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REVIEW

Agriculture: the real nexus for enhancing bioavailable micronutrients in food crops

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Abstract

Human existence requires that agriculture provide at least 50 nutrients (e.g., vitamins, minerals, trace elements, amino acids, essential fatty acids) in amounts needed to meet metabolic demands during all seasons. If national food systems do not meet these demands, mortality and morbidity rates increase, worker productivity declines, livelihoods are diminished and societies suffer. Today, many food systems within the developing world cannot meet the nutritional needs of the societies they support mostly due to farming systems that cannot produce enough micronutrients to meet human needs throughout the year. Nutrition transitions are also occurring in many rapidly developing countries that are causing chronic disease (e.g., cancer, heart disease, stroke, diabetes, and osteoporosis) rates to increase substantially. These global developments point to the need to explicitly link agricultural technologies to human health. This paper reviews some ways in which agriculture can contribute significantly to reducing micronutrient malnutrition globally. It concludes that it is imperative that close linkages be forged between the agriculture, nutrition and health arenas in order to find sustainable solutions to micronutrient malnutrition with agriculture becoming the primary intervention tool to use in this fight.
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Keywords: Bioavailability; Iron; Zinc; Selenium; Vitamins; Micronutrient malnutrition; Nutritional quality; Human health; Biofortification

Contents

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Introduction

Micronutrient malnutrition (e.g., Fe, Zn, I, Se, vitamin A, folic acid, etc.) is at crisis proportions globally afflicting over 3 billion people (i.e., over half the world's population) mostly among women, infants and children in resource-poor families in the Global South [1,2]. The consequences to human health, felicity, livelihoods, and national development are staggering causing increased mortality and morbidity rates, decreased worker productivity, poverty and diminished cognitive ability in children with lower educational potential born to deficient mothers [3–5]. Dr. Bro Harlem Brundtland (Director General, World Health Organization, United Nations), declared at the World Economic Forum in 2000 that:

> Nutrition is a key element to any strategy to reduce the global burden of disease. Hunger, malnutrition, obesity and unsafe food all cause disease, and better nutrition will translate into large improvements in health among all of us, irrespective of our wealth and home country [4].

Further, the World Health Organization's 2002 World Health Report states that inadequate food and malnutrition leads to a downward spiral of increased susceptibility to illness, sickness and loss of livelihood ending in death. Current trends in micronutrient malnutrition continue to be increasing in many developing nations. For instance, the global burden of Fe deficiency has risen from about 35% of the world's population in 1960 to over 50% in 2000 [4], and Fe deficiency among poor women is increasing at an alarming rate in many developing countries and current intervention programs (i.e., food fortification and supplementation programs) to alleviate the problem have not proven to be effective or sustainable in many countries [6]. This global crisis in micronutrient malnutrition is the result of dysfunctional food systems that cannot consistently deliver enough micronutrients to meet the nutritional requirements of all.

Agriculture and nutrition: the nexus for good health

Because agriculture is the primary source of all micronutrients for human consumption, agricultural systems must be contributing to dysfunctional food systems that are failing to meet the nutritional needs of every one [7]. How can agriculture be changed in ways that will result in enough micronutrient output of farming systems to assure adequate nutrition? Importantly, if agricultural technologies are to be directed at improving the nutritional quality of food crops, they must encompass a holistic food system perspective (see Fig. 1) to assure that the interventions will be sustainable, and adopted by farmers and consumers [8]. Further, the agriculture sector must embrace a specific goal of improving human nutrition and health, and the nutrition and health sectors must implement agricultural interventions as a primary tool to fight micronutrient malnutrition.

Humans require at least 50 known nutrients (see Table 1), in adequate amounts, consistently, to live healthy and productive lives. Unfortunately, global food systems are failing to provide adequate quantities of all of these essential nutrients to vast numbers of people in the developing world. Advances in crop production, incurred during the "green revolution", were dependent mostly on improvements in cereal cropping systems (i.e., rice, wheat and maize) and resulted in greatly increased food supplies for the world preventing massive starvation. However, cereals as normally eaten, only supply needed carbohydrates for energy and a small amount of protein but few of the micronutrients in required amounts. This change in agricultural production

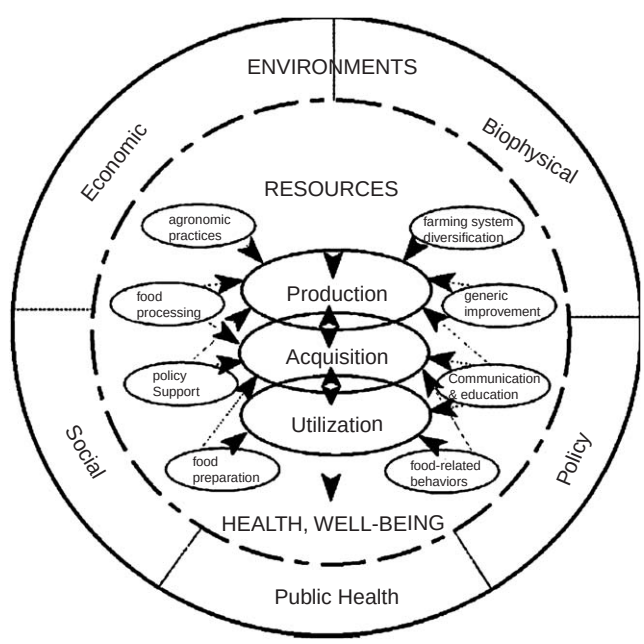

Fig. 1. Holistic food system model [8].

Table 1. The known 50 essential nutrients for sustaining human life[a]

Water and energy [2]	Protein (amino acids) [9]	Lipids (fatty acids) [2]	Macrominerals [7]	Microelements [17]	Vitamins [13]
Water	Histidine	Linoleic acid	Na	Fe	A
Carbohydrates	Isoleucine	Linolenic acid	K	Zn	D
	Leucine		Ca	Cu	E
	Lysine		Mg	Mn	K
	Methionine		S	I	C
	Phenylalanine		P	F	B_1 (thiamin)
	Threonine		Cl	B	B_2 (riboflavin)
	Tryptophan			Se	B_3 (pantothenic acid)
	Valine			Mo	B_6
				Ni	Folic acid
				Cr	Biotin
				Si	Niacin
				As	B_{12} (cobalamin)
				Li	
				Sn	
				V	
				Co (in B_{12})	

[a]Numerous other beneficial substances in foods are also known to contribute to good health.

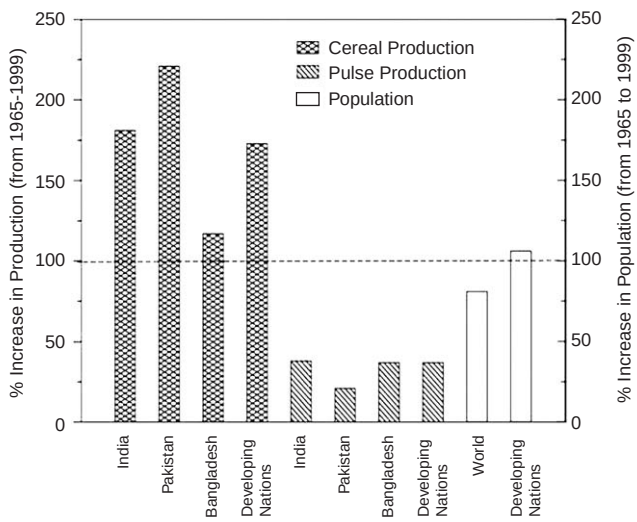

Fig. 2. The percent changes in cereal and pulse production and in population between 1965 and 1999 for selected nations, developed and undeveloped nations, and the world.

towards systems of cereal monocultures and away from more varied cropping systems and traditional foods appears to be contributing to micronutrient malnutrition by limiting food-crop diversity [9]. This has had the unforeseen consequences of reducing available micronutrient supplies to the poor formerly dependent on more diverse cropping systems which provided more traditional micronutrient-rich food crops (e.g., pulses, fruits, and certain vegetables) that are now in low supply and no longer affordable to this sector of society (see Fig. 2) [7,10]. Nutrition transitions are also causing increased rates of chronic diseases (e.g., cancer, heart disease, diabetes, obesity, osteoporosis, etc.) in many rapidly developing nations where societies are switching from traditional diets to more calorie-rich diets derived from adopting developed nation's food systems [11,12].

Agricultural tools for better health

There are numerous ways in which modern agriculture can contribute to increasing the output of micronutrients in staple food crops (primarily edible seeds and cereal grains) from farming systems in order to meet human needs [9]. Some examples of these approaches include:

- Field site selection (e.g., identify soil types with relatively high available levels of Zn and Se).
- Agronomic practices
  - Type and rates of macronutrient fertilizers use (i.e., N, P, K, Mg, Ca, S).
    - ---- Affects levels of protein, fats, vitamins, anti-nutrients, etc.
  - Micronutrient fertilizers (type, application method and rates).
    - ---- Effective for Zn, Mo, Ni, Se, Cl, Li, I.
    - ---- Limited effectiveness for Fe, Cu, Mn, B, Cr, and V.
  - Diversify cropping systems.
    - ---- Legume–cereal rotations.
    - ---- Select micronutrient-dense varieties.

Table 2. Antinutrients in plant foods that reduce Fe and Zn bioavailability, and examples of major dietary sources (modified from Ref. [21])

Antinutrients	Major dietary sources
Phytic acid or phytin	Whole legume seeds and cereal grains
Certain fiber (e.g., cellulose, hemicellulose, lignin, cutin, suberin, etc.)	Whole cereal grain products (e.g., wheat, rice, maize, oat, barley, rye)
Certain tannins and other polyphenolics	Tea, coffee, beans, sorghum
Hemagglutinins (e.g., lectins)	Most legumes and wheat
Goitrogens	*Brassicas* and *Alliums*
Heavy metals (e.g., Cd, Hg, Pb, etc.)	Contaminated leafy vegetables and roots

Table 3. Examples of substances in foods that promote Fe, Zn and vitamin A bioavailability and major dietary sources (modified from Ref. [21])

Substance	Nutrient	Major dietary sources
Certain organic acids (e.g., ascorbic acid, fumarate, malate, citrate)	Fe and/or Zn	Fresh fruits and vegetables
Hemoglobin	Fe	Animal meats
Certain amino acids (e.g., methionine, cysteine, histidine, and lysine)	Fe and/or Zn	Animal meats
Long-chain fatty acids (e.g., palmitate)	Zn	Human breast milk
Fats and lipids	Vitamin A	Animal fats, vegetable fats
Selenium	I	Sea foods, tropical nuts grown in high Se soils
Iron, zinc	Vitamin A	Animal meats
β-carotene	Fe, Zn	Green and orange vegetables
Meat factor(s)	Fe, Zn	Beef, pork, chicken, fish, etc.
Inulin and other non-digestible carbohydrates (prebiotics)	Ca, Fe(?), Zn(?)	Chicory, garlic, onion, wheat, Jerusalem artichoke

---- Increase production of fruits, vegetables, and edible legume seeds.

- Utilize traditional micronutrient-rich indigenous food crops.
- Genetically modify food crops to improve bioavailable micronutrient content of staple food crops (e.g., breed for micronutrient efficiencies and increased bioavailable levels of micronutrients in edible portions).
- Genetically modify food crops to improve bioavailable micronutrient content of staple food crops by breeding for increased levels of promoter substances.
- Genetically modify food crops to improve bioavailable micronutrient content of staple food crops by breeding for decreased levels of inhibitor substances.

For more in-depth discussions of agricultural interventions for improving human nutrition refer to the following references [7,9,13–21].

Several physiological barriers to metal accumulation in food crops have to be addressed before genetically modifying plants in ways that will increase the density of micronutrient metals in staple seeds and grains [22]. Furthermore, because plant foods contain substances (i.e., antinutrients and promoters; see Tables 2 and 3) that influence the bioavailability[1] of these nutrients to humans, it is necessary to demonstrate the efficacy of micronutrient enrichment of plant foods towards improving the nutritional health of targeted populations. This requires that the bioavailability of Fe, Zn, provitamin A carotenoids and other micronutrients in select micronutrient-enriched genotypes of staple plant foods be demonstrated to assure human health impact before advancing genotypes in breeding programs [21].

Physiology of micronutrient accumulation

The physiological basis for micronutrient efficiency in crop plants and the processes controlling the accumulation of micronutrients in edible portions of seeds are not understood with any certainty [23]. Because of the complexity and volume of literature available, these

[1]Bioavailability is defined as the amount of a nutrient that is potentially available for absorption from a meal and once absorbed, utilizable for metabolic processes in the body.

subjects will not be covered in this short review. For an in-depth discussion of these topics the reader is referred to the following references [21,22,24–27]. These processes that determine micronutrient concentrations in edible plant tissues are briefly discussed below.

There are several barriers to overcome in genetically modifying plants to accumulate more micronutrient metals (e.g., Fe and Zn) in edible tissues [22]. These barriers are the result of tightly controlled homoeostatic mechanisms that regulate metal absorption, translocation and redistribution in plants allowing adequate, but non-toxic levels of these nutrients to accumulate in plant tissues. The first and most important barrier to micronutrient absorption resides at the root–soil interface (i.e., the rhizosphere). To increase micronutrient metal uptake by roots, the available levels of the micronutrient in the root–soil interface (i.e., the rhizosphere) must be increased to allow for more absorption by root cells. This could be enhanced by changing root morphology and by stimulating certain root-cell processes that modify micronutrient solubility and movement to root surfaces, such as by stimulating the rate of root-cell efflux of H^+, metal chelating compounds and metal reductants, and by increasing root absorptive surface area such as the number and extent of fine roots and root hairs. Second, absorption mechanisms (e.g., transporters and ion channels), located in the root-cell plasma membrane, must be sufficiently active and specific enough to allow for the accumulation of micronutrient metals once they enter the apoplasm of root cells from the rhizosphere. Third, once taken up by root cells, the micronutrients must be efficiently translocated to and accumulated in edible plant organs. For seeds and grains, phloem sap loading, translocation and unloading rates within reproductive organs are important characteristics that must be considered in increasing micronutrient metal accumulation in edible portions of seeds and grains [26]. Finally, to be effective, the micronutrient metal species accumulated in edible portions must be bioavailable to people that eat the seeds in a meal [9,26,28]. Unfortunately, current knowledge of all of these processes is very limited for most micronutrient metals and much more basic research is needed before we can efficiently genetically modify food crops to accumulate more bioavailable forms of micronutrients in seeds and grains through modern genetic engineering techniques.

Breeding for micronutrient-enriched staple food crops: the CGIAR HarvestPlus Program

Recently, the genetic potential for increasing the concentrations of bioavailable Fe, Zn, and provitamin A carotenoids (as well as Se and I) in edible portions of several staple food crops (including rice, wheat, maize, beans and cassava) has been reviewed [21]. Developing micronutrient enriched staple plant foods, either through traditional plant breeding methods or via molecular biological techniques, is a powerful intervention tool that targets the most vulnerable people (resource-poor women, infants and children; [8,29]). These tools should be fully exploited by the nutrition and public health communities to combat micronutrient malnutrition [21]. Biofortifying these crops (i.e., "biofortification" is a word coined to refer to increasing the bioavailable micronutrient content of food crops through genetic selection via plant breeding) that feed the world's poor can significantly improve the amount of these nutrients consumed by these target populations [17]. Furthermore, it is a sustainable intervention unlike traditional interventions that depend on supplementation and fortification programs that have not proved to be sustainable in many developing nations [18,30]. Additionally, increasing the micronutrient metals stored in seeds and grains of staple food crops increases crop productivity when these seeds are sown to micronutrient-poor soils [23]. Much of the developing world has significant areas of such soils [31]. Enhancing seeds with micronutrient metals will act as an incentive to farmers cultivating micronutrient-poor soils to adopt the micronutrient enriched seeds for use on their farms [21].

Breeding criteria

Certain criteria must be met before new lines of micronutrient-enriched staple food crops are distributed globally to national agricultural research programs. Meeting these conditions will assure that targeted people at risk of developing micronutrient malnutrition will benefit from such action. These criteria include:

- Crop productivity (i.e., yield) must be maintained or increased to guarantee widespread farmer acceptance
- The micronutrient enrichment levels achieved must have significant impact on human health.
- The micronutrient enrichment traits must be relatively stable across the targeted edaphic environments and climatic zones.
- Ultimately, the bioavailability of micronutrients in enriched lines must be tested in humans to assure that they improve the micronutrient status of people preparing and eating them in traditional ways within normal household environments.
- Consumer acceptance must be tested (taste and cooking quality must be acceptable to household members) to assure maximum impact on nutritional health.

Meeting these conditions will require a new way of thinking and performing research by most agriculturalists,

a holistic food systems view of agricultural production. It will necessitate that researchers cooperate with various specialists in disciplines not normally associated with agricultural research, including nutritionists, public health officials, sociologists, political scientists, food technologists and economists to assure that their efforts will have meaningful impact on human nutrition and health [8].

The question of yields

The effects of biofortifying staple plant foods with micronutrients on crop productivity have been addressed in a number of recent reviews [24,32–34]. Briefly, increasing the micronutrient stores in seeds results in more seedling vigor and viability enhancing the performance of seedlings when the seeds are planted in micronutrient-poor soils. This improved seedling vigor is associated with the production of more and longer roots under micronutrient-deficient conditions, allowing seedlings to scavenge more soil volume for micronutrients and water early in growth, an advantage that can lead to improved yields compared to seeds with low micronutrient stores grown on the same soils. For example, Fig. 3 shows the effects of seed micronutrient enrichment on grain yields of wheat grown on farms in Bangladesh (unpublished data from John Duxbury, Department of Crop and Soil Sciences, Cornell University, 2000). In this experiment micronutrient-enriched grains were sown to farmers' fields having low micronutrient stores in three districts in Bangladesh. Seven out of the nine farms had significant increases in wheat grain yield when produced from micronutrient-enriched grain compared to a control of farmers' grain not so enriched. These data clearly show the advantage of using biofortified wheat grain on wheat productivity in these regions of Bangladesh.

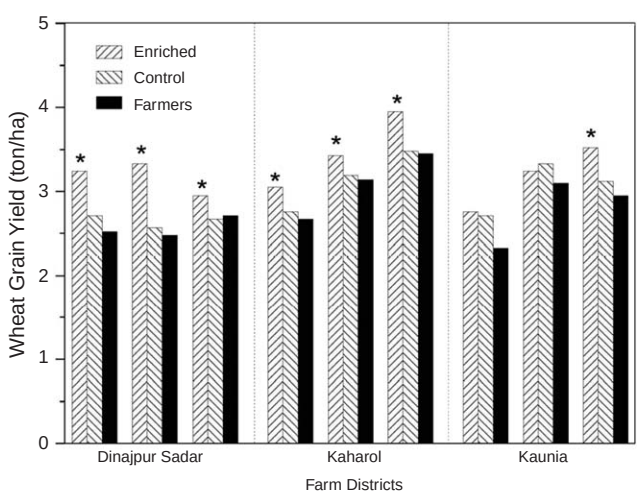

Fig. 3. Effects of micronutrient enrichment of wheat grain on grain yields from nine farms in three districts of Bangladesh. The enriched and control grains were produced on an experimental farm. The enriched grains were produced from foliar applications of micronutrient to mother plants during their reproductive growth stage. Asterisks indicate significant difference from control and farmers' grain (unpublished data from Dr. John Duxbury, Department of Crop and Soil Sciences, Cornell University, 2000).

Many of those countries where micronutrient deficiencies in humans are a problem are also the countries that have large areas of micronutrient-poor/deficient soils [31]. Thus, improving seed vigor with respect to micronutrient stores should be very beneficial to agricultural production in these countries. Additionally, disease resistance and stress tolerance are improved in seedlings grown from micronutrient-dense seeds that would also aid agricultural production in target countries [26]. Thus, selecting for these traits in staple food crops is a "win–win" opportunity. It has potential to enhance crop yields without additional farmer inputs and to improve their nutritional quality simultaneously.

The genetic potential

During the past decade scientists at several Consultative Group on International Agricultural Research (CGIAR) Centers, including the International Rice Research Institute (IRRI), the Centro Internacional de Mejoramiento de Maiz y Trigo (CIMMYT), the Centro Internacional de Agricultura Tropical (CIAT) and the International Institute of Tropical Agriculture (IITA), have been collecting data on the potential for breeding to significantly increase the levels of bioavailable Fe, Zn, and provitamin A carotenoids in edible portions of rice, wheat, maize, beans and cassava [17,21,24,32–34]. These findings show that substantial genetic diversity exists within the genomes of these major staples that could be used in breeding programs to significantly improve the density of Fe, Zn and provitamin A carotenoids in the major staples that feed the world.

The importance of bioavailability

As previously mentioned, determining the total amount of a micronutrient in a plant food is not enough to predict the impact of the food on meeting human micronutrient requirements. One must also know the bioavailable amount of the micronutrient in a plant food as eaten in a common diet to be able to determine nutritional impact.

Determining the bioavailability of micronutrients in plant foods to humans is pervaded with numerous complexities (see Fig. 4). Numerous factors interact to determine the ultimate bioavailability of a particular micronutrient to an individual eating a mixed diet within a given environment. Because of this complexity, the data obtained using various bioavailability model systems

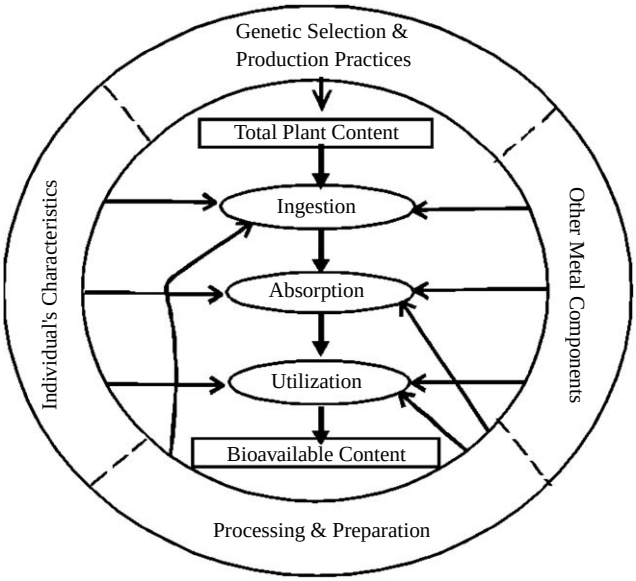

Fig. 4. A model of the complexities of nutrient bioavailability in humans [21].

are always ambiguous [35,36]. Only data from feeding trials in micronutrient-deficient test populations under free living conditions can delineate the effectiveness of using micronutrient-enriched varieties of plant foods as an intervention tool. Unfortunately, it is impractical to test in this way the bioavailability of selected micronutrients in numerous genotypes of staple plant foods that can be generated in plant breeding programs [24]. Therefore, one must use a bioavailability model to screen large numbers of promising lines of micronutrient-enriched genotypes identified in such breeding programs before advancing them within these programs.

Current breeding efforts to screen large numbers of promising micronutrient-dense lines of staple plant foods (rice, maize, wheat, beans and cassava) at several CGIAR Centers (IRRI, CIMMYT, CIAT, and IITA) for bioavailable Fe relies on an in vitro Caco-2 cell model [37]. The bioavailability of Zn in promising staple food crops lines is not currently being performed using Caco-2 cells. However, progress is being made at adopting this model to determine Zn bioavailability from plant foods using cell metallothionein levels as a proxy for Zn absorption. Nevertheless, it is reasonable to assume that the data obtained for Fe bioavailability will also reflect bioavailable Zn levels in promising genotypes because most of the plant food factors that inhibit or promote Fe bioavailability also inhibit or promote Zn bioavailability [38,39].

Dietary micronutrient inhibitors and enhancers

Plant foods (especially seeds and grains) contain various antinutrients (see Table 2) in amounts depending on both genetic and environmental factors that can reduce the bioavailability of dietary non-heme Fe, Zn and other nutrients to humans [40]. Some dietary substances that promote the bioavailability of Fe and Zn in the presence of antinutrients are also known (see Table 3). Their levels are also influenced by both genetic and environmental factors. Current plant molecular biological and genetic modification approaches now make it possible to reduce or eliminate antinutrients from staple plant foods, or to significantly increase the levels of promoter substances in these foods [9,41]. Given these options (i.e., to decrease antinutrients or increase promoters in staple plant foods), which is the wisest path to pursue?

Plant breeders could breed for genotypes that contain lower concentrations of antinutrients or molecular biologists could alter plant genes in ways that reduce or even eliminate antinutrients from staple food crops. However, doing so is not without risk and should be done with caution because many antinutrients are major plant metabolites that may play important roles in plant metabolism, in plant stress resistance and in plant resistance to crop pests or pathogens. Additionally, some of the antinutrients, such as phytate and polyphenols, may have important beneficial roles in human diets by acting as anticarcinogens or by promoting health in other ways such as in decreasing the risk of heart disease or diabetes [42–44]. Thus, plant breeders and molecular biologists should be aware of the possible negative consequences of changing antinutrients in major plant foods before they attempt to alter food crops in this fashion [24].

Many promoter substances (Table 3) are normal plant metabolites and even small changes in their concentration may have significant effects on the bioavailability of micronutrients from staple plant foods [45]. Furthermore, increasing the levels of promoter substances in staple plant foods may also enhance the bioavailable levels of micronutrients from other dietary food sources that also contain antinutrients. Therefore, it is highly recommended that plant breeders and molecular biologists closely scrutinize the strategy of increasing promoter substances in food crops when attempting to improve food crops as sources of micronutrients for people [21].

Importance of diet composition

The bioavailability of micronutrients in plant foods can be greatly affected by the composition of the diet eaten [35,46,47]. Various food processing techniques, meal components and meal preparation techniques can modify plant foods in ways that either promote or reduce the amount of bioavailable micronutrients in these foods [48]. For example, eating some animal

protein (e.g., beef, fish, pork, poultry) with plant foods high in antinutrients, such as phytic acid, can ameliorate the negative effects of the antinutrients on Fe and Zn bioavailability [49–51]. The mechanisms responsible for this are still a mystery as is the actual identity of the "meat factors" although the sulfur-containing amino acid, cysteine, has been implicated in the past, and recently, meat-derived glucosamine glycans have been suggested to be involved in promoting Fe bioavailability from plant foods (personal communication from Dr. Ray Glahn, USDA-ARS, US Plant, Soil and Nutrition Laboratory, Ithaca, NY). Additionally, food preparation techniques can be used to reduce the level of antinutrients such as phytate in staple plant food meals such as seed germination and fermentation before consumption [52].

Much more research is needed before we fully understand the complex factors affecting micronutrient bioavailability in common diets eaten by target populations. Such research should be given a high priority by funding organizations. Such knowledge is greatly needed if we are to efficiently improve the micronutrient status of afflicted people globally.

Conclusions

There are ample compelling global human health and nutritional reasons to elicit the agricultural community to pursue improving the micronutrient nutritional quality of staple food crops as a primary objective in their work targeted for the developing world. Furthermore, accomplishing this goal would improve crop productivity when micronutrient-dense seeds and grains are planted to micronutrient-poor soils, thus assuring farmer adoption of the micronutrient-enriched seeds once they are developed. Current evidence strongly supports the contention that there is enough genetic diversity within the genomes of staple food crops to accomplish this task. Succeeding in linking agriculture to human health issues would dramatically contribute to improving the health, livelihood, and felicity of numerous resource-poor, micronutrient-deficient people in many developing countries, and would contribute greatly to sustaining national development efforts in these countries. Importantly, finding sustainable solutions to micronutrient malnutrition will not be forthcoming in the foreseeable future if we do not start to adopt agriculturally based tools to attack this important global crisis in human health and well being.

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