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Mini review

The influence of plant-based food on bioavailability of iron

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Summary. Iron is a vital micronutrient essential for various physiological functions, including oxygen transport and cellular respiration, DNA, RNA and protein synthesis, gene expression regulation and cell proliferation. Maintaining proper iron levels is crucial for metabolic functions. Inadequate iron intake depletes reserves, leading to iron deficiency anaemia (IDA). The World Health Organization aims to reduce IDA in women of reproductive age by 50% by 2030, though no country is currently on track to meet this goal. IDA causes fatigue, decreased concentration, and, in pregnancy, can lead to premature birth and low infant birth weight. It also affects children's physical and cognitive development. Conversely, excessive iron, particularly in its free form, can cause oxidative damage and contribute to conditions like hemochromatosis and infections. Plant-based foods contain non-haem iron, which is less readily absorbed. Plant-based foods often contain compounds that inhibit iron absorption, which can be beneficial or detrimental depending on an individual's iron status. Compounds like phytic acid and flavonoids can inhibit iron absorption, while vitamin C and carotenoids can enhance it. Those with iron deficiency should avoid high-phytate and flavonoid foods, while those with iron overload may benefit from their consumption to help manage iron levels.

Keywords: iron deficiency anemia (IDA), iron dietary uptake, flavonoids, non-heme iron, nutraceuticals, phytate, polyphenols.

INTRODUCTION

Iron is an essential micronutrient for human health, playing a critical role in various physiological functions. It is a key component of metal-containing proteins, which are involved in numerous biological processes. Haemoproteins are proteins that incorporate iron within a haem (protoporphyrin ring) structure bound to the protein. These proteins play a key role in biological processes, including serving as oxygen transporters (haemoglobin, myoglobin, neuroglobin, etc.), activators of oxygen (catalases, peroxidases, cytochrome P450 enzymes, etc.) and electron transfer proteins (Yehuda and Mostofsky 2010; Ying-wu and Jiangyun 2013). In addition to haemoproteins, another major group of iron proteins includes those that contain iron-sulphur clusters. They are mainly involved in redox processes and are an important part of the electron transfer chain in mitochondria, responsible for cellular respiration, and Krebs cycle. The third group of iron-containing proteins encompasses those that do not fit into the previously mentioned categories. These proteins are involved in crucial processes such as DNA, RNA and protein synthesis, regulation of gene expression, and the processes of cell proliferation and differentiation (Gari et al. 2012; Paul et al. 2016).

Although iron is the fourth most abundant mineral in the Earth's crust, comprising approximately 4.5%, it constitutes less than 0.005% of human body weight, with around 4 g in men and 3 g in women (Powers and Buchanan 2019).

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The majority of iron, about 52%, is incorporated into haemoglobin and is found in erythrocytes or their precursors in bone marrow. Approximately 40% of the body's iron is stored in reserves, bound to storage proteins such as ferritin and hemosiderin. Iron in myoglobin within muscles accounts for about 7.5%, while 0.5% is present in the active centres of various enzymes. Additionally, 0.1% of iron is bound to transferrin, a protein responsible for transporting iron in the bloodstream. (Andrews 1999; Lieu et al. 2001).

THE SIGNIFICANCE OF IRON LEVEL REGULATION

Given iron's critical role in the body, it is essential to maintain its adequate levels for normal metabolic functions. When daily iron intake falls short of the body's requirements, iron reserves compensate for the deficiency. However, if insufficient intake persists over time, these reserves become depleted, leading to iron deficiency. Prolonged deficiency can ultimately result in the development of iron deficiency anaemia (IDA) (Pasricha et al. 2020). WHO defines IDA as blood haemoglobin levels less than 140 g/L for men over the age of 15, less than 130 g/L for nonpregnant women over the age of 15 years (Goddard et al. 2011). IDA is present in one-quarter of the world's population, with even higher prevalence in women of reproductive age, pregnant women and children, and presents a huge burden on the global economy. In May 2012 65th World Health Assembly set a Comprehensive Implementation Plan on Maternal, Infant and Young Child Nutrition which included six major targets, one of them being reducing IDA in women of reproductive age. This goal was to reduce the prevalence of IDA in women of reproductive age by 50% by 2025. As no country was assessed to be on track to meet this goal by 2025, the target has been extended to 2030 (WHO/UNICEF discussion paper 2021). IDA is characterized by symptoms including fatigue, lethargy, and impaired concentration. During pregnancy, IDA is associated with premature childbirth, an increased risk of complications during delivery and a lower birth weight of the infant. Additionally, IDA can have long-term consequences, potentially affecting the physical and cognitive development of children (Lozoff et al. 2006; Katz et al. 2013; Symington et al. 2019; Pasricha et al. 2021).

Conversely, excessive iron levels in the body, particularly in its free, unbound form, can be detrimental as well. Iron acts as a prooxidant and can generate reactive oxygen species (ROS) through the Fenton reaction, leading to oxidative damage to lipids, proteins, DNA, organelles and cells. Genetic disorders that cause unregulated iron absorption result in iron overload and conditions such as hemochromatosis. Additionally, hemolytic anaemias can lead to elevated levels of free iron. These conditions are associated with oxidative stress, which can damage various tissues and organs (Fibach and Rachmilewitz 2017; Sousa et al. 2020). In these conditions, amounts of iron stored in the liver can reach 25-30 g, which is an extremely high amount compared to liver iron storages in most people which vary from 300 mg in menstruated women to 1 g in adult men. (Pietrangelo 2006). Free iron inside cells promotes the production of ROS, and if cells' antioxidant defence capacities are overcome it can result in cell death through ferroptosis (Dixon et al. 2012; Lesjak et al. 2022; Živanović et al. 2024). The most common treatment for iron overload and hemochromatosis involves the use of iron-chelating agents (Fibach and Rachmilewitz 2017). In addition to its role as a prooxidant and pro-ferroptosis agent, elevated iron levels are also associated with an increased susceptibility to infections. Bacteria have evolved mechanisms to extract iron from human proteins, which supports their growth in environments where iron is limited. As bacteria can proliferate more rapidly and form biofilms more readily in the presence of excess iron, individuals with iron overload are at a higher risk for infections caused by intracellular and bloodborne pathogens (Ganz 2003).

The human body lacks specialized mechanisms for controlling iron excretion. Daily iron losses, estimated at approximately 1-2 mg, occur through non-specific processes such as the shedding of epithelial cells, sweating, and minor physiological and non-physiological bleeding, including menstruation. Greater iron losses can occur due to significant blood loss or lactation. Since there are no dedicated mechanisms for iron excretion, the regulation of iron levels in the body primarily occurs at the level of absorption.

Daily dietary iron intake typically ranges from 1 to 2 mg but can increase to about 3 mg when the body's needs are elevated, such as during menstruation or lactation. This intake represents only 10 to 20% of the total iron content in the consumed food (Conway and Henderson 2019).

IRON METABOLISM WITHIN THE BODY

Iron exists in two primary forms in food: haem iron and non-haem iron. Haem iron is found in animal-based foods, such as meat and fish, whereas non-haem iron is present in plant-based foods, including fruits and vegetables. The main place of iron absorption is the duodenum with haem and non-haem iron being absorbed through different mechanisms. Namely, acidic gastric conditions and proteases release haem from proteins which are then absorbed in enterocytes through haem-carrier protein 1 (HCP1). Inside enterocytes, the haem is degraded by the haem-oxygenase 1 (HO-1) which leads to the release of iron in the form of Fe^{3+} and the transformation of the porphyrin ring to the biliverdin. Released iron then enters into the iron metabolism (Shayeghi et al. 2005). On the other hand, in plants, non-haem iron can be present in two forms, ferri- (Fe^{3+}) and ferro- (Fe^{2+}) iron. Ferro-iron is the only form that can be absorbed, thus ferri-iron needs to be reduced. Duodenal cytochrome B (DcytB) is the enzyme responsible for the reduction of Fe^{3+} to Fe^{2+}. DcytB needs vitamin C as a cofactor for its function. Divalent metal ion transporter 1 (DMT-1) is a protein transporter located on the apical side and transports Fe^{2+} inside enterocytes (McKie et al. 2001; Srai et al., 2002). Once inside the cell, Fe^{2+} is transported by the chaperone proteins (PCBP1 and PCBP2) either to the ferritin (FTH; protein responsible for storing iron) or to the basal side of the cell. On the basal membrane, Fe^{2+} is exported, through a protein transporter named ferroportin 1 (FPN1) into the circulation. Once exported from enterocytes, Fe^{2+} is immediately oxidized to Fe^{3+} by the hephaestin after which it binds to transferrin. Transferrin transports iron through the bloodstream to various tissues where it is needed. Cells have transferrin receptors (transferrin receptor 1) that bind to transferrin-iron complexes. This complex is then internalized via endocytosis, forming vesicles within the cell from which iron is released into the cytosol. The primary iron storage sites in the body are the liver, spleen macrophages, and bone marrow (Sharp and Srai 2007; Hentze et al. 2010; Conway and Henderson, 2019; Katsarou and Pantopoulos 2020).

Old erythrocytes are recycled by the macrophages in the spleen. Namely, macrophages phagocytose erythrocytes, followed by the release of haemoglobin and consequently the haem. Haem is degraded by the HO-1 and released iron can be either stored in the ferritin or released back into the circulation through FPN1 (Hentze et al. 2010).

The master regulator of iron metabolism is hepcidin. It is a small peptide hormone produced mainly by the liver and in smaller amounts by the kidneys, macrophages, adipocytes and pancreatic beta cells. Hepcidin expression is suppressed by low iron levels, hypoxia and increased erythropoiesis, while high iron levels and inflammation promote hepcidin production (Viatte and Vaulont 2009). Hepcidin functions by regulating levels of iron in circulation. Namely, hepcidin binds to the FPN1, this complex is then internalized in the cell after which FPN1 is ubiquitinated and degraded resulting in the inhibition of the export of iron into circulation (De Domenico et al. 2004; Nemeth et al. 2004; Bilesbølle et al. 2020). In the enterocytes, rather than regulating levels of FPN1, it regulates DMT-1. Increased hepcidin expression as a response to elevated levels of iron in circulation results in decreased expression of DMT-1 and subsequently a lower rate of iron absorption (Mena et al. 2008).

IRON ABSORPTION FROM PLANT-BASED FOODS

Even though fruits and vegetables can be rich sources of non-haem iron (spinach – 260, lettuce – 64.6, parsley – 89.4, dill – 118, broccoli – 29, tomato – 35.9, strawberry – 19.5 and banana – 27.5 μg/g, apricot juice – 1.56 and peach juice– 1.53 mg/L), non-haem iron is not easily absorbed. Namely, plants contain numerous compounds that can impact the absorption and bioavailability of non-haem iron from plant-based food. Some of them can make iron more readily absorbed, such as organic acids, vitamin C and carotenoids, on the other hand, compounds such as phytic acid and polyphenols, particularly flavonoids, can have an inhibitory effect on iron absorption and its bioavailability from food (Tokalioğlu and Gürbüz 2010; Shubham et al. 2020).

Vitamin C (ascorbic acid) increases iron absorption through the reduction of Fe^{3+} to Fe^{2+} in the duodenum making it bioavailable and readily absorbable through DMT1. The necessary amount of ascorbic acid for a positive effect on non-haem iron absorption is 30-100 mg per day, corresponding to the recommended daily intake. Vitamin C can counter, to some degree, the inhibitory effects of phytic acid and polyphenols on non-haem iron bioavailability (Gillooly et al. 1983; Ballot et al. 1987; Hallberg et al. 1989; Siegenberg et al. 1991; Car and Frei 1999; Teucher et al. 2004; Villano et al. 2016).

Carotenoids are a class of plant secondary metabolites present in many fruits and vegetables such as carrots, tomatoes, pumpkin, spinach, broccoli, pepper and mango. Most common in foods are zeaxanthin, lycopene, β-carotene, α-carotene and β-cryptoxanthin. They have antioxidant activity and some, such as β-carotene serve as provitamin A (Santos et al. 2021). Gautam et al. tested the influence of carrot and amaranth, as sources of β-carotene, on the bioavailability of iron from different cereal meals and showed that they can significantly enhance the bioavailability of iron. This was the first study showing that carotenoids can improve non-haem iron bioavailability, although it is important to take into account that this was an *in vitro* digestion study (Gautam et al. 2010). Wu et al. (2015) tested extracts from *Gynura bicolour* on iron bioavailability in rats. Results have shown that ether extracts, that are rich in β-carotene and chlorophyll, although containing significant amounts of polyphenols as well, used simultaneously with iron supplementation, substantially improved iron status in the IDA model (Wu et al. 2015). Infante et al. (2017) developed sorghum cookies enriched with sweet potato carotenoids, which improved iron deficiency in Wistar rats as well as iron supplementation. However, it cannot be said whether the presence of carotenoids played an important role in the increase of iron bioavailability since no group was receiving sorghum cookies without sweet potato carotenoids fortification.

Phytic acid, inositol hexaphosphate, is the primary storage of phosphor in plants and cannot be digested by humans. Phytate forms a complex with iron that is non-absorbable by humans, making it an anti-nutrient in foods. Food preparation plays an important role in the bioavailability of non-haem iron from phytate-containing foods (sorghum, rice, maize, wheat, oath, quinoa, soy, peas and beans). Processes such as milling, grinding, soaking, germination, fermentation and the addition of vitamin C or phytase (an enzyme that hydrolyses phosphate groups from inositol) can increase non-haem iron bioavailability. Still, even small amounts of phytates in meals, as low as 2 mg per meal, can significantly reduce the bioavailability of iron (Siegenberg et al. 1991; Hurrell et al. 2003; Hurrell 2004; Hurrell and Egli 2010; Kruger et al. 2012). Petry and collaborators (2013) investigated iron absorption from genetically modified beans with reduced phytic acid content in human subjects. They compared two types of beans: one with higher polyphenol content and one with lower. They found that iron absorption was greater from both types of beans with lower phytic acid compared to those with higher phytic acid, and the highest iron absorption occurred in beans with both low phytic acid and low polyphenol content (Petry et al. 2013). Additionally, in another study, Petry and collaborators (2014) showed that lowering phytic acid content through dephytinization results in increased iron absorption. Reddy and collaborators (2021) demonstrated that iron absorption from finger millet with low phytic acid was three times higher in healthy Indian women compared to finger millet with high phytic acid. This shows that choosing plant genotypes that have low concentrations of phytic acid can be a good strategy to enhance iron absorption from food and a possible way to combat and prevent iron deficiency and IDA.

Flavonoids are one of the most diverse classes of plant secondary metabolites and are widely distributed in plants. Fruits and vegetables in the human diet contain varying amounts of flavonoids (blueberry – 180, green tea – 138, parsley – 233, banana – 13, carrot – 0.6, and broccoli – 12 mg flavonoid aglycone/ 100 g fresh weight of edible portion) and humans, through their diet, take significant amounts of flavonoids, especially people with predominantly plant-based diets. For example, the daily dietary intake of flavonoids in the USA is 20–34 mg, in Japan 63 mg, in Finland 24 mg and Netherlands 74 mg (Beecher 2003; Bhagwat et al. 2014).

Flavonoids are made of two phenolic rings connected with C3 moiety and are divided into several subclasses. It is well known that they can complex non-haem iron between two neighbouring hydroxyl or carbonyl and hydroxyl groups. In B-ring 3'- and 4'-hydroxyl groups can strongly complex iron, while in C-ring complexing iron sites are 3-hydroxyl and 4-carbonyl, and 5-hydroxyl and 4-carbonyl groups. In case of quercetin, the strength of iron binding is as follows 3-4 > 4-5 > 3'-4' in complexes containing 1 iron and 1 quercetin. The 3-4 chelation site is also preferred in complexes of 1 iron and two or three molecules of quercetin. pH also plays an important role in iron complexing by flavonoids. Namely, phenolic groups are deprotonated in alkaline conditions resulting in stronger bonds with iron. It is also estimated that quercetin binds stronger to Fe^{3+} than to Fe^{2+}, and when quercetin binds to Fe^{2+} it will autooxidise to Fe^{3+} (Leopoldini et al. 2006; Ren et al. 2008; Perron and Brumaghim 2009; Mladěnka et al. 2011; Taharovski et al. 2014).

Many foods containing polyphenols have been studied for their impact on iron absorption. Generally, foods high in polyphenols tend to inhibit iron absorption, with the extent of inhibition correlating with the concentration of polyphenols (Gyllooly et al. 1983). Furthermore, Petry and collaborators (2010) have shown that the addition of bean polyphenols to a test meal in the amount of 50 mg resulted in 14% reduction of iron absorption, while the addition of 200 mg of bean polyphenols inhibited iron absorption by 45% in women.

It has been known for a long time that the consumption of food rich in flavonoids, such as tea, can result in low bioavailability of non-haem iron (Disler et al. 1975; Rossander et al. 1979; Delimont et al. 2017). Studies with quercetin showed that it can complex iron and inhibit its intestinal absorption which is non-desirable in cases of IDA. On the other hand, it complexes iron in serum which can be beneficial in iron overload, whereas quercetin can offer additional protection from iron toxicity through antioxidant activity. Moreover, quercetin activates the Nrf2 pathway, which promotes the expression of not just enzymes involved in the antioxidant defence of the cell, but also the expression of ferritin H and L chains and FPN1 (Baccan et al. 2012; Lesjak et al. 2014, 2019; Živanović et al. 2024). Additionally, quercetin can promote the expression of hepcidin in the liver which would additionally suppress iron absorption in the duodenum and iron transport to the circulation. On the other hand, myricetin is a flavonoid, which can suppress hepcidin expression which could have an enhancing effect on iron absorption (Tang et al. 2014; Mu et al. 2016; Lesjak et al. 2019). Hart and collaborators (2015) examined the effect of black beans on iron absorption and showed that they have an inhibitory effect. They found that polyphenols, abundant in black beans, affect iron absorption: catechin, kaempferol–3–glucoside and kaempferol promote it, while myricetin, quercetin, and their glucosides inhibit it, leading to an overall negative effect on iron absorption due to their higher concentration.

Although vegetarian and vegan diets are associated with numerous health benefits, including improved outcomes in cancer and ischemic heart disease, these dietary patterns may also pose an increased risk of inadequate intake of essential nutrients, particularly iron. While plant-based foods such as legumes and dark green leafy vegetables are good sources of iron, they also contain compounds such as phytic acid and polyphenols, which inhibit iron absorption and reduce its bioavailability. In a systemic review written by Haider and collaborators (2017) is shown that people with vegetarian and vegan diets have lower iron body stores compared to people who consume meat and animal products. This makes vegetarians more prone to the development of IDA especially during increased body needs for iron such as during periods of growth in children, pregnancy, gastrointestinal bleeding and severe injuries (Haider et al. 2017). Similar conclusions are drawn in meta-studies performed by Koller and collaborators (2023), as well as Pawlak and collaborators (2018). Specifically, vegetarians and vegans tend to have higher iron intakes compared to omnivores; however, they also exhibit lower iron status. These studies highlight that while plant-based diets offer numerous health benefits, it is crucial to ensure adequate intake of essential nutrients like iron. This can be achieved through the consumption of foods with highly bioavailable iron or by employing food preparation techniques that enhance iron absorption, such as fermentation, germination and cooking. Since the high content of vitamin C in foods has a beneficial effect on iron absorption it is recommended to eat cereals and other grain products together with fresh fruits such as citrus fruits, blueberries and strawberries. Additionally, it is well known that coffee and teas have lower iron bioavailability due to the high content of tannins, so their consumption should be 1 to 2 hours after a meal. Lastly, while prolonged or routine use of iron supplements is not recommended due to the potential for adverse effects, short-term, periodic use of iron supplements may be beneficial in addressing iron deficiencies when necessary (Pawlak et al. 2018).

CONCLUSIONS

Iron plays an important role in the human organism. It is part of numerous proteins and enzymes with essential roles such as the transport of oxygen and cell respiration. Because of that, intake of necessary amounts of iron is imperative. Since the human body does not possess specific mechanisms for the removal of excess iron, and high concentrations of iron can have detrimental effects on human health, iron absorption is a tightly regulated process and only small amount of iron present in food ends up being taken by the body. Plant-based foods are usually rich in iron, but it may not be readily absorbable. Plants comprise numerous compounds that can act as iron chelators and suppressors of iron absorption. Phytic acid and flavonoids are the main inhibitors of iron absorption and people suffering from iron deficiency and IDA should avoid consumption of them together with iron supplementation. On the other hand, in people suffering from iron overload or being at risk from iron loading it could be beneficial to consume foods with a lot of iron absorption inhibitors to combat iron loading.

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