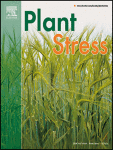
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**Review**

**Iron homeostasis in plants and its crosstalk with copper, zinc, and manganese**

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**Highlights**

* •

Micronutrients are vital for plant growth and development.

* •

The optimal concentration of each element is critical. However, in excess it affects normal physiology of the plant.

* •

Iron is the third most limiting nutrient.

* •

Hormones and small molecules affect Fe uptake.

* •

Crosstalk between different nutrients are poorly understood.

**Abstract**

Micronutrients like copper (Cu), manganese (Mn), Iron (Fe), and Zinc (Zn) are essential for plants, and their functions are tightly linked for vital metabolism. The normal concentration range for each of these metals in the plant is narrow, with both deficiencies and excesses causing severe physiological implications. Maintaining an optimum level of these redox-active metals in the plant requires balanced activities of transporters that mediate import into the cell, proper distribution to where it is needed and storage, and use in metalloproteins and metalloenzymes within the cell. Understanding the complexities of interaction between Fe and other micronutrients and how it defines the health of the plants would facilitate improved plant growth strategies on soils with the low/high levels of these metals, with implications for agriculture and phytoremediation. The review briefly discusses the role of these metals in plant and expands on iron homeostasis and its crosstalk with Cu, Zn, and Mn.

* [Previous article in issue](https://www.sciencedirect.com/science/article/pii/S2667064X21000051)
* [Next article in issue](https://www.sciencedirect.com/science/article/pii/S2667064X21000087)

**Keywords**

Iron

Metal homeostasis

Nutrient stress

Nutrient crosstalk

Plant metabolism

Rhizosphere

**1. Introduction**

Micronutrients play a central role in plant metabolism maintenance, growth and production, stress tolerance and disease resistance ([Shahzad and Amtmann, 2017](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0001)) Micronutrients like copper (Cu), manganese (Mn), Iron (Fe), and Zinc (Zn) are essential for plants at an optimal concentration. However, they are toxic at supra-optimal levels ([Shingles et al., 2004](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0002)). Plants maintain equilibrium in uptake, utilization, and storage of these metals to sustain appropriate ion [homeostasis](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/homeostasis) ([Grotz and Guerinot, 2006](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0003)). Being transition metals, they undergo redox changes under biological conditions; regulates biochemical functions by establishment and maintenance of stable coordinative linkages with electron pair donor atoms of organic ligands in a defined geometry and functional as well as structural components of [metalloproteins](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/metalloprotein" \o "Learn more about metalloproteins from ScienceDirect's AI-generated Topic Pages) ([Krämer and Clemens, 2006](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0004)). Plants maintain a strict balance in the uptake, transport, utilization, and storage of these metals to sustain appropriate ion homeostasis because these metals have the potential to become toxic at supra-optimal concentrations (production of reactive oxygen species via Fenton reaction) causing [oxidative stress](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/oxidative-stress) ([Grotz and Guerinot, 2006](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0003)). This review briefly discusses the role of each of the four micronutrients (Fe, Cu, Zn, and Mn) in plant metabolism, illustrates iron homeostasis in plants and its crosstalk with transition metals- Cu, Zn, and Mn.

Iron (Fe) is one of the most abundant element in the environment, yet the third most limiting nutrient in plants primarily due to its low solubility, especially in alkaline and [calcareous soils](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/calcareous-soil) ([Rout and Sahoo, 2015](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0005)). Fe is essential for many vital processes such as DNA synthesis, energy production (respiration), energy conversion (photosynthesis) and nitrogen reduction ([Rout and Sahoo, 2015](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub#bib0005)). Fe competes with other transition metals such as Cu, Zn, and Mn in its uptake, transport and chemical reaction within plant cells ([Rout and Sahoo, 2015](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub#bib0005)). Fe deficiency is a common nutritional disorder in many crop plants, resulting in reduced yields and reduced nutritional quality ([Rout and Sahoo, 2015](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub#bib0005); [McLean et al., 2009](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0006)). As plants are the primary source of iron for humans, the poor bioavailability of iron in plants is often related to Fe deficiency anemia in humans affecting nearly 25% of the world's population ([McLean et al., 2009](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub#bib0006)). Therefore, increasing iron concentration in [staple foods](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/staple-food) is considered to be an effective method to alleviate Fe deficiency in humans. Importantly, successful soil fortification strategies need a comprehensive understanding of how iron acquisition in plants is affected by similar oxidation state metals sharing [rhizosphere](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/rhizosphere" \o "Learn more about rhizosphere from ScienceDirect's AI-generated Topic Pages) and how other metals relative concentration regulates biological processes involving Fe.

**2. The physiological relevance of Fe, Cu, Zn and Mn in plants**

**2.1. Iron**

Fe typically found in two oxidation states, ferric (Fe+3) or ferrous (Fe+2). The oxidative state of ferrous (Fe+2) form readily changes, and this allows it to participate in various cellular functions, however, its regulation is crucial to avoid cellular toxicity. Iron is not readily available in neutral to [alkaline soils](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/alkaline-soils), rendering plants iron-deficient despite its abundance. Iron is a cofactor for redox enzymes such as cytochrome (Cyt) oxidase, [peroxidase](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/peroxidase" \o "Learn more about peroxidase from ScienceDirect's AI-generated Topic Pages), [catalase](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/catalase" \o "Learn more about catalase from ScienceDirect's AI-generated Topic Pages), iron-sulfur proteins, and [ferredoxin](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/ferredoxin" \o "Learn more about ferredoxin from ScienceDirect's AI-generated Topic Pages) ([Guerinot, 1994](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0007)). Fe is also an active cofactor of many enzymes necessary for plant hormone synthesis (such as ethylene) and enzymes such as [lipoxygenase](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/lipoxygenase" \o "Learn more about lipoxygenase from ScienceDirect's AI-generated Topic Pages) and 1-aminocyclopropane acid-1-carboxylic oxidase ([Siedow, 1991](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0008)). Fe participates in chlorophyll biosynthesis and stabilization, Fe is an integral component of respiratory and photosynthetic electron transport system and also acts as a cofactor in [electron transport chain](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/electron-transport-chain) carriers (Cyt f, [Cyt](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/cytochrome" \o "Learn more about Cyt from ScienceDirect's AI-generated Topic Pages) b559, and Cyt b563) ([Grotz and Guerinot, 2006](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0003); [Briat et al., 2010](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0009)) . Being crucial element Fe ensure the electron flow through the PSII-b6f/RieskePSI complex, thus indispensable for CO2 fixation ([Nishio et al., 1985](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0010); [Briat et al., 2015](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0011)). Iron in [leghemoglobin](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/leghemoglobin" \o "Learn more about leghemoglobin from ScienceDirect's AI-generated Topic Pages) and [nitrogenase](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/nitrogenase" \o "Learn more about nitrogenase from ScienceDirect's AI-generated Topic Pages) enzyme is critical for [nitrogen fixation](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/nitrogen-fixation) in leguminous plants ([Phillips, 1980](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0012)). [Chlorosis](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/chlorosis" \o "Learn more about Chlorosis from ScienceDirect's AI-generated Topic Pages) is the most apparent Fe-deficiency symptom in plants, which not only significantly affects plant growth, and development but also the [product quality](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/product-quality) as well as quantity ([Bashir et al., 2016](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0013)). Fe deficiency responses include stunted [root growth](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/root-growth) ([Mineral Nutrition of Higher Plants 1995](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0014); [Satbhai et al., 2017](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0015)) and up-regulation of genes involved in Fe uptake ([Colangelo and Guerinot, 2004](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0016)). In contrast to the limited availability of Fe, its overload in plants can result in [oxidative stress](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/oxidative-stress) via Fenton reaction ([Nishio et al., 1985](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0010)). Bronzing (coalesced tissue necrosis), acidity, and/or blackening of the roots are symptoms of plants exposed to above-optimal iron levels ([Laan et al., 1991](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0017)).

**2.2. Copper**

Two standard forms of Cu under physiological conditions have been reported, the reduced form of Cu i.e., Cu+, which binds favorably with sulfur-containing compounds having a [thioether](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/sulfide" \o "Learn more about thioether from ScienceDirect's AI-generated Topic Pages) or a thiol group, while the oxidized form i.e., Cu2+, coordinates mostly with imidazole nitrogen groups or oxygen ([Meharg, 2012](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0018)). This variable valency of Cu offer it various degree of freedom to interact with a wide-range of bio-molecules, in particular with proteins, to drive the biochemical reactions or stabilize structural integrity ([Festa and Thiele, 2011](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0019)). In model plant [Arabidopsis](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/arabidopsis) thaliana Six Cu-family transporters (COPT1-COPT6) have been identified, each with a distinct tissue-specific expression as well as [subcellular localization](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/subcellular-localization" \o "Learn more about subcellular localization from ScienceDirect's AI-generated Topic Pages) pattern ([Festa and Thiele, 2011](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0019)). COPT1, the most extensively studied Cu transporter so far, is thought to be mostly responsible for root Cu acquisition ([Festa and Thiele, 2011](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0019)). Copper plays a significant role in photosynthesis, respiration, and protection against oxidative stress ([Meharg, 2012](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0018)). At least 30 copper-containing enzymes are known which includes (i) oxidases, such as [cytochrome oxidase](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/cytochrome-c-oxidase" \o "Learn more about cytochrome oxidase from ScienceDirect's AI-generated Topic Pages), [diamine oxidase](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/diamine-oxidase" \o "Learn more about diamine oxidase from ScienceDirect's AI-generated Topic Pages), phenol oxidase, DOPA oxidase, [tyrosinase](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/tyrosinase" \o "Learn more about tyrosinase from ScienceDirect's AI-generated Topic Pages), phenolase, [polyphenol oxidase](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/catechol-oxidase" \o "Learn more about polyphenol oxidase from ScienceDirect's AI-generated Topic Pages), [laccase](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/laccase" \o "Learn more about laccase from ScienceDirect's AI-generated Topic Pages), [plastocyanin](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/plastocyanin" \o "Learn more about plastocyanin from ScienceDirect's AI-generated Topic Pages); (ii) anti-oxidative enzyme (Cu-Zn [superoxide dismutase](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/superoxide-dismutase); (iii) dioxygen carriers such as [hemocyanin](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/hemocyanin" \o "Learn more about hemocyanin from ScienceDirect's AI-generated Topic Pages) . Plastocyanin is the most abundant [copper protein](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/copper-protein) involved in electron transport between the [cytochrome b6f complex](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/cytochrome-b6f-complex" \o "Learn more about cytochrome b6f complex from ScienceDirect's AI-generated Topic Pages) to [photosystem I](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/photosystem-i" \o "Learn more about photosystem I from ScienceDirect's AI-generated Topic Pages) (PSI) in the [thylakoid](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/thylakoid" \o "Learn more about thylakoid from ScienceDirect's AI-generated Topic Pages) lumen of chloroplasts ([Meharg, 2012](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0018)). Copper deprivation causes a defect in photosynthetic electron transport due to a lack of plastocyanin (PC) ([Meharg, 2012](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0018)). Copper is also involved in the synthesis of a [molybdenum cofactor](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/molybdenum-cofactor) thereby linking Cu metabolism with [nitrogen assimilation](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/nitrogen-assimilation) and [phytochrome](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/phytochrome" \o "Learn more about phytochrome from ScienceDirect's AI-generated Topic Pages) biosynthesis ([Yamasaki et al., 2008](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0020)). Cu plays an essential role in many processes such as pollen formation, pollen viability, pollination and lipid desaturation. Moreover, the biosynthesis of lignin, quinones, and [carotenoids](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/carotenoid" \o "Learn more about carotenoids from ScienceDirect's AI-generated Topic Pages) are also influenced by Cu status ([Mineral Nutrition of Higher Plants 1995](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub#bib0014); [Hajiboland, 2012](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0021)). Copper also serves to intensify flavor, color in flowers and vegetables as well as sugar content and storage life of fruit. Typical deficiency symptoms of copper are [dieback](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/dieback) of stems and twigs, yellowing of leaves, stunted growth and pale green leaves that wither easily ([Mineral Nutrition of Higher Plants 1995](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub#bib0014))

**2.3. Zinc**

Zn2+ acts as a catalytic or structural co-factor in many enzymes and [regulatory proteins](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/regulatory-protein) ([Mineral Nutrition of Higher Plants 1995](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub#bib0014)). Zn serves as a cofactor for large number of enzymes involved in DNA transcription, protein, [nucleic acid](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/nucleic-acid), carbohydrate, and [lipid metabolism](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/lipid-metabolism) ([Hajiboland, 2012](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0021); [Coleman, 1998](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0022); [Ishimaru et al., 2011](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0023)). Zn is an integral component ofplant enzymes such as carbonic anhydrase, [alcohol dehydrogenase](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/alcohol-dehydrogenase), [alkaline phosphatase](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/alkaline-phosphatase), Cu-Zn SOD, RNA polymerase and [phospholipase](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/phospholipase" \o "Learn more about phospholipase from ScienceDirect's AI-generated Topic Pages) and also involved in the reaction of other enzymes where Zn is not the primary component ([Hajiboland, 2012](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0021)).

Unlike Fe and Cu, once taken up Zn maintains a stable redox state inside cells and is consequently safe in the proximity to sensitive biomolecules like DNA. Zn has a strong tendency to form tetrahedral complexes and this is the reason it is identified as a major constituent element of proteins associated with DNA and RNA synthesis, such as transcription factors (DNA-binding Zn finger motifs), reverse transcriptase and RNA polymerases ([Suzuki et al., 2012](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0024); [Broadley et al., 2007](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0025); [Bashir et al., 2016](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0013)). Transcription factors having DNA-binding [Zn finger motifs](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/zinc-finger-motif) not only offers DNA-binding, but also facilitates protein-protein interactions ([Bashir et al., 2016](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0013)). Among the various identified Zn finger proteins from *Arabidopsis*, 176 members of C2H2 type functions as part of an extensive regulatory network that senses and responds to different environmental stimuli ([Sinclair and Krämer, 2012](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0026)). Zn deficit in plants results in (i) the development of abnormalities in plants which become visible as deficiency symptoms such as stunted growth, chlorosis and smaller leaves, [spikelet](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/spadix) sterility, (ii) reduction in rate of [protein synthesis](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/protein-synthesis) as Zinc is constituent of RNA polymerase which regulates protein synthesis, (iii) higher tendency for infection and diseases as Zn plays a critical role in providing integrity or membrane stability, particularly in preventing the leakage of root membranes ([Ciftci-Yilmaz and Mittler, 2008](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0027)). During Zn deficiency, shoot growth is usually more inhibited than root growth ([Mineral Nutrition of Higher Plants 1995](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub#bib0014)).

**2.4. Manganese**

Though Mn available in three oxidation states in the soil, Mn2+ is the only phytoavailable form and the other two forms Mn3+ and Mn4+ are sparingly soluble ([Mineral Nutrition of Higher Plants 1995](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub#bib0014)). Mn has a profound influence on three physiological processes in plants: (i) Mn participates in the structure of the water-splitting system of photosystem II (PSII), which provides the necessary electrons for photosynthesis ([Graham and Webb, 2018](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0028)), (ii) Mn is required for N metabolism, it functions in [nitrate reduction](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/nitrate-reduction), by acting as an activator for the enzymes [nitrite reductase](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/nitrite-reductase) and hydroxylamine reductase, and (iii) Mn is essential for the biosynthesis of aromatic [amino acids](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/amino-acid) (tyrosine) and secondary products like lignin and [flavonoids](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/flavonoid" \o "Learn more about flavonoids from ScienceDirect's AI-generated Topic Pages) ([Buchanan et al., 2000](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0029)). Mn is an crucial constituent of Mn-superoxide dismutase (Mn-SOD), a major antioxidant enzyme ([Lidon et al., 2004](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0030)). Mn in plants also participates in carbohydrate and lipid biosynthesis ([Mineral Nutrition of Higher Plants 1995](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub#bib0014)). Besides, this Mn also serve as a cofactor of many enzymes, like Mn-catalase, Mn-peroxidases, TCA cycle decarboxylases, RNA polymerases and numerous [glycosyltransferases](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/glycosyltransferase" \o "Learn more about glycosyltransferases from ScienceDirect's AI-generated Topic Pages) ([Lidon et al., 2004](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0030)). The Mn-peroxidases generate hydrogen peroxide, which is thought to be involved in cell wall stabilization and pathogen resistance ([Socha and Guerinot, 2014](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0031)).

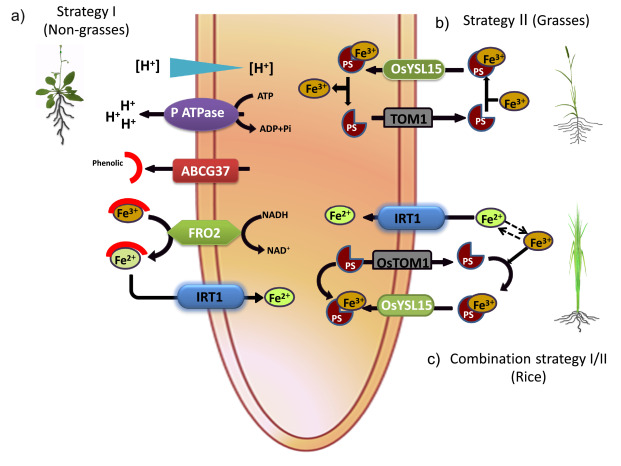
Mn deficiency in plants is frequently confused with Fe deficiency. However, Mn deficiency appears as interveinal chlorosis (yellow leaves with green veins) of the young leaves, sometimes with tan, sunken spots in the chlorotic areas between the veins as well as plants reduced growth and stunted in size ([Heine et al., 2011](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0032)). Mn deficiency is a widespread problem, most often occurring in [sandy soils](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/sandy-soil), organic soils with a pH above 6 and heavily weathered soils. It is usually aggravated by cold and wet conditions ([Dučić and Polle, 2005](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0033)). In contrast, higher than the required concentration of Mn in plants, like other discussed micronutrients, cause ROS production via the Fenton mechanism ([Heine et al., 2011](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub#bib0032)).

**3. Iron homeostasis in plants**

Due to the narrow optimal window for the iron concentration, plants have evolved multifaceted strategies for iron uptake, storage and metabolism. and they regulate these processes to maintain [homeostasis](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/homeostasis) for optimum plant development. While low iron availability severely affects plant growth and development, its high bioavailability can also be harmful. Excess iron inside a cell leads to the formation of [hydroxyl radicals](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/hydroxyl-radical), which leads to cellular damage. Why iron is critical to plant metabolism and how Iron deficiency or excess affect plants have been discussed previously, this section details on how plants maintain Fe balance through uptake, and transport; Fe toxicity effects.

**3.1. Fe uptake strategies in plants- reduction and chelation**

Plants have evolved two main approaches (strategy I and II) for uptake of Fe from the [rhizosphere](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/rhizosphere" \o "Learn more about rhizosphere from ScienceDirect's AI-generated Topic Pages) ([Grotz and Guerinot, 2006](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0003)). The strategy I (reduction strategy) occurrs in most non-grass plants, and it is well characterized in the model plant [Arabidopsis](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/arabidopsis) thaliana ([Fig. 1](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "fig0001)a). Under low Fe condition, protons are released by the H+-ATPase AHA2 in the rhizosphere. The released protons reduce the soil pH and enhance the Fe3+ solubility. Soluble Fe3+then enters the [apoplast](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/apoplast" \o "Learn more about apoplast from ScienceDirect's AI-generated Topic Pages) where it is chelated by coumarin-family phenolics which are exported by the ABCG37 transporter ([Mladěnka et al., 2010](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0034)). The chelated form of Fe3+ is reduced to Fe2+ by [plasma membrane](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/plasma-membrane) ferric chelate reductase FRO2 (FERRIC REDUCTION OXIDASE 2). With the help of high-affinity Iron-Regulated Transporter1 (IRT1), this converted Fe2+ is transported into the root epidermal cells ([Mineral Nutrition of Higher Plants 1995](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub#bib0014)).



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Fig. 1. Iron uptake strategies in plants (a) Strategy I is a reduction based strategy found in most plants except grasses, this includes acidification of the rhizosphere by the [plasma membrane](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/plasma-membrane) H+-ATPase (P-ATPase) which increases the solubility of Fe3+. The soluble Fe3+ is then chelated by the phenolics and exported by the ABCG37 transporter. FRO2 reduces chelated Fe3+ to Fe2+ and then Fe2+ is taken inside the plant cell by the Iron-Regulated Transporter - IRT1 transporter. (b) Strategy II is chelation strategy found in grasses, includes a phytosiderophore mediated transport, YS1 and TOM1; and (c) A combination strategy (Strategy I/II) located in rice. OsTOM1 transporter mediates the PS secretion through the plasma membrane. The OsYSL15 transporter exploited by rhizosphere formed Fe3+-PS to enters in to the root cells. In addition to Fe3+-PS uptake, rice also possesses the components of the Fe2+ uptake system.

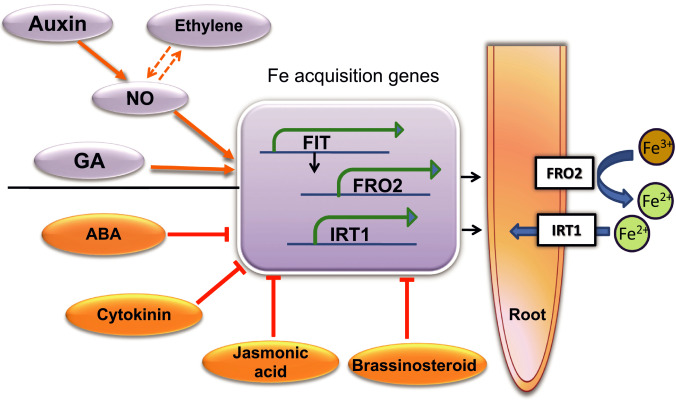
Strategy II is confined to grasses, similar to that used by many bacteria and fungi and is also known as a chelation-based strategy ([Morrissey and Guerinot, 2009](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0035)). This method may have evolved as an adaptation to alkaline soils where rhizosphere acidification is difficult to achieve ([Fig. 1](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub#fig0001)b). It is based on biosynthesis and secretion of [phytosiderophores](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/phytosiderophore" \o "Learn more about phytosiderophores from ScienceDirect's AI-generated Topic Pages) (PS; a class of mugineic acids compounds) in the rhizosphere, which chelates Fe3+, and form PS-Fe (III) complex. The complex employs YS/YSL family transporters to enter into the root ([Morrissey and Guerinot, 2009](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub#bib0035)). The chelation strategy is less sensitive to pH than the reduction strategy, and there is a strong correlation between the amount of PS released and resistance to Fe limiting soils. Interestingly, graminaceous species such as rice can utilize both strategies I/II (combination strategy, [Fig. 1](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub#fig0001)c) to optimize Fe levels ([Krohling et al., 2016](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0036)).

Following symplastic entry, Fe binds with various chelators and preventing it from participating in the generation of reactive oxygen species ([Morrissey and Guerinot, 2009](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub#bib0035)). Organic acids, such as citrate, bind with Fe3+; nicotinamide (NA) forms stable complexes with both Fe2+ and Fe3+. Plant cells reduce free Fe availability within cells by storing the excess Fe in iron complexes called phytoferritin ([Briat et al., 2010](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0009); [Morrissey and Guerinot, 2009](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub#bib0035)). Fe-chelator complexes also play roles in short and or long-distance transport of Fe to the sink tissues where it is essential for iron-dependent enzymes ([Krohling et al., 2016](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0036)) Although most of the Fe is located in chloroplasts, the vacuole is necessary for the redistribution of Fe in the early stages of plant development ([Morrissey and Guerinot, 2009](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub#bib0035)). A large proportion of Fe used in the [plastids](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/plastid) and mitochondria and iron transporters specific for each type of [organelle](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/organelle) has been identified ([Kim and Guerinot, 2007](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0037)). Leaves and seeds are two crucial sinks of iron. In leaves, iron re-enters the [symplast](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/symplast" \o "Learn more about symplast from ScienceDirect's AI-generated Topic Pages) and is reduced to Fe2+, mainly by the action of FRO proteins, used later for photosynthesis. However, in *Arabidopsis*, this process is mediated by an [oligopeptide](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/oligopeptide" \o "Learn more about oligopeptide from ScienceDirect's AI-generated Topic Pages) transporter family protein known as OPT3 ([Kim and Guerinot, 2007](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub#bib0037)). The terminal destination of iron is often considered to be the seed, where Fe is essential during germination.

**3.2. Genetic regulation of the Fe uptake**

Both local, as well as systemic signals, are known to involved in the modulation of Fe deficiency response in plants ([Connorton et al., 2017](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0038); [Schikora and Schmidt, 2001](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0039)). Moreover, these signals are believed to be transmitted by a [signal transduction](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/signal-transduction) cascade, which ultimately results in transcriptional regulation of downstream Fe uptake effector genes. bHLH transcription factors play key role in regulating Fe uptake. The bHLH protein FIT (bHLH29) is crucial to this regulatory network, and is controlled by a suite of proteins, which either activate FIT or enhance its degradation. MYB transcription factors (MYB10 and MYB72) are involved in Fe acquisition and distribution. Although there are several candidates for the long distance transmission of the Fe signal in plants, including the metal chelator [nicotianamine](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/nicotianamine" \o "Learn more about nicotianamine from ScienceDirect's AI-generated Topic Pages) (NA) have been identified ([Vert et al., 2003](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0040); [Curie and Briat, 2003](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0041)), a local Fe sensor’s identity remains elusive.

Hormones and other small molecules such as nitric oxide (NO) play crucial roles in signaling, modulation of gene expression and root architecture alteration in response to changes in Fe availability. However, it is a multifaceted system where one hormone can affect the synthesis of another, and there is likely to be a multidimensional interaction among the intricate signaling pathways through which hormones work ([Curie and Briat, 2003](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub#bib0041)). Auxin and ethylene under iron deficiency identified as involved in root hair proliferation ([Hindt and Guerinot, 2012](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0042)) and control of [root growth](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/root-growth) by NO and auxin ([Ramírez et al., 2008](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0043)). It has been reported that [brassinosteroids](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/brassinosteroid" \o "Learn more about brassinosteroids from ScienceDirect's AI-generated Topic Pages) are involved in inhibiting iron uptake. The application of BRs to cucumber (*Cucumis sativus*) seedlings resulted in substantial reduction of increase in FRO activity under iron deficiency ([Wang et al., 2012](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0044)). [Gibberellin](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/gibberellin" \o "Learn more about Gibberellin from ScienceDirect's AI-generated Topic Pages) (GA) positively regulates iron uptake by promoting the induction of *BHLH038, BHLH039, FRO2* and *IRT1* ([Matsuoka et al., 2014](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0045)). Again, the responses of reduced Fe conditions in the plant are believed to be positively regulated by Auxin, ethylene, gibberellin and NO, and negatively controlled by hormones [cytokinin](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/cytokinin" \o "Learn more about cytokinin from ScienceDirect's AI-generated Topic Pages), [abscisic acid](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/abscisic-acid" \o "Learn more about abscisic acid from ScienceDirect's AI-generated Topic Pages), brassinosteroids and [jasmonic acid](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/jasmonic-acid" \o "Learn more about jasmonic acid from ScienceDirect's AI-generated Topic Pages) [[Fig. 2](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "fig0002); ([Curie and Briat, 2003](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub#bib0041); [Ramírez et al., 2008](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0043); [Wang et al., 2012](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub#bib0044); [Matsuoka et al., 2014](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub#bib0045))]. NRAMP, a metal [transport protein](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/translocator-protein) family contains seven members, three of which are involved in Fe transport. Similarly, eight proteins of YSL family aid in the intercellular transport of Fe chelates, specifically Fe complex to nicotianamine. Fe is imported into the vacuole by vacuolar iron transporter 1 (VIT1) ([Grotz and Guerinot, 2006](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0003)) and iron-regulated transporter protein-2 (IREG2) transporters ([Schaaf et al., 2006](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0046)) and exported to the cytoplasm by natural resistance-associated macrophage proteins NRAMP3 and NRAMP4 ([Lanquar et al., 2005](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0047)).



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Fig. 2. Schematic diagram of hormone and small molecule effects on regulation of the reduction based strategy iron deficiency response. Auxin, ethylene, [gibberellin](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/gibberellin" \o "Learn more about gibberellin from ScienceDirect's AI-generated Topic Pages) and NO are positive regulators of the Fe acquisition genes FIT, FRO2, and IRT1, while [cytokinin](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/cytokinin" \o "Learn more about cytokinin from ScienceDirect's AI-generated Topic Pages) and [jasmonic acid](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/jasmonic-acid" \o "Learn more about jasmonic acid from ScienceDirect's AI-generated Topic Pages), [brassinosteroids](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/brassinosteroid" \o "Learn more about brassinosteroids from ScienceDirect's AI-generated Topic Pages) and ABA negatively regulate FRO2 and IRT1 in a FIT-independent manner.

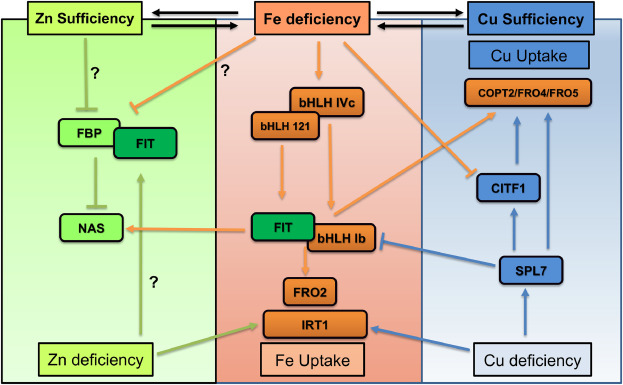
**3.3. Iron toxicity in plants**

Many plants produce chelate reductase enzyme to facilitate Fe absorption, plants lower its production during Fe excess. Supra-optimal Fe accumulation in plant tissues results in ROS via Fenton reaction. It is controlled by several enzymatic (superoxide dismutase, [catalase](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/catalase" \o "Learn more about catalase from ScienceDirect's AI-generated Topic Pages), and peroxidase) and non-enzymatic (glutathione, [carotenoids](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/carotenoid" \o "Learn more about carotenoids from ScienceDirect's AI-generated Topic Pages), ascorbate, [tocopherol](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/tocopherol" \o "Learn more about tocopherol from ScienceDirect's AI-generated Topic Pages), ubiquinol, [uric acid](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/uric-acid) and lipoic acid) antioxidants which can directly react with ROS to neutralize them. Additionally, high concentrations of Fe in soil and around rhizosphere may cause indirect damage by affecting optimum absorption of other essential metals. High levels of Fe in the soil solution result in its precipitation over the roots, forming a crust of [ferric oxide](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/ferric-oxide) that alters the absorption of other nutrients like Zn ([Morrissey and Guerinot, 2009](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub#bib0035)). Too much iron interferes with chlorophyll synthesis; pigment disruption of photosynthetic complexes promotes changes in electron transport, which causes a reduction in the [net assimilation rate](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/net-assimilation-rate) of CO2 and starves the plant of essential sugars that it needs to survive and store for harsher seasons ([Lanquar et al., 2005](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0047)).

**4. Fe and its crosstalk with Cu, Zn, and Mn**

The homeostasis of Fe, Cu, Zn, and Mn is vital to plant metabolism; it is a complex multi-level phenomenon that is tightly regulated to safeguard the cells to maintain their optimal concentration for biological functions to avoid oxidative injuries due to their accumulation ([Mishra and Dubey, 2005](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0048)). The property of these metals, to exist in interchangeable ionic forms and affinity for protein functional groups, make them useful in biochemical redox reactions within cells ([Mineral Nutrition of Higher Plants 1995](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub#bib0014)). It is well known that plants suffering from a deficiency of these nutrients have severely impaired cellular metabolism, significantly reduced growth and development ([Bashir et al., 2016](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0013)) and lower levels of tolerance to disease infection ([González-Guerrero et al., 2016](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0049)). Several reports demonstrate that these metals interact and influence each other's existence in plants ([Bashir et al., 2016](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0013); [Mineral Nutrition of Higher Plants 1995](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub#bib0014)). Though found in multiple oxidation states in the rhizosphere, the most prevalent and biologically critical divalent forms of all these metals compete for (i) some universal metal transporters like IRT1 and NRAMPs for uptake ([Grotz and Guerinot, 2006](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0003)); (ii) metal [binding proteins](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/binding-protein) with overlapping metal cofactor specificities ([Agrios, 2005](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0050)); and (iii) shared transport and inter-compartment storage pool within plants. Metal binding proteins tend to select essential divalent metal ions with a ranked order of preference according to Irving-Williams series for binding proteins, and competitive metals must be kept out of binding sites for the weaker binding ions to avoid mis-metallation ([Wintz et al., 2003](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0051)). Though some studies have tried to answer the complexity of metal interactions by an integrated approach combining [transcriptome](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/transcriptome" \o "Learn more about transcriptome from ScienceDirect's AI-generated Topic Pages), [metabolome](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/metabolome" \o "Learn more about metabolome from ScienceDirect's AI-generated Topic Pages) and [enzyme activities](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/enzyme-activity) data, comprehensive understanding of the metal crosstalks is still a long way to go. Deficiency or excess of any nutrient can cause an imbalance in other nutrients for uptake because of their interactions ([Briat et al., 2015](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0011); [Foster et al., 2014](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0052)). [Membrane transport](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/membrane-transport) systems are likely the first to regulate such crosstalk between metals. Genetic and molecular techniques have helped identify a range of gene families in plants that are likely to be tangled in the transition of metal transport ([Rouached et al., 2010](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0053)) Some of the metal transport families can support multiple metal entries, e.g., IRT1, IRT2 (Fe2+, Zn2+, and Mn2+) and NRAMPs (Fe2+ and Mn2+) ([Grotz and Guerinot, 2006](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0003)). IRT1(A member of ZIP family protein) mediate the transport of various metals, however; it is the primary root Fe transporter in *Arabidopsis* ([Grotz and Guerinot, 2006](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0003)). In rice, Fe-regulated ZIP family transporter OsZIP1–4 and the [heavy metal](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/heavy-metal) [ATPase](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/atpase" \o "Learn more about ATPase from ScienceDirect's AI-generated Topic Pages) family transporter OsHMA2 can also transport either Fe2+ or Zn2+ ([Hall and Williams, 2003](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0054); [Banakar et al., 2017](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0055)a)

Crosstalk between Fe and Cu has been documented in many previous reports. Fe and Cu serve as critical cofactors for components of the [electron transport chain](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/electron-transport-chain) in the mitochondrion and the chloroplast ([Mineral Nutrition of Higher Plants 1995](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub#bib0014)). Fe is found in the center of Fe-S clusters, which act as an electron acceptor and donor in some vital cellular processes including [nitrogen fixation](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/nitrogen-fixation), sulfate assimilation, and ethylene biosynthesis ([Banakar et al., 2017](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0056)b) Fe and Cu interact to influence uptake of each other ([Mineral Nutrition of Higher Plants 1995](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub#bib0014)). Root ferric-chelate reductase activity is a reliable biomarker for plant Fe uptake activity, and thus an indicator of Fe sufficiency/deficiency status ([Mineral Nutrition of Higher Plants 1995](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub#bib0014)). Studies in *Arabidopsis*, cucumber and pumpkin plants suggest that Fe status modulates Cu uptake and accumulation in leaves ([Waters and Armbrust, 2013](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0057); [Waters et al., 2012](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0058)[Waters et al., 2014](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0059)). Below optimal concentration of Cu inhibited the activity of ferric-chelate reductase, suggesting that Cu may be required for synthesis or activity of ferric-chelate reductase. Also when Cu was increased above optimal concentrations, lower ferric-chelate reductase activity was recorded ([Waters and Armbrust, 2013](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub#bib0057)). Increased Cu results in more efficient or rapid synthesis of [Cu proteins](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/copper-protein), which replaces the Fe proteins, thus reducing the Fe demand and generating a feedback inhibition of ferric-chelate reductase activity. However, the toxic concentration of copper in cells suppressed ferric-chelate reductase activity suggesting that Cu blocked expression rather than a function of the ferric- chelate reductase ([Waters and Armbrust, 2013](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub#bib0057)). Another Fe chelator, nicotinamide (NA), demonstrated the ability to bind both Fe and Cu ([Von Wirén et al., 1999](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0060)). Fe-deficient plants have been shown to accumulate additional Cu in leaf tissues, including both grasses and [dicots](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/magnoliopsida" \o "Learn more about dicots from ScienceDirect's AI-generated Topic Pages) ([Waters et al., 2012](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub#bib0058)). Metal uptake genes *FRO3* and *COPT2* upregulated in *Arabidopsis* under both Fe and Cu deficiency ([Agrios, 2005](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0050)). Low Fe induces expression of *COPT2* mRNA to increase cofactor availability for Cu-dependent enzymes such as Cu/Zn-SOD, which replaces Fe-SOD when Fe is scarce ([Puig, 2014](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0061)). It has been recently reported that in addition to COPT2, iron deficiency also leads to upregulation of *FRO4* and *FRO5* genes involved in copper uptake and their expression is regulated by FIT and bHLH Ib TFs which finally leads to copper accumulation under iron deficiency ([Cai et al., 2021](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0062)) ([Fig. 3](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "fig0003)).



1. [Download : Download full-size image](https://ars.els-cdn.com/content/image/1-s2.0-S2667064X21000075-gr3.jpg)

Fig. 3. Schematic representation of crosstalk of iron with zinc and copper in Arabidopsis. Under iron deficiency, the bHLH IVc interact with bHLH121 to form heterodimers and positively regulate the expression of bHLH Ib TFs and FIT which to promote the expression of Fe uptake–associated genes (*IRT1* and *FRO2*) and also Cu uptake–associated genes (*COPT2, FRO4* and *FRO5*). This results in increase in copper concentration under iron deficiency. SPL7 is a central regulator of Cu homeostasis and it is responsible for the upregulation of *COPT2, FRO4* and *FRO5* under Cu deficiency conditions and negatively regulates the expression of four bHLH Ib genes. CITF1 is also activated under Cu deficiency conditions by SPL7 to positively regulate the expression of *COPT2, FRO4* and *FRO5* but it gets repressed under Fe deficiency. FIT is upregulated under Zn deficiency and positively regulate Zn homeostasis gene (NAS).  [FBP](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/binding-protein), an antagonistic partner, interacts with FIT and sequesters it to negatively regulate the expression of NAS genes in response to the excessive Zn stress or low iron. *IRT1* is also upregulated under Fe, Cu, and Zn deficiencies. Arrows indicate positive regulation; blunt arrows indicate negative regulation; question mark indicate unknown mechanism.

In addition to uptake, there are several examples where depending on bioavailability, many plants alternate use of Cu- versus Fe in enzymes catalyzing the same biochemical reaction such as [cytochrome oxidase](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/cytochrome-c-oxidase" \o "Learn more about cytochrome oxidase from ScienceDirect's AI-generated Topic Pages) versus diiron oxidase, Cu versus haem [nitrite reductases](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/nitrite-reductase) ([Von Wirén et al., 1999](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub#bib0060)). In chloroplasts, both FeSODs and CuSODs are present, both functions equivalently to scavenge reactive oxygen species. Fe deficiency in *Arabidopsis* and some other plants showed low levels of FeSOD activity and higher accumulation of CuSOD in the cells ([Waters and Armbrust, 2013](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub#bib0057)). This observation supported the model that Fe-deficient plants require additional Cu to supply CuSOD proteins, allowing replacement of FeSOD proteins with CuSOD proteins. The relative concentration switch between FeSODs to CuSODs is physiologically significant to protect plants against oxidative damage. Moreover, three of the eight micro-RNAs that respond to Fe deficiency also regulate transcripts of Cu-containing proteins ([Waters et al., 2012](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub#bib0058)).

Zn, unlike Fe and Cu, is not redox active; in a large number of enzymes it acts as a functional, structural, or regulatory cofactor and plays a critical role in stabilizing RNA and DNA structure ([Ciftci-Yilmaz and Mittler, 2008](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0027)). Fe and Zn interact due to the chemical similarity between their divalent cations and basic transporter proteins ([Sinclair and Krämer, 2012](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub#bib0026)). While in many plants, the antagonistic relationship between Fe and Zn is reported ([Saenchai et al., 2016](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0063)), others showed a more complicated relationship in their uptake and distribution. It has been notified that Zn interferes with uptake and translocation with Fe. In contrast, Fe interferes with Zn translocation only at higher Zn concentrations ([Dučić and Polle, 2005](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0033)). Higher availability of Fe completely suppresses Zn absorption in chickpea shoots and reduces the rate of Zn absorption in grasses ([Saenchai et al., 2016](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0063); [Ray et al., 2014](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0064)). Inadequate levels of Fe in *Arabidopsis* enhances Zn accumulation but later than Cu and to lower relative levels ([Waters and Armbrust, 2013](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub#bib0057)). The possible reason for this might be that the Fe deficiency leads to the induced *Iron Regulated Transporter 1* (*IRT1*) expression. IRT1 has a broad range of substrates among divalent metals that also transports zinc, manganese, cobalt, and cadmium ([Zhang et al., 1991](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0065); [Vert et al., 2002](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0066); [Arrivault et al., 2006](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0067)).

The Zn concentration influences Fe uptake and Zn deficient plants have been shown to accumulate significantly higher Fe in shoots than the Zn sufficient plants ([Imtiaz et al., 2003](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0068)). Inversely, the physiological deficiency of Fe is due to excess of Zn. It has been advocated that the *Arabidopsis* grown under Zn excess leads to redcued *IRT1* expression in root ([Connolly et al., 2002](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0069)). FIT is involved in regulating both Fe and Zn homeostasis and its activity is regulated by a FIT-binding protein (FBP) which sequesteres it so that it cannot form heterodimer with Ib bHLH TFs in the [stele](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/stele) and fail to activate *NAS* gene expression to maintain iron and zinc homeostasis ([Chen et al., 2018](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0070)) ([Fig. 3](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub#fig0003)). A member of Cation Diffusion Facilitator family (MTP3), a P1B-typeATPase protein (HMA3) and ZIF1 (vacuolar [membrane proteins](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/membrane-protein) belongs to major facilitator transporter family) have been reported to offer are required for Zn tolerance ([Arrivault et al., 2006](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0067); [Haydon et al., 2012](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0071); [Becher et al., 2004](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0072); [Van De Mortel et al., 2006](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0073)).

Higher concentrations of Cu in the soil solution, relative to zinc, can reduce the availability of zinc to a plant (and vice-versa) due to competition for the same sites for absorption into the plant root. The higher Cu could also achieve after the application of a Cu fertilizer. The use of [Zn fertilizers](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/zinc-fertilizers) has been reported to affect the Cu concentration in wheat tissues ([Imtiaz et al., 2003](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0068)). Fe, Zn, and Cu equimolar concentrations application advocated that Cu and Zn are favorable metals than Fe for sensors and or ligands ([Van De Mortel et al., 2006](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub#bib0073)). This is because Fe ligands have a wide range of affinities and hence affecting Fe homeostasis. The various metal ion ligands and their transporters are listed in [Table 1](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "tbl0001).

Table 1. Metal ion ligands and transporters.

| **Name** | **Function** | **Found in** | **References** |
| --- | --- | --- | --- |
| Mugineic acid (MA) | It chelates metal ions (Fe, Zn and Cu) and make them available for uptake by plants | Graminaceous monocots | [Connorton et al., 2017](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub#bib0038) |
| Nicotinamide (NA) | It chelates iron as well as other divalent metals, such as copper, zinc and manganese and is involved in their transport in plants. | Monocots as well as dicots | [Connorton et al., 2017](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub#bib0038) |
| YS1 | It is involved in the uptake of metal-MA complexes from the rhizosphere into the plant cell. | Monocots | [Connorton et al., 2017](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub#bib0038) |
| YSL transporters | It aids in the intercellular transport of a complex of metals with nicotianamine | Monocots as well as dicots | [Connorton et al., 2017](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub#bib0038) |
| IRT1 | It is the primary root iron transporter but it can also transport zinc and manganese. | *Arabidopsis* | [Grotz and Guerinot, 2006](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub#bib0003) |
| OsZIP1–4 and OsHMA2 | It transports either Fe2+ or Zn2+ | *Oryza sativa* | [Banakar et al., 2017](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub#bib0055)a |
| Ctr/COPT transporters | These proteins are thought to be involved in copper uptake and transport | *Arabidopsis* | [Festa and Thiele, 2011](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub#bib0055) |
| NRAMP transporters | These are involved in iron and manganese transport. | Monocots and dicots | [Grotz and Guerinot, 2006](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub#bib0003) |
| CDF transporters | These efflux Mn2+, Zn2+, and Fe2+, into subcellular compartments or out of the cytoplasm | Monocots and dicots | [Gustin et al., 2011](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub#bib0079) |

An antagonism exists between Fe and Mn. At equimolar concentrations of Fe and Mn, Mn interfered with Fe uptake and transport ([Gayomba et al., 2015](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0074)). It is the relative amount of the two metals in the rooting medium that is more important than their absolute level ([Lingle et al., 1963](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0075)). Mutation in Fe transporter IRT1 demonstrated the role of IRT1 in Mn transport, and it uncouples with Mn and Fe transport ([Rogers et al., 2000](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0076)). Broad [substrate specificity](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/substrate-specificity) of the majority of Mn translocation transporters (like NRAMPs) substantiatinly influences the Mn homeostasis ([Socha and Guerinot, 2014](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0031)). Mn deficiency is reported to upregulate AtNRAMP1 transcription ([Ramírez et al., 2008](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0043)). Similarly, in *Arabidopsis* Mn transporters (NRAMP3 and NRAMP4) advocated to involved in Mn export ([Lanquar et al., 2010](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0077)). Metal [transport protein](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/translocator-protein), YSL mediate cellular uptake of metals complexed to [phytosiderophores](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/phytosiderophore" \o "Learn more about phytosiderophores from ScienceDirect's AI-generated Topic Pages) (PS) or its biosynthetic precursor nicotinamide (NA) ([Yen et al., 2001](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0078)) and also identified as Mn ligands ([Gustin et al., 2011](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0079)). Furthermroe, the ZIP transport family has also been advocated to have a broad susbstrate specificity for Fe2+, Mn2+and Zn2+. The CDFs/MTP family proteins have been identified to efflux Mn2+, Zn2+, and Fe2+ into subcellular compartments or out of the cytoplasm by acting as act as proton antiporters ([Gustin et al., 2011](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0079)). These findings suggest complex crosstalks exists for the regulation of metals in cells and these pathways are interconnected to regulate metal homeostasis to maintain a stable metabolism.

**5. Iron homeostasis and plant stress tolerance**

Though iron is highly abundant in soil, the concentration of free iron in most soils is far below than what is required for optimal growth. As a result, iron is tightly regulated in plants; both sub or supra optimum levels of iron can affect plant response under biotic and abiotic stresses. Plants have developed an adaptive mechanism to enhance iron uptake under Fe deficiency conditions. Iron is a critical enzyme cofactor, predominantly in several components of the cellular electron transport system (ETS). Deficiency of iron causes a decrease in the Fe-dependent components of ETS resulting in saturation of ETS intermediates. Under such reduced condition, high potential electrons could pass-on to O2 and generate superoxide radical (O2**.−**) and other reactive oxygen species ([Tewari et al., 2005](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0080)). Iron starvation primarily affects plant chloroplasts, decreasing photosynthetic activity, plastidic [pigments](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/photosynthetic-pigment) and proteins. Both the utilization of ribulose-1,5-bis-phosphate by Rubisco and its regeneration by the Calvin cycle appear compromised in Fe-starved plants ([Tognetti et al., 2007](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0081)). Additionally, Fe is a constituent of some of the key antioxidant enzymes associated with detoxification like catalase, [ascorbate peroxidase](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/ascorbate-peroxidase" \o "Learn more about ascorbate peroxidase from ScienceDirect's AI-generated Topic Pages), superoxide dismutase. Therefore, iron starvation makes plants more prone to [chlorosis](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/chlorosis" \o "Learn more about chlorosis from ScienceDirect's AI-generated Topic Pages) and less efficient in reducing the toxic effects of ROS, as a result more oxidative damage increasing the severity of oxidative stress. Studies have shown that an exogenous supply of iron plays a crucial role in the enhancement of plant tolerance against various abiotic stresses ([Tripathi et al., 2018](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0082)) . According to [Yadav et al. (2017)](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0083), overexpression of native [ferritin](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/ferritin" \o "Learn more about ferritin from ScienceDirect's AI-generated Topic Pages) (*MusaFer1*) in transgenic banana cv. Rasthali which accumulated more iron and displayed improved tolerance to oxidative stress compared with untransformed control plants ([Yadav et al., 2017](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0083)).

Among abiotic stresses salinity and drought largely affect Fe homeostasis in plants ([Tripathi et al., 2018](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0082)). Elevated salt concentration in soil reduces the osmotic potential that results in disturbed water availability to plant root cells, making it difficult to acquire and transport along with essential nutrients like Fe. This creates in-sufficiency of iron and resulting Fe complex proteins involved in photosynthesis, causing symptoms like leaf chlorosis ([Tripathi et al., 2018](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0082)). Similarly, drought condition limits the transport of nutrients from root to shoot due to the reduced rate of transpiration. It has been demonstrated that the exogenous application of Fe to plants under drought condition can enhance tolerance as it leads to the production of assimilates ([Sultana et al., 2001](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0084); [Khan et al., 2003](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0085)). Fe application in [sunflower](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/helianthus-annuus) and soybean under drought stress has been shown to improved yield ([Tripathi et al., 2018](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0082)).

Iron in plants has been found to reduce [heavy metal](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/heavy-metal) toxicity. Studies have shown that Fe reduces Cd toxicity by alleviating complex proteins, photosynthetic pigment synthesis and chloroplast quality in almond seedlings and [Indian mustard](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/brassica-juncea) ([Nada et al., 2007](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0086)). [Shao et al. (2008)](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0087) reported that soil application of Fe fertilizer effectively enhanced rice grain, shoots and roots by limiting Cd concentration ([Shao et al., 2008](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0087)). [Gratão et al. (2005)](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0088) investigated the effect of Fe nutrition in improving oxidative stress defence induced by heavy metals ([Gratão et al., 2005](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0088)). The report suggested that increase in antioxidant [enzyme activities](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/enzyme-activity) may alleviate toxic effects of heavy metals. Fe plaque is usually formed in rice root surfaces under flooded condition. It has been proposed by many researchers that the presence of iron plaque on rice roots may act as a barrier to reduce the uptake of potentially phytotoxic metals into the plant tissues. Strategies like Iron [Biofortification](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/biofortification" \o "Learn more about Biofortification from ScienceDirect's AI-generated Topic Pages) of crops and creating transgenic varieties over-expressing genes for iron uptake, transportation and accumulation are being extensively studied to improve the overall health of crops and their ability to tolerate stress.

Interestingly, the buildup of Fe reserves within cells can also negatively impact plants, causing Fe toxicity. Fe excess generates highly reactive ·OH-radicals by reacting with H2O2 in the Fenton reaction eventually causing oxidative cell damage. Fe excess in *[Nicotiana plumbaginifolia](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/nicotiana-plumbaginifolia" \o "Learn more about Nicotiana plumbaginifolia from ScienceDirect's AI-generated Topic Pages)* grown hydroponically showed inhibition of photosynthesis accompanied by [photoinhibition](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/photoinhibition" \o "Learn more about photoinhibition from ScienceDirect's AI-generated Topic Pages), increased reduction of [photosystem](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/photosystem" \o "Learn more about photosystem from ScienceDirect's AI-generated Topic Pages) 11, higher [thylakoid](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/thylakoid" \o "Learn more about thylakoid from ScienceDirect's AI-generated Topic Pages) energization, and seemed to stimulate [photorespiration](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/photorespiration) ([Kampfenkel et al., 1995](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0089)). Study in young *E. uniflora* plants indicated that toxic levels of Fe enhanced oxidative stress, which was ameliorated through changes in the activities of [antioxidative enzymes](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/antioxidative-enzymes" \o "Learn more about antioxidative enzymes from ScienceDirect's AI-generated Topic Pages) and the contents of the antioxidants AA and GSH ([de Oliveira Jucoski et al., 2013](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0090)). Most recently, a new form of cell death that is dependent on intracellular iron has been reported and termed “Ferroptosis”. It is the iron-dependent cell death pathway characterized by the accumulation of lipid reactive oxygen species ([Distéfano et al., 2020](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0091)).

The iron status also regulates plant response to [biotic stresses](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/biotic-stress). Pathogen infecting plants take up all required nutrients. Iron plays dual roles for host and pathogen, either as a nutrient or as essential cofactor constituent to initiate or avoid immune responses. Iron in plant cells mainly exists in a complex with ferritin, transferrin, haemoglobin, and other proteins. During a pathogen attack, iron accumulates in the [apoplast](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/apoplast" \o "Learn more about apoplast from ScienceDirect's AI-generated Topic Pages) to elevate the oxidative response, which in turn activates the expression of PR genes. The translocation of iron to the apoplast causes intracellular iron deficiency activating iron uptake genes and PR genes ([Naranjo-Arcos and Bauer, 2016](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0092)). Thus, plants use iron-withholding strategies to reduce pathogen virulence or to locally increase iron levels to activate a toxic oxidative burst ([Verbon et al., 2017](https://www.sciencedirect.com/science/article/pii/S2667064X21000075?via%3Dihub" \l "bib0093)).

**6. Conclusion**

Based on researches done so far and our extensive review of the literature shows that micronutrients like Fe, Cu, Zn and Mn in soils are essential factors for normal healthy growth and development of plants. The metals when not in equivalent ratios show the potential risk of interactions affecting absorption and bioavailability, translocation within plants, storage, and the related physiological effects. Plants need to supply appropriate amounts of each of these micronutrients to the precise target apo-metalloproteins and meanwhile avoid adventitious metal binding to non-target metal binding sites or other cellular compounds. This requires a complex and inter-related cooperation of metal homeostasis networks that differ with plant type and soil properties. Despite significant literature on individual metal homeostasis on these micronutrients, gaps remain in our understanding of how they overlap in plants and the related physiological effects. We still need to identify more molecular players in these metal crosstalks. Hence, a better understanding of the complexities with which these micro-nutrients interact and influence each other would improve fortification strategy for enhanced crop yield.

**Declaration of Competing Interest**

The authors declare no conflict of interest.

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