention to improve iron status, including haemoglobin, SF, and total body iron. The findings from three trials suggest that among the individuals who were iron deficient at baseline reported the greatest benefits from biofortified staple crops. Therefore, it can be concluded that iron-biofortified staple food crops might improve the iron status, and reduce the prevalence of anemia. But, a very limited number of research trials are available on this topic which indicates a considerable need for more studies in this area.

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