MICRONUTRIENT MALNUTRITION AND BIOFORTIFICATION: RECENT ADVANCES AND FUTURE PERSPECTIVES

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1 INTRODUCTION

Malnutrition is one of the major causes of human mortality worldwide, accounting for >20 million people per year (WHO, 2007). Malnutrition is also a prominent factor in increasing illness, disability, and underdeveloped mental and physical growth (WHO and FAO, 2002). An appropriate diet composed of fruits, vegetables, and animal products is required to meet micronutrient and energy requirements. However, these products are out of reach for most of the global population. While almost all plants can synthesize and accumulate micronutrients, the edible parts of some staple crop plants contain inadequate quantities of micronutrients, such as iron (Fe), zinc (Zn), vitamin A, folate, etc. (DellaPenna, 2007). Biofortification of staple crops with micronutrients has therefore been proposed as a potential strategy to combat the problem of malnutrition through the enrichment of target food crops to fill the gap in micronutrient ingestion by humans and animals (Welch and Graham, 1999, 2004; Nestel et al., 2006).

Micronutrient deficiency is increasing due to an ever-increasing global population. Iron and Zn deficiency can cause serious health problems such as impaired cognitive and mental development, decreased growth, anemia, immune system impairment, and increased death rate (Black, 2003). Micronutrient malnutrition not only increases disease burden, but also deteriorates social welfare and economic productivity on a global scale (Stein, 2010). Currently, micronutrient malnutrition evolving from Zn and Fe deficiencies is affecting 3 billion people worldwide with serious health effects. The major reason for increased prevalence of Zn and Fe deficiencies has been traced back to staple food-based diets that are low in nutrition, for example, Zn and Fe. In developing countries, mineral deficiency causes low work productivity that leads to a decrease in gross national product. In the United Kingdom for instance, 11%–38% of the children are reported to suffer anemia before reaching 2 years of age. In Canada and America, 10% of the population is at risk of Zn deficiency.

Micronutrient malnutrition evolving from Zn and Fe deficiency is now affecting 3 billion people worldwide and has serious health effects. The WHO reported that roughly 25% of the world's population

Table 1 Micronutrient Deficiencies in Humans Living World-Wide and Their Effect on Human Health

Micronutrient	Effects	Deficient Number of People
Iron	Anemia, impaired motor and cognitive development, increased risk of maternal mortality, premature births, low birthweight, low energy	~1.6 billion
Zinc	Weakened immune system, more frequent infections, stunting	~1.2 billion
Iodine	Brain damage in newborns, reduced mental capacity, goiter	~1.8 billion
Vitamin A	Severe visual impairment, blindness, increased risk of severe illness and death from common infections such as diarrhea and measles in preschool age children; (in pregnant women) night blindness, increased risk of death	209 million preschool going children and pregnant women

Data from Karumbunathan, V., Zimmermann, M.B., 2012. Global iodine status in 2011 and trends over the past decade. J. Nutr. 142, 744–750, Micronutrient Initiative. 2009. Vitamin A: The Scope of the Problem, MI, Ottawa (www.micronutrient.org/English/View. asp?x=577&id=440), and WHO. 2009. Global Health Risks: Mortality and Burden of Disease Attributable to Selected Major Risks. World Health Organization, Geneva.

experience anemia (Table 1). An expected 17.3% of individuals worldwide are at the risk of Zn deficiency (Wessells et al., 2012). In South Asia, 95% of the population consume a rice-pulse diet and have serious health issues. In developing countries, Zn is ranked 5th among the 10 main micronutrients deficiency, whereas on a worldwide scale, Zn deficiency is ranked 11th among 20 micronutrients deficiencies (Shekari et al., 2015).

The basic reason for Fe and Zn deficiency is high consumption of food with little diversity, mainly consuming one or two staples in developing countries. In developing countries, people mostly depend upon cereal and animal-based food due to acute poverty. Zn and Fe concentrations are low in cereal crops, and most is lost during processing (Frano et al., 2014; Welch and Graham, 1999). The major staple crops in these countries are wheat, maize, and rice. Wheat fulfills 60% of the daily energy requirement. In wheat grain, Zn and Fe are found in the aleurone layer, which is lost during milling and processing, and this issue is further aggravated due to the presence of phytate that limit the bioavailability of nutrient. There are numerous ways to enhance micronutrient levels in the human diet's dietary diversity, including supplementation, food fortification, and biofortification.

Biofortification mitigates micronutrient malnutrition by enhancing micronutrient levels and bioavailability in edible parts of staple crops through breeding and fertilization. Among the scientific community, biofortification is widely accepted as a better strategy compared to supplementation and/ or food fortification due to the fact that it is more cost-effective and sustainable.

2 HUNGER AND "HIDDEN HUNGER"

Malnutrition is a broad term to indicate the conditions that may arise from both undernutrition and overnutrition. Undernutrition is associated with stunting (low height for age), wasting (low weight for height), being underweight (low weight for age) and micronutrient deficiencies, whereas overnutrition

is associated with obesity, diet-related noncommunicable diseases (e.g., heart disease, stroke, diabetes and cancer) and being overweight (WHO, 2016a,b). Undernutrition is defined as the provision of an insufficient quantity of food (hunger) or the provision of a sufficient quantity of food but with low levels of essential food elements (i.e., hidden hunger). Hunger is usually understood to refer to the suffering associated with lack of food, but can also refers to conditions when a sufficient quantity of food is provided with low levels of minerals and vitamins.

Developing countries have made substantial improvements in reducing hunger, and the global hunger index (GHI) has been significantly reduced from 1992 to 2016. Since 2000, a 29% decrease in GHI has been observed in developing countries (Anon., 2016). Although conditions are improving, efforts are still needed to achieve a zero-hunger rate throughout the world, as about 50 countries (including some highly populated countries like India, Pakistan, Bangladesh, and Indonesia) have serious threats of hunger (Fig. 1).

Hidden hunger is of more concern due to deficiency of essential food elements such as vitamin A, Zn, Fe, and iodine. The prevalence and consequences of "hidden hunger" can be more insidious as it signifies deficiencies of protein, essential vitamins, and minerals. It may be due to inadequate intake of food in terms of either quantity and/or quality, poor utilization of nutrients due to infections or other illnesses, and/or a combination of these factors. Increased micronutrient requirements during specific periods of life, such as pregnancy and lactation, also cause micronutrient deficiencies in humans and animals.

The most commonly recognized micronutrient deficiencies across all ages, in order of prevalence, are caused by a lack of iodine, Fe, or Zn. Less common, but significant from a public health standpoint,
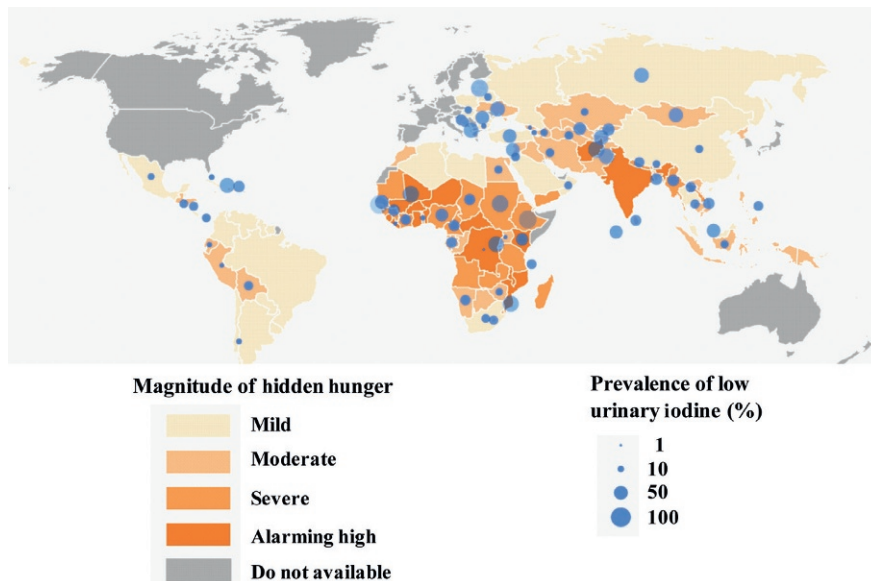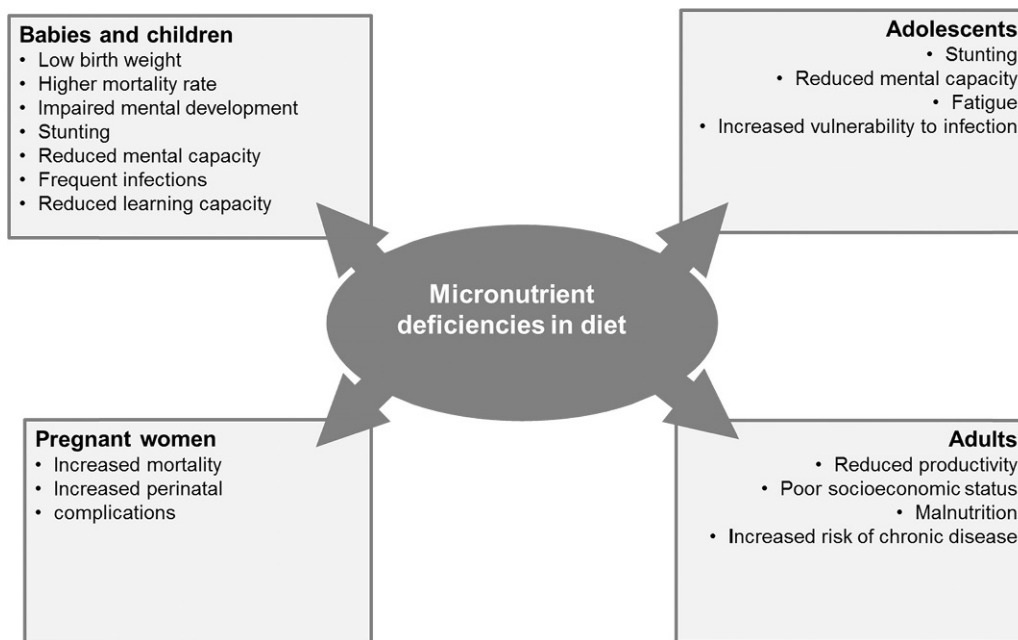

FIG. 1

Global map presenting hidden hunger index based on the prevalence estimates (HHI-PD) in 149 countries and prevalence of low urinary iodine concentration in 90 countries with 2007 Human Development Index (Muthayya et al., 2013).

FIG. 2

Effect of micronutrient deficiencies in diet on babies, adolescents, adults, and pregnant women.

is vitamin A deficiency, with an estimated 190 million preschool children and 19 million pregnant women affected (WHO, 2009). Low intakes of other essential micronutrients, such as calcium, vitamin D, and B vitamins such as folate, are also common (Allen et al., 2006). Pregnant women and children are generally more affected by hidden hunger, as it impairs their health throughout the lifecycle and increases the mortality rate due to micronutrient deficiencies (Fig. 2).

3 REMEDIES OF MICRONUTRIENT MALNUTRITION

Several strategies including food diversity, food supplements, food fortification, and biofortification can be adopted to reduce micronutrient malnutrition. These strategies have their own advantages and weaknesses as discussed below.

3.1 DIETARY DIVERSIFICATION

A single food cannot provide all the nutrients required for the human body. A balanced food intake is required to fulfill all the human body's nutritional requirements. A combination of natural foods that can provide all the nutrients required for growth and development of the human body is called balanced nutrition. Micronutrients are even more critical as their concentration in foods is dependent on soil resources, genetic diversity, micronutrient application, and the husbandry of food crops. Long-term dietary

diversification ensures a healthy diet containing an adequate combination of macronutrients such as carbohydrates, fats, and proteins, essential micronutrients, and dietary fiber content. Although dietary diversity is an effective way to prevent hidden hunger in a sustainable way (Thompson and Amoroso, 2010), micronutrient concentration in the same food product may vary depending upon the husbandry practices. While legumes, cereals, vegetables, fruits, and other animal-sourced foods provide adequate nutrition for most of the population, some population groups such as pregnant women may need supplements due to higher requirements (FAO, 2013). Children at different growth stages may also require varying amounts of nutrients. Therefore, a combination of diverse types of healthy foods is required for normal human nutrition and health. However, it is difficult to overcome micronutrient malnutrition in large populations through dietary diversification alone, as the majority of these people are living in developing countries where access to a healthy food is not possible for everyone at all times.

3.2 FOOD SUPPLEMENTS

Here the term "supplementation" is referred to as adding micronutrient(s) into a person's diet to remedy deficiencies. Use of supplements to fulfill nutritional requirements may be effective in developed parts of the world where supplements are relatively inexpensive compared to available government resources and individual incomes. However, in poor/developing countries supplementation programs can be expensive and difficult to sustain because the people live in remote, rural areas where access is not easy. One of the most cost-effective interventions was vitamin A supplementation to improve child survival in various parts of world (Edejer et al., 2005). The efforts to provide food supplements to more people increased significantly in near past (UNICEF, 2013). Over 70% of children aged 6–59 months old need vitamin A supplements at least once in every 6 months to significantly reduce vitamin A deficiency-related mortality. However, it is often challenging to supply continuous funding for such programs due to fluctuations in these fragile economies (UNICEF, 2007). Vitamin A supplementation is often integrated into national health policies because it is associated with a reduced risk of all-causes of mortality (Imdad et al., 2010). Vitamin A supplements were typically targeted to susceptible populations between 6 months and 5 years of age (UNICEF, 2007). Supplementation for other deficient micronutrients such as amino acids, folic acid, Zn, Fe, etc., is less common. In some countries, Fe-folate supplements are prescribed to pregnant women, however, this is not common in developing countries due to inadequate resources. Nevertheless, the WHO recommends an oral Fe and folic acid supplementation with 30–60 mg of elemental Fe (or equivalent) and 400 µg folic acid for pregnant women on a daily basis to prevent maternal anemia, puerperal sepsis, low birth weights, and preterm births (WHO, 2016a,b). The WHO recommendation also states that folic acid supplements should be commenced as early as possible (ideally before conception) to prevent neural tube defects. In a randomized controlled trial by WHO held in Bangladesh, weekly Zn supplements protected against episodes of pneumonia, diarrhea, and suppurative otitis media, and also prevented deaths (WHO, 2013). The results of this study led to the inclusion of Zn supplements in the UNICEF/WHO management recommendations for diarrhea and also revealed additional benefits in the management of respiratory diseases.

3.3 FOOD FORTIFICATION

Food fortification is the process whereby nutrients are added to food to maintain or improve the quality of the diet of a group, community, or population. Food fortification is required due to insufficient intake of vitamins and minerals, due to the consumption of predominantly processed foods.

Commercial food fortification adds trace amounts of micronutrients to foods during processing, which helps consumers achieve the required levels of micronutrients in their diet. Fortification of table salt with iodine is an example of a sustainable and relatively cost-effective public health strategy. About 71% of the world's population has access to iodized salt, and the number of iodine-deficient countries has decreased from 54 to 32 since 2003 (Andersson et al., 2012). Other examples of fortification include B-group vitamins, Fe, and Zn in wheat flour and cooking oil fortification with vitamin A. However, fortification may be more effective for urban consumers, who frequently buy commercially processed and fortified foods, but for rural consumers, it is difficult to access the value of fortified foods. Several shortcomings can be attributed to food fortification. People may resist fortified foods, cooking properties may be lowered, it can be difficult to determine the appropriate concentrations of micronutrients, and the bioavailability of nutrients may be reduced. Thus, active coordination among stakeholders such as policy makers, researchers, economists, etc., is required for efficient and sustainable use of food fortification strategies.

3.4 BIOFORTIFICATION

Biofortification is a relatively new intervention to improve human nutrition worldwide, with a special emphasis on the populations of poor and developing countries. There are several ways to improve the nutritional value of food crops, and these are discussed in the following sections. The basic goal of biofortification is to reduce mortality and morbidity rates related to micronutrient malnutrition and to increase food security, productivity, and the quality of life for poor populations in developing countries. As biofortification is very cost-effective and easy to disseminate to the masses, its importance is greater for developing countries. Several biofortified crops have been released so far including orange sweet potatoes, maize, cassava, and squash, Fe-enriched beans, sorghum, lentils, and pearl millet, and Zn-enriched rice, wheat, lentils, sorghum, and cowpeas. Biofortification could provide a range of certain micronutrients for people who don't have access to other interventions. As staple foods are comparatively cheap and accessible to the majority of people, the biofortification of staple crops is a primary target. Although the efficiency of biofortification is not comparable to food supplementation, it can still help reduce the micronutrient intake gap and increase the daily intake of vitamins and minerals throughout a person's life, and this may have significant impact on human health by reducing malnutrition (Bouis et al., 2011). Indeed, improved micronutrient concentrations in several crops (beans, maize, pearl millet, rice, sweet potato, and vitamin A-fortified cassava) have significantly improved the micronutrient levels in humans (Tanumihardjo, 2013; Talsma, 2014). Biofortification of orange sweet potato for vitamin A has significantly improved vitamin A intake of mothers and young children (Hotz et al., 2012).

4 BIOFORTIFICATION APPROACHES

Biofortification can be agronomic and/or genetic. Genetic biofortification can be accomplished either through conventional breeding or through genetic engineering to enhance micronutrient levels in edible plant parts.

Mineral elements deficiencies in food crops may be due to different factors, such as soils which are deficient in one or more minerals, lowered availability of minerals to plants due to different factors

such as alkaline soils, reduced distribution/translocation of minerals, and accumulation of minerals in nonedible parts of food crops. Thus, it is extremely important to address these issues to increase the mineral levels in the edible parts of the crop plants.

4.1 AGRONOMIC INTERVENTIONS

Nongenetic measures to improve the micronutrient concentrations of food plants could be more efficient, and several strategies and measures can be adopted to increase micronutrient concentrations in the edible parts of food plants. These include management practices, fertilization of target elements, and improving soil organic matter to increase nutrient availability in soil, and its uptake by roots.

There is evidence that agronomic biofortification not only increases yields but also the nutritional quality of staple crops (Valença et al., 2017). Micronutrient fertilization is most effective when using a combination of inorganic and organic fertilizers, highlighting the importance of integrated soil fertility management. Fertilizer application is an immediate and effective route to enhance trace elements concentrations in crops; nevertheless, genetic biofortification may be more cost effective in the long term. Selenium fertilization in Finland has already been adopted, and its impact on increasing selenium concentrations in Finnish foods and optimum dietary intake by humans has been reported (Broadley et al., 2006). The biofortification of crops with vitamins through agronomic measures is not feasible; however, agronomic measures have shown enormous potential to increase mineral concentrations.

4.2 GENETIC BIOFORTIFICATION

Soil or foliar applications of minerals can increase their concentrations in phloem-fed tissues, such as fruits, seeds, and tubers (White et al., 2009; Cakmak et al., 2010a,b). However, limited mobility of minerals in phloem restricts the impact of agronomic biofortification. For example, low mobility of Zn in the phloem restricts the Zn accumulation in the edible parts of the food crops (Broadley et al., 2007; Cakmak et al., 2010a). Genetic variation for grain mineral-element concentration can be exploited by genetic strategies to increase Zn concentrations in edible portions. Furthermore, genetic variation for nutrient acquisition, uptake, and translocation to shoot through xylem may also be exploited (White and Broadley, 2009). The Consultative Group on International Agricultural Research (CGIAR) has explored genetic variability, for mineral concentrations and stability over different environments to enhance the mineral content of major staple crops such as wheat, maize, rice, cassava, and beans. There is considerable genetic variation for Zn and Fe concentrations in most edible crops. Significant variation for mineral elements in edible roots has been reported; for example, a 2.2-fold variation among 20 carrot genotypes (Nicolle et al., 2004), and >14-fold variation in root Zn concentrations among 600 cassava genotypes (Chávez et al., 2005) have been reported.

Genetic biofortification refers to the breeding of plants (both conventional breeding and using genetic engineering technologies) to develop food crops with improved micronutrient concentrations, lower levels of antinutrients, and increased levels of compounds that enhance the bioavailability of nutrients (Bouis, 2003). Agronomic interventions and conventional breeding have the potential to deliver the required targets; nevertheless, when genotypic variation for any specific nutrient is low, then conventional breeding is unable to achieve the target (Beyer, 2010). Under such conditions, genetic engineering can contribute to increase the micronutrient content in staple crops, and its potential has been successfully demonstrated. Genetically modified (GM) tomato crops have been developed with

increased provitamin A concentrations (De Steur et al., 2015). Enhanced uptake from soil, improved transport of micronutrients to shoot and grains, augmented sequestration of minerals to endosperm, and reduction in antinutritional factors in grains are the major targets of biofortification research, and genetic biofortification can target these aspects for mineral biofortification. Despite the potential of GM technology to improve human health, problems in approval of GM-biofortified crops caused by regulatory barriers significantly hinder the effectiveness of GM technology for biofortification. On the other hand, conventionally biofortified crops are significantly contributing to the amelioration of mineral deficiencies (Finkelstein, 2015).

5 REDUCTION IN MALNUTRITION THROUGH BIOFORTIFICATION

Malnutrition is a concern all over the world and 60%, 30% and 15% of the world's population has been assessed as being Zn, Fe, or iodine (I) deficient, respectively (Yang et al., 2007). Biofortification focuses on improving the nutritional characteristics of crops, enhancing both their mineral concentrations and mineral bioavailability in the edible parts of crop plants, and can be accomplished by agronomic mediation, plant development and production, and utilizing hereditary characteristics. Breeding crops that are high in vitamins and minerals is a cost effective, relatively simple, and easy approach to combat micronutrient deprivation. The efficient utilization of conventional breeding approaches, application of micronutrients to crop plants, and the utilization of biotechnology to enhance micronutrient values of staple crops could ameliorate deficiencies of Zn, Fe, vitamin A, I, and some other minerals and proteins as well. Moreover, mineral-enriched plants can be more resistant to biotic and abiotic stresses and can produce higher yields under some circumstances (Frossard et al., 2000; Nestel et al., 2006).

5.1 ZINC DEFICIENCY

Zinc is an essential element for plants and animals, including humans, and is a component of thousands of functional proteins. >2 billion people are suffering from Zn deficiency (Myers et al., 2014). The breeding of crop varieties mainly focuses on the accumulation of high Zn contents in grains and the utilization of Zn fertilizers to enhance Zn levels (Bouis et al., 2011). Although a plant breeding approach is probably going to be the most economically viable approach over an extended period, utilization of fertilizers is the quickest method to enhance Zn concentration in the diet.

The Zn Nutrient Initiative (ZNI) is a program of the International Zn Association (IZA), which reports Zn scarcity in soils, crops, and ultimately, in humans over expanded utilization of Zn fertilizers, with the aim to promote consciousness of improved crop yield, enhanced nutritive quality of crops, enhanced human nutrition, and enhanced grower income, and to secure both quantity and quality of food (Das and Green, 2011).

Biofortification Challenge Program in 2003 through the Consultative Group on International Agricultural Research (CGIAR), has provided a stage from which to investigate genetic range for micronutrients prevailing in germplasm worldwide and to use this diversity for growing high-Zn genotypes. In Pakistan, the Zn-rich wheat variety "Zincole 2015" has been released by Pakistan Agricultural Research Council (PARC) to reduce Zn deficiency in humans. In recent studies, about 30% of the estimated average requirement of Zn in the human diet was achieved by genetic modification of rice (Kurniawan et al., 2016).

Recently, an advance has been made through the foliar application of Zn to improve Zn concentrations in cereals, especially in wheat (Cakmak, 2008, 2009). Foliar application of Zn not only improves grain yield, but also increases grain Zn concentrations. Shivay et al. (2008) reported that Zn application to soil, as Zn-coated urea or $ZnSO_4$, improved yield as well as the Zn content in wheat grain. Shivay and Prasad (2012) demonstrated that the use of Zn ($ZnSO_4 \cdot 7H_2O$) in Zn-deficient soils significantly enhanced rice grain yield and Zn content in grain of rice.

In wheat, foliar application of Zn, particularly at advanced stages of plant development, was effective at improving the Zn content of both the entire grain and endosperm alone, while soil applications of Zn were not so effective (Cakmak et al., 2010b). In contrast, application of Zn fertilization to soil significantly increased wheat grain Zn content in Australia (Graham et al., 1992) and India (Shivay et al., 2008). In Turkey, the combination of soil and foliar Zn fertilization to cereals remains a useful option for increasing grain Zn contents (Yilmaz et al., 1998).

Foliar Zn application can greatly improve Zn concentrations in the cereal grains; furthermore, soil application and foliar spraying of either $ZnSO_4$ or Zn-chelates can increase grain Zn concentrations in plants with satisfactory Zn translocation through the phloem. Correspondingly, soil or foliar application of Zn can improve Zn accumulation in the leaves, tubers, and fruit (Broadley et al., 2007). The microbial metabolite secretions due to increased microbial action could also significantly contribute to Zn biofortification (Neumann and Romheld, 2000). Utilization of Zn solubilizing bacteria significantly improved Zn concentrations in the roots and shoots of wheat and soybean plants (Madhaiyan et al., 2010).

The molecular mechanisms of Zn uptake and distribution have been well studied in crop plants (Bashir et al., 2012; Yamaguchi et al., 2012; Suzuki et al., 2012). Several groups have also attempted to increase the Zn content of edible parts through transgenic technology (Palmgren et al., 2008; Jou et al., 2012; Takahashi et al., 2012; Bashir et al., 2012; Masuda et al., 2013; Yamaji et al., 2013; Slamet-Loedin et al., 2015; Tiong et al., 2015). The strategies for Zn biofortification significantly overlap with Fe biofortification, and hence are discussed together in the section of Fe biofortification.

5.2 IRON DEFICIENCY

Fe deficiency causes anemia in more than 2 billion people worldwide, and increasing the Fe content in the human diet could address this in most cases. Cereal grains contain very low levels of Fe, but Fe levels can be increased, and the concentration of antinutritional compounds such as phytate can be reduced, to increase the bioavailability of Fe (Zimmermann and Qaimm, 2004).

Inorganic Fe fertilization of soils is generally impractical as the Fe in many s inorganic Fe fertilizers are quickly converted to unavailable or less-available forms of Fe through oxidation and precipitation reactions. However, the use of Fe-chelates as Fe fertilizers in soils can be effective and practical as well (Rengel et al., 1999), and the accessibility of Fe can be improved in the rhizosphere by soil acidification.

The uptake and distribution of Fe is well understood, particularly in cereals, and different approaches could be utilized to increase the Fe content of crop plants (Vigani et al., 2013; Bashir et al., 2013; Bashir et al., 2016; Masuda et al., 2013; Slamet-Loedin et al., 2015). These approaches include (1) increasing uptake of Fe by regulating the expression of Fe transporters, (2) increasing synthesis and/or secretion of metal chelators, (3) increasing Fe storage capacity of plant cells through expression of the Fe storage protein ferritin, and (4) regulating cellular metal homeostasis to increase Fe translocation to seeds.

The proteins responsible for mineral uptake (transporters) often transport more than one metal; thus, Fe and Zn share their routes of uptake from the soil through the root, root-to-shoot translocation, and loading to seeds. Transgenic rice plants overexpressing *OsIRT1* (Rice iron-regulated transporter-like protein, 1) exhibited enhanced accumulation of Fe and Zn in their grains (Lee et al., 2009). Rice lines overexpressing rice yellow stripe like 15 (*OsYSL15*) also accumulate more Fe in their seeds. Overexpressing rice *YSL2* (*OsYSL2*) resulted in a decrease in the root-to-shoot translocation of metals; however, restricting the expression of *OsYSL2* to phloem through sucrose transporter promoter (*OsSUT1*) significantly increased Fe and Mn concentrations in rice seeds (Ishimaru et al. 2010), suggesting that regulation of metal transporters in terms of spatial and temporal expression is important to significantly increase Fe levels in rice grains. Regulating the expression of MAs efflux transporter *TOM1*also slightly increases seed Fe, Zn, and Cu concentrations (Nozoye et al., 2011).

Furthermore, increasing the synthesis and/or secretion of Fe and Zn chelators could also significantly enhance metal accumulation in seeds. Nicotianamine (NA) and mugineic acids (MAs) are important metal chelators in plants (Beneš et al., 1983; Takagi, 1976). Biofortification through regulating NA synthesis to increase Fe and Zn concentration in edible parts has been reported by several groups (Johnson et al., 2011; Slamet-Loedin et al., 2015; Masuda et al., 2013; Aung et al., 2013; Wirth et al., 2009).

Ferritin, is a soluble and nontoxic form of Fe, thus increasing ferritin production could be effectively utilized for Fe biofortification (Harrison and Arosio, 1996; Briat et al., 2010). Several groups have successfully demonstrated that rice lines overexpressing ferritin encoding genes could accumulate up to three times more Fe in seed endosperms (Paul et al., 2012; Goto et al., 1999; Lucca et al., 2001; Qu et al., 2005). Attempts to increase the availability of Fe through regulating the expression of phytase to degrade phytic acid have also been reported (Wirth et al., 2009).

Regulating the expression of transporters controlling the distribution of metals within plant cells could significantly improve metal homeostasis and could lead to increased metal accumulation in seeds (Bashir et al., 2016). In this regard, the vacuolar transporters are of particular interest, as changes in the expression of *vacuolar iron transporter 1* (*VIT1*) significantly alters Fe localization in *Arabidopsis* seeds (Kim et al., 2006). In rice, VIT1 and VIT2 are functional vacuolar transporters that contribute to Fe, Mn, and Zn homeostasis. Disrupting the expression of *OsVIT1* and/or *OsVIT2* leads to increased metal accumulation in rice seeds (Zhang et al., 2012). In contrast, changing the expression of a mitochondrial Fe transporter negatively affects Fe localization in rice seeds (Bashir et al., 2013).

Combining different approaches could produce better results than a single approach to enhance metal concentrations in edible plant parts (Masuda et al., 2012). Several other candidates could also be utilized for Fe and Zn biofortification (Bashir et al. 2012). For example, MAs, play a role in metal uptake and homeostasis (Bashir and Nishizawa, 2006; Bashir et al., 2006; Bashir et al., 2017), and the regulation of MAs by manipulating deoxymugineic acid synthase (*DMAS*) genes, although not tested, could significantly enhance metal accumulation in seeds.

5.3 VITAMIN A DEFICIENCY

Vitamin A (VA) influences visual function, direction of distinction of epithelial tissues, and embryonic advancement, combats sicknesses, and contributes to cell development and skin fitness, including gene translation (Ross et al., 2011). Its deficiency can cause blindness and increase the risk of disease and death for small children. According to an estimate, 140 million children and 7 million pregnant women

are vitamin A deficient, primarily in Africa and South and Southeast Asia (Sommer and Davidson, 2002). Dependence on rice has prompted vitamin A deficiency that specifically affects about 0.2–0.5 million youngsters consistently.

One of the methodologies to ameliorate vitamin A deficiency is the utilization of diet high in vitamin A or a type of vitamin A such as β-carotene, food supplements, etc. Humans can convert β-carotene (a vitamin A precursor) into vitamin A; however, cereals do not provide β-carotene, thus transgenic rice was developed (Ye et al., 2000; Paine et al., 2005). This transgenic rice is called golden rice because of the yellowish color of its grains, and it can provide β-carotene that can be easily converted to vitamin A (Grune et al., 2006; IRRI, 2013). It was suggested that a cup of golden rice could provide up to 50% of the Recommended Dietary Allowance (RDA) of vitamin A (Tang et al., 2009).

A newly released variety of potato expressing three bacterial genes (*Erwinia herbicola*), encoding the enzymes phytoene synthase, lycopene β-cyclase, and phytoene desaturase, contains up to 114 mg of carotenoids and 47 mg of β-carotene per gram dry weight (Diretto et al., 2007). Maize grains have also been biofortified with β-carotene and other basic micronutrients important to maintaining one's well-being.

5.4 IODINE DEFICIENCY

Iodine is an essential component of the thyroid hormones thyroxine and triiodothyronine, which regulate growth and development and maintain a basal metabolic rate. However, only 30% of the body's iodine is stored in the thyroid gland, and the precise role of the 70% distributed in other tissues is unknown. Goiter is an important symptom of iodine deficiency and results from the lack of thyroxine, inducing the production of thyroid-stimulating hormone, which in turn, causes inflammation in thyroid gland (Dunn, 2003). Contrary to other micronutrient deficiencies, I deficiency is common not only in the developing world, but also in well-developed countries (Landini et al., 2011). Urinary I survey data collected from school-aged children on a global basis revealed that 29.8% (241 million children) had insufficient iodine intake (Andersson et al., 2012). According to the same survey study, the highest proportions of low dietary I intake among school-aged children were in regions of Europe (43.9%) and Africa (39.3%), whereas the largest number of children with low dietary I intake were in Southeast Asia (76 million) and Africa (58 million). India is one of the worst affected countries in the world, with >50 million cases of goiter and more than 2 million cases of cretinism. Fortification of salt with iodine has resulted in a considerable reduction in iodine-deficient people worldwide. Raising the iodine content of the edible portion of crop plants could significantly reduce iodine inadequacy. Fertilization with dissolvable iodide as well as iodate salts has been used in agriculture, and iodinization of irrigation water is a good method for effective enhancement of iodine levels in crops, hence adding additional iodine to human diets (Lyons et al., 2004).

In leafy vegetables and root crops, iodine concentrations can be enhanced by fertilization; however, iodine is not readily transportable in the phloem, so the levels in tubers, fruits, and seeds are often not greatly increased. Nevertheless, the iodine content of plant produce can be enhanced by I fertilization to nutritionally acceptable levels (Dai et al., 2004). Since humans require I in trace amounts, iodine fertilization to agricultural land using aeroplanes could enhance the iodine concentration of the edible parts of crop plants and fulfill nutritional requirements in the human diet (Graham et al., 2007). Weng et al. (2013) suggested a creative way to deal with I supplementation via vegetables on soils growing with organic fertilizers containing iodine.

Recently, Cakmak et al. (2017) reported on the opportunities in I biofortification of wheat, rice, and maize through fertilizer strategy. It was shown that foliar I application is highly effective in increasing grain I concentrations in these three main staple crops. Among different forms of I, KIO_3 is the optimal form and can be used up to 0.05% (w/v) in foliar spray solutions for the purpose of agronomic biofortification of cereal crops with I. In this study, iodine concentration of polished rice was increased from 6 to $220 \mu g\,kg^{-1}$ by foliar I application. It was suggested that such an enhancement in grain I concentration can help mitigate human I deficiency caused by low dietary I intake. In general, foliar I application had superior effect on grain I concentration as compared to soil applications. It was suggested that root-absorbed iodine may not be readily available for grain deposition, whereas foliar-applied I prior to grain filling could be translocated at higher rates through phloem towards the grain tissue (Cakmak et al., 2017).

6 CLIMATE CHANGE AND BIOFORTIFICATION

Climate change could negatively influence food security, affecting numerous crops and regions, with the most serious impacts anticipated for South Asia and Southern Africa (Lobell et al., 2008). Climate change could reverse the recent achievements regarding the reducing malnutrition and up to 1 billion people may suffer (WFP, 2009). The environment has a considerable impact on the up take of micronutrients in common bean, field pea, lentils, and chickpea (Hidoto et al., 2017); for example, the Fe content is influenced by genotype and environment interactions (Chandel et al., 2010; Suwarto, 2011).

It is evident that rising temperatures and changing precipitation patterns will negatively influence crop yields worldwide (Funk and Brown, 2009; Godfrey et al., 2010), therefore, biofortification efforts will be adversely influenced with such seasonal variations. Smallholder growers who rely on rain-fed agriculture for their livelihood are dependent upon rain and its timing, and intra-seasonal precipitation patterns can determine the success or failure of their crops, especially in sub-Saharan Africa where rain-fed farming is used on 96% of all arable land (FAO, 2007).

The International Food Policy Research Institute (IFPRI) has evaluated climate change consequences for food security and human prosperity utilizing two markers: per capita calorie utilization and number of malnourished children. It is expected that by 2050, the decrease in calorie accessibility will enhance child malnutrition by 20% worldwide without climate change, and with climate change, child malnourishment levels could be much greater.

Plant growth and development are temperature related, and high temperatures combined with low rainfalls can negatively influence crop yields (Easterling et al., 2007). Higher temperatures can shorten the growing season, speed the evaporation of water from soil, and stress plants, all of which tend to reduce yields and the nutritional value of crops. Protein and micronutrient levels are reduced when crops are grown at elevated CO_2 concentrations (Myers et al., 2014).

Crop production would be significantly affected by a progressively warming planet (Easterling et al., 2007), increasing malnutrition and making humans more susceptible to infectious diseases. The net outcomes could be a decrease in labor efficiency and an expansion of poverty and mortality (Schmidhuber and Tubiello, 2007). Fischer et al. (2005) stated that climate change will increase the number of undernourished individuals in 2080 by 5%–26%, or by between 5 and 10 million people under a moderate impact scenario, or 120–170 million people under a more severe impact scenario.

Increases in population and food demand require the development of crop cultivars with higher yields, and this can reduce micronutrient concentrations in edible plant parts. Therefore, under climate change, there is a need to develop more efficient cultivars that maintain adequate micronutrient concentrations.

7 CONCLUSION AND FUTURE RESEARCH THRUSTS

Recent reports and developments conclude that increase in concentration of micronutrients can be retained in the edible parts during processing, and after consumption by humans, the nutrients are bioavailable. Biofortification is offering proven technology to combat malnutrition, especially for those living in poor and developing countries where most people rely on staple food crops which are inherently low in micronutrient concentrations. Biofortification of crops is being introduced in many countries as a strategy to eradicate micronutrient deficiencies and thus improve human health. Enhanced fertilization with micronutrients, conventional plant breeding, and genetic engineering are used to develop biofortified cultivars. To date maize, rice, wheat, beans, pearl millet, sweet potato, and cassava have been biofortified with increased concentrations of Fe, Zn, and provitamin A. To increase micronutrient concentrations in edible crops, future research should focus on (i) integration of agronomic and genetic strategies to increase mineral transport to phloem-fed tissues and (ii) identification of the mechanisms effecting mineral-homeostasis in plant cells. Confidently, using a combination of strategies (e.g., enhancing efficiency of crops to take up mineral nutrients and/or enhanced production of vitamins/proteins using conventional breeding and genetic engineering tools) followed by enhanced fertilization of targeted nutrients should be considered. There is a need to refine planning, and monitor and evaluate biofortification programs, considering the available biofortification technologies and stakeholders who fund biofortification programs. Although the HarvestPlus consortium is performing a decent job, nevertheless, it is required to set indicators to evaluate the performance of biofortification programs and set priorities. Regarding production and consumption of biofortified staples, there is a need to develop communication and marketing strategies considering ethical values. The same strategies may not be effective to all countries to make it acceptable and to convince the people to pay for micronutrient-enriched food; therefore, countries should be guided to follow favorable strategies for their people.

Food safety and quality assurance are vital, and assessment of possible risks for excessive intake must be addressed. Bearing environmental changes in mind, possible allergies and toxicities related to enhanced micronutrient intake still require intensive work. International standards and national policies on food content information and health claims must be highlighted. Biofortification strategy should be adapted for living with the regulatory framework for a specific country. Measures should be taken to balance biofortification approaches, and harmonization with other public strategies must be emphasized. Though improvements by conventional breeding have not been subjected to regulations, the transgenic approach requires an appropriate regulatory framework for its adaptation.

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