Food Research 7 (1) : 76 - 92 (February 2023)
Journal homepage: https://www.myfoodresearch.com

FOOD RESEARCH

REVIEW

Bioavailability of iron and its potential to improve the immune system and ward off COVID-19: a review

*Subroto, E., Indiarto, R. and Andoyo, R.

Department of Food Industrial Technology, Faculty of Agro-Industrial Technology, Universitas Padjadjaran, Jl.Raya Bandung-Sumedang Km. 21, Jatinangor, Sumedang 40600, Indonesia

Article history:
Received: 8 September 2021
Received in revised form: 24 October 2021
Accepted: 22 February 2022
Available Online: 15 January 2023

Keywords:
Iron,
Bioavailability,
Fortification,
Immune system,
COVID-19

DOI:
https://doi.org/10.26656/fr.2017.7(1).701

Abstract

Iron is a mineral that plays an important role, especially to prevent anaemia through the production of red blood cells. Iron also plays a role in physiological processes, such as the activation of enzymes and hormones, as well as increasing the immune system in warding off various viral infections. Therefore, iron bioavailability needs to be considered to take the greatest benefit of iron. This review discussed the factors that can affect the bioavailability of iron, various technologies to increase the bioavailability, and its potential in enhancing the immune system. Iron bioavailability can be increased by fortification, fermentation, the addition of vitamin C, and iron encapsulation. Under conditions of adequate iron intake, iron plays an important role in enhancing the immune system through controlling lymphocytes and T cell proliferation. However, excess iron consumption can be at risk of weakening the host's immune response to viruses. Therefore, the appropriate level of iron intake must be maintained accurately to be used optimally and has the potential to ward off viral infections, including the Sars-CoV-2 virus as the cause of COVID-19.

1. Introduction

Minerals are essential micronutrients that maintain various metabolic systems in the body (Nosratpour and Jafari, 2019). Iron (Fe) is one of the micro minerals that have an important role, especially in the transport of oxygen from the lungs to cells or tissues, oxidative metabolism, formation of haemoglobin, electron transport media in cells, preventing anaemia, supports various physiological processes such as enzyme and hormone activation, and immune cell formation (Nair and Iyengar, 2009; Quintaes and Diez-Garcia, 2015; Gharibzahedi and Jafari, 2017). Iron can be found widely in animal meat (30-70% is heme), chicken liver, eggs, seafood, beans, and green vegetables such as broccoli, kale, and spinach (Geissler and Singh, 2011; Gharibzahedi and Jafari, 2017).

Iron deficiency can harm the body, including anaemia, pale skin, headaches, fatigue or lethargy, and decreased immunity (Zand *et al*., 2015). The recommended iron requirement is about 8-15 mg per day, depending on the sex and age of the individual. The Recommended Dietary Allowance (RDAs) of Iron for children < 13 years is 7-11 mg per day, for adolescents 14-18 years is 11 mg per day for males and 15 mg/day for females, for adults 19-50 years is 8 mg per day for males and 18 mg for females, and elderly people > 51 years is 8 mg per day (Institute of Medicine, 2001). Iron needs must be met by consuming foods rich in iron minerals, but not all iron can be absorbed and utilized by the body because the bioavailability value is different for each ingredient (Abbaspour *et al*., 2014; Dasa and Abera, 2018). Bioavailability is the fraction of nutrients that can be digested and available for use and provides benefits to the body. The bioavailability of iron depends on the iron content and the presence of other compounds that can increase or inhibit iron absorption (Oliveira *et al*., 2014; Kiewlicz and Rybicka, 2020).

Adequate iron intake is believed to improve the immune system and fight various infectious diseases through several mechanisms, such as controlling lymphocytes and T cell proliferation (Gorji and Ghadiri, 2021), as well as the activation of peroxidation enzymes that will produce oxides that can destroy viruses (Oppenheimer, 2001; Maggini *et al*., 2018). Sufficient iron intake can have the potential as an immune modulator and ward off COVID-19, which is becoming a worldwide pandemic. However, under certain conditions when infected with a virus or disease, iron intake must be controlled because some viruses or infectious microorganisms can utilize iron in the body to carry out

*Corresponding author.
Email: *edy.subroto@unpad.ac.id*

eISSN: 2550-2166

growth and replication, the infection can then become more dangerous (Nairz *et al*., 2014; Nairz and Weiss, 2020). Therefore, it is very important to study how to increase the bioavailability of iron and the mechanism of iron in boosting the immune system and inhibiting viral infections. This reviewed aimed to summarize the bioavailability of iron and various technologies to improve it, the role of iron in enhancing the immune system, and its potential in warding off various viral infections, including the Sars-CoV-2 virus, as the cause of COVID-19.

2. Iron absorption

Iron contained in the body can be in the form of functional iron compounds, iron reserves, and iron transport. Functional iron is iron that forms compounds such as haemoglobin, myoglobin, hormones, and enzymes. Reserve iron is iron that is stored and prepared when the input of iron elements into the body is reduced, such as serum ferritin and hemosiderin. At the same time, transport iron is iron that functions in transporting one compartment to another (Shubham *et al*., 2020). The iron is obtained from food intake, which mainly contains ferrous ions either in the free state or chelated in complex compounds such as lactoferrin or other iron-binding proteins (Cherayil, 2010; Kell *et al*., 2020; Habib *et al*., 2021).

Iron taken from food will be absorbed in the duodenum and proximal jejunum. The iron absorption process goes through 3 phases, namely the luminal, mucosal, and corporeal phases (Dasa and Abera, 2018). The absorption and metabolism of iron in the body can be seen in Figure 1. The luminal phase is the phase where the iron in the food is processed and ready to be absorbed. In the stomach, food mixes with stomach acid and then releases iron from its bonds with other compounds thanks to the stomach acid. With the help of the ferric reductase enzyme, Fe^{3+} is converted into $Fe^{2+,}$ which is ready to be absorbed. This occurs when iron undergoes a reduction process (Shubham *et al*., 2020). Iron absorption occurs in the intestinal mucosa. The absorption is the mucosal phase. Fe^{2+} that enters enterocytes crosses the apical membrane via divalent metal transporter I (DMTI). Within these enterocytes, the incoming iron can be stored as serum ferritin, or transported to the plasma by the basolateral membrane. The iron that is not stored will be released into the circulation from the basolateral membrane and then through the transmembrane protein ferroportin (Larson and Coyne, 2013).

The corporeal phase is the last phase of the iron absorption process. This phase includes the transportation process, taking the iron for use, and storing the iron itself. After the iron is absorbed, it circulates in the bound form of transferrin and into the hepatic portal system. The system is the main iron storage area. Hepatocytes will bind iron with the help of transferrin receptors 1 and 2 and then be stored in the form of ferritin. In addition, iron that binds to transferrin will be carried to the spinal cord to form red blood cells. In the reticuloendothelial system, old red blood cells are phagocytosed by macrophages. Sources of iron from food are generally found in 2 forms, namely heme and non-heme (Shubham *et al*., 2020). Non-heme iron is iron found in plants or vegetables. This non-heme iron has a relatively lower bioavailability than iron in the form of heme, and its absorption can be affected by inhibitory materials from the components in the material itself or inhibitors from outside (Hurrell and Egli, 2010). At the same time, heme iron is found in meat or animals. In contrast to non-heme iron, heme has high bioavailability. Its absorption is not easily affected by inhibitory materials (Shubham *et al*., 2020).

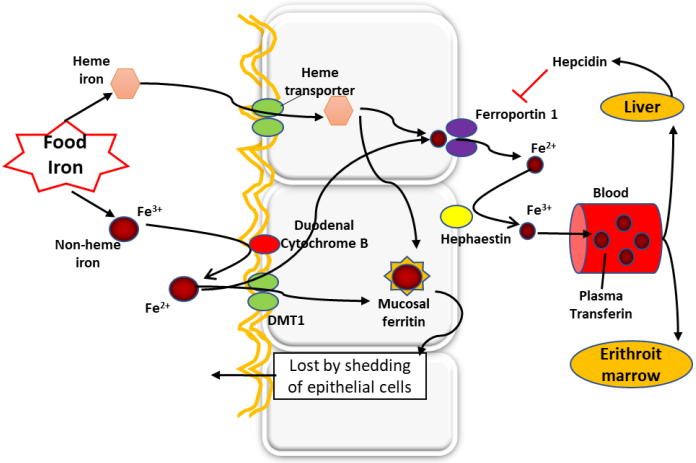

Figure 1. The absorption and metabolism of iron

2.1 Factors affecting the absorption of iron

Iron absorption can be affected by the components in food. Some components can increase iron absorption, such as ascorbic acid and some other organic acids. However, some can inhibit iron absorption, such as phytic acid and polyphenols. Several process conditions also greatly determine iron absorption. Several factors that can affect iron absorption can be seen in Table 1.

2.1.1 Phytic acid

Phytate or myo-inositol hexaphosphate (IP-6) is a natural compound contained in many legumes (such as peanuts and soybeans) and cereals (such as wheat and sorghum). Phytic acid has antioxidant properties but can also act as an inhibitor of the absorption of various minerals, including iron. Phytic acid will form complex compounds with iron to form complex iron compounds that are difficult to digest (Armah *et al*., 2015). Phytic acid can chelate iron to form insoluble complexes in the

https://doi.org/10.26656/fr.2017.7(1).701

Table 1. Some compounds and treatments that can affect iron absorption

Compounds/ Treatments	Effect on iron absorption	References
Phytate	Phytate forms complex iron compounds that are difficult to digest and absorb	Armah *et al*. (2015)
	The presence of phytate reduced the bioavailability of iron by 5-15%.	Gupta *et al*. (2013)
Polyphenols	The presence of polyphenolic compounds reduced iron absorption by up to 90%.	Speer *et al*. (2019)
	Polyphenols from EGCG, green tea extract, and grape seed extract inhibit iron absorption through a basolateral inhibition mechanism in Caco-2 cells.	Ma *et al*. (2011)
	8 mg of quercetin reduced the absorption of iron on the basolateral membrane by 5%.	Lesjak *et al*. (2019)
	Polyphenols formed iron-polyphenol complex ions. 100 mg of tannin reduced iron absorption by 5 mg.	Jaramillo *et al*. (2015)
Animal protein	The bioavailability of heme iron decreased by 53% when chicken meat was added, while it decreased by 32% when fish meat was added.	Pizarro *et al*. (2016)
Calcium	Calcium as a non-competitive inhibitor of DMT1 reduces the absorption of non-heme iron.	Shawki and Mackenzie, 2010)
	100 mg of calcium can reduce iron absorption by 18%, while 200 mg of calcium can reduce iron absorption by 27%.	Walczyk *et al*. (2014)
Heating processes	Heating to 80°C causes a decrease in heme iron by as much as 12%.	Gandemer *et al*. (2020)
	Heating to 60°C causes a decrease in heme iron by as much as 7%.	Florek *et al*. (2016)
	The decrease in iron levels in meat boiled for 5 hours was 19%, and heme iron oxidation occurred.	Njoumi *et al*. (2017)

digestive tract, so it cannot be absorbed in the digestive tract because there is no phytase enzyme in intestinal digestion (Gibson *et al*., 2010). Research conducted by Andrews *et al*. (2014) found that levels of phytic acid around 50 – 150 M can inhibit iron absorption by 20%. The bioavailability of iron could be estimated by calculating the molar ratio between phytate and iron. The molar ratio of phytate and iron (Phy: Fe) above 1 indicates the adverse effect on iron absorption. The value of a good molar ratio between phytate and iron is less than 0.4 (Castro-Alba *et al*., 2019). Phytic acid is easily damaged by heating, therefore to get the benefits of iron minerals from legumes and cereals, these materials should be processed through a heating process. Other processes or methods that can reduce phytic acid are germination, soaking, fermentation, and enzymatic treatment by phytase (Gupta *et al.,* 2015). Other inhibitors, such as tannic acid and oxalic acid, are also known to reduce iron solubility and inhibit iron absorption (Milman, 2020).

2.1.2 Polyphenols

Polyphenols are compounds that can inhibit the absorption of iron. Polyphenols can form complex compounds with iron that cannot be digested by the intestines and are fermented by microbes in the large intestine so that these complex compounds are excreted through faeces (Lesjak *et al*., 2019). Research conducted by Jaramillo *et al*. (2015) found that 100 mg of tannin could reduce the absorption of 5 mg of non-heme iron. Research conducted by Delimont *et al*. (2017) found that rats who consumed 100g/L of green tea polyphenols for 8 weeks experienced a significant decrease in hepatic iron levels. Research conducted by Lesjak *et al*. (2019) showed that rats given 8 mg of quercetin experienced a 5% decrease in iron expenditure on the basolateral membrane. Quercetin can chelate iron in the body. This chelating process can occur in the lumen, causing a decrease in iron absorption at the basolateral membrane (Lesjak *et al*., 2014; Xiao *et al*., 2018). However, polyphenols can be reduced through several methods of processing, including fermentation, oxidation, heating, and ripening (Manach *et al.,* 2004).

2.1.3 Calcium

Calcium is one of the ions that can inhibit the absorption of iron. The presence of calcium will reduce the affinity between DMT1 and iron (Candia *et al*., 2018). Absorption of non-heme iron into the blood occurs through DMT1, which is located in the apical membrane of enterocytes (Mónica *et al*., 2018). In addition, calcium can also cause interference with iron transport in mucosal cells (Andrews *et al*., 2014). Research conducted by Shawki and Mackenzie (2010) found that the molar ratio of Ca: Fe with a ratio of 10:1 decreased the absorption of non-heme iron due to non-competitive competition in DMT1. Meanwhile, Walczyk *et al*. (2014) reported that the addition of 100 mg of calcium in beverages could reduce iron absorption by 18%, while the addition of 200 mg of calcium in beverages could reduce iron absorption by 27%. Thompson *et al*. (2010) incubated Caco-2 cells for 4 hours with 30 μM iron ammonium citrate and 2.2 mM calcium chloride. This study found that calcium did not change DMT1, but the content of DMT1 decreased in the incubated cell membranes because calcium caused

https://doi.org/10.26656/fr.2017.7(1).701

localization changes in DMT1. This causes a decrease in the absorption of non-heme iron. However, calcium has a less strong inhibitory ability when compared to polyphenols and phytic acid, which can form complexes causing irons to not be absorbed. In addition, the inhibitory effect of calcium can be overcome through the addition of organic acids, including ascorbic acid (Walczyk *et al*., 2014).

2.1.4 Animal protein

Some food sources of animal protein, such as casein, whey, fish, chicken meat, and egg whites, can affect the absorption of iron (Ems *et al*., 2021). The bioavailability of heme iron decreased in the presence of 150 g of chicken and fish about 53% and 32%, respectively, whereas the bioavailability did not decrease when beef was added. This may be due to the formation of luminal carriers that transport iron to the mucous cell membranes, which can inhibit iron absorption. The presence of collagen, casein, and albumin also did not affect the bioavailability of heme iron (Pizarro *et al*., 2016). On the other hand, the absorption of other minerals such as zinc is substantially higher in the presence of protein from animal sources than in vegetable protein. The addition of animal protein to plant foods can also increase the bioavailability of zinc. This is inversely proportional to heme iron which decreased significantly in the presence of animal protein (Villarroel *et al*., 2011; Maares and Haase, 2020).

2.1.5 Heating process

Various types of food processing can also affect the stability and bioavailability of iron compounds contained in foods. Research reported by Gandemer *et al*. (2020) showed that meat roasted at 80°C decreased heme iron levels by 12%. Meanwhile, Florek *et al*. (2016) reported that meat heated at 60°C decreased heme iron levels by 7%. Research conducted by Njoumi *et al*. (2017) showed that meat boiled at 100°C for 5 hrs decreased heme iron levels by 19%. The decrease in iron levels is caused by the partial conversion of heme iron compounds into non-heme iron caused by myoglobin oxidation. This occurs due to oxidative cleavage of the heme porphyrin ring during the heating process, making it more difficult for iron to be absorbed by duodenal enterocytes (Gandemer *et al*., 2020).

3. Various technologies to increase the bioavailability of iron

Various methods or technologies have been developed to increase the bioavailability of iron in foods. This is to facilitate the fulfilment of iron needs for the body so that it can reduce iron deficiency or anaemia. Some of these methods include fermentation, fortification, the addition of ascorbic acid, and iron encapsulation, as presented in Table 2.

3.1 Fermentation

The bioavailability of minerals, including iron, in grains, is generally hampered by the presence of anti-nutritional substances such as tannins and phytic acid (Luo *et al*., 2010). One solution to increase bioavailability is fermentation. Fermentation can liberate micronutrients such as iron-bound by phytic acid and oxalic acid, which act as inhibitors of their absorption. In the fermentation process, complex compounds are broken down into simpler compounds by microbial activity. According to Ahmed *et al*. (2020), the fermentation of 54-72 hrs can significantly reduce anti-nutritional substances such as phytic acid (PA), oxalic acid (OA), and tannins in bread from Koreeb seed flour. This is due to the increased activity of degrading enzymes such as phenyl oxidase and phytase formed during fermentation. The bioavailability of iron increased from 36% to 50% after fermentation for 72 hrs. Therefore, fermentation can be an alternative to increasing the bioavailability of iron in foodstuffs.

Processed foods such as bread that were treated with fermentation affected iron bioavailability. Fermentation with sourdough produces higher bioavailability than fermentation with yeast. This is due to the degradation of phytic acid by phytase in grains produced by yeast and lactic acid bacteria. These microorganisms can dephosphorylate phytate, forming inositol phosphate ester and free inorganic phosphate that the level of inhibition is lower (Lopez *et al*., 2003).

Bread processed with sourdough fermentation resulted in efficient transport of iron sources and increased iron absorption, which was higher than fermentation using conventional yeast (Bryszewska *et al*., 2019). During fermentation, sourdough produces organic acids such as lactic acid. These organic acids can increase the absorption of Fe (Khodaii *et al*., 2019). The mechanism of organic acids in iron absorption is by lowering the pH, and then low pH can lead to the breakdown of phytate and release of Fe from the Fe-phytate complex. Free Fe then forms Fe-organic acid complexes that can be dissolved at intestinal pH. The Fe-organic acid complex can delay the rate of gastric emptying, resulting in a longer Fe contact time in the duodenum (Salovaara *et al*., 2003; Khodaii *et al*., 2019).

3.2 Iron fortification

Food fortification is one way to reduce micronutrient deficiencies, including iron in humans. Iron fortification in food facilitates the fulfilment of iron needs for the

https://doi.org/10.26656/fr.2017.7(1).701

Table 2. Various methods or technologies to increase the bioavailability of iron

Methods/ Technologies	Results	References
Fermentation	Fermentation reduced levels of anti-nutrients, such as PA, OA and tannins. Fe bioavailability increased from 36% to 50% after 72 hours of fermentation.	Ahmed *et al*. (2020)
	Sourdough fermentation resulted in higher Fe bioavailability than yeast fermentation.	Lopez *et al*. (2003)
	Fe-sulfate fortified bread can be effectively transported both conventionally fermented and sourdough.	Bryszewska *et al*. (2019)
	Sourdough fermentation increased iron absorption.	Khodaii *et al*. (2019)
Fortification	Rice biofortification provided more than 50% estimated average requirement (EAR) in children.	Taleon *et al*. (2020)
	Bread fortified with Fe showed high bioavailability of Fe, namely 160.6-428.3%.	Singh *et al*. (2016)
	Fe fortification through the germination process was a promising method to increase the bioavailability of Fe in brown rice.	Wei *et al*. (2013)
	Biofortification-GMO increased the expression of proteins responsible for micronutrient absorption. Biofortification increased the concentration of micronutrients.	Balk *et al*. (2019)
	Biofortification caused plant roots to absorb siderophores produced by microorganisms so that iron absorption increased.	Khan *et al*. (2019)
	Fortification with the addition of iron-fortified yeast results in 72-82% of iron being lysed during digestion and releasing iron.	Sabatier *et al*. (2017)
	Fortification of 20 mM $FeSO_4$ on soybean germination showed that the stability of the iron contained was strongly affected by water content.	Makowska *et al*. (2018)
	Fortification through overexpression of the NAS gene showed increased iron levels in plants and increased iron bioavailability	Lee *et al*. (2009)
Addition of ascorbic acid	Ascorbic acid increased Fe absorption through the mechanism of Fe^{3+} to Fe^{2+} reduction agent, which allows more effective transport through the duodenal microvilli.	Habeych *et al*. (2016); Shubham *et al*. (2020).
	Ascorbic acid had a high potential to increase Fe absorption	Singh and Prasad, 2018).
	As a reducing agent, Fe^{3+} to Fe^{2+} to increase iron bioavailability.	Aride *et al*. (2010)
	Iron supplementation with vitamin C for 2 weeks increased the haemoglobin level in anaemia patients to 2.0 g/dL compared to only 1.84 g/dL without vitamin C.	Li *et al*. (2020)
	Haemoglobin level was positively correlated with iron intake along with vitamin C, which increased to 1.5 g/L.	Péneau *et al*. (2008)
Encapsulation	Encapsulation with ultrasonication pretreatment resulted in a 10-fold increase in iron content compared to the control	Rojas *et al*. (2019)
	Encapsulation through liposome formation increased the efficiency of iron encapsulation (85.5%) compared to the fatty acid ester (FAE) method (81.8%), but the FAE method was simpler and cheaper.	Abbasi and Azari (2011)
	Niosome-encapsulation resulted in an encapsulation efficiency of 72–84% and caused only minimal changes in the sensory, rheological, and stability properties.	Gutiérrez *et al*. (2016)
	The formation of solid lipid nanoparticles (SLN) resulted in an encapsulation efficiency of 92.3%, a particle size of 25 nm, and a 4-fold increase in bioavailability.	Hosny *et al*. (2015); Siddique and Park (2019)
	Encapsulation of ferrous sulfate in SLN increased iron absorption by 24.9% higher than that of free iron	Zariwala *et al*. (2013)
	Microencapsulation of ferrous fumarate in Double Fortified Salt (DFS) resulted in a premix formulation of Fe that could retain 93% Fe after 3 months of storage at 35 ºC.	Yadava *et al*. (2012)

human population and is cheaper than supplementation. Food fortification has a slower effect than supplementation in increasing iron bioavailability, but fortification carries a lower risk and has long-term sustainable benefits (Khan *et al*., 2019; Finlayson-Trick *et al*., 2020). The food selected for fortification must be in the form of food commonly consumed by the community. In addition, chemical interactions between foodstuffs and iron must be synergistic or not contradictory. Eating foods that have been fortified with iron regularly, can increase iron levels in the body (Detzel and Wieser, 2015).

The staple food that can be fortified with iron is rice. Rice can be biofortified through genetic engineering to contain higher iron content (Bashir *et al*., 2013). Several countries in Europe usually fortify micronutrients in bakery products, cakes, and biscuits (Agrahar-Murugkar,

https://doi.org/10.26656/fr.2017.7(1).701

2020). Bouhouch *et al*. (2016) reported that children and women who consumed iron-fortified biscuits showed a significant reduction in the risk of anaemia. Legumes can also be fortified either directly or through a milling process into flour and then fortified with iron (de Escalada Pla *et al*., 2020). Another suitable material for iron fortification is milk. Studies show that children aged 6–59 months who consume iron-fortified milk are less likely to have anaemia than they do not consume iron-fortified milk (Semba *et al*., 2010). Drinking water can also be a medium for iron fortification. Lamounier *et al*. (2010) reported that children who consumed drinking water fortified with iron showed a significant decrease in anaemia sufferers.

Most of the fortification process is carried out during the processing of foods. Fortification through the biofortification method has a similar goal but starts at the level of agricultural cultivation. Biofortification is carried out through agronomic (fertilization) and genetic (plant breeding) interventions. Various studies have shown that iron fortification shows success in efforts to increase iron bioavailability. The iron fortification approach is carried out through direct addition to food, biofortification, and encapsulation (Nosratpour and Jafari, 2019).

Biofortification is an effort to breed certain plants such as wheat, rice, corn, and tubers to improve the bioavailability of micronutrients, such as iron, in foodstuffs since plant cultivation. Biofortification carried out on rice plants resulted in iron bioavailability of fortified germinated brown rice almost 4 times higher than normal germination or without germination. Fortification through germination has an impact on decreasing the ability of phytic acid and phenolic compounds to inhibit the amount of iron bioavailability (Taleon *et al*., 2020). Thus, iron fortification by germination is a suitable method to increase the iron content and iron bioavailability in brown rice (Wei *et al*., 2013).

The fortification of iron directly into processed foods can be conducted by directly spraying it onto the finished product. This method has the advantage that it can avoid degradation factors during food processing. Iron-fortified foods such as bread showed a very high iron bioavailability, which increased up to 428.30% (Singh *et al*., 2016). However, direct fortification has several drawbacks; namely, iron in fortified foods is unstable and can affect the sensory properties of the product. Therefore, the technology that is currently being developed is the fortification with encapsulated fortification preparations, either micro- or nanoencapsulation (Darwish *et al*., 2021).

Micro- and nanoencapsulation are the latest techniques that involve coating bioactive compounds or minerals into a matrix with different capsule sizes. The encapsulation can increase the retention time of minerals and the controlled release of minerals. The encapsulation also improves bioavailability, solubility, and physicochemical stability (Nosratpour and Jafari, 2019). Yadava *et al*. (2012) succeeded in microencapsulating ferrous fumarate in salt to prevent iodine and iron deficiency. However, the two compounds can react to produce unwanted products, so it must be controlled so that the two compounds are separated. One of which is by microencapsulation to produce a stable double fortified salt (DFS) product. Ferrous fumarate is an inexpensive, bioavailable source of iron, and has a bland taste. However, it is reddish-brown, it needs to be agglomerated, disguised, and encapsulated to become an effective Fe-premix. Microencapsulation of ferrous fumarate in DFS resulted in Fe-premix formulation made by hydroxypropyl methylcellulose (HPMC) based polymer, which could retain 93% Fe after 3 months at 35ºC and 60% of RH. All Fe-premix formulas have good bioavailability, high particle density, and are organoleptically acceptable.

3.3 Addition of ascorbic acid/vitamin C

Vitamin C can increase iron absorption by reducing ferric ions (Fe^{3+}) to form ferrous ions (Fe^{2+}) so that they are easily absorbed (Aride *et al*., 2010). These changes allow transport through the duodenal microvilli more effectively. In addition, vitamin C also plays a role in the release of iron from ferritin and transferritin into red blood cells. Some iron supplements intentionally add or combine with vitamin C to increase iron bioavailability. Research conducted by Astuti *et al*. (2018) showed a significant increase in serum ferritin in supplementation in the group of individuals who did not take vitamin C with the group who then routinely took vitamin C supplements. Serum ferritin increased, which was initially an average of 9.54 g/dl to 41.89 g/dl. Research conducted by Singh and Prasad (2018) showed an increase in the bioavailability of iron in kidney beans added with vitamin C from 1.04% to 11.57%.

Generally, iron absorption is increased in the presence of organic acids, especially ascorbic acid (Habeych *et al*., 2016; Shubham *et al*., 2020). Ascorbic acid affects the absorption of Fe in several types of food, such as chickpeas, kidney beans, green beans, and wheat bread. The presence of ascorbic acid naturally in food samples can increase the absorption of mineral content, but it is necessary to add 10 mg of ascorbic acid to the sample to increase the bioavailability of Fe minerals (Singh and Prasad, 2018). Therefore, the addition of

https://doi.org/10.26656/fr.2017.7(1).701

ascorbic acid has a high potential to increase the absorption of Fe in food.

3.4 Iron encapsulation

Encapsulation is the process of coating the main material with a coating membrane to facilitate the control of target release. Iron encapsulation is commonly used for the composition of dry products such as baby food and powdered drink mixes. The encapsulation coating component in the form of lipid-based microcapsules can prevent colour damage and increase the bioavailability of iron and iodine in fortified salt. Another study on iron encapsulation by coating hydrogenated oil from palm oil and soybeans showed that mono, diacylglycerols, and maltodextrins did not interfere with iron bioavailability (Hurrell, 2004).

Iron encapsulation can be conducted by various methods. Abbasi and Azari (2011) used liposomes and fatty acid ester (FAE) methods in their study to microencapsulate iron in fortified milk. They reported that the liposome method had a higher encapsulation efficiency (85.5%) than using a method of FAE (81.8%). In another study, encapsulation using the liposome method used ferrous glycinate. Ding *et al*. (2009) reported that liposome encapsulation could significantly improve iron stability by preventing the interference of ferrous glycinate from the environment. The study showed that the liposome encapsulation method was effective for iron fortification. Gutiérrez *et al*. (2016) applied the encapsulation method in iron fortification in yoghurt using niosomes as an iron coating. Niosomes require surfactants as stabilizers in their use. The results showed that the encapsulation efficiency ranged from 72 –84%, with minimal changes in the characteristics of fortified yoghurt. Another study used niosomes in the encapsulation of iron and vitamin D. The results showed that niosomes were stable at room temperature storage. It is also known that niosomes must be stored at temperatures above the precipitation temperature because niosomes can rupture at 4°C resulting in iron and vitamin D leaking from the encapsulation (Wagner *et al*., 2016).

Nanoencapsulation is a process of coating the bioactive components with nano-size in a shell that implicates dispersion, incorporation, and absorption of bioactive compounds from small vesicles (Vishali *et al*., 2019). Nanoencapsulation can improve bioavailability, stability, oxidation prevention, release control, and targeted absorption. Thus, nanoencapsulation is suitable as an approach to iron fortification. Hosny *et al*. (2015) carried out iron encapsulation using the solid lipid nanoparticles (SLN) method. The results showed an increase in iron bioavailability 4 times. Zariwala *et al*. (2013) encapsulated ferrous sulfate in SLN, and the result showed that iron absorption increased up to 24.9% compared to ferrous sulfate without encapsulation. This is due to lipids increasing intestinal absorption by several mechanisms, namely: The lipophilic characteristics of solid lipids promote the transport of particles across bimolecular lipid membranes such as intestinal enterocytes. Lipid particles are bioadhesive, which helps adhere to the GI tract, thereby increasing cellular absorption. Lipids can also improve the permeability of the GI tract. In addition, lipids increase bioavailability by attenuating efflux transporters, such as p-glycoprotein in the apical gut mucosa. On the other hand, the approach using liposomes and solid lipid nanoparticles has a weakness in changing the sensory attributes of the product caused by the iron oxidation reaction and the addition of iron salts (Cengiz *et al*., 2019; Siddique and Park, 2019). Another study encapsulated iron by applying O-palmitoyl chitosan (OPC) into liposomes. OPC can increase iron encapsulation efficiency while increasing iron absorption in Caco-2 cells. This shows that the use of OPC liposomes is very promising for micronutrient delivery agents in the digestive process (Zariwala *et al*., 2018).

4. The role of iron in immune system improvement

Various sources of food in nature have bioactive properties that are beneficial to human health and biological systems. Various bioactive ingredients from plants, and animal products, as well as various micronutrients such as polyphenols, peptides, vitamins, and minerals, are known to be able to improve the immune system (Rezaharsamto and Subroto, 2019; Cámara *et al*., 2021; Indiarto *et al*., 2021). Iron is a mineral that is bioactive and has an important role in the biological system, especially in improving the immune system. Increasing the immune system, in general, is through the mechanism of controlling lymphocytes and T cell proliferation (Subroto and Indiarto, 2020). Insufficient iron intake can cause decreased immunity which can predispose individuals to infection because iron deficiency will affect the ability of adaptive antibody responses mediated by T cells and innate immunity. In innate immunity, iron can play a role in controlling the activity of enzymes that produce antimicrobial substances such as nitric oxide and hydroxyl radicals. Innate immunity also provides iron chelation so that it is not easily used by microbes for their growth needs (Cherayil, 2010; Nairz and Weiss, 2020). Iron also plays a role in the activation and control of NF-B, which is a transcription factor required for the expression of various genes involved in the inflammatory response and the body's defence system (Vallabhapurapu and Karin, 2009). Another role of iron

https://doi.org/10.26656/fr.2017.7(1).701

is through a mechanism in controlling HIF-1α, which is innate immunity resulting from the response of anti-microbial peptides by macrophages and cytokine expression (Nizet and Johnson, 2009). The studies on the role of iron in improving the immune system can be seen in Table 3.

In the adaptive immune system, iron plays a major role in the formation or production of lymphocyte cells or T cells that function in the body's defence system from microbial attacks and various other infections (Ganz and Nemeth, 2015; Nairz and Weiss, 2020). It is known that the formation of lymphocyte cells requires the availability of iron, where the production of lymphocyte cells is very dependent on how much iron is obtained through TfR1, it can support the proliferation involved to lead to the production of lymphocyte cells. Therefore, in conditions of iron deficiency, the production of lymphocytes or T cells can be disrupted (Cherayil, 2010).

Anaemia or iron deficiency is considered the most common deficiency of nutrition experienced by most of the population worldwide (Miller, 2013). In conditions of iron deficiency, adverse effects that can occur include decreased neutrophil function, namely through decreased myeloperoxidase activity and possible interference with intracellular bactericidal activity, decreased number of T -lymphocytes, impaired proliferative response induced by T-lymphocytes, impaired interleukin-2 production by lymphocytes, impaired natural killer cell activity, and decreased production of macrophage inhibitory factors (Cherayil, 2010; Calder, 2020; Nairz and Weiss, 2020). Besides that, Iron deficiency can cause thymus atrophy and have many effects on immune function in humans. Its effects are wide-ranging and include impaired adaptive immune system and innate immunity, inhibition of T helper 1 cytokine production, and T lymphocyte proliferation (Calder, 2020). Each of these disorders can be overcome by meeting the needs of bioactive compounds, including adequate iron intake.

Anaemia has been an important factor in the development of these immune system-degrading mechanisms. This mechanism became clear after it was known that these conditions would increase hepcidin in iron homeostasis. The increase in hepcidin expression is strongly influenced by pro-inflammatory cytokines such as TNF, IL-1, and IL-6, which will further decrease the ability of macrophages and enterocytes to regulate macrophages and enterocytes by FPN resulting in intracellular iron chelation. Increased expression of hepcidin has also been known to occur in several infectious conditions such as lupus, rheumatoid, and intestinal inflammation (Demirag *et al*., 2009; Cherayil, 2010). Maggini *et al*. (2018) reported that iron-adequate individuals experienced 50-60% lower T lymphocyte proliferation compared to iron-deficient individuals. This is a clear case for individuals who are iron deficient and therefore more susceptible to infection. Nevertheless, the relationship between deficiency of iron and sensitivity to infection is complex because many factors can affect the immune system both internally and externally (Oppenheimer, 2001; Cherayil, 2010; Ward *et al*., 2011; Ganz, 2018; Calder, 2020).

In other studies, it is quite surprising that infection can increase when the iron status in the body is excessive, especially infections by microorganisms that spend part of their life cycle intracellularly, such as mycobacteria and plasmodia (Cherayil, 2010; Ganz, 2018; Calder, 2020). This indicates that the condition of abundant iron can have a detrimental effect on being more easily infected. Iron at levels above a certain threshold may be associated with an increased risk of malaria and other infections, such as pneumonia. Therefore, iron intervention in areas of malaria-endemic is not recommended, especially during the peak season

Table 3. The studies on the role of iron in improving the immune system

Treatments	Results	References
Effect of iron status on macrophage polarization.	Adequacy of iron in macrophages was able to prevent pro-inflammatory responses by decreasing the expression of IL-6, IL-12, iNOS, IL-1β, and TNFα; and reduced LPS-	Agoro *et al*. (2018)
Effect of iron on support immune function.	Iron synergizes with vitamins and trace elements (selenium, copper, and zinc) to support cellular immunity.	Maggini *et al*. (2007)
Effect of iron on T cell proliferation.	Older Canadian women who are iron deficient have a 50-60% lower proliferation rate than those with adequate iron requirements.	Ahluwalia *et al*. (2004)
The role of iron on the interleukin-6 (IL-6).	There is a positive correlation between iron serum levels and serum levels of IL-6.	Hassan *et al*. (2016)
The role of lactoferrin on the physiological responses of T-cells.	Lactoferrin has a positive impact on immunoregulatory Th1 and Th2 cell activities.	Fischer *et al*. (2006)
The effect of iron on the immune system.	Iron affected the immune system by increasing the level of IL-6, the activity of neutrophils, monocytes, and the level of IgG4.	Ekiz *et al*. (2005)

https://doi.org/10.26656/fr.2017.7(1).701

of malaria transmission (Neuberger *et al*., 2016).

There are several principle mechanisms to explain the detrimental effect of excessive iron administration on the susceptibility of infection, including (i) iron overload causes inflammatory damage, (ii) excess iron leads to impaired immune function, (iii) microorganisms need iron and provide it to support the growth of pathogens (Nairz and Weiss, 2020). Lastly, several mechanisms of immunity have been developed to defend iron from pathogens. Iron preparations in the chelated form with other compounds are known to be safer in preventing infection. Studies have shown that the intensive administration of iron to iron-deficient children raised the risk of respiratory tract infections. However, when the administration of iron is carried out together with n-3 -rich oils, it can reduce the detrimental effects of excessive iron intake (Calder, 2020). In conditions of sufficient iron status, the presence of intracellular iron is in a chelated state it is not easily taken up by infectious microbes. However, in the conditions of excess iron intake, some of the iron is in a free state, it is easily taken up by infectious microbes to carry out growth and reproduction (Cherayil, 2010).

5. The role of iron in warding off virus infections and COVID-19

Iron is a micronutrient mineral that has an important role in responding to T-cell differentiation and proliferation. Iron can also encourage the formation or production of various cytokines, especially through hepcidin or directly (Maggini *et al*., 2007). However, iron can control or regulate the ratio between cytotoxic T cells and helpers to prevent excessive cytokine storms. Furthermore, iron is also an important component for neutrophil myeloperoxidase activity in enhancing defences to ward off viral attacks (Maggini *et al*., 2018; Nairz and Weiss, 2020). Under conditions of sufficient iron levels, iron will help increase the M2 macrophage phenotype and decrease the M1 pro-inflammatory response. Inhibition of the pro-inflammatory response may occur by decreasing nuclear translocation of NF-B by controlling IL-12, IL-6, IL-1β, iNOS, and TNFα expression (Agoro *et al*., 2018).

Iron can inhibit various types of viral infections, including the HIV and influenza A virus. Iron oxide nanoparticles take strong antiviral oppose influenza virus strain A/H1N1 through alteration of RNA transcription. In addition, iron oxide enzymes can shut off influenza A viruses and increase protective efficiencies, possibly by peroxidation of the viral lipid envelope (Qin *et al.,* 2019; Gorji and Ghadiri, 2021). The ability of iron to improve the immune system and inhibit infection with several types of viruses such as influenza strain A / H1N1 makes iron has good potential in inhibiting infection with the Sars-CoV-2 virus. This virus has become the cause of the COVID-19 pandemic that afflicts almost all countries in the world. The sars-CoV-2 virus has characteristics that are almost the same as the influenza virus, which is included in the envelope viruses group. This virus is covered by a lipid component on the outside it can be peroxidated by various oxidizing agents (Abu-Farha *et al*., 2020). Iron can activate iron oxide enzymes which are thought to be able to oxidize the fatty layer of the Sars-CoV-2 virus, viral growth and replication are inhibited (Oppenheimer, 2001; Maggini *et al*., 2018). The studies on the role of iron against viral infections can be seen in Table 4.

However, to obtain a good immune response and the ability to ward off viruses, an appropriate and accurate iron intake is needed. Iron deficiency decreases the immune system's ability to limit viral infections, mainly when the virus invades immune cells. Anaemia or severe iron deficiency conditions will greatly affect the immune system when a viral infection occurs (Nairz and Weiss, 2020). However, under conditions of excessive iron intake, it can also attenuate the host's immune response to the virus (Cherayil, 2010). Hepcidin, a protein hormone that plays a role in regulating iron levels in the blood, can play a role in helping infected individuals to get optimal benefits from iron therapy (Wessling-Resnick, 2018). Various studies on the role of iron as an antiviral have discussed of the pros and cons. This is because the virus also requires iron, ferritin, and transferrin for the process of growth, survival, replication, and entry into host cells. In the condition that both the host and the virus need iron, the innate immune response controlled by hepcidin will control the metabolism of iron to limit its availability during infection so that viral infections do not develop more severely (Gorji and Ghadiri, 2021).

In another study, it was even reported that the Sars-CoV-2 virus could attack haemoglobin in red blood cells through a series of cellular actions, which in turn can make red blood cells unable to carry oxygen (Liu and Li, 2020). Excess iron intake, especially iron that is in a state of free unbound iron, can stimulate iron to be easily utilized by viruses that infect the body it can produce various harmful responses, such as hyperferritinemia, hypercoagulation, inflammation, and immune dysfunction that often occur in humans COVID-19 sufferers (Kernan and Carcillo, 2017; Cavezzi *et al*., 2020). Liu and Li (2020) reported that pathogenically the Sars-CoV-2 virus could utilize iron from the blood by attacking haemoglobin which causes iron ions in the porphyrin ring to dissociate or be released and then free

https://doi.org/10.26656/fr.2017.7(1).701

Table 4. The studies on the role of iron against viral infections

Treatments	Results	References
The role of Ferric ammonium citrate on the inhibition of virus infections.	Ferric ammonium citrate inhibited the infections of Enterovirus 71 (EV71), Zika virus, HIV virus, and Influenza A virus by blocking endosomal viral release and inducing viral fusion.	Wang *et al*. (2018)
Effect of Iron oxide nanoparticles on H1N1 influenza A virus.	Iron oxide nanoparticles can act as antiviral in strain A/H1N1 by the inhibition of RNA transcription.	Kumar *et al*. (2019)
The role of iron oxide nanozyme on inactivation of influenza virus.	Iron oxide nanozyme inhibited enveloped viruses including influenza virus, by catalysing the lipid peroxidation.	Qin *et al*. (2019)
Effect of iron on Malawian children who are anaemic and HIV-infected.	Iron can be improved $CD4^+$ T cell percentage, thereby improving immunity in HIV-infected children in anaemic conditions.	Esan *et al*. (2013)
Relationship between the Iron status of Chinese children with recurrent respiratory tract infection.	Children in China who have recurrent respiratory infections mostly have low iron in their hair.	Mao *et al*. (2014)
The role of lactoferrin on inhibition of the herpes virus.	Lactoferrin from bovine inhibited the replication of herpes simplex virus type 1 and 2.	Marchetti *et al*. (1998)
The role of lactoferrin on inhibition of the hepatitis C virus.	Lactoferrin from bovine can inhibit the Hepatitis C virus in the human hepatocyte cell line PH5CH8 effectively.	Ikeda *et al*. (1998)

in the blood circulation. Haemoglobin that loses iron can no longer bind and transport oxygen to be circulated throughout the body and can have dangerous consequences. Therefore, the presence of iron in the body needs to be limited to an adequate level and not excessive; and it is better to consume iron in the form of chelated ions as it is not easily taken up by the infecting virus (Habib *et al*., 2021).

Several studies have reported that iron in the form of chelated ions is safer and not easily exploited by viruses. Iron in the form of lactoferrin or other iron chelators is believed to be able to overcome these problems. The chelated iron can still be utilized by the body but is difficult for viruses to use in reproduction. Even iron chelators such as lactoferrin are also reported to act as immune modulators and can prevent inflammation by inhibiting pro-inflammatory cytokines such as IL-1 and IL-6 (Cherayil, 2010; Habib *et al*., 2021). The use of iron chelating agents such as deferiprone has been reported to be effective in prolonging the life of patients infected with HIV (Liu *et al*., 2020). Iron chelating can also inhibit the enlargement of host cells infected by viruses through the mechanism of controlling mitochondrial activity, resulting in the inhibition of host cell macromolecular synthesis (Drakesmith and Prentice, 2008). Iron chelating agents such as CP511 and CP502 have also been reported to be effective in inhibiting HIV replication and able to control cell proliferation (Crowe *et al*., 2004).

Clinical research on the effectiveness of iron in boosting the immune system and warding off COVID-19 is still ongoing and developing. Still, various studies have proven that adequate iron consumption can provide good health effects by improving the immune system. Thus, a more in-depth study is needed regarding clinical trials of the potential of iron in warding off COVID-19 either through the mechanism of increasing the immune system or other inhibitory mechanisms such as the destruction of lipid membranes and inhibition of viral RNA synthesis or replication.

6. Conclusion

The bioavailability of iron can be affected by substances that inhibit the absorption of iron, such as phytate, polyphenols, calcium, and animal protein. However, iron bioavailability can be increased in several ways, including by fermentation, addition of ascorbic acid, fortification, and encapsulation which can increase the ease of iron in food to be absorbed and prevent iron damage. Iron plays an important role in enhancing the immune system by controlling the proliferation of T cells. However, excessive consumption of iron can be at risk of weakening the host's immune response to viral infections. Therefore, the appropriate level of iron intake must be maintained accurately in order to optimally improve the immune system and ward off COVID-19.

Conflict of interest

The author declared no conflict of interest.

Acknowledgements

The authors would like to thank the Rector of Universitas Padjadjaran and the Ministry of Education, Culture, Research, and Technology of the Republic of Indonesia for the support provided for the publication of this article.

https://doi.org/10.26656/fr.2017.7(1).701

References

Abbasi, S. and Azari, S. (2011). Efficiency of novel iron microencapsulation techniques: Fortification of milk. *International Journal of Food Science and Technology*, 46(9), 1927–1933. https://doi.org/10.1111/j.1365-2621.2011.02703.x

Abbaspour, N., Hurrell, R. and Kelishadi, R. (2014). Review on iron and its importance for human health. *Journal of Research in Medical Sciences*, 19(2), 164–174.

Abu-Farha, M., Thanaraj, T.A., Qaddoumi, M.G., Hashem, A., Abubaker, J. and Al-Mulla, F. (2020). The role of lipid metabolism in COVID-19 virus infection and as a drug target. *International Journal of Molecular Sciences*, 21(10), 3544. https://doi.org/10.3390/ijms21103544

Agoro, R., Taleb, M., Quesniaux, V.F.J. and Mura, C. (2018). Cell iron status influences macrophage polarization. *PLoS ONE*, 13(5), e0196921. https://doi.org/10.1371/journal.pone.0196921

Agrahar-Murugkar, D. (2020). Food to food fortification of breads and biscuits with herbs, spices, millets and oilseeds on bio-accessibility of calcium, iron and zinc and impact of proteins, fat and phenolics. *LWT - Food Science and Technology*, 130, 109703. https://doi.org/10.1016/j.lwt.2020.109703

Ahluwalia, N., Sun, J., Krause, D., Mastro, A. and Handte, G. (2004). Immune function is impaired in iron-deficient, homebound, older women. *The American Journal of Clinical Nutrition*, 79(3), 516–521. https://doi.org/10.1093/ajcn/79.3.516

Ahmed, M.I., Xu, X., Sulieman, A.A., Na, Y. and Mahdi, A.A. (2020). The effect of fermentation time on in vitro bioavailability of iron, zinc, and calcium of kisra bread produced from koreeb (*Dactyloctenium aegyptium*) seeds flour. *Microchemical Journal*, 154, 104644. https://doi.org/10.1016/j.microc.2020.104644

Andrews, M., Briones, L., Jaramillo, A., Pizarro, F. and Arredondo, M. (2014). Effect of Calcium, Tannic Acid, Phytic Acid and Pectin over Iron Uptake in an In Vitro Caco-2 Cell Model. *Biological Trace Element Research*, 158, 122–127. https://doi.org/10.1007/s12011-014-9911-0

Aride, P.H.R., Ferreira, M.S., Duarte, R.M., de Oliveira, A.M., de Freitas, D.V., dos Santos, A.L.W., Nozawa, S.R. and Val, A.L. (2010). Ascorbic Acid (Vitamin C) and Iron Concentration in Tambaqui, *Colossoma macropomum*, Iron Absorption. *Journal of the World Aquaculture Society*, 41, 291–297. https://doi.org/10.1111/j.1749-7345.2010.00370.x

Armah, S.M., Boy, E., Chen, D., Candal, P. and Reddy, M.B. (2015). Regular Consumption of a High-Phytate Diet Reduces the Inhibitory Effect of Phytate on Nonheme-Iron Absorption in Women with Suboptimal Iron Stores. *The Journal of Nutrition*, 145(8), 1735–1739. https://doi.org/10.3945/jn.114.209957

Astuti, N.D., Wirjatmadi, B. and Adriani, M. (2018). The Role of Addition of Vitamin C in Iron Supplementation on Ferritin Serum Levels in Anemia Adolescent Females. *Health Notions*, 2(3), 332–338.

Balk, J., Connorton, J.M., Wan, Y., Lovegrove, A., Moore, K.L., Uauy, C., Sharp, P.A. and Shewry, P.R. (2019). Improving wheat as a source of iron and zinc for global nutrition. *Nutrition Bulletin*, 44(1), 53–59. https://doi.org/10.1111/nbu.12361

Bashir, K., Nozoye, T., Ishimaru, Y., Nakanishi, H. and Nishizawa, N.K. (2013). Exploiting new tools for iron bio-fortification of rice. *Biotechnology Advances*, 31(8), 1624–1633. https://doi.org/10.1016/j.biotechadv.2013.08.012

Bouhouch, R.R., El-fadeli, S. andersson, M., Aboussad, A., Chabaa, L., Zeder, C., Kippler, M., Baumgartner, J., Sedki, A. and Zimmermann, M.B. (2016). Effects of wheat-flour biscuits fortified with iron and EDTA, alone and in combination, on blood lead concentration, iron status, and cognition in children : a double-blind randomized controlled trial. *The American Journal of Clinical Nutrition*, 104(5), 1318–1326. https://doi.org/10.3945/ajcn.115.129346

Bryszewska, M.A., Tomás-cobos, L., Gallego, E., Villalba, M., Rivera, D., Laure, D., Saa, D.L.T. and Gianotti, A. (2019). In vitro bioaccessibility and bioavailability of iron from breads fortified with microencapsulated iron. *LWT - Food Science and Technology*, 99, 431–437. https://doi.org/10.1016/j.lwt.2018.09.071

Calder, P.C. (2020). Nutrition, immunity and COVID-19. *BMJ Nutrition, Prevention and Health*, 3(1), 74–92. https://doi.org/10.1136/bmjnph-2020-000085

Cámara, M., Sánchez-Mata, M.C., Fernández-Ruiz, V., Cámara, R.M., Cebadera, E. and Domínguez, L. (2021). A review of the role of micronutrients and bioactive compounds on immune system supporting to fight against the COVID-19 disease. *Foods*, 10(5), 1088. https://doi.org/10.3390/foods10051088

Candia, V., Ríos-Castillo, I., Carrera-Gil, F., Vizcarra, B., Olivares, M., Chaniotakis, S. and Pizarro, F. (2018). Effect of various calcium salts on non-heme iron bioavailability in fasted women of childbearing age. *Journal of Trace Elements in Medicine and Biology*, 49, 8–12. https://doi.org/10.1016/j.jtemb.2018.04.029

Castro-Alba, V., Lazarte, C.E., Bergenståhl, B. and Granfeldt, Y. (2019). Phytate, iron, zinc, and calcium content of common Bolivian foods and their estimated mineral bioavailability. *Food Science and Nutrition*, 7(9), 2854–2865. https://doi.org/10.1002/fsn3.1127

Cavezzi, A., Troiani, E. and Corrao, S. (2020). COVID-19: Hemoglobin, Iron, and Hypoxia beyond Inflammation. A Narrative Review. *Clinics and Practice*, 10(2), 24–30. https://doi.org/10.4081/cp.2020.1271

Cengiz, A., Kahyaoglu, T., Schröen, K. and Berton-Carabin, C. (2019). Oxidative stability of emulsions fortified with iron: the role of liposomal phospholipids. *Journal of the Science of Food and Agriculture*, 99(6), 2957–2965. https://doi.org/10.1002/jsfa.9509

Cherayil, B.J. (2010). Iron and immunity: Immunological consequences of iron deficiency and overload. *Archivum Immunologiae et Therapiae Experimentalis*, 58, 407–415. https://doi.org/10.1007/s00005-010-0095-9

Crowe, W.E., Maglova, L.M., Ponka, P. and Russell, J.M. (2004). Human cytomegalovirus-induced host cell enlargement is iron dependent. *American Journal of Physiology-Cell Physiology*, 287(4), C1023–C1030. https://doi.org/10.1152/ajpcell.00511.2003

Darwish, A.M.G., Soliman, T.N., Elhendy, H.A. and El-Kholy, W.M. (2021). Nano-encapsulated Iron and Folic Acid-Fortified Functional Yogurt Enhance Anemia in Albino Rats. *Frontiers in Nutrition,* 8, 654624. https://doi.org/10.3389/fnut.2021.654624

Dasa, F. and Abera, T. (2018). Factors Affecting Iron Absorption and Mitigation Mechanisms: A review. *International Journal of Agricultural Science and Food Technology*, 4(1), 024–030. https://doi.org/10.17352/2455-815x.000033

de Escalada Pla, M.F., Flores, S.K. and Genevois, C.E. (2020). Innovative strategies and nutritional perspectives for fortifying pumpkin tissue and other vegetable matrices with iron. *Food Science and Human Wellness*, 9(2), 103–111. https://doi.org/10.1016/j.fshw.2020.02.005

Delimont, N.M., Haub, M.D. and Lindshield, B.L. (2017). The impact of tannin consumption on iron bioavailability and status : A narrative review. *Current Developments in Nutrition*, 1(2), 1–12. https://doi.org/10.3945/cdn.116.000042

Demirag, M.D., Haznedaroglu, S., Sancak, B., Konca, C., Gulbahar, O., Ozturk, M.A. and Goker, B. (2009). Circulating Hepcidin in the Crossroads of Anemia and Inflammation Associated with Rheumatoid Arthritis. *Internal Medicine*, 48(6), 421–426. https://doi.org/10.2169/internalmedicine.48.1578

Detzel, P. and Wieser, S. (2015). Food Fortification for Addressing Iron Deficiency in Filipino Children : Benefits and Cost-Effectiveness. *Annals of Nutrition and Metabolism*, 66(Suppl. 2), 35–42. https://doi.org/10.1159/000375144

Deugnier, Y., Battistelli, D., Jouanolle, H., Guyader, D., Gueguen, M., Loréal, O., Jacquelinet, C., Bourel, M. and Brissot, P. (1991). Hepatitis B virus infection markers in genetic haemochromatosis: A study of 272 patients. *Journal of Hepatology*, 13(3), 286–290. https://doi.org/10.1016/0168-8278(91)90070-R

Ding, B., Xia, S., Hayat, K. and Zhang, X. (2009). Preparation and pH stability of ferrous glycinate liposomes. *Journal of Agricultural and Food Chemistry*, 57(7), 2938–2944. https://doi.org/10.1021/jf8031205

Drakesmith, H. and Prentice, A. (2008). Viral infection and iron metabolism. *Nature Reviews Microbiology*, 6, 541–552. https://doi.org/10.1038/nrmicro1930

Ekiz, C., Agaoglu, L., Karakas, Z., Gurel, N. and Yalcin, I. (2005). The effect of iron deficiency anemia on the function of the immune system. *Hematology Journal*, 5(7), 579–583. https://doi.org/10.1038/sj.thj.6200574

Ems, T., St Lucia, K. and Huecker, M.R. (2021). Biochemistry, Iron Absorption. Treasure Island, Florida, USA: StatPearls Publishing.

Esan, M.O., van Hensbroek, M.B., Nkhoma, E., Musicha, C., White, S.A., ter Kuile, F.O. and Phiri, K.S. (2013). Iron Supplementation in HIV-Infected Malawian Children With Anemia: A Double-Blind, Randomized, Controlled Trial. *Clinical Infectious Diseases*, 57(11), 1626–1634. https://doi.org/10.1093/cid/cit528

Finlayson-Trick, E.C., Fischer, J.A., Goldfarb, D.M. and Karakochuk, C.D. (2020). The Effects of Iron Supplementation and Fortification on the Gut Microbiota: A Review. *Gastrointestinal Disorders*, 2 (4), 327–340. https://doi.org/10.3390/gidisord2040030

Fischer, R., Debbabi, H., Dubarry, M., Boyaka, P. and Tomé, D. (2006). Regulation of physiological and pathological Th1 and Th2 responses by lactoferrin. *Biochemistry and Cell Biology*, 84(3), 303–311. https://doi.org/10.1139/o06-058

Florek, M., Junkuszew, A., Greguła-kania, M., Bojar, W., Kaliniak, A., Bracik, K., Krupa, P. and Gruszecki, T.M. (2016). Effect of sex, muscle, and

processing temperature on heme iron content in lamb meat. *Animal Science Papers and Reports*, 34(3), 257–268.

Gandemer, G., Scislowski, V., Portanguen, S. And Kondjoyan, A., (2020). The Impact of Cooking of Beef on the Supply of Heme and Non-Heme Iron for Humans. *Food and Nutritions Sciences*, 11(7), 629–648. https://doi.org/10.4236/fns.2020.117045

Ganz, T. (2018). Iron and infection. *International Journal of Hematology*, 107(1), 7–15. https://doi.org/10.1007/s12185-017-2366-2

Ganz, T. and Nemeth, E. (2015). Iron homeostasis in host defence and inflammation. *Nature Reviews Immunology*, 15(8), 500–510. https://doi.org/10.1038/nri3863

Geissler, C. and Singh, M. (2011). Iron, Meat and Health. *Nutrients*, 3(3), 283–316. https://doi.org/10.3390/nu3030283

Gharibzahedi, S.M.T. and Jafari, S.M. (2017). The importance of minerals in human nutrition: Bioavailability, food fortification, processing effects and nanoencapsulation. *Trends in Food Science and Technology*, 62, 119–132. https://doi.org/10.1016/j.tifs.2017.02.017

Gibson, R.S., Bailey, K.B., Gibbs, M. and Ferguson, E.L. (2010). A review of phytate, iron, zinc, and calcium concentrations in plant-based complementary foods used in low-income countries and implications for bioavailability. *Food and Nutrition Bulletin*, 31(Suppl. 2), 134–146. https://doi.org/10.1177/15648265100312s206

Gorji, A. and Ghadiri, M.K. (2021). Potential roles of micronutrient deficiency and immune system dysfunction in the coronavirus disease 2019 (COVID -19) pandemic. *Nutrition*, 82, 111047. https://doi.org/10.1016/j.nut.2020.111047

Gupta, R.K., Gangoliya, S.S. and Singh, N.K. (2013). Reduction of phytic acid and enhancement of bioavailable micronutrients in food grains. *Journal of Food Science and Technology*, 52(2), 676–684. https://doi.org/10.1007/s13197-013-0978-y

Gutiérrez, G., Matos, M., Barrero, P., Pando, D., Iglesias, O. and Pazos, C. (2016). Iron-entrapped niosomes and their potential application for yogurt fortification. *LWT - Food Science and Technology*, 74, 550–556. https://doi.org/10.1016/j.lwt.2016.08.025

Habeych, E., van Kogelenberg, V., Sagalowicz, L., Michel, M. and Galaffu, N. (2016). Strategies to limit colour changes when fortifying food products with iron. *Food Research International,* 88(Part A), 122–128. https://doi.org/10.1016/j.foodres.2016.05.017

Habib, H.M., Ibrahim, S., Zaim, A. and Ibrahim, W.H. (2021). The role of iron in the pathogenesis of COVID-19 and possible treatment with lactoferrin and other iron chelators. *Biomedicine and Pharmacotherapy*, 136, 111228. https://doi.org/10.1016/j.biopha.2021.111228

Hassan, T.H., Badr, M.A., Karam, N.A., Zkaria, M., El Saadany, H.F., Abdel Rahman, D.M., Shahbah, D.A., Al Morshedy, S.M., Fathy, M., Esh, A.M.H. and Selim, A.M. (2016). Impact of iron deficiency anemia on the function of the immune system in children. *Medicine*, 95(47), e5395. https://doi.org/10.1097/MD.0000000000005395

Hosny, K.M., Banjar, Z., Hariri, A.H. and Hassan, A.H. (2015). Solid lipid nanoparticles loaded with iron to overcome barriers for treatment of iron deficiency anemia. *Drug Design, Development and Therapy*, 9, 313–320. https://doi.org/10.2147/DDDT.S77702

Hurrell, R. and Egli, I. (2010). Iron bioavailability and dietary reference values. *The American Journal of Clinical Nutrition*, 91(5), 1461S–1467S. https://doi.org/10.3945/ajcn.2010.28674F

Hurrell, R.F. (2004). Phytic acid degradation as a means of improving iron absorption. *International Journal for Vitamin and Nutrition Research*, 74(6), 445–452. https://doi.org/10.1024/0300-9831.74.6.445

Ikeda, M., Sugiyama, K., Tanaka, T., Tanaka, K., Sekihara, H., Shimotohno, K. and Kato, N. (1998). Lactoferrin Markedly Inhibits Hepatitis C Virus Infection in Cultured Human Hepatocytes. *Biochemical and Biophysical Research Communications*, 245(2), 549–553. https://doi.org/10.1006/bbrc.1998.8481

Indiarto, R. Subroto, E., Angeline and Selly. (2021). Ginger rhizomes (*Zingiber officinale*) functionality in food and health perspective : a review. *Food Research*, 5(1), 497–505. https://doi.org/10.26656/fr.2017.5(1).361

Institute of Medicine (US) Panel on Micronutrients. (2001). Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. Washington, DC., USA: National Academies Press.

Jaramillo, Á., Briones, L., Andrews, M., Arredondo, M., Olivares, M., Brito, A. and Pizarro, F. (2015). Effect of phytic acid, tannic acid and pectin on fasting iron bioavailability both in the presence and absence of calcium. *Journal of Trace Elements in Medicine and Biology*, 30, 112–117. https://doi.org/10.1016/j.jtemb.2014.11.005

Kell, D.B., Heyden, E.L. and Pretorius, E. (2020). The Biology of Lactoferrin, an Iron-Binding Protein That Can Help Defend Against Viruses and Bacteria. *Frontiers in Immunology*, 11, 1221. https://doi.org/10.3389/fimmu.2020.01221

Kernan, K.F. and Carcillo, J.A. (2017). Hyperferritinemia and inflammation. *International Immunology*, 29(9), 401–409. https://doi.org/10.1093/intimm/dxx031

Khan, A., Singh, J., Upadhayay, V.K., Singh, A.V. and Shah, S. (2019). Microbial biofortification: A green technology through plant growth promoting microorganisms. In Shah S., Venkatramanan V. and Prasad R. (eds). Sustainable Green Technologies for Environmental Management, p. 255–269. Singapore: Springer. https://doi.org/10.1007/978-981-13-2772-8_13

Khodaii, Z., Zadeh, M.N., Kamali, J. and Natanzi, M.M. (2019). Gene Reports Enhanced iron absorption from lactic acid fermented bread (an *in vivo*/*ex vivo* study). *Gene Reports*, 15, 100389. https://doi.org/10.1016/j.genrep.2019.100389

Kiewlicz, J. and Rybicka, I. (2020). Minerals and their bioavailability in relation to dietary fiber, phytates and tannins from gluten and gluten-free flakes. *Food Chemistry*, 305, 125452. https://doi.org/10.1016/j.foodchem.2019.125452

Kumar, R., Nayak, M., Sahoo, G.C., Pandey, K., Sarkar, M.C., Ansari, Y., Das, V.N.R., Topno, R.K., Bhawna, Madhukar, M. and Das, P. (2019). Iron oxide nanoparticles based antiviral activity of H1N1 influenza A virus. *Journal of Infection and Chemotherapy*, 25(5), 325–329. https://doi.org/10.1016/j.jiac.2018.12.006

Lamounier, J.A., Capanema, F.D., da Silva Rocha, D., de Oliveira, J.E.D., da Silva, M.C. and de Almeida, C.A.N. (2010). Iron Fortification Strategies for the Control of Childhood Anemia in Brazil. *Journal of Tropical Pediatrics*, 56(6), 448–451. https://doi.org/10.1093/tropej/fmq001

Larson, D.S. and Coyne, D.W. (2013). Understanding and exploiting hepcidin as an indicator of anemia due to chronic kidney disease. *Kidney Research and Clinical Practice*, 32(1), 11–15. https://doi.org/10.1016/j.krcp.2013.01.001

Lee, S., Jeon, U.S., Lee, S.J., Kim, Y.K., Persson, D.P., Husted, S., Schjørring, J.K., Kakei, Y., Masuda, H., Nishizawa, N.K. and An, G. (2009). Iron fortification of rice seeds through activation of the nicotianamine synthase gene. *Proceedings of the National Academy of Sciences*, 106(51), 22014–22019. https://doi.org/10.1073/pnas.0910950106

Lesjak, M., Balesaria, S., Skinner, V., Debnam, E.S. and Srai, S.K.S. (2019). Quercetin inhibits intestinal non-haem iron absorption by regulating iron metabolism genes in the tissues. *European Journal of Nutrition*, 58(2), 743–753. https://doi.org/10.1007/s00394-018-1680-7

Lesjak, M., Hoque, R., Balesaria, S., Skinner, V., Debnam, E.S., Srai, S.K.S. and Sharp, P.A. (2014). Quercetin inhibits intestinal iron absorption and ferroportin transporter expression in vivo and in vitro. *PLoS ONE*, 9(7), e102900. https://doi.org/10.1371/journal.pone.0102900

Li, N., Zhao, G., Wu, W., Zhang, M., Liu, W., Chen, Q. and Wang, X. (2020). The Efficacy and Safety of Vitamin C for Iron Supplementation in Adult Patients With Iron Deficiency Anemia: A Randomized Clinical Trial. *JAMA Network Open*, 3 (11), e2023644. https://doi.org/10.1001/jamanetworkopen.2020.23644

Liu, W., Zhang, S., Nekhai, S. and Liu, S. (2020). Depriving Iron Supply to the Virus Represents a Promising Adjuvant Therapeutic Against Viral Survival. *Current Clinical Microbiology Reports*, 7 (2), 13–19. https://doi.org/10.1007/s40588-020-00140-w

Liu, W. and Li, H. (2020). COVID-19: Attacks the 1-Beta Chain of Hemoglobin and Captures the Porphyrin to Inhibit Human Heme Metabolism. *ChemRxiv*. [Accepted]. https://doi.org/10.33774/chemrxiv-2021-dtpv3-v10

Lopez, H.W., Duclos, V., Coudray, C., Krespine, V., Feillet-Coudray, C., Messager, A., Demigné, C. and Rémésy, C. (2003). Making bread with sourdough improves mineral bioavailability from reconstituted whole wheat flour in rats. *Nutrition*, 19(6), 524–530. https://doi.org/10.1016/S0899-9007(02)01079-1

Luo, Y.W., Xie, W.H. and Cui, Q.X. (2010). Effects of phytase, cellulase, and dehulling treatments on iron and zinc in vitro solubility in faba bean (*Vicia faba L.*) flour and legume fractions. *Agriculture Food Chemistry*, 58(4), 2483–2490. https://doi.org/10.1021/jf903275w

Ma, Q., Kim, E., Lindsay, E.A. and Han, O. (2011). Bioactive Dietary Polyphenols Inhibit Heme Iron Absorption in a Dose-Dependent Manner in Human Intestinal Caco-2 Cells. *Journal of Food Science*, 76 (5), H143–H150. https://doi.org/10.1111/j.1750-3841.2011.02184.x

Maares, M. and Haase, H. (2020). A Guide to Human Zinc Absorption: General Overview and Recent Advances of In Vitro Intestinal Models. *Nutrients*, 12(3), 762. https://doi.org/10.3390/nu12030762

Maggini, S., Pierre, A. and Calder, P.C. (2018). Immune function and micronutrient requirements change over the life course. *Nutrients*, 10(10), 1531. https://doi.org/10.3390/nu10101531

Maggini, S., Wintergerst, E.S., Beveridge, S. and Hornig, D.H. (2007). Selected vitamins and trace elements support immune function by strengthening epithelial barriers and cellular and humoral immune responses. *British Journal of Nutrition*, 98(Suppl. 1), 29–35. https://doi.org/10.1017/S0007114507832971

Makowska, A., Zielińska-Dawidziak, M., Niedzielski, P. and Michalak, M. (2018). Effect of extrusion conditions on iron stability and physical and textural properties of corn snacks enriched with soybean ferritin. *International Journal of Food Science and Technology*, 53(2), 296–303. https://doi.org/10.1111/ijfs.13585

Manach, C., Scalbert, A., Morand, C., Rémésy, C. and Jiménez, L. (2004). Polyphenols: Food sources and bioavailability. *American Journal of Clinical Nutrition*, 79(5), 727–747. https://doi.org/10.1093/ajcn/79.5.727

Mao, S., Zhang, A. and Huang, S. (2014). Meta-analysis of Zn, Cu and Fe in the hair of Chinese children with recurrent respiratory tract infection. *Scandinavian Journal of Clinical and Laboratory Investigation*, 74 (7), 561–567. https://doi.org/10.3109/00365513.2014.921323

Marchetti, M., Pisani, S., Antonini, G., Valenti, P., Seganti, L. and Orsi, N. (1998). Metal complexes of bovine lactoferrin inhibit in vitro replication of herpes simplex virus type 1 and 2. *Biometals*, 11(2), 89–94. https://doi.org/10.1023/A:1009217709851

Miller, J.L. (2013). Iron deficiency anemia: A common and curable disease. *Cold Spring Harbor Perspectives in Medicine*, 3, a011866. https://doi.org/10.1101/cshperspect.a011866

Milman, N.T. (2020). A Review of Nutrients and Compounds, Which Promote or Inhibit Intestinal Iron Absorption: Making a Platform for Dietary Measures That Can Reduce Iron Uptake in Patients with Genetic Haemochromatosis. *Journal of Nutrition and Metabolism*, 2020, 7373498. https://doi.org/10.1155/2020/7373498

Mónica, A., Lautaro, B., Fernando, P. and Miguel, A. (2018). Calcium and zinc decrease intracellular iron by decreasing transport during iron repletion in an *in vitro* model. *European Journal of Nutrition*, 57(8), 2693–2700. https://doi.org/10.1007/s00394-017-1535-7

Nair, K.M. and Iyengar, V. (2009). Iron content, bioavailability and factors affecting iron status of Indians. *The Indian Journal of Medical Research*, 130(5), 634–645.

Nairz, M., Haschka, D., Demetz, E. and Weiss, G. (2014). Iron at the interface of immunity and infection. *Frontiers in Pharmacology*, 5, 152. https://doi.org/10.3389/fphar.2014.00152

Nairz, M. and Weiss, G. (2020). Iron in infection and immunity. *Molecular Aspects of Medicine*, 75, 100864. https://doi.org/10.1016/j.mam.2020.100864

Neuberger, A., Okebe, J., Yahav, D. and Paul, M. (2016). Oral iron supplements for children in malaria -endemic areas. *Cochrane Database of Systematic Reviews*, 2016(2), CD006589. https://doi.org/10.1002/14651858.CD006589.pub4

Nizet, V. and Johnson, R.S. (2009). Interdependence of hypoxic and innate immune responses. *Nature Reviews Immunology*, 9(9), 609–617. https://doi.org/10.1038/nri2607

Njoumi, S., Bellagha, S., Icard-vernière, C., Picq, C., Amiot, M.J. and Mouquet-rivier, C. (2017). Effects of cooking and food matrix on estimated mineral bioavailability in Mloukhiya, a Mediterranean dish based on jute leaves and meat. *Food Research International*, 105, 233-240. https://doi.org/10.1016/j.foodres.2017.11.020

Nosratpour, M. and Jafari, S.M. (2019). Bioavailability of Minerals (Ca, Mg, Zn, K, Mn, Se) in Food Products. In Melton, L., Shahidi, F. and Varelis, P. (Eds.). Encyclopedia of Food Chemistry, p. 148–154. Cambridge, United Kingdom: Academic Press. https://doi.org/10.1016/B978-0-08-100596-5.21618-1

Oliveira, F., Rocha, S. and Fernandes, R. (2014). Iron metabolism: From health to disease. *Journal of Clinical Laboratory Analysis*, 28(3), 210–218. https://doi.org/10.1002/jcla.21668

Oppenheimer, S.J. (2001). Iron and Its Relation to Immunity and Infectious Disease. *The Journal of Nutrition*, 131(2), 616S-635S. https://doi.org/10.1093/jn/131.2.616S

Péneau, S., Dauchet, L., Vergnaud, A.-C., Estaquio, C., Kesse-Guyot, E., Bertrais, S., Latino-Martel, P., Hercberg, S. and Galan, P. (2008). Relationship between iron status and dietary fruit and vegetables based on their vitamin C and fiber content. *The American Journal of Clinical Nutrition*, 87(5), 1298–1305. https://doi.org/10.1093/ajcn/87.5.1298

Pizarro, F., Olivares, M., Valenzuela, C., Brito, A., Weinborn, V., Flores, S. and Arredondo, M. (2016). The effect of proteins from animal source foods on heme iron bioavailability in humans. *Food Chemistry*, 196, 733–738. https://doi.org/10.1016/

j.foodchem.2015.10.012

Qin, T., Ma, R., Yin, Y., Miao, X., Chen, S., Fan, K., Xi, J., Liu, Q., Gu, Y., Yin, Y., Hu, J., Liu, X., Peng, D. and Gao, L. (2019). Catalytic inactivation of influenza virus by iron oxide nanozyme. *Theranostics*, 9(23), 6920–6935. https://doi.org/10.7150/thno.35826

Quintaes, K.D. and Diez-Garcia, R.W. (2015). The importance of minerals in the human diet. In de la Guardia, M. and Garrigues, S. (Eds). Handbook of Mineral Elements in Food, p. 1–18. Hoboken, New Jersey, USA: John Wiley and Sons. https://doi.org/10.1002/9781118654316.ch1

Rezaharsamto, B. and Subroto, E. (2019). A Review On Bioactive Peptides Derived From Various Sources Of Meat And Meat By-Products. *International Journal of Scientific and Technology Research*, 8 (12), 3151–3156.

Rojas, M.L., Alvim, I.D. and Augusto, P.E.D. (2019). Incorporation of microencapsulated hydrophilic and lipophilic nutrients into foods by using ultrasound as a pre-treatment for drying: A prospective study. *Ultrasonics Sonochemistry*, 54, 153–161. https://doi.org/10.1016/j.ultsonch.2019.02.004

Sabatier, M., Egli, I., Hurrell, R., Hoppler, M., Gysler, C., Georgeon, S., Mukherje, R., Richon, P.A., Vigo, M., Foman, J.T., Zeder, C. and Schaffer-Lequart, C. (2017). Iron bioavailability from fresh cheese fortified with iron-enriched yeast. *European Journal of Nutrition*, 56(4), 1551–1560. https://doi.org/10.1007/s00394-016-1200-6

Salovaara, S., Alminger, M.L., Eklund-Jonsson, C., Andlid, T. and Sandberg, A.-S. (2003). Prolonged transit time through the stomach and small intestine improves iron dialyzability and uptake *in vitro*. *Journal of Agriculture and Food Chemistry*, 51, 5131–5136. https://doi.org/10.1021/jf0208233

Semba, R.D., Moench-pfanner, R., Sun, K., de Pee, S., Akhter, N., Rah, J.H., Campbell, A.A., Badham, J., Bloem, M.W. and Kraemer, K. (2010). Iron-fortified milk and noodle consumption is associated with lower risk of anemia among children aged 6 – 59 mo in Indonesia 1 – 3. *The American Journal of Clinical Nutrition*, 92(1), 170–176. https://doi.org/10.3945/ajcn.2010.29254

Shawki, A. and Mackenzie, B. (2010). Interaction of calcium with the human divalent metal-ion transporter-1. *Biochemical and Biophysical Research Communications*, 393(3), 471–475. https://doi.org/10.1016/j.bbrc.2010.02.025

Shubham, K., Anukiruthika, T., Dutta, S., Kashyap, A.V., Moses, J.A. and Anandharamakrishnan, C. (2020). Iron deficiency anemia: A comprehensive review on iron absorption, bioavailability and emerging food fortification approaches. *Trends in Food Science and Technology*, 99, 58–75. https://doi.org/10.1016/j.tifs.2020.02.021

Siddique, A. and Park, Y.W. (2019). Effect of iron fortification on microstructural, textural, and sensory characteristics of caprine milk Cheddar cheeses under different storage treatments. *Journal of Dairy Science*, 102(4), 2890–2902. https://doi.org/10.3168/jds.2018-15427

Singh, P. and Prasad, S. (2018). Determination of ascorbic acid and its influence on the bioavailability of iron, zinc and calcium in Fijian food samples. *Microchemical Journal*, 139, 119-124. https://doi.org/10.1016/j.microc.2018.02.019

Singh, P., Prasad, S. and Aalbersberg, W. (2016). Bioavailability of Fe and Zn in selected legumes, cereals, meat and milk products consumed in Fiji. *Food Chemistry*, 207, 125–131. https://doi.org/10.1016/j.foodchem.2016.03.029

Speer, H., D'Cunha, N.M., Botek, M., McKune, A.J., Sergi, D., Georgousopoulou, E., Mellor, D.D. and Naumovski, N. (2019). The Effects of Dietary Polyphenols on Circulating Cardiovascular Disease Biomarkers and Iron Status: A Systematic Review. *Nutrition and Metabolic Insights*, 12, 117863881988273. https://doi.org/10.1177/1178638819882739

Subroto, E. and Indiarto, R. (2020). Bioactive monolaurin as an antimicrobial and its potential to improve the immune system and against COVID-19: a review. *Food Research*, 4(6), 2355–2365. https://doi.org/10.26656/fr.2017.4(6).324

Taleon, V., Gallego, S., Orozco, J.C. and Grenier, C. (2020). Retention of Zn, Fe and Phytic Acid in Parboiled Biofortified and Non-Biofortified Rice. *Food Chemistry: X*, 8, 100105. https://doi.org/10.1016/j.fochx.2020.100105

Thompson, B.A.V., Sharp, P.A., Elliott, R. and Fairweather-Tait, S.J. (2010). Inhibitory effect of calcium on non-Heme iron absorption may be related to translocation of DMT-1 at the apical membrane of enterocytes. *Journal of Agricultural and Food Chemistry*, 58(14), 8414–8417. https://doi.org/10.1021/jf101388z

Vallabhapurapu, S. and Karin, M. (2009). Regulation and Function of NF-κB Transcription Factors in the Immune System. *Annual Review of Immunology*, 27 (1), 693–733. https://doi.org/10.1146/annurev.immunol.021908.132641

Villarroel, P., Flores, S., Pizarro, F., de Romana, D.L.

and Arredondo, M. (2011). Effect of dietary protein on heme iron uptake by Caco-2 cells. *European Journal of Nutrition*, 50(8), 637–643. https://doi.org/10.1007/s00394-011-0173-8

Vishali, D.A., Monisha, J., Sivakamasundari, S.K., Moses, J.A. and Anandharamakrishnan, C. (2019). Spray freeze drying: Emerging applications in drug delivery. *Journal of Controlled Release*, 300, 93–101. https://doi.org/10.1016/j.jconrel.2019.02.044

Wagner, M.E., Spoth, K.A., Kourkoutis, L.F. and Rizvi, S.S.H. (2016). Stability of niosomes with encapsulated vitamin D3 and ferrous sulfate generated using a novel supercritical carbon dioxide method. *Journal of Liposome Research*, 26(4), 261–268. https://doi.org/10.3109/08982104.2015.1088868

Walczyk, T., Muthayya, S., Wegmüller, R., Thankachan, P., Sierksma, A., Frenken, L.G.J., Thomas, T., Kurpad, A. and Hurrell, R.F. (2014). Inhibition of Iron Absorption by Calcium Is Modest in an Iron-Fortified, Casein- and Whey-Based Drink in Indian Children andIs Easily Compensated for by Addition of Ascorbic Acid. *Journal of Nutrition*, 144(11), 1703–1709. https://doi.org/10.3945/jn.114.193417

Wang, H., Li, Z., Niu, J., Xu, Y., Ma, L., Lu, A., Wang, X., Qian, Z., Huang, Z., Jin, X., Leng, Q., Wang, J., Zhong, J., Sun, B. and Meng, G. (2018). Antiviral effects of ferric ammonium citrate. *Cell Discovery*, 4, 14. https://doi.org/10.1038/s41421-018-0013-6

Ward, R.J., Crichton, R.R., Taylor, D.L., Corte, L.D., Srai, S.K. and Dexter, D.T. (2011). Iron and the immune system. *Journal of Neural Transmission*, 118(3), 315–328. https://doi.org/10.1007/s00702-010-0479-3

Wei, Y., Shohag, M.J.I., Ying, F., Yang, X., Wu, C. and Wang, Y. (2013). Effect of ferrous sulfate fortification in germinated brown rice on seed iron concentration and bioavailability. *Food Chemistry*, 138(2–3), 1952–1958. https://doi.org/10.1016/j.foodchem.2012.09.134

Wessling-Resnick, M. (2018). Crossing the iron gate: Why and how transferrin receptors mediate viral entry. *Annual Review of Nutrition*, 38, 431–458. https://doi.org/10.1146/annurev-nutr-082117-051749

Xiao, L., Luo, G., Tang, Y. and Yao, P. (2018). Quercetin and iron metabolism: What we know and what we need to know. *Food and Chemical Toxicology*, 114, 190–203. https://doi.org/10.1016/j.fct.2018.02.022

Yadava, D., Li, Y.O., Diosady, L.L. and Wesley, A.S. (2012). Optimisation of Polymer Coating Process for Microencapsulating Ferrous Fumarate for Salt Double Fortification with Iodine and Iron. *Journal of Microencapsulation*, 29(8), 729–738. https://doi.org/10.3109/02652048.2011.651493

Zand, N., Christides, T. and Loughrill, E. (2015). Dietary intake of minerals. In de la Guardia, M. and Garrigues, S. (eds). Handbook of Mineral Elements in Food, p. 23–36. Hoboken, New Jersey, USA: John Wiley and Sons.

Zariwala, M.G., Bendre, H., Markiv, A., Farnaud, S., Renshaw, D., Taylor, K.M.G. and Somavarapu, S. (2018). Hydrophobically modified chitosan nanoliposomes for intestinal drug delivery. *International Journal of Nanomedicine*, 13, 5837–5848. https://doi.org/10.2147/IJN.S166901

Zariwala, M.G., Elsaid, N., Jackson, T.L., López, F.C., Farnaud, S., Somavarapu, S. and Renshaw, D. (2013). A novel approach to oral iron delivery using ferrous sulphate loaded solid lipid nanoparticles. *International Journal of Pharmaceutics*, 456(2), 400–407. https://doi.org/10.1016/j.ijpharm.2013.08.070

https://doi.org/10.26656/fr.2017.7(1).701