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REVIEW

Assessment of Biofortification Approaches Used to Improve Micronutrient-Dense Plants That Are a Sustainable Solution to Combat Hidden Hunger

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Abstract
Malnutrition causes diseases, immune system disorders, deterioration in physical growth, mental development, and learning capacity worldwide. Micronutrient deficiency, known as hidden hunger, is a serious global problem. Biofortification is a cost-effective and sustainable agricultural strategy for increasing the concentrations or bioavailability of essential elements in the edible parts of plants, minimizing the risks of toxic metals, and thus reducing malnutrition. It has the advantage of delivering micronutrient-dense food crops to a large part of the global population, especially poor populations. Agronomic biofortification and biofertilization, traditional plant breeding, and optimized fertilizer applications are more globally accepted methods today; however, genetic biofortification based on genetic engineering such as increasing or manipulating (such as CRISPR-Cas9) the expression of genes that affect the regulation of metal homeostasis and carrier proteins that serve to increase the micronutrient content for higher nutrient concentration and greater productivity or that affect bioavailability is also seen as a promising high-potential strategy in solving this micronutrient deficiency problem. Data that micronutrients can help strengthen the immune system against the COVID-19 pandemic and other diseases has highlighted the importance of tackling micronutrient deficiencies. In this study, biofortification approaches such as plant breeding, agronomic techniques, microbial fertilization, and some genetic and nanotechnological methods used in the fight against micronutrient deficiency worldwide were compiled.

Keywords Biofertilizer · Climate change · COVID-19 · CRISPR/Cas9 · Genetic improvement · Nanoencapsulation

1 Introduction

Insufficient energy intake and inability to reconstruct body tissues as a taking less than the required amount of any nutrient is called undernourishment. Today, more than 820 million people in the world are hungry, two billion people are suffering from micronutrient deficiencies and 2 billion people are overweight or obese (FAO 2019; UNEP 2021). Undernutrition and micronutrient deficiencies contribute substantially to the global burden of disease; people have micronutrient deficiencies for at least one including iron (Fe), zinc (Zn), iodine (I), selenium (Se), calcium (Ca), and vitamins such as folate and vitamin A (Beal et al. 2017; FAO 2020a, b; Kumssa et al. 2015; World Health Organization (WHO) and UNICEF 2017) (Fig. 1). Fe deficiency is seen in 20–25% of the world population and Zn deficiency is seen in 17.3% (Cooper et al. 2012). Fe and Zn are two important nutrients in human nutrition and they are among the most common micronutrient deficiencies in the world. Zn deficiency is a serious health problem and is common in South Asian and sub-Saharan African countries (Shahzad et al. 2014; Shekari et al. 2015) (Fig. 1). Furthermore, 2 billion people suffer from I deficiency (Horton et al. 2008), and 254 million pre-school children have vitamin A deficiency. It was reported that symptoms of night blindness were detected in 5.2 million pre-school children and low serum retinol concentrations were detected in 190 million children due to vitamin A deficiency (Sherwin et al. 2012). Vitamin A and I deficiency are most common in South Asian and sub-Saharan African countries (Stevens et al. 2015; Zimmermann 2009) (Fig. 1). Moreover, I deficiency is seen in more developed regions such as Europe, the USA, and

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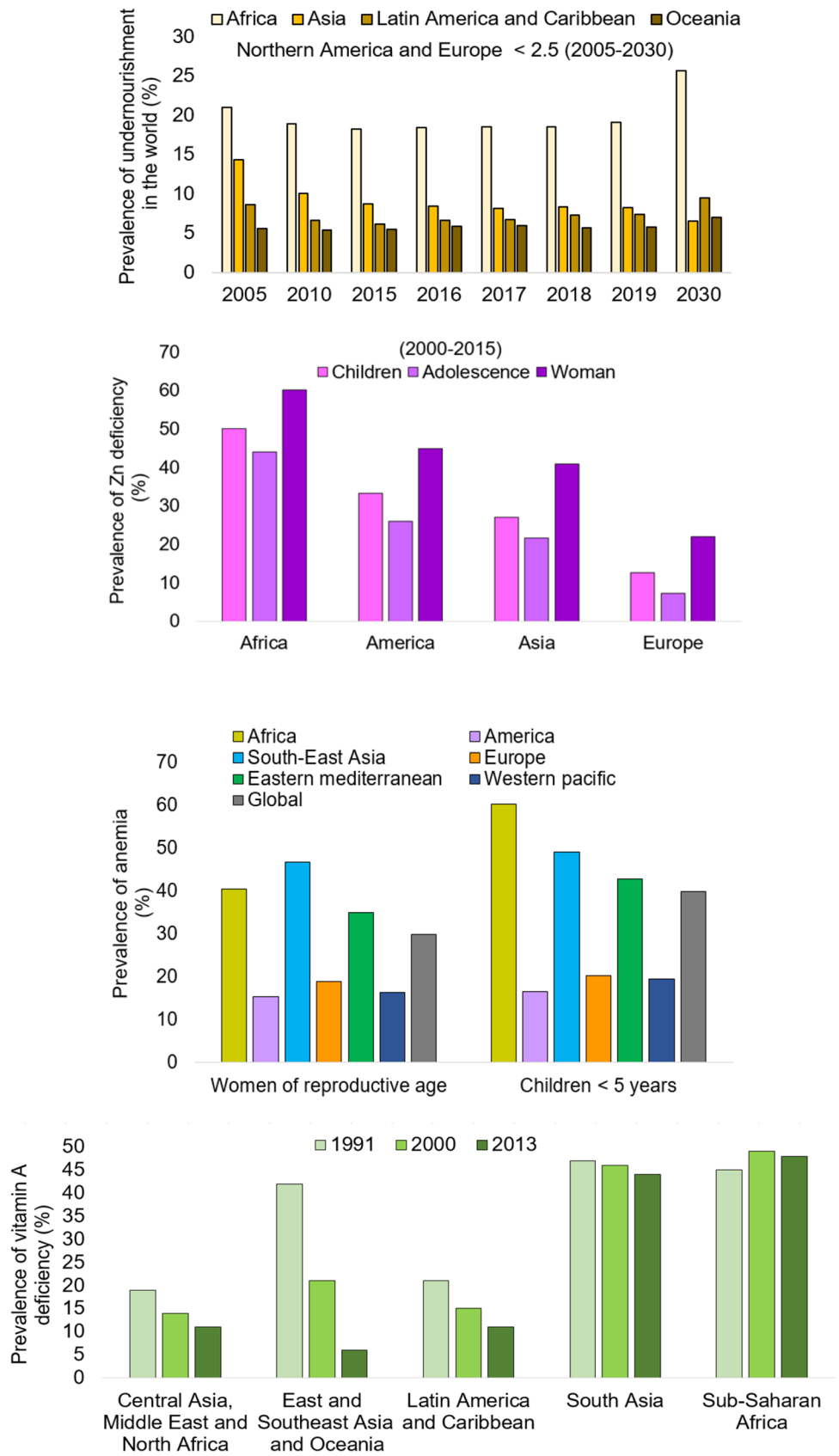


Fig. 1 Prevalence of undernourishment (based on FAO 2020a, b) and zinc deficiency (based on ECA 2015; Gupta et al. 2020; Wessells and Brown 2012), WHO geographic distribution of anemia prevalence (based on WHO 2019), and estimated prevalence of vitamin A deficiency (based on Stevens et al. 2015)

Australia more mildly (Zimmermann 2009). I deficiency leads to stillbirth, cretinism, goiter, thyroid inflammation, and impaired cognitive development (Landini et al. 2011). Vitamin A, Zn, Fe, and I deficiencies were reported to cause deaths in approximately 20% of children aged under five (Prentice et al. 2008; Stewart et al. 2010). Anemia is also seen in approximately 24.8% of the world's population (mostly common in South Asian and sub-Saharan African countries) and the most common causes include nutrient deficiencies such as Fe deficiency, as well as vitamin B12 and vitamin A deficiencies (Chaparro and Suchdev 2019; WHO 2021) (Fig. 1). Deficiency of Se (especially in China, Africa, and Northern Europe), another micronutrient, affects 0.5–1.0 billion people worldwide and can be prevented by dietary supplementation containing Se in "Keshan disease," a fatal cardiomyopathy disease in humans (Alloway 2013).

Micronutrient deficiencies, which threaten human health, are directly and indirectly related to all environmental factors. Factors such as low or high light and temperature, excessive rain, high CO_2, flooding, pathogenic diseases, soil type, and the antagonistic effects of micronutrients (Cu–Zn, Fe-Cu, Fe–Mn, Cu-Mn) lead to micronutrient deficiency in plants (Giri et al. 2017; Liu et al. 2014; Moraghan and Mascagni 1991; Neenu and Ramesh 2020). Micronutrient deficiencies are global phenomena that are seen in soils ranging from neutral to alkaline, as well as soils with anaerobic conditions in arid regions (Kalra et al. 2020; Monreal et al. 2015; Voortman and Bindraban 2015). The critical concentrations of micronutrients in soils vary based on the soil test procedure, product, soil type, and soil pH. Soils in regions with arid climates are generally alkaline with high soil pH, while soils in regions with humid climates are generally acidic with low pH (Brady and Weil 2002). Soil pH is one of the most important factors controlling the availability of all plant nutrients, microbial activity, and crop growth (Zhang et al. 2019). Temperature and amount of precipitation change soil pH by affecting the intensity of leaching and soil mineral weathering. Micronutrient availability generally decreases as soil pH increases, with the exception of Mo. High pH and $CaCO_3$, low organic matter content and soil moisture, and flooding-induced electrochemical changes are the main factors of low Zn availability in plants (Graham 2004). Silica and calcareous sandy soils with neutral or alkaline pH cause Mn immobility, which leads to Mn deficiency in plants (Rengel 2000). With increasing pH, the solubility of free Fe decreases 1000-fold, which reduces the availability of Fe in alkaline and calcareous soils ($pH > 7$) (Hiradate et al. 2007). The calcareous soils common in the arid areas of the world are poor in micronutrients such as Fe and Zn (FAO 2016).

Soil moisture and temperature are important for the uptake of micronutrients. Low temperature and humidity affect the micronutrient availability causing a decrease in root activity, dissolution rates, and nutrient diffusion. In addition, wet soil conditions at low temperature further reduce the availability of micronutrient cations (Choudhary and Suri 2014; Kumar et al. 2016). Low soil temperature decreases the production of phytosiderophores and mobilization and uptake of soil Fe by Gramineae members, while high soil temperature decreases Fe uptake by increasing the microbial decomposition of phytosiderophores and stimulating CO_2 production (Marschner et al. 1986).

Climatic change, which is a result of the increase in greenhouse gases, causes decreases in crop production, yield, and quality, and thus nutritional deficiency in humans (Myers et al. 2014). Increasing temperature with climate change and changes in precipitation amount and density affect the leaching density and soil minerals, and cause changes in soil pH (Abdalla and Smith 2016). Moreno-Jiménez et al. (2019) stated that increasing drought, which is also a result of climatic change, will limit the availability of essential micronutrients, especially Fe and Zn. The findings showed that aridity negatively affected the uptake of Cu, Fe, Mn, and Zn by reducing soil pH and organic matter. Heat stress causes deterioration in root activity (such as nutrient-uptake proteins), reducing the concentration of nutrients in plant tissues (Heckathorn et al. 2014). Giri et al. (2017) reported that nutrient uptake and assimilation protein levels decreased in tomato roots exposed to severe heat stress (40–42 °C). For this reason, they pointed out that increases in heat stress with global warming may reduce crop production and nutrient quality due to its negative effect on root-nutrient relationship.

It is known that increased CO_2, another factor that negatively affects plant nutrient content, causes a decrease in Zn and Fe concentrations in plants such as wheat and rice (Myers et al. 2014). High CO_2 alters the balance of plant carbon metabolism and mineral composition and nutrient-use efficiency. In a recent study, the effect of increased CO_2 on the intake of Fe, Zn, and protein for the populations of 151 countries was investigated. The results reveal that countries in North Africa, south and Southeast Asia and the Middle East, and sub-Saharan Africa are among the hardest hit. Considering the population of 2050 and the CO_2 ratio (~550 ppm), it is estimated that increased CO_2 could cause Zn deficiency in an additional 175 million people and Fe deficiency in 311 million children (0–4 years old). In addition, 122 more million people could be added to the 622 million who do not receive enough protein (Smith and Myers 2018). Smith and Myers (2019) reported that CO_2, which would increase further until 2050, may cause a 17–30% decrease in the amounts of vitamins such as thiamin, riboflavin, and folate in rice.

Changes in climatic parameters alter the susceptibility of crops to pathogens, resulting in changes in their physiological and normal functions, reduced biosynthetic capacity, and

eventual plant death. This decline in agricultural production and product yield and quality is one of the most important obstacles to achieving the goal of feeding the starving population on a global scale (Dong and Ronald 2019). In addition, climate change can facilitate the spread of many pathogens, including viruses, localized in certain regions due to geographical barriers and climate constraints (Savo et al. 2016). It has been reported that climate change may cause gradual substitution of species, decrease in species diversity, and shrinking of ecosystems (Nunez et al. 2019). These and similar changes may lead to increased contact between wildlife and humans (Rodó et al. 2021). Therefore, global warming poses a great risk in the spread of existing infectious diseases and the emergence of those that are not yet seen.

Despite the warnings of scientists that the climate crisis should be taken seriously and numerous international agreements (Montreal Protocol, UN Framework Convention on Climate Change, Kyoto Protocol, Paris Climate Agreement, etc.), countries have delayed in taking adequate and necessary measures to reduce carbon emissions. Therefore, various policies and strategies (reducing emissions, green technology, etc.) need to be put into effect urgently to reduce greenhouse gas emissions and limit the CO_2 impact, before it is too late.

The critical deficiency levels of micronutrients in crop plants are generally in the range between 1 and 5 for Cu, 50–100 for Fe, 15–20 for Zn, and 10–20 for Mn (mg kg^{-1} DM) (Alloway 2013). Most plants can accumulate micronutrients whereas some main crops, particularly the edible parts of plants, contain insufficient amounts of Fe and Zn (Wakeel et al. 2018). Basic crops such as rice, wheat, and maize contain low amounts of Zn and Fe (Shariatipour and Heidari 2020). Processing cereals before consumption is another factor that reduces their micronutrient content. The presence of large amounts of micronutrients such as Fe and Zn in parts other than the endosperm, which are lost during procedures (milling, polishing, etc.) (Ozturk et al. 2006) and the rare measurement of toxic elements such as cadmium (Cd) and arsenic (As), which threatens food safety, are considered an important problem. Zn and Fe were mostly localized to the aleurone layer of the wheat grain. Consumption of the wheat grain, usually by milling, results in the removal of the Zn-rich parts, leaving behind the Zn-poor endosperm. It is also known that 75% of folate is lost in whole wheat during this process. Cakmak et al. (2010b) reported that the amount of Zn in white flour does not meet the requirements for daily diet. In addition, compounds such as phytate localized to the aleurone layer of wheat and rice aggravate this problem by reducing the bioavailability in terms of Zn. During milling, about 90% of the phytic acid is removed from the cereal grains, but the remaining 10% still acts as a potent inhibitor (Dary and Hurrell 2006). The B vitamin and Fe are mostly found in the germ and bran layers of rice, and therefore significant losses occur during the milling process. For example, it has been reported that 80% of the thiamine amount is removed during the milling of brown rice into white rice. In addition, other nutrients such as niacin, Fe, and riboflavin in the bran layer are also lost (Abbas et al. 2011). Polished grains are more preferred because the removal of insoluble fibers by polishing facilitates cooking, chewing, and digestion. This process also extends the shelf life of grain but induced important losses in mineral content. Proteins, fats, minerals, and vitamins in the outer grain layers are denser than the inner parts, but polishing causes a significant decrease in the concentration of mineral elements in the grain (Hansen et al. 2012). It has been reported that there was a significant reduction in the amount of micronutrients such as Mn, Zn, Ni, Cu, Fe, and thiamine in polished rice (Pourcel et al. 2013; Yao et al. 2020). For this reason, increasing the micronutrient levels or bioavailability in the edible parts of plants such as the endosperm, which is especially poor in Fe and Zn, by biofortification is considered a potential sustainable strategy in the combating against malnutrition.

If minerals are not found in sufficient quantities in the soil, their deficiencies lead to a reduction in product quality and thus deterioration of human health (WHO 2009). The reason for the increasing interest in the problem of micronutrient malnutrition is that it is a public health problem not only in poor countries but also in developed countries (Fig. 1). As mentioned above, I and Fe deficiency, which are the most common micronutrient deficiencies in the world, are also common in European countries. In addition, it has been reported that consumption of foods rich in energy but insufficient in terms of micronutrients negatively affects micronutrient intake in industrialized countries (Allen et al. 2006).

Micronutrients are essential for their vital physiological functions, and their deficiency causes serious health disorders. Zn is a micronutrient that is effective in many events such as reproduction and neurotransmission, especially the immune system. Its deficiency causes learning impairment, physical growth and reproductive health, a decrease in immune resistance, and an increase in the rate of infection (Verma et al. 2021; Wessels and Rink 2020). Fe acts as an important cofactor for various enzymes involved in plant and human metabolism. its deficiency causes deterioration in the immune system and anemia. Inadequacy of essential micronutrients such as vitamins A and D, Fe, Se, Cu, and Zn may cause an insufficient immune system against viral and bacterial infections (Bae and Kim 2020). For example, due to the antiviral and immune-enhancing properties of Se and Zn, it has been reported to be effective in reducing symptoms against SARS-CoV-2 infection (Zhang et al. 2020). It is seen how critically important micronutrients are in the

formation of a well-functioning immune system during the COVID-19 pandemic (WHO 2020). The recent research shows that the essential nutrients like vitamin A, vitamin B (folate, vitamin B6, and vitamin B12), vitamin C, vitamin D, and the minerals such as Fe, Cu, Se, and Zn can help strengthen people's resilience to the COVID-19 pandemic (Cámara et al. 2021;Richardson and Lovegrove 2021; Wessels and Rink 2020). The antiviral property of Cu is attributed to its regulatory role on some enzymes that are critical to the functions of immune cells (Gombart et al. 2020). It has been reported that vitamins A, D, E, and K strengthen the body's defense mechanism against COVID-19 infection and prevent complications such as cytokine storm (Samad et al. 2021). A recent study has shown that vitamin D supplementation can play an important role in the treatment of COVID-19 patients (Sooriyaarachchi et al. 2021). In another study, a high prevalence of vitamin D deficiency was seen in countries such as Italy, Spain, and France, which have higher COVID-19 mortality rates compared to other European countries (Kehoe et al. 2019). Vitamin C has been proposed as an effective agent in improving the neutrophil response, which is responsible for the high cytokine levels produced during the cytokinin storm (Colunga Biancatelli et al. 2020). Data from a previous study showed that vitamin E and Se are effective on the control of viral replication and mutations, and that RNA viruses can convert more virulent strains in case of malnutrition from these micronutrients (Beck et al. 1995). It has been found that there is a direct relationship between Se deficiency and lower recovery rates in COVID-19 cases, and that Se is effective in reducing the risk of COVID-19 by inactivating the viral spike protein (Kieliszek and Lipinski 2020; Zhang et al. 2020). Therefore, it has been suggested that Se supplementation such as Zn may be a natural treatment to combat the virus in COVID-19 patients with low blood levels (Schiavon et al. 2020). It has been stated that feeding with different crops biofortified in terms of Se in the human diet can provide Se supplementation (Newman et al. 2019). These results emphasize that regular consumption of foods biofortified in terms of Se can be a sustainable and practical method for human health. Iodine is an essential microelement regulating growth, development, and basal metabolic rate. Derscheid et al. (2014) reported that I could support the innate immune system in the fight against infections. Also, recent data have shown that Japanese, known for their high I intake, have a very low number of COVID-19 deaths compared to other countries. Because it supports the innate immune system, I has been suggested as a therapeutic and preventive agent in the fight against the COVID-19 pandemic (Verheesen and Traksel 2020). Given the positive impact of this micronutrient resistance on human immune function, it is also likely to increase people's resistance to potential future pandemics. Gastélum-Estrada et al. (2021) reported that consumption of biofortified foods (tomato, acerola, mushrooms, wheat, chickpea, etc.) in addition to vaccination would strengthen the immune system and suggested it as a realistic approach that could help reduce the risk of COVID-19 disease.

COVID-19 has caused a decline in household incomes, especially for those living in poor areas (FAO 2020a, b; World Bank 2020). This decrease in income levels has also caused changes in food consumption patterns and increased dependency on basic crops that are more affordable instead of expensive foods (Clapp and Moseley 2020; FAO et al. 2020; Klassen and Murphy 2020; Laborde et al. 2020). On the other hand, biofortified crops will also help poor families survive during crises such as COVID-19 or after natural disasters (droughts, floods, heavy rainfall, cyclones, and pests). In these processes, since vulnerable communities living in poor geographies use basic foods, biofortification is important in terms of ensuring that these people continue to consume valuable minerals and vitamins.

Micronutrient deficiencies increase susceptibility to many infectious diseases, including COVID-19 (Akhtar et al. 2021; Huizar et al. 2021). Therefore, the COVID-19 pandemic, which is a global health crisis that defines our century, has drawn attention to the importance of biofortification, which is an effective strategy to combat micronutrient deficiency. In addition, considering that climatic change may cause hundreds of millions of people to suffer from nutritional deficiencies in the future, it is obvious how important it is to fortify foods. Therefore, the intake of nutritious and adequate micronutrients in daily diets will increase the resilience of the rapidly increasing global population in the face of crises. Biofortification, which is used to improve the nutritional value of plants, is presented as a sustainable solution to overcome many nutritional problems with breeding, microbial, agricultural, or fertilization approaches, as well as genetic engineering and biotechnological strategies (Fig. 2).

2 The Uptake of Micronutrients

Optimal uptake of micronutrients from soil solutions is vital since micronutrient deficiencies in crops tend to cause low intakes in the diets of animals and humans. Therefore, the uptake of some micronutrients from the soil has been briefly reviewed. Fe in the rhizosphere is taken up into root cells by two different strategies based on non-Graminaceae plants (strategy I) and Graminaceae plants (strategy II) (Fig. 3). In strategy I plants, after the soil is acidified by H-ATPase AHA2 and solubilized in the Fe rhizosphere, Fe^{3+} is reduced to ferrous Fe^{2+} by ferric chelate reductase (FRO2) and taken into the root epidermal cells by the metal carrier IRT1 (plasma membrane–localized Fe^{2+} transporter) (Conte and Walker 2011; Ivanov et al. 2012). Some plants

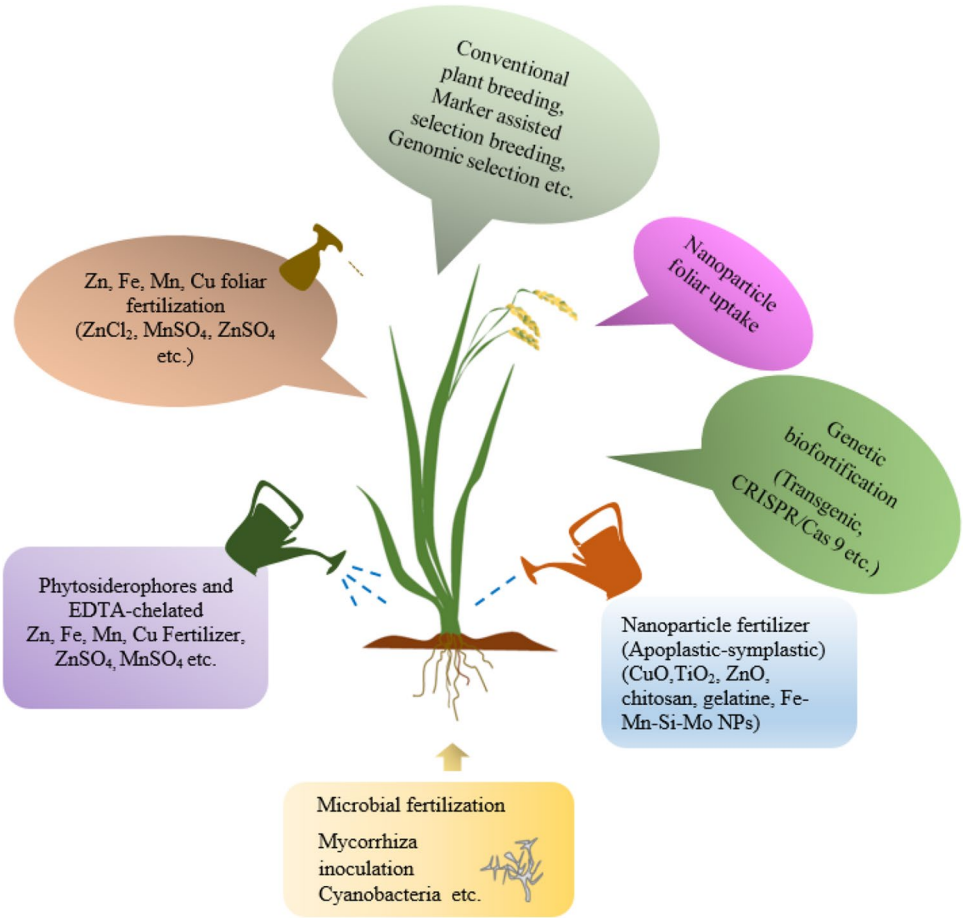


Fig. 2 Different approaches for biofortification

use a chelation strategy to get Fe from the soil. This strategy is based on the phytosiderophore secretion by the roots. In strategy II plants, after substances such as mugineic acid are secreted into the rhizosphere by phytosiderophore transporters, ferric iron Fe^{3+} is chelated and Fe-phytosiderophore chelates are transported to stem cells by YELLOW-STRIP1 (YSL), a transmembrane peptide transporter localized in the plasma membrane (Curie et al. 2001; Li et al. 2018).

Zn uptake in plants is generally through transmembrane transporters in the ZIP (ZRT and IRT-like protein) family, which are localized in the plasma membrane of root epidermal cells (Tiong et al. 2014). Excess Zn prevents the uptake of Mn, Fe, and Cu. In Cu deficiency, plants induce the expression of the gene encoding the transcription factor, SPL7, and a major plasma membrane Cu uptake transporter, COPT1, to increase Cu uptake (Fig. 3). As a result of many human activities, including the administration of Cu-containing solutions against some disease-causing pathogens, pollution occurs due to excessive Cu accumulation in soils. Excess Cu causes oxidative stress in plants and leads chlorophyll to lose its function by preventing the uptake of other basic metals such as Mg (Karimi et al. 2012). Manganese (Mn) is abundant in the earth and seawater and is taken by plants as Mn^{2+}. The uptake of Mn^{2+}, which is abundant in acidic soils, is carried out by the carrier protein NRAMP1 (also NRAMP 3, 4 in vacuolar membrane, YSL 6 in rice, etc.), which is localized in the plasma membrane in plants (Fig. 2). Mn deficiency is common mostly in alkaline soils. On the other hand, like most metal micronutrients, Mn is toxic at high concentrations, and in particular, high Mn^{2+} in acidic soils prevents the uptake of other cations such as Fe. Mo, which is less in the soil, is taken into the plant as MoO_4^{-2} by MOT1 and MOT2 carriers (Tejada-Jiménez et al. 2013).

3 Biofortification Strategies

3.1 Plant Breeding and Agronomic Strategy

Biofortification is an important strategy to overcome this micronutrient deficiency that threatens human health. Traditional plant breeding is based on the traditional manipulation of plant genomes to improve crops and increase some essential nutrients. Broad research programs such as HarvestPlus and BioCassava Plus used traditional breeding methods to

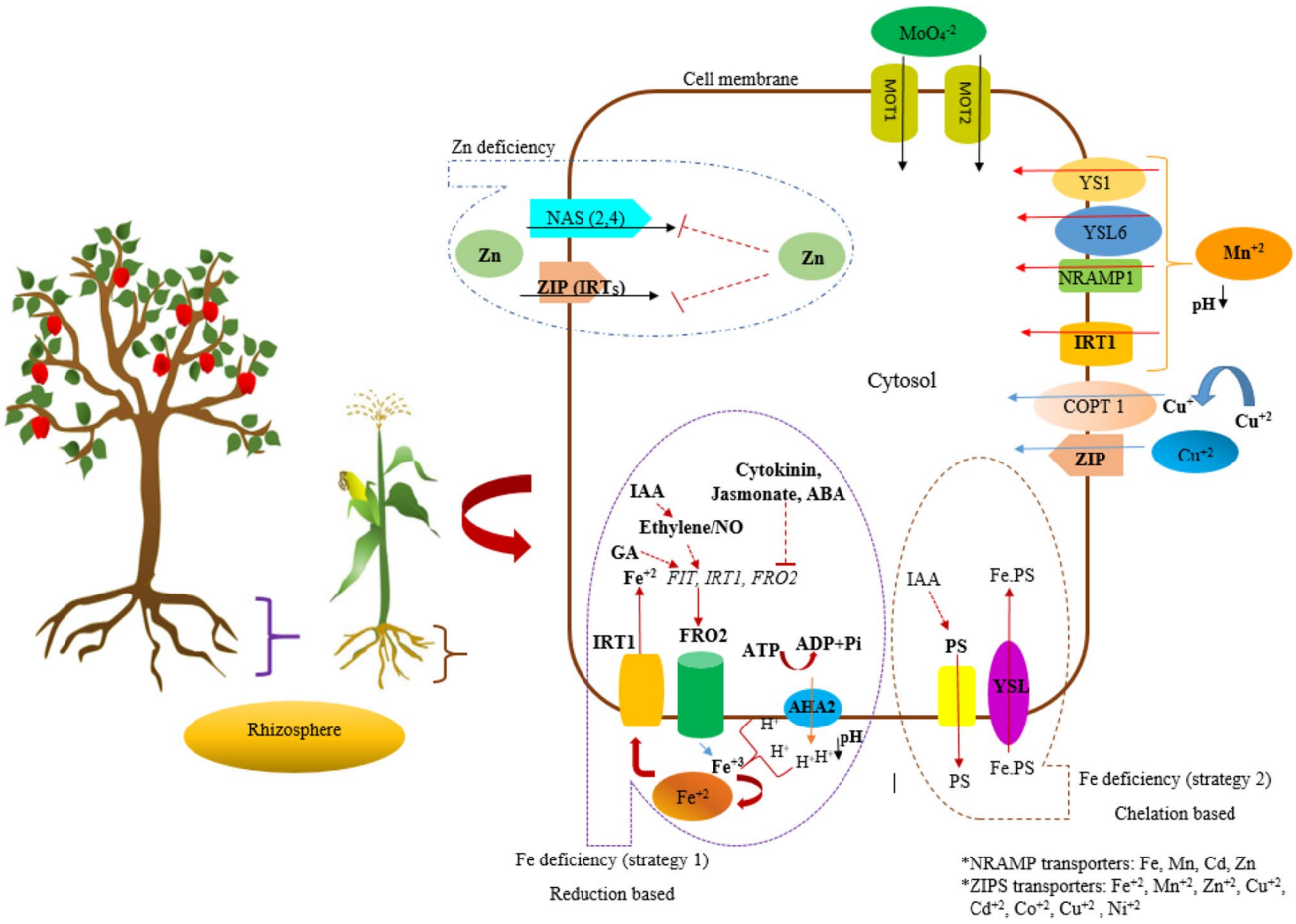


Fig. 3 Uptake mechanism of Fe, Zn, Cu, Mn, and Mo from soil to plant

develop biofortified crops (Garg et al. 2018). Biofortified crops with higher vitamin A, Fe, and Zn are also important in maintaining immune systems for vulnerable people whose nutritional diets depend on one or two food products such as corn, rice, and wheat. Therefore, biofortified crop varieties with Zn and vitamin A are now available in Africa and Asia. For example, it was reported that increasing the β-carotene content of *Ipomoea batatas* L. biofortified by the traditional breeding method reduced vitamin A deficiency in children in South Africa; on the other hand, consuming rice fortified in Fe, which was developed by the HarvestPlus program, increased ferritin in Filipino women (Low et al. 2017).

The agronomic strategy of biofortification is mainly based on the application of mineral fertilizers, particularly Fe and Zn, in order to increase the solubility and mineral content of micronutrients in the soil (White and Broadley 2009). The effective and proven role of Zn in boosting the human immune system against viruses and other health threats may be a good reason to grow wheat and rice varieties with high Zn content. It was reported in the studies that these micronutrient deficiencies in the soil can be eliminated by the fertilization method. An increase in micronutrient concentration and grain yield was reported in areas with micronutrient deficiencies after the application of fertilizer and micronutrient combination to soils and leaves (Cakmak et al. 2010a; Imtiaz et al. 2010). For example, in countries such as Australia, the USA, Canada, and in the European region which have different climate characteristics and micronutrient deficiencies in the soils, fertilizers and micronutrients are applied to the soil to increase the grain crop yield and fruit yield in trees. The effective and proven role of Zn in boosting the human immune system against viruses and other health threats may be a good reason to grow wheat and rice varieties with high Zn content. Fe and Zn fertilization is one of the methods to increase the accumulation and yield of minerals in grains (Alloway 2008). It was determined in the studies that the amount of Zn and Fe increases in Fe- and Zn-applied wheat, rice, and corn (Aref 2010; Stomph et al. 2011). Inorganic Fe fertilization of soils is not practical since Fe in inorganic Fe fertilizers is transformed into forms, which cannot be taken by plants, through oxidation and precipitation. Therefore, the use of Fe-chelates

as Fe fertilizer and acidification of the soil are preferred to increase Fe uptake and access (Wakeel et al. 2018). It was found that the International HarvestPlus biofortification program, which adopts traditional breeding, and foliar Zn application to increase Zn concentrations in the edible parts of grains such as wheat, corn, and rice in the sub-project study, are more effective than the application to soil and that the highest increase in Zn amount is achieved in wheat (Cakmak and Kutman 2018; www.harvestzinc.org). Madhaiyan et al. (2010) reported that Zn-solubilizing bacteria increased the Zn concentration in roots and shoots of wheat and soybean. Green fertilization using nitrogen-fixing plants such as clover, vetch, and broad bean and Zn-coated urea (fertilizer) increase the concentration of Zn in grain and straw. Pooniya and Shivay (2015) stated that surface fertilization with Zn-enriched urea provides higher Zn uptake in basmati rice than fertilization with $ZnSO_4$ in soil applications and that Zn-enriched urea improved productivity and all the quality parameters (physical, chemical, and cooking quality; rice grain length, breath, and their ratio before and after cooking) of *Basmati* rice. Soil microbiological parameters and yield and quality parameters of rice showed significantly positive correlations. This positive correlation was attributed to the increase in nutrient intake and mobilization.

Rapid urbanization and industrialization are the most important factors causing soil pollution all over the world (Hu et al. 2020). Activities such as mining, traffic, wastewater irrigation, pesticide use, and reuse of sewage sludge cause heavy metal pollution in arable lands (Huang et al. 2016). Therefore, the emission of various heavy metals in agricultural soils changes the ecological function of the soil and endanger human health by accumulating in crops (Li et al. 2020). In addition, heavy metals can accumulate in the soil due to the application of manure and inorganic fertilizers (Martin et al. 2006). The application of Zn at proper concentrations in cereals grown in soils with high Cd content reduces the uptake and accumulation of Cd; however, the continuous use of some micronutrient fertilizers at high concentrations for long term increases the accumulation of toxic metals such as Cd (Shahzad et al. 2014). Cd, which is the most toxic metal for humans and all other living organisms among all heavy metals, is easily taken up by plants due to its high mobility in both soil and plant systems. The presence of Zn in the soil and in the plant has a vital role in the accumulation of Cd, which is a toxic element because Zn competes with Cd for the same membrane transporters, reduces the uptake and accumulation of Cd, and reduces the oxidative damage that will occur in the plant. Other elements that are effective in preventing Cd accumulation are Fe and Mn. Fe deficiency can accelerate Cd accumulation. Fe and Mn compete with Cd for the same membrane transporter and prevent Cd uptake from the root. Moreover, they reduce the accumulation of Cd in the crop by preventing the formation of Fe plaques that adsorb Cd on the root surface and the reactive oxygen species (ROS) formed in the cell as a cofactor of antioxidant enzymes from damaging the plasma membrane (Liu et al. 2008; Sarwar et al. 2010). Therefore, applying Fe to Cd-contaminated soils can increase the Fe concentration in the crop and also decrease the Cd concentration. On the other hand, in addition to increasing the micronutrients such as Fe and Zn in the edible parts of plants by fertilization, it is necessary to recycle micronutrients considering the possibility of increased fertilization costs in the future and environmental concerns. For example, it was determined that Zn concentration in *Triticum aestivum* L. species can increase and have similar effects with $ZnCO_3$ when sewage sludge and liquid-treated sludge are applied to soil (McGrath et al. 2012).

It was reported that Se, another micronutrient required in human nutrition, is utilized to develop tolerance against abiotic stresses such as high temperature, freeze, drought, salinity, and heavy metals (Feng et al. 2013). Se not only promotes plant growth and development but also increases the resistance against various abiotic stresses by increasing the capacity of enzymatic antioxidants such as catalase, superoxide dismutase, peroxidase, and non-enzymatic antioxidants such as vitamin E and ascorbate against oxidative stress caused by ROS (Domokos-Szabolcsy et al. 2017; Hasanuzzaman et al. 2010). Broccoli and garlic are good candidates for biofortification studies since they naturally accumulate Se (Hsu et al. 2011). Agronomic crop biofortification by Se has been considered a cost-effective method for growing wheat with high Se content. The foliar fertilization of wheat with Se or adding it during the soaking process during seed germination are shown as effective alternatives to obtain biofortified foods in terms of Se. In fact, increasing Se content in wheat is a food strategy that increases Se uptake by people (Masarovičová and Kráľová 2012). Therefore, Se biofortification of foods may be a sustainable and practical method that can increase Se uptake by the human population.

Salt is considered the ideal way for people to eliminate I deficiency for some reasons such as its universal consumption, cheap processing, and the ability of a small number of manufacturing companies to carry out this business (Horton et al. 2008; Zimmermann et al. 2008). The most effective universal strategy to reduce I deficiency is accepted as salt iodization (fortification of consumed salt with I). Therefore, it was reported that the addition of soluble iodide and iodate salts to irrigation water in agriculture can reduce I deficiency by increasing the amount of I in the edible parts of crop plants (Lyons et al. 2004). Furthermore, it was stated that the concentration of I can be increased in plants such as wheat, corn, and rice with surface applications of KIO_3. Similar to the results obtained in Fe and Zn biofortification studies, the foliar fertilization of I is more effective on I concentration

than soil applications (Budke et al. 2020; Cakmak et al. 2017). Budke et al. (2020) reported that foliar fertilization of I is a promising method for biofortifying apples with I. The long-distance transport of I in plants occurs primarily in the xylem, while the mobility in the phloem is estimated to be low (Humphrey et al. 2019). In the study using radioactive I isotope, it has been detected that I can accumulate by penetrating through the stomata and the cuticle of epidermal cells of the leaves (Humphrey et al. 2019). It has been suggested that this is an effective approach to biofortifying leafy vegetables. Cakmak et al. (2017) stated that foliar-applied I was transported to the seed in the head and early milk development stages of some cereal species and diffusion was effective in the accumulation of I in the grain.

3.2 Microbial Biofertilizers

The population is rapidly increasing all over the world, and thus the nutritional needs of people are increasing, as well. Due to the increasing nutritional needs, people are trying to obtain more products from the resources they have. Water and soil pollution is one of the most important disadvantages of fertilization. Selective breeding, which is one of the biofortification techniques, is a method used to biofortify the main crops by crossing plant varieties naturally rich in micronutrients (Malik and Maqbool 2020). However, there are some limiting factors in selective breeding such as low heritability and lack of genetic diversity. Plant breeding and agronomic biofortification strategies are difficult to sustain as they require long monitoring and continuous support respectively (Kaur et al. 2020). Therefore, some studies and transgenic programs are carried out in developing countries on the use of different biofertilizers to improve basic crops with micronutrients (Garg et al. 2018; Kaur et al. 2020; Malik and Maqbool 2020). The use of biofertilizers is considered a more advantageous approach because it reduces environmental pollution, is cheap and easy to produce, is sustainable in agriculture, and is easily accessible. Various microorganisms such as bacteria, fungi, cyanobacteria, actinomycetes, and mycorrhizae, expressed by Gadd (2010) as the invisible engineers of the soil, support micronutrient uptake with various properties such as dissolution of micronutrients in the soil, production of phytohormones, nitrogen fixation, and oxidation and chelation and improve plant growth (Rana et al. 2020; Yadav 2020). Besides Fe, Zn is the most abundant metal in living organisms, is the only metal found in all enzyme classes, and has a role in nucleic acid, lipid, protein, auxin synthesis, and chlorophyll reactions. All these show how important it is as a micronutrient. The main cause of Zn deficiency is that Zn available in the soil is not suitable for plant uptake. Therefore, microbial biofortification is suggested as a strategy that can be used to eliminate Zn deficiency (Dotaniya et al. 2016).

Mycorrhiza inoculation is seen as an alternative option to increase productivity without polluting soil and water and disturbing the ecological balance. In addition, the chance of success increases when mycorrhiza-inoculated soil, plant, seed, etc. are used. The use of arbuscular mycorrhizal fungi (AMF), generally known as a biofertilizer, in breeding studies is increasing all over the world. The microorganisms in the soil and the plants share a symbiotic life. The use of AMF in agricultural crops aims to meet the micronutrient needs economically, use water, and protect the soil (Palta et al. 2010). AMF provides root development and ensures the uptake of nutrients such as phosphorus (P), nitrogen (N), Ca, copper (Cu), manganese (Mn), sulfur (S), Fe, and Zn. Gashgari et al. (2020) reported that the inoculation of AMF (*Rhizophagus irregularis*) in medicinal plants such as *Mentha pulegium* and *Petroselinum hortense* increases the biomass of plants and primary metabolites such as sugar, amino acids, fatty acids, secondary metabolites such as polyphenols, and minerals such as Ca, K, Mg, P, Na, Fe, Cu, Mn, and Zn, and suggested that AMF is a promising approach that can be used in the food and pharmaceutical industry. The use of AMF for growing nutrient-rich crops is considered to be a more economical strategy than costly chemical fertilizers for Himalayan communities that suffer from hidden hunger due to Fe and Zn deficiencies (Kumar et al. 2016). It was reported that *Pseudomonas* spp. and *Pseudomonas chlororaphis* isolated from corn promote Fe uptake and germination, plant growth, and crop production (Sharma et al. 2003). Some microorganisms secrete Fe-chelating compounds called siderophores that facilitate the uptake of microelements such as Fe. Fe^{3+} ions have very low solubility at neutral pH and thus cannot be used by organisms; however, siderophores facilitate Fe uptake by plants under different pH conditions.

3.3 Genomic Approaches

Applications of micronutrients to soil or to the leaves by surface spraying increase micronutrient concentrations in the edible parts of plants such as fruits, seeds, and bulbs; however, factors such as the accumulation of micronutrients in the non-edible parts of the plants such as leaves, limited mobility of some micronutrients, and differences in soil composition of geographies limit the accumulation of micronutrients in crops (Cakmak 2008; Cakmak et al. 2010a; Kalra et al. 2020). Increasing the micronutrient content of crops by agronomic methods is a short-term solution, and these fertilizers are also quite expensive for farmers in low-income countries. Since the excessive use of high-cost inorganic fertilizers in agriculture reduces biodiversity, increases the proliferation of algae, and causes air and water pollution (at this point, the interest in biofertilizers has increased) (Jewell et al. 2020), plant breeding is accepted

as a more sustainable strategy (Bouis and Saltzman 2017). However, this method depends on the diversity in the genetic pool of the targeted crop. Lack of genetic diversity and low heritability prevent biofortification with traditional breeding (Marques et al. 2021). Another disadvantage is that it requires a long-term comprehensive selection to introduce the function into a specific culture. In order to overcome such obstacles, various alternative applications are being developed.

Identification of genes controlling biofortification traits in cereals is seen as one of the strategies that can help reduce global micronutrient deficiencies by increasing the concentrations of micronutrients. The improvement of crops by genetic improvement for micronutrient content in crops is considered a more effective approach. Thus, genomic approaches such as marker-assisted selection (MAS) and quantitative trait loci (QTL) mapping and genomic selection (GS) are seen as cost-effective approaches for selecting desired plants and have been widely used for the biofortification of wheat.

Considering the example of wheat biofortification, advances in genomics have accelerated the improvement of several agriculturally important crops. However, being polyploid and having a large genome are compelling factors in wheat breeding. Thus, without a genome sequence, it has been difficult to design molecular markers and map loci that regulate the desired trait (Ali and Borrill 2020). A wheat landrace Chinese Spring genome sequence (RefSeqv1.0) representing 94% of the whole wheat genome was published in 2018, and the high contiguity of this genome assembly was reported to be effective in genetic mapping of loci involved in Fe and Zn accumulation (Appels et al. 2018). The analysis of gene families related to biofortification and the interpretation of loci identified by QTL and genome-wide association study (GWAS) will be helpful. For example, wheat natural resistance-associated macrophage proteins (NRAMPs) were identified using phylogenetic trees from rice orthologs. However, it was also stated that RefSeqv1.1 gene annotations are not perfect due to the missing two of the 24 NRAMP genes (Ali and Borrill 2020). Such limitations are being developed with ongoing studies. On the other hand, the rice *OsIRT1* gene (*LOC_Os03g46470*) has an important role in Fe uptake (Lee and An 2009). The OsIRT1 promoter and/or its coding sequence were used in multi-biofortification studies in rice (Bonneau et al. 2018) and three orthologous *TaIRT1* genes with conserved gene structure were found in the wheat genome on chromosome group 4. It has been determined that these genes encode protein sequences with 73.0–74.2% identity with *OsIRT*.

MAS determines whether the plant carries the genomic regions required for the expression of a trait and whether it has the target trait (Lema 2018). Identifying quantitative trait loci (QTL) requires statistical methods, high-resolution genetic maps, and a large number of molecular markers. A good understanding of the genetic basis of micronutrients at the molecular level and identification of the important effects of QTLs help in the production of biofortified varieties through marker-assisted breeding. For example, more than 80 QTLs have been identified and mapped on 12 chromosomes for Zn and Fe content in rice. These identified QTLs and candidate genes can significantly enhance the efficacy of breeding programs to improve the Zn and Fe content in rice (Sharma et al. 2019). For the Mn concentration of the cereals, several QTLs were mapped on the 3, 7, and 8 chromosomes of the rice (Liu et al. 2017). Rice chromosome 3 is evolutionarily conserved across the cultivated cereals and shares large blocks of synteny with maize and sorghum (Minx et al. 2005). More than 133 agronomic genes/traits per QTL were found to be associated with chromosome 3 (Wu et al. 2002). The regions on chromosome 7 are related to the plant shoot and root development (Uddin and Fukuta 2020). Chromosome 8 has been reported to be effective in yield-related traits such as grain length and weight (Kang et al. 2018). In this study, one major QTL region was determined and the *LOC_Os07g15370* (*OsNRAMP5*) gene was identified as the possible gene causing the high amount of Mn accumulation in rice grain (Liu et al. 2017). In a study conducted in wheat, a total of 16 QTLs were identified that contributed to the Se content at the seedling stage (Wang et al. 2017). MAS is an indirect selection process in which the desired trait is selected with DNA (such as intersimple sequence repeat (ISSR), simple sequence repeat (SSR), random amplified polymorphic DNA, and single nucleotide polymorphisms (SNPs)) and RNA markers known as molecular markers or specific markers such as morphological and biochemical. It is a technique that is routinely used in conventional breeding programs and facilitates the breeding and selection of suitable genotypes (Vlcko and Ohnoutkova 2019). This genomic approach has been used in the development of provitamin A in maize cultivars where germplasm with high β-carotenoid content was selected (Masuka et al. 2017). MAS provides high success in the development of nutrient-rich maize grain. As a result of MAS studies, provitamin A content increased from 1.60 to 5.25 µg/g and from 1.80 to 8.14 µg/g (Goredema-Matongera et al. 2021). In strategies such as genomic selection, QTL mapping, SNPs are used to identify genomic regions that affect nutritional characteristics. For example, more than 20 SNPs have been identified that have a direct effect on the accumulation of Zn content in maize (Hindu et al. 2018).

3.4 Micronutrient Biofortification Using Transgenic Approaches

3.4.1 Advantages and Disadvantages of Transgenic Approaches

Increasing micronutrients in plants by genetic engineering is shown as a sustainable and cost-effective alternative to traditional fortification programs (Dunwell 2014; Kumar et al. 2019; Van Der Straeten et al. 2020). The aim of traditional breeding and genetic engineering, using for biofortification, is to manipulate the gene sequence of plants to accumulate micronutrients in the edible parts of plants and increase their bioavailability and plant diversity for human consumption (Kaur et al. 2020). In transgenic approach, new cultivars with desired traits can be developed by transferring new genes or overexpressing of the genes already present, or by blocking genes that provide inhibitor synthesis (Malik and Maqbool 2020). On the other hand, conventional breeding is insufficient for a particular crop/micronutrient combination. Nutritional-related genes from multiple parents can be combined into a single genotype by conventional backcross, but this method is very time consuming and laborious. Also, it is quite difficult to combine more than one trait with the traditional method, given the difficulty of simultaneous selection of multiple traits (Van Der Straeten et al. 2020). Today's transgenic technologies save time in the design and development of a multi-nutrient product. The genetic engineering allows the simultaneous addition of multiple micronutrients (multi-fortification) in a single product and can increase the amount and accumulation of multiple micronutrients in products (Van Der Straeten et al. 2020). In this way, many new traits are transferred to a crop more quickly. For example, a simultaneous increase in Fe, Zn, and β-carotene content was achieved in polished rice (Singh et al. 2017).

There are no evolutionary and taxonomic restrictions in genetic engineering (Garg et al. 2018), and synthetic genes can be designed and used (Hirschi 2009). That is, using various genes from different sources, many crops rich in nutrients such as vitamins, minerals, amino acids, and fatty acids can be developed. With this, well-defined gene or genes are transferred by genetic engineering; there is no risk of transferring untargeted genes to the products to be developed (CAST 2020).

Genetic biofortification aims to increase the uptake and transport of micronutrients to the shoots by genetic engineering, increase of density of micronutrients to edible portions of the cereal grains such as endosperm, and reduce the anti-nutrient factors. It can be used to develop higher quality crops in terms of more bioavailability by increasing the mineral and vitamin levels in the starchy endosperm of cereal seeds. Conventional breeding cannot develop rice enriched with vitamin A, but it has been achieved by genetic engineering (Ye et al. 2000). In this study, biosynthesis of provitamin A in endosperm was achieved with a combination of transgenes using recombinant DNA technology (Ye et al. 2000).

The phytic acid, which is the main storage form of phosphorus, is a food inhibitor that chelates micronutrients and prevents bioavailability (Gupta et al. 2015). In other words, phytic acid acts as an anti-nutritional agent by blocking the absorption of minerals such as Fe, Zn, and Ca (Akond et al. 2011; Feil 2001). The transgenic method can be used to reduce the phytic acid content in foods and to help alleviate malnutrition by improving the nutritional value of the grain which becomes poor due to such anti-nutrients. In addition, transgenic technology can also be used to simultaneous incorporation of genes involved in increasing the micronutrient concentration and reducing the concentration of anti-nutrients that reduce the bioavailability of nutrients (Garg et al. 2018).

On the other hand, for the plant development strategy with the transgenic approach, it is necessary to have sufficient basic knowledge about the micronutrient metabolism of the plant, so it may require a higher entry cost than traditional methods (Strobbe et al. 2018). In addition, the potential discovery of new genes involved in micronutrient metabolism is less likely than with conventional methods (CAST 2020).

Although genetic biofortification is a potential strategy to combat malnutrition, a skeptical approach to gene technologies is seen as an important obstacle for the development of genetically modified plants, especially in European Union countries. This technology is under strict control in many countries.

3.4.2 Transgenic Approaches for İmprovement of Zn and Fe Content in Plants

Many crops have been successfully modified using the transgenic approach to overcome the micronutrient deficiency. The single or multiple gene overexpressions were used to modulate biochemical pathways such as transport of micronutrient. Studies showed that Zn accumulation occurs in plants with the overexpression of the transporters such as transmembrane transporters in the ZIP (ZRT and IRT-like protein) family and has an important role in the acquisition of Zn^{+2} from the root-soil interface. It is also known that nicotianamine synthase (NAS) genes are expressed in the Zn^{2+} deficiency and that Zn plays a role in intercellular and long-distance transport (Cardini et al. 2021). The ZIP member IRT1 is also a major root Fe transporter. The *IRT2* gene, a close homologue of *IRT1*, encodes a high-affinity Fe transporter. Studies have shown that expression of both *IRT1* and *IRT2* genes is induced in the root upon Fe starvation (Vert et al. 2001; Wairich et al. 2019). Different methods

are used to increase Fe uptake and content in cereals, such as the modulation of the expression of ferritin, the Fe storage protein, to increase the Fe storage capacity, regulation of metal homeostasis for its transport to shoots and seeds, and increasing the synthesis of metal chelators. Wirth et al. (2009) reported that when compared to wild type, the amount of Fe and Zn in rice increased significantly with the co-expression of *Arabidopsis* synthase, bean ferritin, and *Aspergillus* phytase and overexpression of ferritin protein in rice and soybean. In another study, it was determined that Fe concentration increased up to 70 times compared to non-transgenic control groups as a result of overexpression of *Arabidopsis* vacuole Fe transporter (*VIT1*) in transgenic cassava plant (Narayanan et al. 2019). Carrier proteins can usually carry more than one metal. It was determined that both Fe and Zn accumulation increased in transgenic rice engineered as a result of induction of overexpression of genes encoding Fe regulator-carrier-like protein 1 (Lee et al. 2009). Increasing the synthesis of metal chelators such as nicotianamine (NA) and mugineic acids (MAs) increases Fe and Zn accumulation in the edible parts of the plants (Slamet-Loedin et al. 2015). Fe accumulation increases in the seed and endosperm with the expression of genes encoding ferritin and genes encoding some carrier proteins such as vacuolar Fe transporter 1 (*VIT1*) responsible for Fe, Zn, and Mn homeostasis (Bashir et al. 2016; Briat et al. 2010). Therefore, transgenic cereals fortified in Fe and Zn are also produced by the modulation of genes that control Fe and Zn homeostasis and regulate bioavailability. However, genetic modulations in the expression of genes encoding transporters affect Cd and Zn concentrations. P, Zn, and Fe are acquired in the form of free ions around the root in plants and the uptake and transport of these minerals in plants involve multiple and complex transport systems (Nussaume et al. 2011). Due to the chemical similarity between Cd and Zn, Zn-regulatory transporter (ZRT), Fe-regulating transporter-like (IRT-like) protein (ZIP), and heavy metal ATPases (HMAs) also serve as Cd transporters (Cun et al. 2014; Takahashi et al. 2012; Uraguchi and Fujiwara 2012). Detterbeck et al. (2016) conducted a study on barley and determined that high Zn concentration is associated with high Cd content. For this reason, genetic biofortification with transgenic methods may be risky for Cd accumulation (Cakmak and Kutman 2018). Moreover, the expression of ferric chelate reductase, which has a role in Fe uptake, and Fe-regulated transporter 1 (IRT1), which is the main transporter for Fe absorption from the soil, is regulated by phytohormones such as auxin, cytokinin, ethylene, and jasmonic acid (Hindt and Guerinot 2012; Kobayashi and Nishizawa 2012). Studies using ethylene and ethylene precursors showed that ethylene regulates the expression of Fe uptake genes (García et al. 2015; Ye et al. 2015). Omic approaches such as reverse transcription PCR (RT-PCR) and microarray evidenced that genes regulating Fe deficiency are sensitive to ethylene (García et al. 2010; Mai et al. 2016).

Plants try to maintain Zn levels by the mechanisms of Zn homeostasis such as Zn uptake, transport, and storage. In a recent study, it was tried to determine how plants meet this Zn condition. It was found that bZIP19 and bZIP23 (Assunção et al. 2010), which are the Zn-deficient *Arabidopsis thaliana* F-group bZIP transcription factors and bind to Zn deficiency response elements (ZDRE) in the promoter regions of target genes required for Zn uptake, transport, and distribution in Zn-deficiency, act as a Zn sensor and bind to Zn^{+2} ions to a Zn sensor motif (ZSM): Cys/His-rich motifs (Lilay et al. 2020). This ZSM deletion or modification prevents Zn to bind, leading to a constitutive transcriptional Zn deficiency response that results in increased Zn accumulation in the plant and seed (Lilay et al. 2020). ZSM is highly conserved in land plants; therefore, the identification of these sensors will contribute to the development of new strategies for eliminating Zn deficiency in crops, increasing yield and quality, and combating global malnutrition due to Zn deficiency. The *Gpc-B1* (Grain protein content-B1) gene taken from wild emmer wheat regulates the protein content as well as the content of micronutrients such as Fe and Zn in the grain. The most important characteristic of this gene is that it encodes the NAM-B1 transcription factor, which mobilizes the macroelement N and the microelements Fe and Zn. Wild emmer wheat has three genes encoding this transcription factor. However, modern bread wheat varieties have lower amounts of protein, Zn, and Fe as they contain a dysfunctional allele gene. Therefore, it is aimed to use the *Gpc-B1* gene in obtaining productive wheat cultivars (Cakmak 2008). In another study, recombinant human lactoferrin (r*HLF*) gene was expressed in rice considering that HLF proteins in breast milk may increase Fe uptake due to their high affinity for Fe and it was determined that both HLF protein and Fe amounts increased in cereal grains (Lönnerdal and Bryant 2006). Many studies have been carried out for the transport of micronutrients in crops and to increase their content (Table 1).

3.4.3 Crop Biofortification for Vitamins with Transgenic Approaches

One of the aims of biofortification is to increase vitamin levels in fortified foods, as well as to reduce or prevent the deterioration of these vitamins after harvest and during long storage. There are different approaches to increase the level of β-carotene in processed basic products. Inducing chromoplast formation and increasing the β-carotene level by transferring the *orange* (*Or*) *gene* to potatoes (Li et al. 2012), increasing the level of β-carotene in polished rice with the

Table 1 Transgenic biofortified crops with enhanced micronutrients

Crops/Cultivar	Nutrient	Gene	Reference
Oryza sativa	Zn and Mn	*TaCNR5*	Qiao et al. (2019)
Oryza sativa L. (cv. EYI105)	Fe and Zn	*OsNAS*$_1$	Diaz-Benito et al. (2018)
Oryza sativa	Fe	*OsYSL13*	Zhang et al. (2018a)
Oryza sativa	Cu	*OsYSL16*	Zhang et al. (2018b)
Indica rice cv. IR64	Fe and Zn	*AtNRAMP3, AtNAS1, PvFER*	Wu et al. (2018)
Oryza sativa	Fe	*OsDMAS1*	Bashir et al. (2017)
Oryza sativa	Fe	*OsYSL9*	Senoura et al. (2017)
Oryza sativa	Fe	*OsFRDL1*	Yokosho et al.(2016)
Indica Rice	Fe and Zn	*OsNAS*$_2$, *sferH-1*	Trijatmiko et al. (2016)
Oryza sativa L. cv. japonica	Fe and Zn	*MxIRT*$_1$	Tan et al. (2015)
Oryza sativa L. cv. japonica	High Zn	*OsPCR1*	Song et al. (2015)
Oryza sativa L.	Vitamin B9	*GTPCHI, ADCS*	Dong et al. (2014)
Triticum aestivum L.	Fe	*OsNAS*$_2$	Beasley et al. (2019)
Triticum aestivum and Zea mays	Vitamin B9	*Gm8gGCHI, GmADCS, LeADCS*	Liang et al. (2019)
Triticum aestivum L.	Fe, Zn, β-carotene	*OsNAS*$_2$	Singh et al. (2017)
Triticum aestivum L.	Fe and Mn	*TaVIT2*	Connorton et al. (2017)
Triticum turgidum and Triticum aestivum	β-carotene	*CCDs*	Qin et al. (2016)
Triticum aestivum L.	Provitamin A	*CtrB, ctrl*	Wang et al. (2014)
Hordeum vulgare	Zn	*Hvzip7*	Tiong et al. (2014)
Zea mays	α-tocopherol	*ZmTMT*	Zhang et al. (2020)
Maize	α-tocopherol	*GmTMT2a f*	Zhang et al. (2013)
Glycine max	β-carotene	*PSY, phytoene desaturese, lycopene β-cyclase*	Schmidt et al. (2015)
Indian soybean	γ-tocopherol	*γ-TMT*	Arun et al. (2014)
Glycine max (L.) Merrill	Fe	*HvNAS1*	Nozoye et al. (2014)
Glycine max L. cv. Kwangan	β-carotene	*PYS, carotene desuturase*	Kim et al. (2012)
Solanum lycopersicum L.	Iodine	*HMT, S3H,SAMT*	Halka et al. (2019)
Solanum lycopersicum L.	Ascorbate	*GMPase, ALO, MIOX2*	Cronje et al. (2012)
Solanum lycopersicum	Ascorbate	*SlGMEs*	Zhang et al. (2011)
Solanum tuberosum L.	Vitamin B6	*PDX-II*	Bagri et al. (2018)
Sweet potato (cv. White Star)	Fe	*HvNAS1*	Nozoye et al. (2017)
Solanum tuberosum L	β-carotene	*StLCYb*	Song et al. (2016)
Manihot esculenta Crantz	Fe and Zn	*VIT1, IRT1, FER1*	Narayanan et al. (2019)
Manihot esculenta Crantz	Vitamin B6	*AtPDX1.1, AtPDX2*	Li et al. (2015)
Sorghum bicolor	Vitamin E, β-carotene	*Psy1, crt1, At-dxs, pmi, hggt*	Che et al. (2016)
Arachis hypogaea L.	Fe and Mn	*AnNRAMP*$_1$	Wang et al. (2019)

Or gene (Bai et al. 2016), suppressing the degradation of provitamin A to increase the β-carotene levels in wheat (Zeng et al. 2015), can be given as examples.

Considering the long post-harvest storage period, it is of great importance to ensure storage stability for vitamins. Long-term stabilization of vitamin B9 was achieved by transferring genes that ensure the expression of folate binding proteins (aminodeoxychorismate synthase and GTP cyclohydrolase I). In polished rice, folate accumulation was increased up to 150 times compared to wild-type rice levels, and it was suggested that this approach may also be effective in increasing the stability of vitamins B1 and B6 (Blancquaert et al. 2015).

Gene transfer can be used to improve crops with multiple micronutrient deficiencies. Sorghum grain is a very low plant in terms of provitamin A, Fe, and Zn bioavailability. It was determined that the transfer of the homogentisate geranylgeranyl transferase (*hggt*) gene, which is required for vitamin E synthesis, to sorghum plant causes an increase in the amounts of major vitamin E (tocochromanols, α-tocotrienol, α-tocopherol, γ-tocopherol) as well as all-trans β-carotene (lutein, zeathanthin, α-carotene, 13-cis β-carotene, and 9-cis β-carotene) (Che et al. 2016) (Table 1). Researchers reported

that this approach is promising for people suffering from vitamin A deficiency by increasing the amount and stability of provitamin A in many food products.

Different simulation studies confirmed that consumption of biologically fortified crops positively affects human nutrition and that regular consumption of these fortified crops can reduce micronutrient deficiencies (De Steur et al. 2017). For example, simulation analysis of Golden Rice which was biologically fortified for provitamin A in Asia showed that vitamin A deficiency can be reduced (de Moura et al. 2016).

3.4.4 Future Perspectives

An efficient biofortification can be achieved by increasing both the concentrations of micronutrients and the bioavailability of micronutrients. The identification of many of the key genes involved in micronutrient uptake, translocation, and storage will facilitate the development of crops (other target micronutrients) enriched by transgenic approaches. Some traits (such as provitamin A in rice seed) that cannot be obtained by plant breeding can be introduced by the transgenic method (CAST 2020).

To help overcome micronutrient deficiencies in developing countries, pulse crops biofortified using conventional plant breeding approaches have been released by HarvestPlus (Jha and Warkentin 2020). However, it has been reported that there are no examples of pulse crop improvement by transgenic biofortification for Fe, Zn, Se, I, carotenoids, or folate (Jha and Warkentin 2020). Previous transgenic studies have found positive results in these plants, at least for other nutrients such as amino acids. The expression of the Brazil methionine-rich storage albumin gene caused an increase in the amount of methionine amino acid by 23% in the transgenic bean plant (Aragão et al. 1999). In a similar study, it was determined that the sunflower seed albumin gene caused a 94% increase in methionine concentration in transgenic lupine plants (Molvig et al. 1997). Therefore, these findings open the door to the use of gene editing (see 3.5.) and transgenic technologies in the development of pulse cultivars with desired traits. Sub-Saharan Africa is one of the regions where Zn deficiency is most prevalent and beans are consumed the most (Philipo et al. 2021), so genetically enriching the common bean with zinc will have a high impact on reducing zinc deficiency.

Transgenic biofortification is certainly not an approach that alone can solve the problem of malnutrition. However, it can be used as a complementary option in reducing the burden of malnutrition. As efforts to block transgenic crops continue, hidden hunger from micronutrient deficiency, a major public health problem, continues to affect poorer populations the most. It is necessary to make arrangements to reduce the negative perception of the society towards transgenic foods and to remove restrictions such as intellectual property that prevent the delivery of biologically enriched foods to the poor.

3.5 Genome Editing Technology

There are different approaches regarding the regulatory effect of the palindromic repeat clusters (CRISPR/Cas) system used in genome editing, which is a genetic engineering technique with the 2020 Nobel Chemistry prize and allows cleaving and recombining DNA strands.

The meganucleases, such as Zn-finger nucleases (ZFNs) and transcription activator-like effector nucleases (TALENs), used in changing the targeted region in any genomes for genome editing (GE) have great potential for crop improvement. These meganucleases have been used to genetically modify plants such as tobacco, *Arabidopsis*, rice, wheat, and barley (Ansari et al. 2020; Jaganathan et al. 2018; Sedeek et al. 2019). ZFN and TALEN are not preferred much because they are costly as compared to CRISPR/Cas, and have limited efficiency and are time consuming and difficult to design these proteins (Shiva Krishna and Suma 2019). Another alternative way to manipulate gene function is the use of mutagenized populations. It is seen as a more effective and easier approach than traditional TILLING (Targeting Induced Local Lesions IN Genomes) approaches, where it is very difficult to find a mutation in a related gene (Ali and Borrill 2020). CRISPR-Cas9 is a two-component system consisting of guide RNA that recognizes the target sequence in the genome and CRISPR-associated endonuclease (Cas) that cuts the targeted sequence. It provides precise editing of any sequence in the genome. Since RNA synthesis is easier and cheaper, it makes the CRISPR/Cas system more advantageous than ZFN and TALEN approaches (Aglawe et al. 2018). In order to determine the effect of *OsZIP9* gene, which is a member of Zn-IRT-related proteins and is involved in Zn uptake, on Zn accumulation, *OsZIP9* was knocked out by the CRISPR/Cas 9 system and mutant rice plants were grown in a hydroponic solution with low Zn concentration. Compared to the wild type, Zn content decreased in roots and shoots of knockout lines. This study reported that OsZIP9 functions as a flux carrier of Zn and increases Zn uptake in rice under Zn-limited conditions (Huang et al. 2020). The CRISPR/Cas9 system was used in rice in order to prevent excessive accumulation of micronutrients with toxic properties such as Cd. The metal transporter gene, *OsNramp5*, was deactivated in the rice plant, Cd accumulation in the shoots and roots of the osnramp5 mutants decreased, and this was found to have a positive effect on growth (Tang et al. 2017). On the other hand, Ishimaru et al. (2012) and Takahashi et al. (2014) found that more Cd accumulated in

OsNramp5 mutants compared to wild type. Therefore, it was stated that it is unlikely that these different results are due to the role of *OsNramp5* directly. There is strong evidence that Cd and Fe share transporters such as OsIRT1, OsIRT2, OsNramp1, and OsNramp5 in rice (Sasaki et al. 2012; Senoura et al. 2011). Expression of these Fe/Cd transporter genes was found to be highly induced in OsNramp5 knockout or knockout lines, especially in the case of Fe deficiency (Takahashi et al. 2014; Yang et al. 2014). It has been reported that the reason for the difference in Cd accumulations may be due to the different degrees of suppression of the expression of *OsNramp5* in the rice lines, as well as the induction of other Fe/Cd transporters (Sasaki et al. 2012; Takahashi et al. 2014).

Fortification of crops with β-carotene (provitamin A) is suggested as a potential strategy to solve the problem of vitamin A deficiency, which is common in developing countries (Endo et al. 2019). In a recent study, β-carotene was rapidly accumulated in rice calluses with the modification of the Orange (*or*) gene, which causes the accumulation of β-carotene in cauliflower by genome editing using CRISPR/Cas9 (Endo et al. 2019). In another study, rice with high carotenoid content was developed by adding a carotenoid biosynthesis cassette with the CRISPR-Cas9-based method (Dong et al. 2020).

CRISPR-Cas9 is seen as a promising strategy in producing more durable and tolerant crops by stimulating the development of multi-resistance to many abiotic and biotic stress factors in non-transgenic but modified by genome-edited plants and in reducing global food scarcity by improving crop quality and yield (Vestergaard et al. 2014). However, off-target effects such as cleaving the wrong genes, altering the function of genes, or genomic instability are among the important disadvantages of this system. CRISPR-Cas9 application can also cause great harm by producing off-target mutations (Naeem et al. 2020). The problem is that large genomes contain identical or substantially similar homologous regions. CRISPR-Cas9 can target these similar regions instead of the region it should cut. Targeting these undesirable regions can create mutations that cause cell death or transformation. However, several strategies have been developed to reduce off-target effects or limitations in CRISPR-mediated genome editing. Various techniques have been reported for the detection of off-target mutations, including in silico detection and different bioinformatics approaches. Off-target detection methods are categorized into two groups, biased tools (to detect and evaluate guide RNA (gRNA) efficiency) and unbiased tools (detects unwanted cleavage sites in living cells at the whole genomic level). The most preferred off-target detection biased and unbiased methods are Elevation (Listgarten et al. 2018) and GUIDE-seq (Tsai et al. 2015). In addition, it is crucial to select Cas variants to reduce off-target effects. For this purpose, studies are underway to develop engineered Cas9 variants with negligible off-target effects and new gene targeting techniques (Naeem et al. 2020). The United States Department of Agriculture has exempted the application of GMO regulations on many crops modified by the CRISPR system whereas the Court of Justice of the European Union has declared that strict GMO regulations will be applied (Callaway 2018). In all these genomic studies, another critical question, besides the legal regulations, is whether these food crops developed with different genomic editing tools will be accepted by the public.

3.6 Biofortification Through Nanoencapsulation

The crop yield is tried to be increased by co-applying micronutrients and N, P, and K (NPK) fertilizers to soils that are deficient in micronutrients in order to meet the nutritional needs of billions of people in the world. The common point with micronutrients in diverse global agricultural ecosystems is that crop deficiencies increase with the low efficiency of crop use. Micronutrient use efficiency (MUE) is defined as the biomass yield per unit input of fertilizer and nutrient content (Meena et al. 2014). It was also reported that the interactions between micronutrients and macronutrients can affect crop yield positively or negatively. In other words, the interaction of fertilizer-micronutrients with macronutrients can occur as a synergistic, antagonistic, or neutral reaction that may affect the yield and quality of the product. It was determined that high amounts of P applied to the soil cause Cu deficiency in plants such as corn, beans, citrus, and tomato. It was reported that NPK fertilization for rice and wheat cultivation in India increases the crop yield whereas the bioavailability of micronutrients such as Zn becomes so limited, and as a result, it poses a big problem in Zn nutrition for humans (Cakmak 2009; Monreal et al. 2015). Despite the increase in crop yield with NPK fertilization, reasons such as the lack of increase in crop yield in regions with less favorable biophysical conditions and hidden hunger in people consuming products with low micronutrient values necessitate sustainable new solutions to produce crops with high crop yield and nutrient quality.

Today, increasing crop yield, food nutrition, and fertilizer-micronutrient use efficiency around the world have required the use of nanotechnology and biotechnological methods (Akhter et al. 2013; De Rosa et al. 2010). New strategies such as nanoencapsulation and microencapsulation, nanomaterials, nanodevices, and nanoparticles are among the methods that aim to increase the micronutrient use efficiency (Monreal et al. 2015). Nanoencapsulation is the technology of encapsulating micronutrients in different materials and coating in nanosizes. Nanocapsules are in the submicron range and function as a vehicle for encapsulating with nanometric films, layers, and coating materials and

transporting the component to the desired site of action. Microencapsulation is the process of coating or packaging small solid, liquid, or gas particles, which constitute the active core, with another thin polymeric secondary material called encapsulant (Gharsallaoui et al. 2007). Microcapsule-micron size ranges between 1 and 1000 μm (Bratovcic and Suljagic 2019). In nanoencapsulation, mesoporous aluminosilicates, which contain a mixture of silica and Al and active sites for ion exchange and adsorption, are used as CuO nanoparticle carriers in the controlled release of macro- and microelements into the soil (Huo et al. 2014). Crop yield and micronutrient concentration are increased by ensuring the uptake of microcapsules, nanocapsules, nanomaterials, and nanoparticles such as Zn, Fe, Mn, and CuO, to which micronutrients are added, by plants. Encapsulation protects micronutrients from various environmental factors such as pH, light, and oxidants. In addition, providing a controlled slow-release with the compounds used in the coating of these nutrients and increasing the solubility of less soluble compounds by encapsulation increase the bioavailability of micronutrients (Karunaratne et al. 2017). Studies on encapsulated micronutrients were mainly performed in the food and pharmaceutical industries. Different coating materials are used depending on the target molecule, cell tissue or organism, and environmental conditions. Polymers such as ethylene–vinyl acetate, gelatin, zein, alginate, chitosan, lignosulfate, pectin, and starch are used for micronutrient coating (Wang et al. 2013). Polymer films are used in microcapsules for the controlled release of commercial fertilizers into the soil solution. Cui et al. (2010) reported that coating the nutrients in water-soluble fertilizers with materials such as resin-polymer, wax, and sulfur will reduce the loss of nutrients in the fertilizer through permeation to the soil and increase the bioavailability of nutrients; thus, the rate of nutrient release can be controlled. Mn oxide nanoparticles accumulate on the root surface, taken into the plant, and then migrate. It was reported that nanostructures containing a core fortified with Zn and a shell around the core consisting of Mn carbonate increase the Zn use efficiency in rice by adding micronutrients to the roots of the plant. Nanoencapsulation of Zn using Mn increases grain yield while reducing nutrient loss (Yuvaraj and Subramanian 2014). In another study, it was determined that ZnO nanoparticles with an average size of 25 nm increase the yield and Zn amount in corn compared to $ZnSO_4$ application and that ZnO nanoparticles can be effective in improving human health (Subbaiah et al. 2016). High water solubility, the ability of nanoparticles smaller than 100 nm to penetrate the plant quickly, having a large surface area that can interact with other molecules, non-toxicity, and the potential to minimize environmental pollution are the main reasons for the use of nanomaterials to increase micronutrient efficiency (Kalra et al. 2020). It was previously mentioned that unlike the application to the soil, the application of microelements such as Fe, Mn, Cu, and Zn as liquid fertilizers to the leaves by the surface spraying method is considered a more effective method in reducing the delay of nutrient uptake. If this foliar application method is used for nanofertilizers, it will provide a great agronomic efficiency since stoma (when the stoma is open) and leaf epidermal cells will be involved in nutrient uptake (Kalra et al. 2020). Some studies showed that nanofertilizers accelerate metabolism with the foliar application and enhance plant growth by supporting meristematic activity. For example, the dry weight of the mint plant increases with N nanofertilization (Rostami et al. 2017), and carbohydrate and protein production in maize increases with Fe nanofertilization (Sharifi et al. 2016). Compared with other fertilizers used in agriculture, the use of nanofertilizers is considered to be a sustainable, low-cost method to increase soil fertility, product yield, and quality. However, overdoses of nanofertilizers can cause some problems at the soil–plant interface and it has been reported that it can cause toxic effects for plants, animals, microorganisms, and plants (Landa 2021).

On the other hand, nanoparticles were obtained by using of extracts and parts of the plant such as leaves, roots, flowers, and seeds; microbes such as bacteria, fungi, algae, and yeast; and biomolecules such as enzymes, proteins, and carbohydrates. This biogenic green synthesis of nanoparticles is more economical and environmentally friendly. Examples are the production of Fe-NPs from green tea and black tea leaves (Mareedu et al. 2021), ZnO-NPs from *Nilgiriantuscilliantus* leaves (Resmi et al. 2021), and nickel oxide-NPs from fennel (*Nigella sativa*) seeds (Boudiaf et al. 2021). These green synthesized nanoparticles are successfully used as an antimicrobial agent, alternative energy source, and catalyst in human health–related issues (El Ramady et al. 2021). It has been reported that these nanonutrients such as nano-Se can support the fight against many diseases, especially COVID-19 (as anti-COVID-19 nanoparticles) (He et al. 2021).

4 Conclusion

Micronutrient deficiency is considered one of the most important problems threatening human health worldwide (WHO 2007). Most of the global population does not have access to fruits, vegetables, and animal products consisting of micronutrients and vitamins necessary for proper nutrition. However, the COVID-19 pandemic, which is currently a global health crisis, along with many diseases caused by micronutrient deficiencies, has highlighted the value of biofortified crops as a practical and cost-effective strategy for delivering essential micronutrients to billions of people. The concentration of minerals and vitamins in

food staples, which are widely consumed by the poor population, can be increased by using different biofortification techniques. One of these strategies, the major advantage of traditional breeding programs, is that breeding biofortified food is more easily accepted by humans on a global scale compared to transgenically fortified food. Since this method is more sustainable and low cost, it draws more attention from poor farmers living in regions where micronutrient deficiencies are most common, such as Africa, Asia, and Latin America (FAO 2017). Although plant breeding and agronomic biofortification used in biofortification of crops are usually successful techniques, they are not considered sufficient to eliminate some micronutrient deficiencies. On the other hand, due to disadvantages such as lack of genetic diversity and low heritability, MAS is used as a complementary and supportive new strategy to increase the success of conventional breeding. However, the greatest risk of MAS is the narrowing of genetic diversity. Although transgenic biofortification, which aims to transport and distribute micronutrients between tissues, increasing their concentration in the edible parts of crops and the efficiency and productivity of biochemical pathways in their synthesis, requires time, effort, and investment at the beginning, it is seen as a more cost-effective and sustainable method in the long term. However, the time-consuming and high-cost legal regulations for the commercial distribution of developed food crops, the difficulties in obtaining approval from governments, the concerns and demands of anti-GMO activists for more testing before distribution, and the low public acceptance are the main disadvantages of this method. Despite these difficulties, traditional and marker-supported plant breeding, genetic applications, and various biofortification strategies based on both the agronomic and nanoencapsulation applications of micronutrients to the soil or surface have promising potential to improve health and the nutritional diets of people living in poor geographies suffering from micronutrient deficiencies.

It is an undeniable fact that the biggest threat to global human health today is the COVID-19 pandemic. The effects of this threat were more severe especially in poor countries due to malnutrition conditions. Worse still, COVID-19, climate change, and malnutrition have converged to make it an even more devastating threat to millions of people. The production of biologically fortified foods that will strengthen human immunity is seen as an approach that will help to overcome COVID-19 and similar pandemics. These biofortification strategies will help vulnerable people to be more resilient against income and food system shocks that may occur due to negative factors such as possible pandemics and natural disasters in the future. Therefore, governments should prevent discrimination against biofortified staple foods by promoting the widespread adoption of fortified staple cultivars and by providing official support. Let us not forget that the lessons to be learned and the global responses to be given from global crises such as COVID-19 and climate change will be an investment in the future of humanity.

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Declarations

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