Industry note: The importance of bioavailability of iron in plant-based foods in the context of treating iron-deficiency anaemia

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1 Introduction

The World Health Organization defines anaemia as the condition of having a low blood haemoglobin (Hb) concentration, i.e., < 13.0, < 12.0 and < 11.0 g/dL for men, non-pregnant women, and children aged 6–59 months, respectively (Pasricha et al., 2018) although Ghosh et al. (2023) have recently suggested that a cut-off value of 11.0 g/dL may be more appropriate for Indian women of childbearing age. The high prevalence of anaemia is a major health issue in India with the National Family Health Surveys reporting that more than 58% of children aged 6–59 months are anaemic with Hb concentrations of < 11.0 g/dL. Sub-optimal iron status, due to low intake of bioavailable iron, is generally regarded as the most common cause of anaemia, especially in low- and middle-income countries (WHO, 2023). There are however, increasing concerns that Hb concentration may not be a satisfactory indicator of iron-deficiency anaemia (IDA), and that in India at least, other causes of anaemia, notably intestinal worm infestation and vitamin B12 deficiency are major contributory factors (Givens et al., 2024). Despite anaemia having a multifactorial aetiology, it remains critical that correctly diagnosed IDA is treated. Iron is an essential nutrient and a deficiency in infancy can seriously retard brain development which may progress into a range of neurological diseases including impaired psychomotor development (Yager and Hartfield, 2002), lower verbal IQ, more frequent inattention, and inadequate executive functioning in young adults (East et al., 2021). In addition, there is good evidence that childhood anaemia can lead to life-long effects including poorer work performance and money earning capacity (Marcus et al., 2021).

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2 The role of millets as suppliers of dietary iron to the diet

There has been considerable interest in the potential of developing IDA-correcting, iron biofortified millets. These contain higher iron concentrations than standard millets. This approach appears to have promise based on several randomised controlled studies (RCTs) in Indian children. Finkelstein et al. (2015) compared feeding iron biofortified pearl millet (8.6 mg Fe/100 g) with a control pearl millet (2.2 mg Fe/100 g) to children aged 12-16 years for six months. The children received about 200–300 g (dry) of pearl millet per day in the form of bhakri (round flatbread) at lunch and dinner. The fortified and non-fortified millet gave daily iron intakes of approximately 21.5 and 5.5 mg, respectively. Those who were iron deficient at baseline and consumed the biofortified millet were 1.64 times more likely to be iron replete by 6 months. Additional findings from studies which compared iron biofortified pearl millet with a non-fortified control in similar aged children also reported improved iron status, cognitive performance, and memory (Scott et al., 2018) and increased light physical activity and decreased sedentary time (Pompano et al., 2022).

Because of the large range of iron concentrations in non-biofortified millets, Anitha et al. (2024) carried out a meta-analysis of human RCTs which examined the effect of millet consumption vs. regular refined rice and/or wheat diets on blood Hb concentration. Thirteen studies from 12 published papers of adequate data quality were included. Overall, these included 297 adolescents, 268 children and 25 adults in the intervention arms and 260 adolescents, 264 children and 25 adults in the control arms. There were five studies each which used finger and pearl millets (one iron-biofortified), one used mixed millet and one sorghum with the intervention period ranging considerably from 28 days to three years.

Table 1 Effect of millet-based diets vs. controls on blood Hb concentration

Determination	*Treatment*			*Controls*			*Overall treatment effect*[1] *(%)*
	Pretest	*Post-test*	*Mean change (%)*	*Pretest*	*Post-test*	*Mean change (%)*	
Haemoglobin (g/dL ± SD)	9.95 ± 1.07	11.31 ± 1.26	+13.6**	10.20 ± 0.99	10.66 ± 1.09	+4.8	+8.8*

Note: ** P < 0.01; [1]mean treatment % change – mean control % change, *P < 0.05 based on Wilcoxon matched-pairs signed rank test.

Source: Derived from Anitha et al. (2024)

The results are summarised in Table 1. The overall heterogeneity was high (I^2 = 80%) and compared with refined rice/wheat diets, the millet diets increased Hb by 8.8% (P < 0.05), equivalent to an average of 0.90 g/dL. It is interesting to note that sub-group analysis showed that the positive treatment effects were only seen in the studies with children, possibly related to few available studies with adults, and because the children's studies expressed lower heterogeneity. Unfortunately, only one of the studies in the meta-analysis reported iron concentrations in the millets/control diet and iron intakes but whilst other limitations in the meta-analysis existed, they give some confidence that, with further research, high-iron millets will have the potential to enhance iron intake and absorption, leading to a reduction in IDA.

However, as noted above, IDA does not represent all anaemia and careful differential diagnosis is important so that the most appropriate dietary treatment(s) can be provided. Despite these promising results, simply measuring iron concentration in food does not inform about the bioaccessibility (the proportion of iron in the food that is released from the food matrix during digestion) or the bioavailability (the proportion of iron in the food that is absorbed from the digestive tract). These are vital characteristics which should be plant breeding targets. It is therefore important to understand the range of factors which can enhance and diminish the bioavailability of iron in plant-based foods.

3 Factors affecting the absorption of iron

The proportion of dietary iron that is absorbed from the digestive tract (bioavailability) depends on:

1 the degree to which iron is released from the food matrix during digestion (bioaccessibility)

2 the biochemical form of the released iron

3 the food consumer's iron status such that those of low status will have a higher absorptive efficiency than those of adequate status.

The process of iron absorption is highly regulated because the body has no controlled process for iron excretion. Dietary iron can be in the form of haem or non-haem. Haem iron is only found in animal and seafood products, notably red meat and is highly bioavailable (typically 20%–30% absorption) whereas non-haem iron is found in plant and animal-based foods and is much less bioavailable (typically 1%–10% absorption). This means that those who consume meat will get haem and some non-haem iron whereas vegetarians and vegans generally only get non-haem iron and thus have a higher risk of IDA. Using a double stable isotope technique, Hallberg et al. (1997) reported the absorption in men of haem and non-haem iron to be 28.6±9.45% and 10.3±8.80% respectively. However, when the subjects were classified as being blood donors or non-donors, the donors had significantly ($P < 0.0001$) higher absorption of both haem and non-haem iron. Serum ferritin was significantly lower in the donors illustrating a control mechanism for iron absorption based on iron status, but also shows that bioavailability of dietary iron from the same source will differ substantially between in iron replete and non-replete subjects (Kalasuramath et al., 2013). Indeed, Hurrell and Egli (2010) proposed that a range of iron bioavailability values should be developed not only based on diet but also on subject iron status and obesity.

In plant-based foods in particular, the bioaccessibility of iron represents a key component of the overall bioavailability. It is predominantly a characteristic of the plant and any processing that it has been subjected to and is a useful target for plant breeders although it does need to be supplemented by analysis of compounds that can influence the absorption of the bioaccessible iron (see below). There are a range of in vitro techniques for assessing bioaccessibility and have been reviewed by Sulaiman et al. (2021). If appropriate, these can be followed by human studies to measure bioavailability which are more complex and costly (Fairweather-Tait and Dainty, 2002; Fairweather-Tait et al., 2020).

As noted above there are a range of dietary factors that can influence the absorption of iron. These can be compounds within plant-based foods or other foods in the diet. There have been a number of reviews on this subject (e.g., Wallace, 2016; Dasa and Abera, 2018; Milman, 2020; Dixit et al., 2021; Malhotra et al., 2023) and it is not the intention to cover this extensively in this paper, rather to identify key factors most relevant to diets in India and in particular, the value of millets as 'smart foods' for delivering dietary iron (Poole and Kane-Potaka, 2020).

3.1 Enhancers of iron absorption

Two dietary factors in particular, i.e., red meat and vitamin C have been shown to enhance the absorption and hence bioavailability of non-haem iron.

3.1.1 Red meat

As noted above haem iron has a substantially higher absorbability than non-haem iron and the primary sources of haem iron are the haemoglobin and myoglobin in red meat with lower concentrations in poultry meat and fish. Haem iron can increase the absorption of non-haem iron when they are consumed together in a meal (Bæch et al., 2003) and this increase occurs even with diets rich is phytates. Kristensen et al. (2005) showed over a 5-day period that including 60 g of Danish pork meat in high phytic acid diets (1,250 µmol/d) increased the fractional absorption of non-haem iron compared with the same diets without the meat. The exact mechanism whereby haem iron increases the absorption of non-haem iron is not fully understood but appears to involve the peptides and amino acids released from hydrolysis of the meat protein (Hooda et al., 2014). Anderson and Frazer (2017) reported that haem iron is presumed to bind to the enterocyte brush border and is then endocytosed into the enterocyte. Iron is then enzymatically released from haem and exported from the cells via ferroportin 1. Although the uptake of non-haem iron by the enterocyte is by a different mechanism to haem iron, its export into the circulation is also via ferroportin 1 (Anderson and Frazer, 2017).

Meat consumption in India has traditionally been low with the result that only about 1% of iron intake is in the form of haem (Ghosh et al., 2019). The Indian National Family Health Survey 2015–2016 (IIPS and ICF, 2017) reported that very few women consume meat daily although about 30% do consume it weekly. The pattern of food consumption by men is similar, although they are less likely than women to stop eating chicken. The Survey also confirmed that diets have changed little since 2005–2006 which seems at odds with other studies which highlight a trend towards increasing meat consumption. For example, the Indian population consumed some 3.1×10^6 t of beef and veal in 2023 somewhat greater than 2.3×10^6 t in 2015 (Statistica, 2024a) although consumption of red meat is not equally distributed by region (Reddit, 2024) and more is consumed in urban than rural areas (Sathyamala, 2018). The increase in the average income and the urban population in India has led to a large increase in the demand for poultry meat with total consumption of poultry meat in India in 2023 was 4×10^6 t compared with 2.9×10^6 t in 2013 (Statistica, 2024b). Unfortunately, poultry meat will not provide much haem iron.

It is therefore difficult to predict to what degree red meat consumption can aid the needed higher iron intake in India, but there would be merit in targeted red meat consumption to vulnerable sections of the population, children and women of

childbearing age in particular who would also benefit from the additional high-quality protein.

3.1.2 Vitamin C

It has been known for a long time that among organic acids, vitamin C (ascorbic acid) provides the greatest enhancement of the absorption of non-haem iron (Milman, 2020). It can overcome the impact of all dietary inhibitors when it is included in a diet high non-haem iron (Ems et al., 2023). Ascorbic acid forms a chelate with ferric (Fe^{3+}) iron in the low pH of the stomach, which persists and remains soluble in the alkaline environment of the duodenum.

Bendich and Cohen (1990) examined the evidence from 24 studies which showed a dose-response relationship of vitamin C on non-haem iron absorption up to a vitamin C intake of 500 mg/d. Similar data were examined in India by the ICMR (2010) when reviewing the recommended dietary allowances for vitamin C, but it did not recommend a change from the then existing value of 40 mg/d for adults. The report indicated that 40 mg/d was associated with good iron absorption and that this intake can be easily achieved. However, more recently ICMR-NIN (2020) has recommended substantially increased intakes of vitamin C of 80 mg/d for men and pregnant women and 115 mg/d for lactating women. Some increases for children and adolescents were also proposed with values of 45 mg/d for 7–9-year-olds rising to 70 and 85 mg/d for 16–18-year-old boys and girls respectively. Such increases in vitamin C recommended intakes will be helpful for improving absorption of non-haem iron if achieved although the study of Rowe and Carr (2020) with > 5,600 adults recorded low dietary intakes of vitamin C of 23 and 34 mg/d in north and south India respectively which reflected frank deficiency seen in 74 and 46% of subjects. Achievement of the ICMR-NIN (2020) intake targets may be a substantial challenge. Clear dietary guidance on how the higher requirements can be achieved are needed.

Cereal grains and millets contain very little vitamin C and therefore reliance on green leafy vegetables and fruit is needed to provide dietary vitamin C. An in vitro study conducted on finger millet and kidney beans in combination with vitamin C or mango showed that addition of vitamin C or mango (a source of vitamin C) increased the bioavailable iron content by 6.8 times (Mamiro et al., 2001). However, a careful consideration of the source of vitamin C needs to be considered to ensure that this approach is effective for the whole diet. For example, a study by Gowri et al. (2001) examined the influence of adding amla fruits (Indian Gooseberry; Emblica officinalis), which are claimed to be a rich source of vitamin C, at 10% and 30% to cooked cereals and pulses or cereal-pulse combinations. Addition of 10% amla showed an increase of 21% in iron in vitro bioavailability from finger millets and 10% and 30% amla added to wheat increased iron bioavailability from 23 to 70% respectively. However, 30% amla gave a 50% reduction in iron bioavailability in rice and 24% in sorghum. Moreover, 10% amla led to reductions in iron bioavailability of 28%–80% in all pulses examined and 37% to 67% in cereal-pulse combinations. Gowri et al. (2001) suggested that the enhancing effect of vitamin C in amla fruits may be substantially inhibited by the tannins in amla although why there are differential effects on different foods is unclear.

3.2 Inhibitors of iron absorption

3.2.1 Phytates

It has been known for a long time that phytic acid/phytate, present in many cereal grains, can substantially reduce the bioavailability of iron and other nutrients (Brouns, 2022) by chelating with them. The study of Ravindran (1991) of common (six varieties), finger (three varieties) and foxtail millets (four varieties), showed that 67.3, 60.0 and 69.9% of total phosphorus was in the form of phytic acid in the proso, finger and foxtail millets respectively which would have implications for the bioavailability of phosphorus as well as iron. They also showed that the concentrations of calcium in the finger millets (mean 240 mg/100 g) was some ten times higher than the other two types (mean 30 mg/100 g) which may also have a depressing effect on iron absorption at least in the short term (Bendich, 2001).

Lestienne et al. (2005a) examined the effect of soaking whole millet grain, and dehulling and grinding, on the phytate content of the various fractions. The phytate concentration in the raw millet grains was 762 mg/100g and this was not significantly affected by dehulling since it was suggested that 60% of the phytates are in the germ. Dehulling did however lead to an 18% reduction in phytase activity and a 51% reduction in iron content. A further reduction in iron content was seen after soaking the dehulled seeds. Overall, dehulling and milling of millets before soaking did have a positive effect on phytate degradation due to improved contact between the phytase and phytate but it was also shown that cooking of millet flour by boiling did not lead to phytate degradation.

Table 2 Iron, *in vitro* iron (Fe) bioaccessibility, phytic acid and iron: phytic acid molar ratio of pearl millet types

Pearl millet cultivar	*Fe (mg/100g)*	*Fe bioacces*[1] *(%)*	*Phytic acid (g/100g)*	*Phytic acid: Fe molar ratio*
ICMV221	8.39	1.82	0.682	8.5
ICMV221J	8.79	8.51	0.957	8.8
ICTP8203	9.01	2.64	0.827	6.1
ICTP8203J	9.10	7.09	0.889	7.8
JBV2	7.02	13.00	0.880	10.6
Mysore local	5.92	16.27	0.681	9.7
Anantapur local	5.59	17.50	0.729	11
GHB558	6.06	5.54	0.785	10.9
GHB744	6.83	6.76	0.735	9.1
RHB173	6.87	11.50	0.958	11.8
HHB67 improved	9.34	3.83	1.007	9.1
HHB223	5.78	8.88	1.051	15.4
HHB226	13.41	5.18	1.080	6.8

Note: [1]Bioaccessibility *in vitro*.

Source: From Krishnan and Meera (2017)

Using an in vitro simulation of gastro-intestinal digestion Lestienne et al. (2005b) assessed the bioavailability of iron in samples of decreased phytate whole pearl millet flour and non-dephytinised or dephytinised samples of two pearl millet grain fractions, one of low fibre and tannin contents and one bran fraction of high fibre and tannin contents. Iron bioavailability of the whole pearl millet flour was significantly improved by the reduced phytate content as was the case for the dephytinised low fibre fraction. Dephytinisation of the bran fraction had no effect on iron bioavailability. Lestienne et al. (2005b) also concluded that not only the phytates play a role in reducing iron bioavailability of pearl millet flour but that the fibre fraction and tannins are also involved. The effect of fibre has been known for some time (Reinhold et al., 1976). Krishnan and Meera (2017) measured the iron and phytic acid concentrations together with in vitro iron bioaccessibility in a range of pearl millet cultivars. Their results are summarised in Table 2.

There was considerable variation in all the variables in Table 2. The authors highlighted that the highest phytic acid concentrations were seen in the so-called hybrid cultivars (HH/RH) with lower values in the so-called open pollinated types (ICMV221, ICPT8203) and Mysore local. They also noted that breeding for higher iron concentration does not guarantee a higher bioaccessibility of the iron. Indeed, the higher iron millets HHB226, ICM/ICT types had some of the lowest iron bioaccessibility values whilst the low iron types (Mysore, Anantapur) had the highest iron bioaccessibility. The authors suggest that this was mainly due to their somewhat low concentration of phytic acid whilst the high iron HHB226 had a high phytic acid content which probably contributed to its low iron bioaccessibility. In fact, there was no significant relationship between phytic acid concentration alone and bioaccessibility ($R^2 = 0.044$) suggesting that phytic acid may have more impact on iron absorption than its bioaccessibility or that other factors may have had a greater effect. Indeed, Krishnan and Meera (2017) reported a multiple linear regression model containing a range of factors:

$$\text{Iron bioaccessibility} = 17.16 - 0.0189x_1 + 0.231x_2 - 29.15x_3 - 1.61x_4 + 1.79x_5 - 0.777x_6$$

where x_1 = polyphenols, x_2 = flavonoids, x_3 = phytic acid, x_4 = soluble dietary fibre, x_5 = insoluble dietary fibre and x_6 = zinc, $R^2 = 0.94$.

Interpretation of this model implies a negative effect on iron bioaccessibility by polyphenols, phytic acid, soluble dietary fibre and zinc, with phytic acid having the largest coefficient. A major problem with multiple linear regression is the risk of multicollinearity which can be associated with high R^2 values, and it is not known if this was tested for before the model was created.

The phytates have also been shown to have a key role in reducing the bioavailability of iron in sorghum. The study of Afify et al. (2011) showed in three varieties of white sorghum that 42-52% of total phosphorus was in the form of phytate. They also showed that soaking and germinating after soaking led to a significant reduction (24.9%–28.7%) in phytate content and whilst these treatments also led to a reduction in iron content (~38%) at the same time, in vitro bioavailability of the remaining iron was increased from 8.0% to 13.2% in the untreated sorghum varieties to 16.7 to 20.6% after soaking and germinating which only slightly more than compensated for the loss of iron.

Phytates are also known to reduce the bioavailability of zinc (Camara and Amaro, 2003) in millets and sorghums and their role and the use of exogenous phytase needs

careful consideration. In addition, the loss of iron that treatments such as soaking, germinating, etc. incur, needs careful balancing against any improvements in its bioavailability.

3.2.2 Polyphenols

Shahidi and Chandrasekara (2013) reviewed the potential role of phenolics in millets for disease risk reduction with a focus on antioxidant activity. They also described a range of flavonoids, which is interesting, since there is increasing evidence that this class of polyphenolics can have benefit for vascular and brain function (Dodd et al., 2019). Polyphenolic compounds in plants have been shown to reduce the absorption of iron and there has been concern that breeding plants such as black beans with higher iron concentration may also increase polyphenolics leading to little if any increase in absorbable iron (Tako et al., 2014). The same researchers also investigated this problem in pearl millet (Tako et al., 2015). They studied whether iron biofortified pearl millet (8.5 mg/100 g) had greater capacity to supply absorbable iron than a standard low iron pearl millet (2.6 mg/100 g) using a broiler bird model. LC-MS analysis identified 15 unique phenolic compounds that were elevated ($P < 0.05$) in the high iron millet and corresponded to a mass/charge ratio (m/z) of 431.09. This elevated mass was reported to represent a range of glycosylated phenolic compounds which have been implicated in reducing iron absorption (Scarano et al., 2023).

Overall, the high iron millet in the study of Tako et al. (2015) did improve the iron status of the birds based on a range of measures compared with the low iron type. However, in vitro assays of absorption using Caco-2 cells, whilst suggesting that the high iron millet should provide more absorbable iron, was associated very low cell ferritin values typical of the presence of high amounts of polyphenolic compounds (and possibly phytates) that inhibit iron absorption. Tako et al. (2015) suggested that reducing the polyphenolics (and phytates) may be something that plant breeding can achieve and emphasised that this was necessary to further improve the nutritional benefits of millets.

As noted above, Krishnan and Meera (2017) also evaluated the association between polyphenol concentrations and in vitro iron accessibility. Their multiple linear regression model implied a negative effect of polyphenols but curiously a positive effect of flavonoids despite them being a family of polyphenols. Flavonoids are often the most common polyphenol in the diet. The variance accounted for (R^2) in iron bioaccessibility by polyphenols alone was very low (0.034) but interestingly the relationship with flavonoids was positive with $R^2 = 0.59$ confirming the positive coefficient in the multiple regression of Krishnan and Meera (2017). The positive association of flavonoids with iron bioaccessibility contradicts the views of Lesjak and Srai (2019) who suggest that the generally negative impact of polyphenols on iron absorption is greatest for flavonoids which are believed to chelate non-haem iron. Whether this is due to different effects on iron bioaccessibility, and intestinal absorption is unclear.

Interestingly, there has been interest in extracting polyphenols from millets as a source of antioxidant compounds for use in food and for their potential health benefits such as inhibiting platelet aggregation and some anti-tumour effects. Using LC-MS, database search and what they described as ‘speculation’, Li et al. (2023) identified the three main polyphenols in foxtail millet as 7-O-β-D-glucopyranosyl-6-C-β-D-glucopyranosyl luteolin, p-coumaric acid and isoscoparin-7-O-β-D-glucoside. They found that the antioxidant activity of the polyphenols was highest when extracted by

boiling compared with a range of other methods. Zhang et al. (2022) described a method for sustainable extraction of millet polyphenols using switchable deep eutectic solvents following high hydrostatic pressure pretreatment.

4 Conclusions

The high prevalence of anaemia is a major health issue in India and many low- and middle-income countries. Despite anaemia having a multifactorial aetiology, it remains critical that adequately diagnosed IDA is corrected. Sub-optimal iron status, due to low intake of bioavailable iron, is generally regarded as the most common cause of anaemia. Iron is an essential nutrient and a deficiency in infancy can seriously retard brain development which may progress into a range of neurological diseases in adulthood. There is considerable interest in the potential of developing IDA-correcting, iron biofortified millets. These have higher iron concentrations than standard millets yet simply measuring iron concentration does not inform about the bioaccessibility or the bioavailability of the iron. These are vital characteristics which, together with iron concentration, should be a component of millet breeding strategy. If the recent increase in the target intakes of vitamin C in India is translated into widespread dietary practice, they will increase the bioavailability of dietary non-haem iron from predominantly plant-based diets. Unfortunately iron-rich plants, including types of millet that have been developed to increase iron intake, contain virtually no vitamin C but are likely to contain phytochemicals including phytates and polyphenols which can reduce iron bioavailability substantially. The impact of these compounds needs a fuller understanding but should also be considered when plant breeding is planned. The ability of millet processing to reduce these undesirable compounds has potential but needs further work with contemporary millet types.

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