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Review

Effectiveness of Agronomic Biofortification Strategy in Fighting against Hidden Hunger

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Abstract: Micronutrient deficiencies (MNDs), also known as hidden hunger, affect more than a quarter of the global population. Agronomic biofortification helps to increase the concentration of a target mineral in food crops and improve human mineral dietary intake. It is a means of providing nutrient-dense foods to a larger population, especially among rural resource-poor settings, providing that they have access to mineral fertilizers. However, the feasibility of agronomic biofortification in combating hidden hunger depends on several factors in addition to fertilizer access, including crop type, genotype, climate, soils, and soil mineral interactions. Consideration of its effectiveness in increasing human mineral intake to the daily requirements and the improvement of human health and the cost-effectiveness of the program is also important. In this paper, we review the available literature regarding the potential effectiveness and challenges of agronomic biofortification to improve crop micronutrient concentrations and reduce hidden hunger.

Keywords: agronomic biofortification; dietary intake; effectiveness; fertilizers; micronutrient deficiencies

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1. Introduction

Micronutrient deficiencies (MNDs), also known as 'hidden hunger', occur when dietary intakes of vitamins and mineral micronutrients are not adequate for optimal human health. MNDs are a public health concern worldwide and have been the focus of intensive research for many years. It is estimated that more than a quarter of the global population is affected by the deficiency of one or more micronutrients [1]. MNDs are a risk factor for many diseases, contributing to the existing high rates of morbidity and mortality. For example, MNDs can lead to reduced resistance to infections, which can cause severe illnesses and developmental challenges, including anemia, mental retardation, blindness, and spinal and brain birth defects. The most prevalent forms of MNDs are iron (Fe), iodine (I), zinc (Zn), and vitamin A [2,3]. In terms of the loss of healthy life years, the deficiency of these micronutrients is responsible for 1.5–12% of the total disability-adjusted life years (DALYs) lost in sub-Saharan Africa (SSA) [4]. It has been estimated that undernutrition and MNDs, combined, cost the world up to USD 3.5 trillion every year [5]. The research also shows that MNDs among women of reproductive age lead to undesirable birth outcomes in newborns, together with a higher risk of physical and cognitive impairment, leading to economic stagnation and intergenerational poverty [6].

Understanding the etiology of MNDs is vital in the process of designing and implementing strategies for the prevention of diet-related diseases [7]. MNDs can be addressed through the implementation of programs. Dietary diversification, food fortification, supplementation, and the genetic and agronomic biofortification of food crops are among the strategies. In addition to improving micronutrient intake, dietary diversification has the potential to improve the intake of many food constituents at the same time. It is typically considered to be the most sustainable and preferred strategy compared to the others. However, the availability and affordability of diversified foods are often barriers in resource-poor societies. Changes in dietary patterns through nutrition education and behavioral change communication also make the strategy tough to achieve [2].

Supplementation of high-dose vitamins and minerals is a strategy that can quickly improve the micronutrient status of individuals or a targeted population [2]. However, supplementation depends on the availability of supplements to the individual at the correct level. In addition, it is not necessarily sustainable because it does not address the root cause of the particular MND or multiple MNDs. Nutrients from supplements can also show different physiological responses and absorption rates than nutrients in food [2]. The procurement of micronutrients in a relatively expensive pre-packaged form is also a challenge in resource-poor communities [2].

Food fortification can have a wider impact and is potentially more sustainable than supplementation. However, fortification is dependent on centrally processed food vehicles and requires the engagement of food-processing industries. Furthermore, some communities can be difficult to reach through the implementation of food fortification, especially those that consume locally produced food sources. The sustainability of the mineral supply to food industries, the bioavailability of fortified minerals, and possible sensory changes as a result of fortification could be additional challenges to this strategy [2]. Overall, food fortification, supplementation, and diet diversification strategies may work well only in urban settings [8,9].

Improvement in the quantity as well as the quality of essential nutrients in the edible portions of crops during plant growth either genetically and/or agronomically is known as biofortification [10]. Biofortification that is achieved through genetic engineering or classical breeding is called genetic biofortification, while agronomic biofortification involves the application of a micronutrient fertilizer either to the soil (basal application) or application directly to the leaves of the crop (foliar application) [11,12]. The focus of this review is agronomic biofortification.

2. Agronomic Biofortification

Agronomic biofortification is the strategy of increasing the micronutrient contents in the edible parts of food crops through the basal and/or foliar application of mineral fertilizers [11,12]. Agronomic biofortification can enrich crops with multiple elements, but the most common ones are Fe, Se, Zn, and I. It may be a suitable approach to reach resource-poor rural populations, provided they have access to chemical fertilizers. Soil-to-plant transfer and the accumulation of minerals in the edible portion of food crops determine the success of biofortification. In addition, the bioavailability of minerals from biofortified crops in the body influences the effectiveness of biofortification programs.

3. Evidence from Agronomic Biofortification

Agronomic biofortification has mainly been carried out on staple cereal crops like rice, wheat, and maize because they dominate diets worldwide, especially among groups vulnerable to MND. Dimpka and Bindraban [13] recommend that micronutrient fertilization should improve the yields as well as the nutrient contents of crops. This is because fertilization programs in developing countries typically focus on nitrogen, phosphorus, and potassium (NPK) and/or sulfur (S) fertilizers, yet crop yields can still be limited by multiple soil micronutrient deficiencies [14]. Basal application of multiple elements in small amounts to the soil has, therefore, been recommended as a sustainable strategy to increase both the yields and the nutrient quality of crops [14–16].

Most research on agronomic biofortification has focused on Se and Zn, and these micronutrients are the focus of this review. Selenium is an essential trace element with many roles in human health; however, it has no known biological roles in plants. Blending or granulating Se with macronutrient fertilizers can be highly effective [12]. For example, crops in Finland showed a 15-fold increase in their Se concentration due to the application of Se with NPK fertilizers [17]. Similarly, in a recent study from Malawi, an 88–97% increase in the Se concentration of maize grain was observed due to the application of 20 g ha^{-1} Se fertilizer [18]. Grain Se increased by about 10-fold as a result of 25 g ha^{-1} Se fertilizer application in Brazil [19]. De Lima Lessa et al. [20] and Chilimba et al. [18] showed approximately linear increments of grain Se concentration with increased Se fertilizer application in their studies conducted in Brazil and Malawi, respectively. Other studies from Kenya and Australia also reported linear increases in grain Se concentrations with increases in the Se fertilizer application dose [21]. On the other hand, studies that compared the effects of Se chemical forms (nanoparticle, sodium selenite, and sodium selenite) on faba bean seed [22] and tomato fruit [23] Se concentrations reported that nanoparticles exerted the smallest effects compared to the other chemical forms. In general, multiple previous studies have reported the positive impact of Se agronomic biofortification on grain Se concentration (Table 1). However, there was no evidence that Se fertilizer application had an effect on crop yield in these studies.

Table 1. Previous reports on impact of Se agronomic biofortification on grain Se concentration.

No.	Crop	Application Method	Application Rate	Grain Se Increase (%)	Reference
1	Wheat	Basal	55.4–21.6 mg ha^{-1} elemental Se	283–1650	[24]
2	Rice	Foliar	30 g ha^{-1} Na_2SeO_3	259	[25]
3	Wheat	Basal	5 g ha^{-1} elemental Se	137	[26]
		Foliar	5 g ha^{-1} elemental Se	51–155	
		Basal and foliar	A total of 10 g ha^{-1} elemental Se	61–364	
4	Soybean	Basal	80 g ha^{-1} Na_2SeO_4	290–331	[27]
5	Maize	Basal	5–20 g ha^{-1} Na_2SeO_4	25–227	[28]
		Foliar	5–20 g ha^{-1} Na_2SeO_4	423–819	
6	Faba bean	Foliar	1 L m^{-2} Se nanoparticles (90 nm) (concentration = 100 mg L^{-1})	1360	[22]
			1 L m^{-2} sodium selenite (concentration = 220 mg L^{-1})	3799	
			1 L m^{-2} sodium selenate (concentration = 240 mg L^{-1})	7426	

In contrast to Se, Zn is an essential plant nutrient and a yield-limiting factor in many production systems. Cakmak [12] showed that Zn fertilization enhances yield as well as crop Zn concentrations. Previous studies reported the positive impact of Zn agronomic biofortification on both yield and grain Zn concentration (Table 2). Joy et al. [29] systematically reviewed studies and reported an incremental effect of Zn fertilizer application on Zn concentrations in maize (20%), rice (7%), and wheat (19%) in 10 African countries. The same review indicated that foliar Zn application resulted in even higher grain Zn concentrations in maize (30%), rice (25%), and wheat (63%). Moreover, the chemical form of Zn has been reported to have a significant impact on both crop yield and grain Zn concentration. For instance, Umar et al. [30] reported that the application of Zn nanoparticles on maize was more effective in improving both the grain yield and Zn concentration. Similar studies on rice [31] and wheat [32] have reported that Zn nanoparticles were effective at increasing grain Zn concentration, but the yield remained unaffected (Table 2).

Table 2. Previous reports on impact of Zn agronomic biofortification on crop yield as well as grain Zn concentration.

No.	Crop	Application Method	Application Rate	Yield Increase (%)	Grain Zn Increase (%)	Reference
1	Maize	Basal	30 kg ha^{-1} elemental Zn	11	15	[33]
2	Chickpea	Basal Foliar Basal and foliar	25 kg ha^{-1} $ZnSO_47H_2O$ 0.5% (*w*/*v*) $ZnSO_47H_2O$ 25 kg ha^{-1} and 0.5% (*w*/*v*) $ZnSO_47H_2O$	10.2 9.2 14.3	24.9 35.4 39.1	[34]
3	Rice	Foliar	0.5% (*w*/*v*) $ZnSO_4{\cdot}7H_2O$	10	66	[35]
4	Rice	Basal	20 mg elemental Zn per 1 kg soil	23.5	80.4	[36]
5	Wheat	Basal Foliar	25 kg ha^{-1} $ZnSO_47H_2O$ 0.5% (*w*/*v*) $ZnSO_47H_2O$	5 3	18 47	[37]
6	Rice	Basal Foliar Basal and foliar	5 kg ha^{-1} elemental Zn 0.5% (*w*/*v*) $ZnSO_4{\cdot}7H_2O$ 5 kg ha^{-1} elemental Zn0.5% (*w*/*v*) & $ZnSO_4{\cdot}7H_2O$		26.5 79.5 89.8	[38]
7	Maize	Basal	ZnO nanoparticle (105 nm) (8 kg Zn ha^{-1}) ZnO (8 kg Zn ha^{-1})	44 11	59 28	[30]
		Foliar	ZnO nanoparticle (105 nm) (2% solution) ZnO (2% solution)	33 11	82 38	
8	Rice	Basal	25–100 mg Zn nanoparticle (30 ± 10 nm) kg^{-1} soil 25–100 mg Zn from $ZnSO_4{\cdot}7H_2O$ kg^{-1} soil	88.3 86.5	24.2 12.6	[31]
9	Wheat	Basal	10–1000 mg ZnO nanoparticle (<100 nm) kg^{-1} soil 10–1000 mg Zn from $ZnSO_4{\cdot}7H_2O$ kg^{-1} soil	5.6–56 8.8–55	23.5–230 12.6–142	[32]

Overwhelming evidence from many countries has shown that the application of Zn fertilizer on Zn-deficient soils improves the yield and/or grain Zn concentration [11,39–52]. However, one study in Pakistan reported little or no significant effect of Zn fertilizer application on rice yield or grain Zn concentration [35]. This was due to the presence of high DTPA-extractable Zn (2.2 to 6.5 mg kg^{-1}) in the soil, while the level of DTPA-extractable Zn in soil considered to be critical for Zn deficiency in rice is 0.5–0.8 mg Zn kg^{-1} [53]. Zia et al. [54] also reported no significant effect on wheat grain Zn concentration as a result of soil Zn application, which, again, may be linked to soil properties.

There are fewer studies on the effect of Fe agronomic biofortification compared to Se and Zn. For example, a study from India reported a 13% yield and 2-fold wheat grain Fe concentration increase due to Fe fertilization [37]. Similarly, another study on finger millet reported a positive impact of Fe fertilization on both grain yield and Fe concentration (Table 3). In contrast, Zhang et al. [55] and Pahlavan-Rad and Pessarakli [56] from China and Iran observed 36% and 21% wheat grain Fe concentration increases, respectively, but the yield remained unaffected. However, studies from Turkey and Canada on the Fe biofortification of barley and wheat, respectively, showed neither yield nor grain Fe concentration improvement [39,57]. This was due to two reasons. First, graminaceous species release phytosiderophores (Fe-mobilizing compounds) to solubilize and absorb Fe from soils with low Fe concentrations, and thus, they can maintain adequate plant growth by satisfying Fe demand without the requirement of Fe fertilization [54,56,58]. The second reason is that when applied to calcareous soils, Fe is rapidly converted into unavailable forms, and the poor mobility of Fe in phloem makes Fe fertilization unsuccessful [11,59]. Furthermore, the crop response to Fe fertilization is more dependent on the synergetic effect of nitrogen fertilizer [39,60]; the details are presented in Section 5.2. The chemical form of Fe is also reported to have a significant impact on both the crop yield and grain Fe concentration. For instance, foliar application of Fe nanoparticles showed a significantly higher impact on wheat grain Fe concentration, but not yield, compared to Fe-EDTA and $FeSO_4$ [61]. On the other hand, Dhaliwal et al. [62] and Taskin and Gunes [63] reported significantly higher yields, but not grain Fe concentration, in chickpea and wheat, respectively, as a result of foliar application of Fe nanoparticles compared to $FeSO_4$ application (Table 3).

Table 3. Previous reports on impact of Fe agronomic biofortification on crop yield as well as grain Fe concentration.

No.	Crop	Application Method	Application Rate	Yield Increase (%)	Grain Fe Increase (%)	Reference
1	Wheat	Foliar	50 mg Fe L^{-1} from 1 to 3 sprays		1.3–22	[64]
2	Wheat	Foliar	6 g L^{-1} (0.84 kg ha^{-1}) FeO_3 nanoparticle 12 g L^{-1} (1.1 kg ha^{-1}) elemental Fe from $FeSO_47H_2O$ 12 g L^{-1} (1.1 kg ha^{-1}) elemental Fe from Fe-EDTA	11.4 13 3.8	17 11.3 5.1	[61]
3	Finger millet	Basal	4 kg ha^{-1} elemental Fe from $FeSO_47H_2O$	18.3	17.8	[65,66]
4	Chickpea	Foliar	0.5% $FeSO_47H_2O$ 0.5% FeO_3 nanoparticle	7.1 43	−2.8 0.16	[62]
5	Wheat	Foliar	0.2% Fe from $FeSO_47H_2O$ 0.2% nano zero-valent Fe (29 to 50 nm)	6.6 −1.9	13.2 12.6	[63]

4. Effect on Human Nutrition and Health

It is suggested that agronomic biofortification potentially improves the daily intake of minerals and helps to alleviate MNDs [18,67]. However, the effectiveness of agronomic biofortification on the improvement of human micronutrient status and health is currently less well studied. The only large-scale effectiveness study that linked agronomic biofortification to the improvement of human Se status and health was reported from Finland. The average dietary intake of Se was 0.04 mg Se/day/10 MJ when Finland started the agronomic biofortification of Se in 1985. After six years of extensive application, the average dietary intake of Se was enhanced to 0.12 mg Se/day. After four years, the mean human plasma Se concentration increased from 0.89 µmol/L to 1.50 µmol/L. The authors concluded that the nationwide agronomic biofortification of Se was found to be effective and safe for increasing the Se intake of the whole population [17]. A randomized control feeding trial study in Malawi to test the effectiveness of the consumption of Se-biofortified maize showed significant increases in serum Se concentrations over a two-month intervention period from 57.6 (17.0) µg L^{-1} (n = 88) to 107.9 (16.4) µg L^{-1} (n = 88) among WRA and from 46.4 (14.8) µg L^{-1} (n = 86) to 97.1 (16.0) µg L^{-1} (n = 88) among SAC without a significant increase among their counterparts who received non-biofortified maize [68].

Lowe et al. [69] also reported an additional daily Zn intake between 3 and 6 mg for refined and whole grain flour, respectively, as a result of an average flour consumption of 224 g d^{-1} of Zn biofortified wheat flour. After 4 weeks of consumption, a significant increase in the plasma Zn concentration of 41.5 µg L^{-1} was observed. A study investigated the impact of zinc-biofortified wheat flour consumption on the zinc status of Pakistani adolescent girls (n = 517) and indicated a moderate increase in the intakes of zinc (1.5 mg/day) and iron (1.2 mg/day) but did not have a significant effect on plasma Zn concentrations [70]. A study on the efficacy of Fe-biofortified pearl millet in improving attention and memory in Indian adolescents (n = 140) indicated a 30% hemoglobin increase due to four months of consumption of Fe-biofortified pearl millet (Fe = 86 ppm) compared to a non-biofortified version (Fe = 21–52 ppm) [71].

Ex ante analysis of the potential of Zn fertilizers to alleviate human dietary Zn deficiency, focusing on ten African countries where dietary Zn supply is low, showed considerable reductions in the DALYs lost due to Zn deficiency, with 0.5–18.6% in Burkina Faso, 8.8–53.8% in Ethiopia, 1.2–22.8% in Ghana, 2.9–28.9% in Kenya, 9.5–29.4% in Malawi, up to 22.2% in Mali, 2.2–24.4% in Nigeria, 2.1–32.7% in Senegal, 1.8–25.8% in Tanzania, and 6.6–27.7% in Zambia. The cost per DALY saved ranged from USD 624 to 5,893 and from USD 46 to 347 due to granular and foliar fertilizer applications, respectively. The scenario of foliar Zn application is predicted to be cost-effective in all nations according to the WHO standard [29]. Joy et al. [72] also reported that the application of Zn fertilizers to wheat in the Punjab and Sindh areas of Pakistan could increase the dietary Zn supply from ~12.6 to 14.6 mg $capita^{-1}$ d^{-1}, with a cost per DALY saved of USD 461–619. Another ex ante analysis aiming to quantify the potential cost-effectiveness of the agronomic biofortification of staple crops with Zn for alleviating Zn deficiency in Ethiopia indicated that biofortification with granular Zn could reduce the burden of Zn deficiency by 29 and 38% with a cost of USD 502 and USD 505 to avert each DALY lost under pessimistic and optimistic scenarios, respectively. Foliar Zn application was predicted to cost USD 226 and USD 496 to avert each DALY lost under pessimistic and optimistic scenarios, respectively [73].

Another study that explored the potential of the agronomic biofortification of rice with Zn and Fe to alleviate human dietary Zn and Fe deficiency was conducted in four regions of China (Northeast (NE), Central China (CC), Southeast/(SE), and (Southwest)/SW). The results showed considerable (0.92–28%) reductions in the DALYs lost due to Fe deficiency. Similarly, reductions in the DALYs lost due to Zn deficiency were in the range of 3–55%. The cost per DALY saved ranged from USD 376 to 4989, from USD 194 to 2730, and from USD 37.6 to 530 for single, dual, and triple foliar Fe and Zn applications, respectively. The combined foliar spray of Fe and Zn in CC, SE, and SW was found to be cost-effective according to The World Bank standard [74].

5. Potential Challenges to Agronomic Biofortification

5.1. Mineral Fertilizer Manufacturing

One of the major challenges of agronomic biofortification as a strategy is the manufacturing of fertilizers containing a suitable quantity of mineral micronutrients, especially in many developing countries, where most fertilizer is imported. Strategies aiming to reduce MNDs are likely to be more effective where the intervention is case-sensitive in local situations [21,75]. To produce a fertilizer blend for a specific location is likely to require the close involvement of public and private fertilizer production and distribution sectors.

5.2. Mineral Fertilizer Application Method

There are two approaches for the application of mineral fertilizers—foliar and basal application. The two approaches have their costs and benefits in terms of logistics, economic feasibility, and final grain mineral concentration.

In the short term, foliar Zn applications are more effective than soil applications at increasing grain Zn concentrations in wheat [35,54]. For example, foliar Zn application to rice and wheat represents an effective agronomic practice to enhance the grain Zn concentration up to 66%, while soil application has no effect [35,41]. Soil applications of Zn are less effective than foliar applications to increase grain Zn concentration. The study by Joy et al. [29] indicated that soil Zn application led to increases in the median Zn concentrations in maize, rice, and wheat grains of 23%, 7%, and 19%, respectively, while foliar application led to increases of 30%, 25%, and 63%, respectively. The authors suggested that Zn fixation in the soil makes foliar applications more cost-effective than soil applications; however, the deployment might be more complicated. Botoman et al. [33] reported that many studies on soil Zn applications are underpowered to detect small increases in crop Zn concentration; they reported a 15% increase in maize Zn concentration as a result of 30 kg ha^{-1} elemental Zn application. A study from Zimbabwe aimed at quantifying the potential health benefits of alleviating dietary Zn deficiency with soil-applied Zn fertilizer and improved soil fertility management (ISFM) to increase maize grain Zn concentration reported that soil Zn fertilizers were estimated to increase the dietary Zn supply from 9.3 to 11.9 mg Zn capita^{-1} day^{-1}, reduce the dietary Zn deficiency prevalence from 68% to 31%, and save 6576 DALYs lost per year. On the other hand, soil Zn fertilizer, together with ISFM, is estimated to increase the dietary Zn supply from 9.3 to 12.5 mg Zn capita^{-1} day^{-1}, reduce the dietary Zn deficiency prevalence from 68 to 25%, and save 7606 DALYs lost per year [76]. Therefore, the report indicates strong effects of other ISFM approaches on the effectiveness of soil-applied Zn.

One benefit of soil application of Zn fertilizer is its potential residual effects in subsequent cropping seasons. For example, Narwal et al. [37] reported that soil application of Zn to wheat has a significant effect for multiple years and could be more effective and economical for wheat in the long run as compared to foliar application. Another study reported that soil application of 28 kg ha^{-1} $ZnSO_4$ fertilizer was an effective strategy to correct soil Zn deficiencies for about 7 years [77]. Similarly, Frye et al. [78] reported the residual effect ranging from 4 to 5 years as a result of soil application of 34 kg ha^{-1} $ZnSO_4$ fertilizer. Similar researchers reported that soil application of $ZnSO_4$ ranging from 18 to 28 kg h^{-1} is adequate to correct Zn deficiency in plants for four to seven years [79–81]. Therefore, the argument is, if the application of Zn fertilization is planned for more than one season, basal application could be a more cost-effective method due to its residual effect, whereas foliar application may provide the highest grain Zn concentration for a single production season.

Some studies have indicated that the combined application of soil and foliar Zn and Fe are more effective than a single soil or foliar application. The results indicate an increase from 25 to 100% grain mineral content due to combined soil and foliar fertilization application [35,38,41,45,53,82]. However, it is very crucial to consider the soil type effect since the combined foliar and basal application method of Zn on wheat is reported to highly depend on the soil type [54].

Ngigi et al. [28] suggested that foliar application of Se was more effective than soil application for maize and beans. However, it is important to consider that Se can act both as an antioxidant and a pro-oxidant, and in its concentrated form, Se is toxic [83], therefore, blended or granular Se applied to soils is the only safe approach for farmers. Ros et al. [84] argued that soil application of Se could result in similar responses to foliar-applied Se fertilizer, and the effects of soil-applied Se lasted longer than foliar-applied Se since residual effects were observed for up to 4 years. Chilimba et al. [18] also reported no significant difference between basal and foliar application of Se. They reported for each gram of Se ha^{-1} applied, the Se concentration in maize grain increased by 11–29 μg Se kg^{-1} and by 11–33 μg Se kg^{-1} for foliar and basal applications, respectively. The only comprehensive nationwide experience that has deployed Se fertilization with basal application, in Finland, reported a 15-fold increase in crop Se content [17].

Soil application of Fe usually has no or only limited residual effects, as Fe^{2+} is rapidly converted into Fe^{3+} in soils; therefore, foliar application has been considered the most effective method, especially for plants that develop grain months after germination [35,37,56,59]. However, other studies found that neither soil nor foliar application of Fe fertilization was an effective method to enhance wheat, barley, or oat Fe concentrations [39,57]. In contrast, regular foliar Fe application could result in a potential environmental hazard [85]. Manzeke-Kangara et al. [60] and Aciksoz et al. [39] argued that the efficiency of soil Fe application is more dependent on other factors, especially the integration of N fertilization and ISFM, compared to the Fe fertilizer application method (foliar or basal).

Studies have suggested the potential of a multi-mineral agronomic biofortification strategy to address multiple mineral deficiencies, based on a site-specific biofortification strategy. Mao et al. [75] reported that combined Se, Zn, and I fertilizers were as effective as singly-applied fertilizers when applied to maize, soybean, potato, and cabbage. This suggests that multi-mineral agronomic biofortification has the potential to address multiple MNDs simultaneously. However, knowledge about the elemental antagonistic and synergetic interaction effect is very critical. Pahlavan-Rad and Pessarakli, [56] reported 8% and 13% increases in wheat grain Fe and Zn concentrations, respectively, as a result of Fe and Zn interaction in their study on the combined application of Fe and Zn fertilization. Even though the mechanism of Zn and Fe interaction is not well understood [86], it has been reported that Zn treatment resulted in Fe accumulation in soybean roots and increased root-to-fruit Fe translocation in tomato plants [87].

5.3. Mineral Interaction Effect

Interactions between phosphorus (P) and Zn and between P and Fe in soils and plants have long been recognized and well documented. Studies have reported that high soil P levels can negatively affect Zn and Fe uptake by crops by inhibiting the mycorrhizal colonization of roots and resulting in impaired nutrient uptake [88,89]. Multiple studies have reported that P deficiency in soil results in a higher accumulation of Zn, whereas Zn deficiency in soil leads to a higher accumulation of P in plants [90–92]. Similarly, Fe deficiency stimulates the absorption of P in both roots and shoots [93–96]. Erdal [97] reported that soil Zn application enhances wheat grain Zn, and at the same time, significantly reduces grain P concentration. Another study also reported the association between Zn fertilization and a reduction in the phytic acid in rice grain, ranging from 14.8 to 30.4% [38]. These findings suggest that agronomic biofortification with Fe and Zn might also be a useful strategy to reduce antinutritional factors, such as phytate, in addition to increasing the grain mineral concentration.

A study that employed a factorial design involving the application of N up to 60 kg ha^{-1} and Zn up to 10 kg ha^{-1} on pearl millet indicated that the highest grain Zn concentration was observed at the application of 20 kg N ha^{-1} and 5 kg Zn ha^{-1} [98]. Similarly, the Zn uptake rate was enhanced by 4-fold due to the increased N application [99]. Similarly, multiple studies have indicated that N significantly enhances grain Zn [34,100] and Fe [36,39,60,101] concentrations. Nitrogen can increase the activity of transporter proteins and nitrogenous compounds, like nicotianamine, which helps to maintain Zn root uptake and shoot translocation [101,102], and by increasing the activity and abundance of Fe transporter proteins, such as yellow stripe 1 (YS1), in root cell membranes [103,104], which positively affects the root uptake and shoot transport of Fe. Similarly, the Se concentration of rice grains increased by 54.6% as a result of a combined Se and N application compared to only Se application as a fertilizer [19]. These findings suggest the application of Zn, Fe, and Se as a fertilizer is more effective when they are applied along with N fertilization and ISFM.

5.4. Environmental Impact

Uncontrolled and excessive mineral fertilizer use could cause contamination risk in the environment from the minerals of interest. It has been reported that about 28 tons of extra Cu per year is released into the soil in parts of the United Kingdom as a result of Cu fertilizer [105]. Furthermore, the long-term application of mineral fertilizer was reported to adversely affect important rhizospheric microorganisms that play major roles in plant nutrition and health [106–108]. In such cases, it is recommended to use nanoparticle fertilization, which potentially reduces the release of excessive mineral fertilizers into the environment. For instance, the application of Fe oxide nanoparticles on wheat [109], Zn oxide on maize [30], and Se nanoparticles on soybean [110] effectively improved grain Fe, Zn, and Se concentrations, respectively, without extra mineral release into the environment.

6. Mineral Fertilizer Application Timing

The timing of mineral application is always critical for its effectiveness in improving grain mineral concentration and/or yield. Foliar Zn applications resulted in a marginal effect on rice grain Zn when applied at the stem elongation plus the booting stage, but much greater increases in grain Zn concentration were achieved when foliar Zn application was performed when the crop had reached the milk stage [35]. Fang et al. [111] suggested foliar Zn application at the heading stage as the best practice to improve the Zn concentration of white rice. Sharma et al. [112] and Zeidan et al. [113] argued that the application of Zn fertilization on wheat at the grain-filling stage is an ideal method to increase grain Zn concentrations. The application of Zn fertilizer at the flowering and pod formation stages of chickpea were reported to result in the maximum grain Zn concentration [34].

The application of Se fertilizer during the vegetative stage of crops has been observed to enable and stimulate the quick uptake of Se by the crop [83], although the optimal timing will likely be context-specific. Wheat grain Se concentration increased more when Se fertilizer was applied at the booting stage compared to the earlier jointing stage [114]. Deng et al. [115] also reported that Se fertilizer treatment on rice resulted in a 2-fold higher grain Se concentration at full-heading application compared to late-tillering application.

The application of Se fertilizer at flowering increased grain Se concentrations more than when Se was applied at earlier stages in winter wheat [116]. Galinha et al. [117] reported that Se fertilizer application at the booting stage was more effective in enhancing wheat grain Se concentration compared to the grain-filling stage.

The maximum Fe concentration was achieved from foliar application during the maximum tillering stage [118]. The combination of soil Zn application at sowing and foliar application of Zn along with urea at the flowering and pod formation stages can be the best strategy to enhance Zn and Fe contents in chickpea grain [34]. A study showed that the grain-filling stage of wheat might be the best crop development stage to apply Fe fertilization to attain the maximum grain Zn concentrations [113]. This finding suggests that it is very critical to understand crops as well as the genotype timing of mineral mobilization, remobilization, and translocation within the plant to achieve the best results with respect to grain mineral concentration.

7. Cost of Mineral Fertilizer

Farmers might be willing to pay for the extra cost incurred due to biofortification for minerals that can increase yields, like Zn. However, covering the cost of minerals that do not increase yield, such as Se, is a challenge for fertilizer policy discussions. Given that Se deficiency leads to health complications, it may be appropriate for public health policies to consider whether agronomic biofortification is cost-effective. Further, Joy et al. [68] argued that the application of 7.3 kilo tons of $ZnSO_4H_2O$ on wheat per year increased the yield by ~7.5% and dietary Zn by 15.9% capita^{-1} day^{-1} and reduced the prevalence of Zn deficiency by ~50%. Therefore, consideration of the cost-effectiveness of minerals like Zn and Fe should not be seen only from the perspective of their impact on the crop yield, but should also include the cost per DALY saved. Manzeke-Kangara et al. [76] argued that the cost of Zn fertilization in Zimbabwe for maize was not likely to be as useful as investing in nitrogen, due to the yield gaps.

8. Conclusions

A large number of studies have investigated the impact of agronomic biofortification with Se, Fe, and Zn on grain mineral concentration, primarily on staple cereal crops. Most studies have suggested that agronomic biofortification is likely to be a feasible strategy to enhance grain mineral concentrations, especially among rural resource-poor settings, providing that they have access to mineral fertilization. It is also clear that agronomic biofortification is dependent on many factors, like the timing and method of mineral application, mineral–mineral and mineral–soil interactions, and the adoption of ISFM and other practices. It is, therefore, important to have the right information on these factors prior to the intervention in order to make agronomic biofortification successful. Very few studies have tried to investigate the effectiveness of agronomic biofortification on the improvement of human dietary intake and health, and further studies are required. Reports on the effectiveness of agronomic biofortification on indigenous crops, like finger millet, teff, and amaranth, in tropical smallholding farming systems are lacking. However, these crops are highly adaptive to the local climate and efficiently withstand biotic and abiotic stresses, which is crucial in the effectiveness of agronomic biofortification. In general terms, it is possible to conclude that agronomic biofortification can be a supplementary strategy to combat MND among resource-poor rural settings where people are dependent on their own produce as a food source, and in which other interventions, like supplementation and food fortification, may not be suitable.

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References

1. World Health Organization. Mineral Nutrition Information System. 2023. Available online: https://www.who.int/teams/nutrition-and-food-safety/databases/vitamin-and-mineral-nutrition-information-system (accessed on 21 February 2023).
2. Allen, L.; De Benoist, B.; Dary, O.; Hurrell, R. *Guidelines on Food Fortification with Micronutrients*; FAO: Rome, Italy, 2006; pp. 11–19.
3. World Health Organization. Micronutrients. 2021. Available online: https://www.who.int/health-topics/micronutrients (accessed on 17 November 2022).
4. Muthayya, S.; Rah, J.H.; Sugimoto, J.D.; Roos, F.F.; Kraemer, K.; Black, R.E. The global hidden hunger indices and maps: An advocacy tool for action. *PLoS ONE* **2013**, *8*, e67860. [CrossRef] [PubMed]
5. Hoddinott, J. The economics of reducing malnutrition in sub-Saharan Africa. In *Global Panel on Agriculture and Food Systems for Nutrition Working Paper*; Cornell University: Ithaca, NY, USA, 2016; Volume 21.
6. Gonmei, Z.; Toteja, G.S. Micronutrient status of Indian population. *Indian J. Med. Res.* **2018**, *148*, 511–521. [PubMed]
7. Bouis, H.; Boy-Gallego, E.; Meenakshi, J.V. Micronutrient malnutrition: Causes, prevalence, consequences, and interventions. *Fertil. Crops Improv. Hum. Health A Sci. Rev.* **2012**, *1*, 29–64.
8. Bouis, H.E.; Welch, R.M. Biofortification—A sustainable agricultural strategy for reducing micronutrient malnutrition in the global south. *Crop Sci.* **2010**, *50*, 20–32. [CrossRef]
9. Kuper, H.; Nyapera, V.; Evans, J.; Munyendo, D.; Zuurmond, M.; Frison, S.; Mwenda, V.; Otieno, D.; Kisia, J. Malnutrition and childhood disability in Turkana, Kenya: Results from a case-control study. *PLoS ONE* **2015**, *10*, e0144926. [CrossRef]
10. White, P.J.; Broadley, M.R. Biofortification of crops with seven mineral elements often lacking in human diets–iron, zinc, copper, calcium, magnesium, selenium and iodine. *New Phytol.* **2009**, *182*, 49–84. [CrossRef]
11. Cakmak, I. Enrichment of cereal grains with zinc: Agronomic or genetic biofortification? *Plant Soil* **2008**, *302*, 1–17. [CrossRef]
12. Cakmak, I. *Agronomic Biofortification*; International Food Policy Research Institute: Washington, DC, USA, 2014; Volume 16, pp. 56–97.
13. Dimkpa, C.O.; Bindraban, P.S. Fortification of micronutrients for efficient agronomic production: A review. *Agron. Sustain. Dev.* **2016**, *36*, 7. [CrossRef]
14. Vanlauwe, B.; Descheemaeker, K.; Giller, K.E.; Huising, J.; Merckx, R.; Nziguheba, G.; Wendt, J.; Zingore, S. Integrated soil fertility management in sub-Saharan Africa: Unravelling local adaptation. *Soil* **2015**, *1*, 491–508. [CrossRef]
15. Voortman, R.L.; Bindraban, P.S. *Beyond N and P: Towards a Land Resource Ecology Perspective and Impactful Fertilizer Interventions in Sub-Sahara Africa (VFRC Reports; 2015/1)*; Virtual Fertilizer Development Centre: Washington, DC, USA, 2015; pp. 49–67.
16. Manzeke, G.M.; Mapfumo, P.; Mtambanengwe, F.; Chikowo, R.; Tendayi, T.; Cakmak, I. Soil fertility management effects on maize productivity and grain zinc content in smallholder farming systems of Zimbabwe. *Plant Soil* **2012**, *361*, 57–69. [CrossRef]
17. Alfthan, G.; Eurola, M.; Ekholm, P.; Venäläinen, E.R.; Root, T.; Korkalainen, K.; Hartikainen, H.; Salminen, P.; Hietaniemi, V.; Aspila, P.; et al. Effects of nationwide addition of selenium to fertilizers on foods, and animal and human health in Finland: From deficiency to optimal selenium status of the population. *J. Trace Elem. Med. Biol.* **2015**, *31*, 142–147. [CrossRef] [PubMed]
18. Chilimba, A.D.; Young, S.D.; Black, C.R.; Meacham, M.C.; Lammel, J.; Broadley, M.R. Agronomic biofortification of maize with selenium (Se) in Malawi. *Field Crop. Res.* **2012**, *125*, 118–128. [CrossRef]
19. Reis, H.P.; de Queiroz Barcelos, J.P.; Junior, E.F.; Santos, E.F.; Silva, V.M.; Moraes, M.F.; Putti, F.F.; dos Reis, A.R. Agronomic biofortification of upland rice with selenium and nitrogen and its relation to grain quality. *J. Cereal Sci.* **2018**, *79*, 508–515. [CrossRef]
20. De Lima Lessa, J.H.; Araujo, A.M.; Ferreira, L.A.; da Silva Júnior, E.C.; de Oliveira, C.; Corguinha, A.P.; Martins, F.A.; de Carvalho, H.W.; Guilherme, L.R.; Lopes, G. Agronomic biofortification of rice (*Oryza sativa* L.) with selenium and its effect on element distributions in biofortified grains. *Plant Soil* **2019**, *444*, 331–342. [CrossRef]
21. Lyons, G.H.; Judson, G.J.; Ortiz-Monasterio, I.; Genc, Y.; Stangoulis, J.C.; Graham, R.D. Selenium in Australia: Selenium status and biofortification of wheat for better health. *J. Trace Elem. Med. Biol.* **2005**, *19*, 75–82. [CrossRef] [PubMed]
22. Sindireva, A.; Golubkina, N.; Bezuglova, H.; Fedotov, M.; Alpatov, A.; Erdenotsogt, E.; Sękara, A.; Murariu, O.C.; Caruso, G. Effects of High Doses of Selenate, Selenite and Nano-Selenium on Biometrical Characteristics, Yield and Biofortification Levels of *Vicia faba* L. Cultivars. *Plants* **2023**, *12*, 2847. [CrossRef] [PubMed]
23. Shiriaev, A.; Pezzarossa, B.; Rosellini, I.; Malorgio, F.; Lampis, S.; Ippolito, A.; Tonutti, P. Efficacy and comparison of different strategies for selenium biofortification of tomatoes. *Horticulture* **2022**, *8*, 800. [CrossRef]

24. Liu, Y.; Huang, S.; Jiang, Z.; Wang, Y.; Zhang, Z. Selenium biofortification modulates plant growth, microelement and heavy metal concentrations, selenium uptake, and accumulation in black-grained wheat. *Front. Plant Sci.* **2021**, *12*, 748523. [CrossRef] [PubMed]
25. Premarathna, L.; McLaughlin, M.J.; Kirby, J.K.; Hettiarachchi, G.M.; Stacey, S.; Chittleborough, D.J. Selenate-enriched urea granules are a highly effective fertilizer for selenium biofortification of paddy rice grain. *J. Agric. Food Chem.* **2012**, *60*, 6037–6044. [CrossRef]
26. Radawiec, A.; Szulc, W.; Rutkowska, B. Selenium biofortification of wheat as a strategy to improve human nutrition. *Agriculture* **2021**, *11*, 144. [CrossRef]
27. Silva, M.A.; de Sousa, G.F.; Corguinha, A.P.B.; de Lima Lessa, J.H.; Dinali, G.S.; Oliveira, C.; Lopes, G.; Amaral, D.; Brown, P.; Guilherme, L.R.G. Selenium biofortification of soybean genotypes in a tropical soil via Se-enriched phosphate fertilizers. *Front. Plant Sci.* **2022**, *13*, 988140. [CrossRef]
28. Ngigi, P.B.; Lachat, C.; Masinde, P.W.; Du Laing, G. Agronomic biofortification of maize and beans in Kenya through selenium fertilization. *Environ. Geochem. Health* **2019**, *41*, 2577–2591. [CrossRef]
29. Joy, E.J.; Stein, A.J.; Young, S.D.; Ander, E.L.; Watts, M.J.; Broadley, M.R. Zinc-enriched fertilisers as a potential public health intervention in Africa. *Plant Soil* **2015**, *389*, 1–24. [CrossRef]
30. Umar, W.; Hameed, M.K.; Aziz, T.; Maqsood, M.A.; Bilal, H.M.; Rasheed, N. Synthesis, characterization and application of ZnO nanoparticles for improved growth and Zn biofortification in maize. *Arch. Agron. Soil Sci.* **2021**, *67*, 1164–1176. [CrossRef]
31. Yang, G.; Yuan, H.; Ji, H.; Liu, H.; Zhang, Y.; Wang, G.; Chen, L.; Guo, Z. Effect of ZnO nanoparticles on the productivity, Zn biofortification, and nutritional quality of rice in a life cycle study. *Plant Physiol. Biochem.* **2021**, *163*, 87–94. [CrossRef]
32. Du, W.; Yang, J.; Peng, Q.; Liang, X.; Mao, H. Comparison study of zinc nanoparticles and zinc sulphate on wheat growth: From toxicity and zinc biofortification. *Chemosphere* **2019**, *227*, 109–116. [CrossRef] [PubMed]
33. Botoman, L.; Chimungu, J.G.; Bailey, E.H.; Munthali, M.W.; Ander, E.L.; Mossa, A.W.; Young, S.D.; Broadley, M.R.; Lark, R.M.; Nalivata, P.C. Agronomic biofortification increases grain zinc concentration of maize grown under contrasting soil types in Malawi. *Plant Direct* **2022**, *6*, e458. [CrossRef] [PubMed]
34. Pal, V.; Singh, G.; Dhaliwal, S.S. Agronomic biofortification of chickpea with zinc and iron through application of zinc and urea. *Commun. Soil Sci. Plant Anal.* **2019**, *50*, 1864–1877. [CrossRef]
35. Phattarakul, N.; Rerkasem, B.; Li, L.J.; Wu, L.H.; Zou, C.Q.; Ram, H.; Sohu, V.S.; Kang, B.S.; Surek, H.; Kalayci, M.; et al. Biofortification of rice grain with zinc through zinc fertilization in different countries. *Plant Soil* **2012**, *361*, 131–141. [CrossRef]
36. Hussain, S.T.; Bhat, M.A.; Hussain, A.; Dar, S.A.; Dar, S.H.; Ganai, M.A.; Telli, N.A. Zinc fertilization for improving grain yield, zinc concentration and uptake in different rice genotypes. *J. Pharmacogn. Phytochem.* **2018**, *7*, 287–291.
37. Narwal, R.P.; Malik, R.S.; Dahiya, R.R. Addressing variations in status of a few nutritionally important micronutrients in wheat crop. In Proceedings of the 19th World Congress of Soil Science, Soil Solutions for a Changing World, Brisbane, QL, Australia, 1–6 August 2010; Volume 3, pp. 1–6.
38. Saha, S.; Chakraborty, M.; Padhan, D.; Saha, B.; Murmu, S.; Batabyal, K.; Seth, A.; Hazra, G.C.; Mandal, B.; Bell, R.W. Agronomic biofortification of zinc in rice: Influence of cultivars and zinc application methods on grain yield and zinc bioavailability. *Field Crop. Res.* **2017**, *210*, 52–60. [CrossRef]
39. Aciksoz, S.B.; Yazici, A.; Ozturk, L.; Cakmak, I. Biofortification of wheat with iron through soil and foliar application of nitrogen and iron fertilizers. *Plant Soil* **2011**, *349*, 215–225. [CrossRef]
40. Cakmak, I. Enrichment of fertilizers with zinc: An excellent investment for humanity and crop production in India. *J. Trace Elem. Med. Biol.* **2009**, *23*, 281–289. [CrossRef] [PubMed]
41. Cakmak, I.; Kalayci, M.; Kaya, Y.; Torun, A.A.; Aydin, N.; Wang, Y.; Arisoy, Z.; Erdem, H.A.; Yazici, A.; Gokmen, O.; et al. Biofortification and localization of zinc in wheat grain. *J. Agric. Food Chem.* **2010**, *58*, 9092–9102. [CrossRef] [PubMed]
42. Cakmak, I. HarvestPlus zinc fertilizer project: HarvestZinc. *Better Crop.* **2012**, *96*, 17–19.
43. Haileselassie, B.; Stomph, T.J.; Hoffland, E. Teff (Eragrostis tef) production constraints on Vertisols in Ethiopia: Farmers' perceptions and evaluation of low soil zinc as yield-limiting factor. *Soil Sci. Plant Nutr.* **2011**, *57*, 587–596. [CrossRef]
44. Jat, S.L.; Shivay, Y.S.; Parihar, C.M. Dual purpose summer legumes and zinc fertilization for improving productivity and zinc utilization in aromatic hybrid rice (*Oryza sativa*). *Indian J. Agron.* **2011**, *56*, 328–333.
45. Kumar, N.; Salakinkop, S.R. Agronomic biofortification of maize with zinc and iron micronutrients. *Mod. Concepts Dev. Agron.* **2018**, *1*, 1–4.
46. Mishra, J.S.; Hariprasanna, K.; Rao, S.S.; Patil, J.V. Biofortification of post-rainy sorghum (*Sorghum bicolor*) with zinc and iron through fertilization strategy. *Indian J. Agric. Sci.* **2015**, *85*, 721–724.
47. Pooniya, V.; Shivay, Y.S. Summer green-manuring crops and zinc fertilization on productivity and economics of basmati rice (*Oryza sativa* L.). *Arch. Agron. Soil Sci.* **2012**, *58*, 593–616. [CrossRef]
48. Prasad, S.K.; Singh, M.K.; Singh, R.E.N.U. Effect of nitrogen and zinc fertilizer on pearl millet (*Pennisetum glaucum*) under agri-horti system of eastern Uttar Pradesh. *Significance* **2014**, *400*, 163–166.
49. Saleem, I.; Javid, S.; Bibi, F.; Ehsan, S.; Niaz, A.; Ahmad, Z.A. Biofortification of maize grain with zinc and iron by using fertilizing approach. *J. Agric. Ecol.* **2016**, *7*, 1–6. [CrossRef]
50. Shivay, Y.S.; Kumar, D.; Prasad, R. Effect of zinc-enriched urea on productivity, zinc uptake and efficiency of an aromatic rice–wheat cropping system. *Nutr. Cycl. Agroecosyst.* **2008**, *81*, 229–243. [CrossRef]

51. Shivay, Y.S.; Prasad, R.; Rahal, A. Relative efficiency of zinc oxide and zinc sulphate-enriched urea for spring wheat. *Nutr. Cycl. Agroecosyst.* **2008**, *82*, 259–264. [CrossRef]
52. Singh, M.V. Micronutrient Deficiencies in Crops and Soils in India. In *Micronutrient Deficiencies in Global Crop Production*; Alloway, B.J., Ed.; Springer: Dordrecht, Switzerland, 2008; pp. 93–125.
53. Yilmaz, A.; Ekiz, H.; Torun, B.; Gultekin, I.; Karanlik, S.; Bagci, S.A.; Cakmak, I. Effect of different zinc application methods on grain yield and zinc concentration in wheat cultivars grown on zinc-deficient calcareous soils. *J. Plant Nutr.* **1997**, *20*, 461–471. [CrossRef]
54. Zia, M.H.; Ahmed, I.; Bailey, E.H.; Lark, R.M.; Young, S.D.; Lowe, N.M.; Joy, E.J.; Wilson, L.; Zaman, M.; Broadley, M.R. Site-specific factors influence the field performance of a Zn-biofortified wheat variety. *Front. Sustain. Food Syst.* **2020**, *4*, 135. [CrossRef]
55. Zhang, Y.; Shi, R.; Rezaul, K.M.; Zhang, F.; Zou, C. Iron and zinc concentrations in grain and flour of winter wheat as affected by foliar application. *J. Agric. Food Chem.* **2010**, *58*, 12268–12274. [CrossRef] [PubMed]
56. Pahlavan-Rad, M.R.; Pessarakli, M. Response of wheat plants to zinc, iron, and manganese applications and uptake and concentration of zinc, iron, and manganese in wheat grains. *Commun. Soil Sci. Plant Anal.* **2009**, *40*, 1322–1332. [CrossRef]
57. Gupta, U.C. Iron status of crops in Prince Edward Island and effect of soil pH on plant iron concentration. *Can. J. Soil Sci.* **1991**, *71*, 197–202. [CrossRef]
58. Sims, J.T.; Johnson, G.V. Micronutrient soil tests. *Micronutr. Agric.* **1991**, *4*, 427–476.
59. Zhang, J.; Wu, L.H.; Wang, M.Y. Iron and zinc biofortification in polished rice and accumulation in rice plant (*Oryza sativa* L.) as affected by nitrogen fertilization. *Acta Agric. Scand. B Soil Plant Sci.* **2008**, *58*, 267–272.
60. Manzeke-Kangara, M.G.; Mtambanengwe, F.; Watts, M.J.; Broadley, M.R.; Lark, R.M.; Mapfumo, P. Can nitrogen fertilizer management improve grain iron concentration of agro-biofortified crops in Zimbabwe? *Agronomy* **2021**, *11*, 124. [CrossRef]
61. Ghafari, H.; Razmjoo, J. Response of durum wheat to foliar application of varied sources and rates of iron fertilizers. *J. Agric. Sci. Technol.* **2015**, *17*, 321–331.
62. Dhaliwal, S.S.; Sharma, V.; Shukla, A.K.; Verma, V.; Behera, S.K.; Singh, P.; Alotaibi, S.S.; Gaber, A.; Hossain, A. Comparative efficiency of mineral, chelated and nano forms of zinc and iron for improvement of zinc and iron in chickpea (*Cicer arietinum* L.) through biofortification. *Agronomy* **2021**, *11*, 2436. [CrossRef]
63. Taskin, M.B.; Gunes, A. Iron biofortification of wheat grains by foliar application of nano zero-valent iron (nZVI) and other iron sources with urea. *J. Soil Sci. Plant Nutr.* **2022**, *22*, 4642–4652. [CrossRef]
64. Aziz, M.Z.; Yaseen, M.; Abbas, T.; Naveed, M.; Mustafa, A.; Hamid, Y.; Saeed, Q.; Xu, M.G. Foliar application of micronutrients enhances crop stand, yield and the biofortification essential for human health of different wheat cultivars. *J. Integr. Agric.* **2019**, *18*, 1369–1378. [CrossRef]
65. Teklu, D.; Gashu, D.; Joy, E.J.; Lark, R.M.; Bailey, E.H.; Wilson, L.; Amede, T.; Broadley, M.R. Genotypic Response of Finger Millet to Zinc and Iron Agronomic Biofortification, Location and Slope Position towards Yield. *Agronomy* **2023**, *13*, 1452. [CrossRef]
66. Teklu, D.; Gashu, D.; Joy, E.J.; Lark, R.M.; Bailey, E.H.; Wilson, L.; Amede, T.; Broadley, M.R. Impact of zinc and iron agronomic biofortification on grain mineral concentration of finger millet varieties as affected by location and slope. *Front. Nutr.* **2023**, *10*, 1159833. [CrossRef]
67. Broadley, M.R.; White, P.J.; Bryson, R.J.; Meacham, M.C.; Bowen, H.C.; Johnson, S.E.; Hawkesford, M.J.; McGrath, S.P.; Zhao, F.J.; Breward, N.; et al. Biofortification of UK food crops with selenium. *Proc. Nutr. Soc.* **2006**, *65*, 169–181. [CrossRef]
68. Joy, E.J.; Kalimbira, A.A.; Sturgess, J.; Banda, L.; Chiutsi-Phiri, G.; Manase, H.; Gondwe, J.; Ferguson, E.L.; Kalumikiza, Z.; Bailey, E.H.; et al. Biofortified maize improves selenium status of women and children in a rural community in Malawi: Results of the addressing hidden hunger with agronomy randomized controlled trial. *Front. Nutr.* **2022**, *8*, 1189. [CrossRef]
69. Lowe, N.M.; Zaman, M.; Khan, M.J.; Brazier, A.K.; Shahzad, B.; Ullah, U.; Khobana, G.; Ohly, H.; Broadley, M.R.; Zia, M.H.; et al. Biofortified wheat increases dietary zinc intake: A randomised controlled efficacy study of zincol-2016 in rural Pakistan. *Front. Nutr.* **2022**, *8*, 1238. [CrossRef]
70. Gupta, S.; Zaman, M.; Fatima, S.; Shahzad, B.; Brazier, A.K.; Moran, V.H.; Broadley, M.R.; Zia, M.H.; Bailey, E.H.; Wilson, L.; et al. The impact of consuming zinc-biofortified wheat flour on haematological indices of zinc and iron status in adolescent girls in rural pakistan: A cluster-randomised, double-blind, controlled effectiveness trial. *Nutrients* **2022**, *14*, 1657. [CrossRef] [PubMed]
71. Scott, S.P.; Murray-Kolb, L.E.; Wenger, M.J.; Udipi, S.A.; Ghugre, P.S.; Boy, E.; Haas, J.D. Cognitive performance in Indian school-going adolescents is positively affected by consumption of iron-biofortified pearl millet: A 6-month randomized controlled efficacy trial. *J. Nutr.* **2018**, *148*, 1462–1471. [CrossRef] [PubMed]
72. Joy, E.J.; Ahmad, W.; Zia, M.H.; Kumssa, D.B.; Young, S.D.; Ander, E.L.; Watts, M.J.; Stein, A.J.; Broadley, M.R. Valuing increased zinc (Zn) fertiliser-use in Pakistan. *Plant Soil* **2017**, *411*, 139–150. [CrossRef] [PubMed]
73. Abdu, A.O.; De Groote, H.; Joy, E.J.M.; Kumssa, D.B.; Broadley, M.R.; Gashu, D. Zinc agronomic biofortification of staple crops may be a cost-effective strategy to alleviate zinc deficiency in Ethiopia. *Front. Nutr.* **2022**, *9*, 1037161. [CrossRef] [PubMed]
74. Zhang, C.M.; Zhao, W.Y.; Gao, A.X.; Su, T.T.; Wang, Y.K.; Zhang, Y.Q.; Zhou, X.B.; He, X.H. How could agronomic biofortification of rice be an alternative strategy with higher cost-effectiveness for human iron and zinc deficiency in China? *Food Nutr. Bull.* **2018**, *39*, 246–259. [CrossRef] [PubMed]
75. Mao, H.; Wang, J.; Wang, Z.; Zan, Y.; Lyons, G.; Zou, C. Using agronomic biofortification to boost zinc, selenium, and iodine concentrations of food crops grown on the loess plateau in China. *J. Soil Sci. Plant Nutr.* **2014**, *14*, 459–470. [CrossRef]

76. Manzeke-Kangara, M.G.; Joy, E.J.; Mtambanengwe, F.; Chopera, P.; Watts, M.J.; Broadley, M.R.; Mapfumo, P. Good soil management can reduce dietary zinc deficiency in Zimbabwe. *CABI Agric. Biosci.* **2021**, *2*, 20210026618. [CrossRef]
77. Robertson, L.S.; Lucas, R.E. Essential micronutrients: Zinc [for both plants and animals, fertilizers]. In *Extension Bulletin-Michigan State University, Cooperative Extension Service (USA)*; Michigan state University Press: East Lansing, MI, USA, 1976; pp. 4–8.
78. Frye, W.W.; Miller, H.F.; Murdock, L.W.; Peaslee, D.E. Zinc Fertilization of Corn in Kentucky. Available online: https://uknowledge.uky.edu/pss_notes/110 (accessed on 22 July 2022).
79. Martens, D.C.; Westermann, D.T. Fertilizer applications for correcting micronutrient deficiencies. *Micronutr. Agric.* **1991**, *4*, 549–592.
80. Singh, M.V.; Abrol, I.P. Direct and residual effect of fertilizer zinc application on the yield and chemical composition of rice-wheat crops in an alkali soil. *Fertil. Res.* **1985**, *8*, 179–191. [CrossRef]
81. Takkar, P.N.; Walker, C.D. The distribution and correction of zinc deficiency. In *Zinc in Soils and Plants: Proceedings of the International Symposium on 'Zinc in Soils and Plants'*; Robson, A.D., Ed.; Springer: Berlin/Heidelberg, Germany, 1993; pp. 151–165.
82. Meena, N.; Fathima, P.S. Nutrient uptake of rice as influenced by agronomic biofortification of Zn and Fe under methods of rice cultivation. *Int. J. Pure Appl. Biosci.* **2017**, *5*, 456–459.
83. Chauhan, R.; Awasthi, S.; Srivastava, S.; Dwivedi, S.; Pilon-Smits, E.A.; Dhankher, O.P.; Tripathi, R.D. Understanding selenium metabolism in plants and its role as a beneficial element. *Crit. Rev. Environ. Sci. Technol.* **2019**, *49*, 1937–1958. [CrossRef]
84. Ros, G.H.; Van Rotterdam, A.M.D.; Bussink, D.W.; Bindraban, P.S. Selenium fertilization strategies for bio-fortification of food: An agro-ecosystem approach. *Plant Soil* **2016**, *404*, 99–112. [CrossRef]
85. Sperotto, R.A.; Ricachenevsky, F.K.; de Abreu Waldow, V.; Fett, J.P. Iron biofortification in rice: It's a long way to the top. *Plant Sci.* **2012**, *190*, 24–39. [CrossRef] [PubMed]
86. Xie, X.; Hu, W.; Fan, X.; Chen, H.; Tang, M. Interactions between phosphorus, zinc, and iron homeostasis in nonmycorrhizal and mycorrhizal plants. *Front. Plant Sci.* **2019**, *10*, 1172. [CrossRef]
87. Ibiang, Y.B.; Innami, H.; Sakamoto, K. Effect of excess zinc and arbuscular mycorrhizal fungus on bioproduction and trace element nutrition of tomato (*Solanum lycopersicum* L. cv. Micro-Tom). *Soil Sci. Plant Nutr.* **2018**, *3*, 342–351. [CrossRef]
88. Lynch, J.; Marschner, P.; Rengel, Z. Effect of internal and external factors on root growth and development. In *Marschner's Mineral Nutrition of Higher Plants*, 3rd ed.; Academic Press: Amsterdam, The Netherlands, 2012; pp. 331–346.
89. Watts-Williams, S.J.; Patti, A.; Cavagnaro, T.R. Arbuscular mycorrhizas are beneficial under both deficient and toxic soil zinc conditions. *Plant Soil* **2013**, *371*, 299–312. [CrossRef]
90. Bouain, N.; Kisko, M.; Rouached, A.; Dauzat, M.; Lacombe, B.; Belgaroui, N.; Ghnaya, T.; Davidian, J.C.; Berthomieu, P.; Abdelly, C.; et al. Phosphate/zinc interaction analysis in two lettuce varieties reveals contrasting effects on biomass, photosynthesis, and dynamics of Pi transport. *BioMed Res. Int.* **2014**, *2014*, 548254. [CrossRef]
91. Khan, G.A.; Bouraine, S.; Wege, S.; Li, Y.; de Carbonnel, M.; Berthomieu, P.; Poirier, Y.; Rouached, H. Coordination between zinc and phosphate homeostasis involves the transcription factor PHR1, the phosphate exporter PHO1, and its homologue PHO1; H3 in Arabidopsis. *J. Exp. Bot.* **2014**, *65*, 871–884. [CrossRef]
92. Ova, E.A.; Kutman, U.B.; Ozturk, L.; Cakmak, I. High phosphorus supply reduced zinc concentration of wheat in native soil but not in autoclaved soil or nutrient solution. *Plant Soil* **2015**, *393*, 147–162. [CrossRef]
93. Briat, J.F.; Rouached, H.; Tissot, N.; Gaymard, F.; Dubos, C. Integration of P, S, Fe, and Zn nutrition signals in Arabidopsis thaliana: Potential involvement of PHOSPHATE STARVATION RESPONSE 1 (PHR1). *Front. Plant Sci.* **2015**, *6*, 290. [CrossRef] [PubMed]
94. Nafady, N.A.; Elgharably, A. Mycorrhizal symbiosis and phosphorus fertilization effects on Zea mays growth and heavy metals uptake. *Int. J. Phytoremediat.* **2018**, *20*, 869–875. [CrossRef] [PubMed]
95. Ward, J.T.; Lahner, B.; Yakubova, E.; Salt, D.E.; Raghothama, K.G. The effect of iron on the primary root elongation of Arabidopsis during phosphate deficiency. *Plant Physiol.* **2008**, *147*, 1181–1191. [CrossRef] [PubMed]
96. Zheng, L.; Huang, F.; Narsai, R.; Wu, J.; Giraud, E.; He, F.; Cheng, L.; Wang, F.; Wu, P.; Whelan, J.; et al. Physiological and transcriptome analysis of iron and phosphorus interaction in rice seedlings. *Plant Physiol.* **2009**, *151*, 262–274. [CrossRef] [PubMed]
97. Erdal, I. Effects of Various Zinc Application Methods on Grain Zinc and Phytic Acid Concentration of Different Cereal Species and Wheat Cultivars Grown in Central Anatolia. Doctoral Dissertation, Graduate School of Natural and Applied Sciences, Ankara University, Ankara, Turkey, 1998.
98. Prasad, S.K.; Singh, R.; Singh, M.K.; Rakshit, A. Zinc biofortification and agronomic indices of pearl millet under semi-arid region. *Int. J. Agric. Environ. Biotechnol.* **2015**, *8*, 171–175. [CrossRef]
99. Monsant, A.C.; Wang, Y.; Tang, C. Nitrate nutrition enhances zinc hyperaccumulation in *Noccaea caerulescens* (Prayon). *Plant Soil* **2010**, *336*, 391–404. [CrossRef]
100. Römheld, V. The role of phytosiderophores in acquisition of iron and other micronutrients in graminaceous species: An ecological approach. *Plant Soil* **1991**, *130*, 127–134. [CrossRef]
101. Kutman, U.B.; Yildiz, B.; Ozturk, L.; Cakmak, I. Biofortification of durum wheat with zinc through soil and foliar applications of nitrogen. *Cereal Chem.* **2010**, *87*, 1–9. [CrossRef]
102. Erenoglu, E.B.; Kutman, U.B.; Ceylan, Y.; Yildiz, B.; Cakmak, I. Improved nitrogen nutrition enhances root uptake, root-to-shoot translocation and remobilization of zinc (65Zn) in wheat. *New Phytol.* **2011**, *189*, 438–448. [CrossRef]

103. Murata, Y.; Harada, E.; Sugase, K.; Namba, K.; Horikawa, M.; Ma, J.F.; Yamaji, N.; Ueno, D.; Nomoto, K.; Iwashita, T.; et al. Specific transporter for iron (III): Phytosiderophore complex involved in iron uptake by barley roots. *Pure Appl. Chem.* **2008**, *80*, 2689–2697. [CrossRef]
104. Curie, C.; Cassin, G.; Couch, D.; Divol, F.; Higuchi, K.; Le Jean, M.; Mission, J.; Schikora, A.; Czernic, P.; Mari, S. Metal movement within the plant: Contribution of nicotianamine and yellow stripe 1-like transporters. *Ann. Bot.* **2009**, *103*, 1–11. [CrossRef] [PubMed]
105. Stuart, J.; Nicholson, F.; Rollett, A.; Chambers, B.; Gleadthorpe, A.D.A.S.; Vale, M. The Defra "Agricultural Soil Heavy Metal Inventory" for 2008 Report 3 for Defra Project SP0569. 2010. Available online: http://pstorage-cranfield-168447862.s3.amazonaws.com/14636414/Defra_SP0569Report3.pdf (accessed on 18 May 2023).
106. Semenov, M.V.; Krasnov, G.S.; Semenov, V.M.; van Bruggen, A.H. Long-term fertilization rather than plant species shapes rhizosphere and bulk soil prokaryotic communities in agroecosystems. *Appl. Soil Ecol.* **2020**, *154*, 103641. [CrossRef]
107. Semenov, M.V.; Krasnov, G.S.; Semenov, V.M.; van Bruggen, A. Mineral and organic fertilizers distinctly affect fungal communities in the crop rhizosphere. *J. Fungi* **2022**, *8*, 251. [CrossRef] [PubMed]
108. Wu, L.; Jiang, Y.; Zhao, F.; He, X.; Liu, H.; Yu, K. Increased organic fertilizer application and reduced chemical fertilizer application affect the soil properties and bacterial communities of grape rhizosphere soil. *Sci. Rep.* **2020**, *10*, 9568. [CrossRef]
109. Sundaria, N.; Singh, M.; Upreti, P.; Chauhan, R.P.; Jaiswal, J.P.; Kumar, A. Seed priming with iron oxide nanoparticles triggers iron acquisition and biofortification in wheat (*Triticum aestivum* L.) grains. *J. Plant Growth Regul.* **2019**, *38*, 122–131. [CrossRef]
110. Xiong, Y.; Xiang, X.; Xiao, C.; Zhang, N.; Cheng, H.; Rao, S.; Cheng, S.; Li, L. Illumina RNA and SMRT Sequencing Reveals the Mechanism of Uptake and Transformation of Selenium Nanoparticles in Soybean Seedlings. *Plants* **2023**, *12*, 789. [CrossRef] [PubMed]
111. Fang, Y.; Wang, L.; Xin, Z.; Zhao, L.; An, X.; Hu, Q. Effect of foliar application of zinc, selenium, and iron fertilizers on nutrients concentration and yield of rice grain in China. *J. Agric. Food Chem.* **2008**, *56*, 2079–2084. [CrossRef] [PubMed]
112. Sharma, P.; Sheikh, I.; Singh, D.; Kumar, S.; Verma, S.K.; Kumar, R.; Vyas, P.; Dhaliwal, H.S. Uptake, distribution, and remobilization of iron and zinc among various tissues of wheat–*Aegilops* substitution lines at different growth stages. *Acta Physiol. Plant* **2017**, *39*, 185. [CrossRef]
113. Zeidan, M.S.; Mohamed, M.F.; Hamouda, H.A. Effect of foliar fertilization of Fe, Mn and Zn on wheat yield and quality in low sandy soils fertility. *World J. Agric. Sci.* **2010**, *6*, 696–699.
114. De Vita, P.; Platani, C.; Fragasso, M.; Ficco, D.B.M.; Colecchia, S.A.; Del Nobile, M.A.; Padalino, L.; Di Gennaro, S.; Petrozza, A. Selenium-enriched durum wheat improves the nutritional profile of pasta without altering its organoleptic properties. *Food Chem.* **2017**, *214*, 374–382. [CrossRef]
115. Deng, X.; Liu, K.; Li, M.; Zhang, W.; Zhao, X.; Zhao, Z.; Liu, X. Difference of selenium uptake and distribution in the plant and selenium form in the grains of rice with foliar spray of selenite or selenate at different stages. *Field Crop. Res.* **2017**, *211*, 165–171. [CrossRef]
116. Chu, J.; Yao, X.; Yue, Z.; Li, J.; Zhao, J. The effects of selenium on physiological traits, grain selenium content and yield of winter wheat at different development stages. *Biol. Trace Elem. Res.* **2013**, *151*, 434–440. [CrossRef]
117. Galinha, C.; Freitas, M.D.C.; Pacheco, A.M.G.; Coutinho, J.; Macas, B.; Almeida, A.S. Selenium supplementation of Portuguese wheat cultivars through foliar treatment in actual field conditions. *J. Radioanal. Nucl. Chem.* **2013**, *297*, 227–231. [CrossRef]
118. Singh, P.; Dhaliwal, S.S.; Sadana, U.S.; Manchanda, J.S. Enrichment of rice cultivars with Fe at different plant growth stages through ferti-fortification. *LS Int. J. Life Sci.* **2013**, *2*, 91–96. [CrossRef]