Review Article

Agronomic Bio-Fortification of Wheat to Combat Zinc Deficiency in Developing Countries

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Abstract | Zinc (Zn) deficiency is well reported problem around the globe causing severe reduction in crop yield and quality. The intake of inadequate foods low in Zn is the major cause of Zn deficiency in humans, especially in developing countries. The deficiency of Zn causes many irregularties in both plants and humans. The Zn deficiency considerably reduced the plant growth, tillers production, chlorophyll synthesis, and crop yield. Moreover, in the case of humans' Zn deficiency causes blindness, lower intelligence quotient (IQ) levels, weaker immune system, and impaired physical and mental development. Wheat crop play a chief role in daily food requirement and calories need in developing countries, however, inherently wheat has lower Zn contents. Moreover, soil Zn deficiency further increasing the problem of low Zn contents in wheat grain. Thus, the finest way to combat the Zn deficiency is to produce the grains of wheat having desirable Zn contents at farmer's field. The breeding and agronomic (fertilizer application) bio-fortification approaches are important ones to increase Zn concentration in wheat grains up to desirable levels. The genetic techniques are costly, and sustainable, however, they are long term and requires large breeding activities and resources. Conversely, agronomic techniques appear to be short term, quick and economic solution to increase the Zn contents to meet human needs. The application of Zn as foliar sprays, seed priming, soil application and soil+foliar application effectively enhanced Zn uptake and grain Zn contents. Zn fertilization also maintains desirable Zn availability in soil solution and maintains the Zn pools in plant tissues during later stages thus resulting in an increase in Zn accumulation in wheat grains. Therefore, in this review, we discussed roles of Zn in plants and humans and possible strategies to combat Zn deficiency in humans. Additionally, challenges for agronomic and breeding strategies and possible benefits of both these strategies also discussed in this review.

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Introduction

Cereal crops including the wheat (*Triticum aestivum)* and rice (*Oryza sativa*) are a major source of food and nutrition for the developing nations (Cakmak, 2008). Among cereals, wheat crop is the major source of food it has chief role in the provision of nutrients, energy and proteins around the globe especially in the developing nations (Shewry, 2009; Chattha *et al.*, 2017a, 2018). The wheat crop provides more than 70% daily calories to people living in the rural area, additionally, it is also a major source of micronutrients including zinc (Zn) for the developing world (Cakmak, 2008). The consumption of wheat resulting in Zn deficiency owing to fact wheat crop is hereditarily lower in Zn and higher in phytic acid (PA) which further reduces the Zn bio-availability to humans (Ma *et al.*, 2008). Additionally, wheat processing in order to make flour further diminishes Zn contents in flour owing to the loss of Zn during processing (Oghbaei and Prakash, 2016). Zn is a crucial nutrient needed for the humans and plant growth (Hafeez *et al.*, 2013). Zn affects diverse aspect of the human's immune system (Shankar and Prasad, 1998), additionally, it is also needs for the proper and optimum functioning of cells mediating innate immunity, and natural killer cells (Prasad, 2008). Zn is also an imperative nutrient for plants and it plays a chief role in the plant metabolism by influencing the activity of different enzymes including carbon anhydrase (CA), and hydrogenase (Maret, 2013). Moreover, Zn also regulates the genes expressions and therefore, improve plant growth in stress conditions (Cakmak, 2000; Gauci *et al.*, 2009).

Among the micro-nutrients, Zn deficiency is a widespread problem both in humans and plants (Welch and Graham, 2004). It has been documented that every year more than 0.5 million children under the age of 5 years died owing to Zn deficiency (Black *et al.*, 2008). Zn deficiency together with Fe and vitamin A deficiencies are considered as top priority challenges and they should be urgently tackled for humanity and global stability (WHO, 2002). Globally, more than 1.1 billion people are at the risk of Zn deficiency (Kumssa *et al.*, 2015) and this problem is more widespread in the developing countries. Moreover, percentage of the population in different areas of the world suffering from Zn deficiency is given in Figure 1. In different countries including Turkey, Pakistan, and Iran most of the soils are Zn deficient which further enhanced the Zn deficiency in crops and consequently in humans (Hotz and Brown, 2004). Zn deficiency is widespread problem in developing countries and particularly in those regions where people consume unbalanced foods and most of the Zn is lost during the making of flour owing to the fact most Zn is stored in the husk (Graham *et al.*, 2001). Moreover, percentage of Zn uptake from animal and cereals in different regions is given in Figure 2 which is clearly describing the difference among the developing and developed nations for the Zn uptake from animal and cereals based food sources.

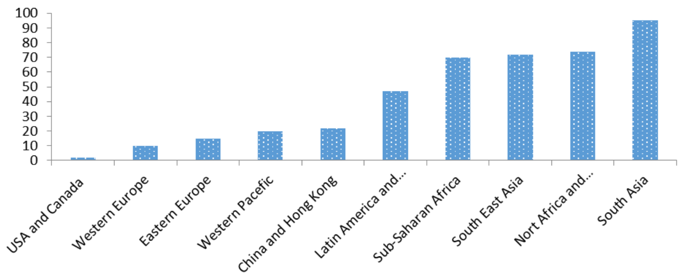

Figure 1: *The percentage of populations suffering from the Zn deficiency in variable regions (Shahid et al., 2010).*

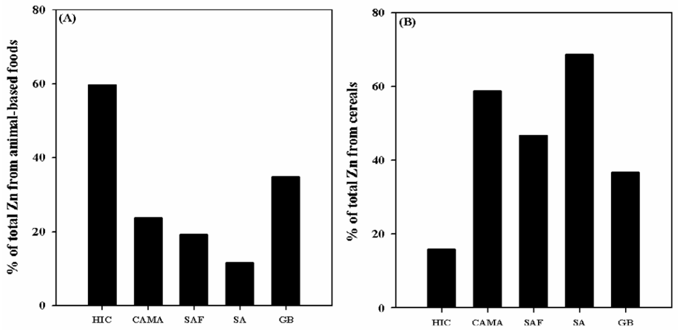

Figure 2: *The % contribution in daily Zn intake from and animal (A) and cereals (B) foods in different regions. HIC: High income countries, CAMA: Central Asia and Middle east, SAF: Sub-Saharan Africa, SA: South Asia, GB: Global. Redrawn and modified from (Wessells and Brown, 2012; Cakmak and Kutman, 2018).*

Bio-fortification is a novel and imperative strategy to solve the problems related to micro-nutrient deficiencies (Dennis and Ross, 2013). This strategy involves the utilization of breeding and agronomic approaches to solve the nutrient deficiency problems. The breeding approach used to develop the genotypes with higher nutrient contents are time taking and costly (Bouis *et al.*, 2011). Conversely, agronomic strategy is a quick solution to combat the problem of Zn deficiency. This technique involves the application of micro-nutrients through different methods including seed treatments, soil, and foliar application (Bouis *et al.*, 2011). The bio-fortified crops have higher concentration of nutrients and mostly wheat, rice, maize (*Zea mays*) potatoes (*Solanum tuberosum*) and beans are subjected to bio-fortification owing to the fact they are important food sources globally (Dennis and Ross, 2013). Improved human health and better crop production can be acheived by increasing the Zn contents in edible crops. Thus, it is the dire need of time to improve the grain Zn and Zn bio-availability in wheat grains in the developing world, where wheat is a staple food (Zhao and McGrath, 2009). Therefore, in this review, we discussed the roles of Zn for humans and plants and causes of Zn deficiency in wheat and possible approaches to reduce the Zn deficiency in humans. Additionally, role of breeding and agronomic approaches to increase wheat grain Zn contents in order to reduce the Zn deficiency in crops and humans also discussed in this review.

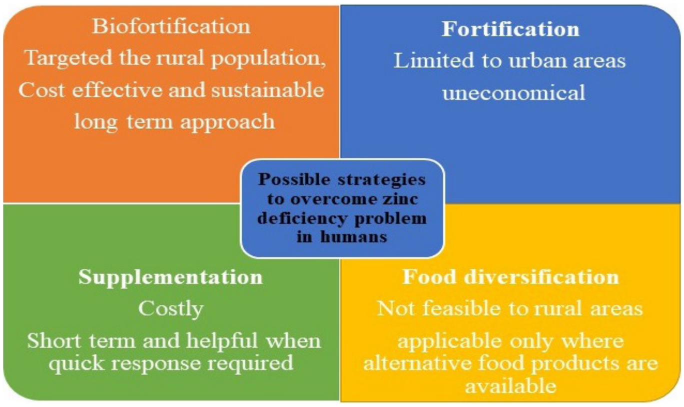

Figure 3: *The possible strategies for combating Zn deficiency in humans.*

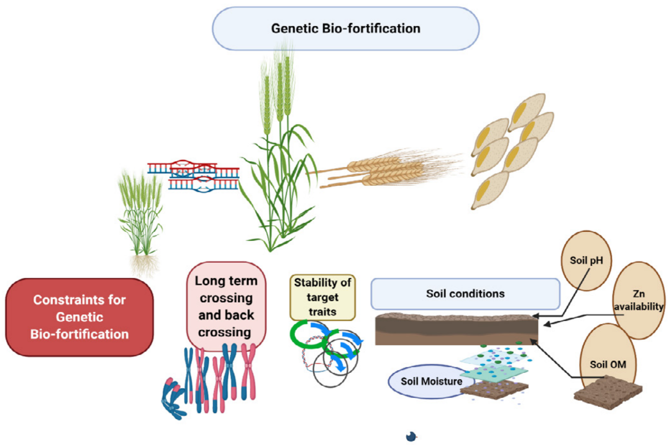

Figure 4: *The constrains of breeding techniques of Zn bio-fortification.*

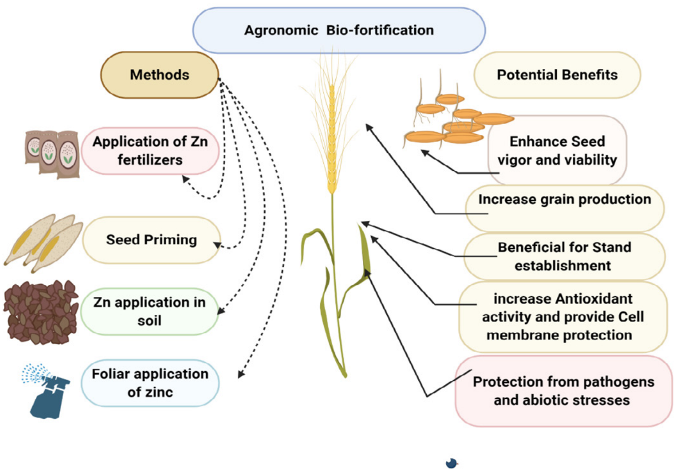

Figure 5: *Potential benefits of agronomic bio-fortification of wheat.*

Roles of Zn in plants

Zinc plays an imperative role in plant growth and development and it is considered as an important nutrient to be involved in the synthesis of proteins and amino acids (Pandey *et al*., 2006; Cabot *et al*., 2019). Zn also required for hormones synthesis (auxin) and its deficiency leads to a reduction in endogenous auxin and tryptophan levels, which therefore, reduced the plant growth (Pedler *et al*., 2000). Zn also affect activities of different enzymes including CA, hydrogenase, and fructose 1,6-bisphosphate involve in carbohydrate metabolisms. The activities of these enzymes substantially declined in Zn deficiency and leads to accretion of carbohydrates in leaves (Taheri *et al*., 2011).

Zn also improves nitrogen metabolism, synthesis of chlorophyll, proteins synthesis, photosynthesis and provides resistance against the stress conditions (Alloway, 2008; Mousavi, 2011; Hassan *et al*., 2020). Moreover, Zn also helps in maintaining the membrane integrity, structural arrangements of different macro-molecules and also helps in the transportion of ions (Cakmak, 2008; Dang *et al*., 2010). The Zn deficient conditions resulting in stunted growths, and leads to reduction in tiller production and chlorophyll synthesis (Hafeez *et al*., 2013). Zn also improves the quality of the crops, however, Zn deficiency reduces the quality and increased the plant's susceptibility to diseases and temperature injuries (Hafeez *et al*., 2013).

Roles of Zn in humans

Zn has a key role in human health, as Zn influences the different features of human immune system (HIS) (Shankar and Prasad, 1998). Zn is essential for the cells that mediated inborn immunity (Prasad, 2008). The Zn supplementation in Table 1 being reduces the anemia and intestinal disturbance (Skrovanek *et al*., 2014) and decrease diarrhea sternness in children's (Haque and Binder, 2006). The Zn supplementation in humans also improves the water and electrolyte absorption (Haque and Binder, 2006) and reduce the chances of disease (sickle cell) in humans and it also affect HIS by influencing the non-specific as well as attained immunity (Bao *et al*., 2008).

The shortage of Zn in human also cause different problems including the poor functioning of the immune system, skin problems, lower IQ levels, joints pain, memory loss, night blindness and problems related to sexual maturation (Maret and Sandstead, 2008; Wang and Busbe, 2005). However, Zn paucity in human beings can be decreased by using the bio-fortified crops enriched with micro-nutrients including Zn (Cakmak, 2002).

Reasons of Zn deficiency in humans

The deficiency of Zn in humans occurs owing to the utilization of foods having low Zn contents/Zn bio-availability and diseases that impaired the intestinal absorption and resulting in an increase in intestinal Zn losses (Maria *et al*., 2002). Moreover, foods with high PA contents and dietary fibers further inhibit Zn availability and retention in humans (Foster *et al*., 2012).

Factors associated with Zn deficiency in field crops

The deficiency of Zn has been reported around the globe from temperate to arid regions (Hafeez *et al*., 2013). Globally, all types of soils are suffering from Zn deficiency and the important factors responsible for the Zn deficiency in crops are discussed below.

Parent material: This is one of the most imperative factors which affects the Zn availability and determines the amount of Zn in soils. The concentration of Zn in soils depends upon the waethering of rocks from which soil is derived (Alloway, 2008; Rashid and Ryan, 2008). Likewise, soil produced from granite and quart rock has low Zn owing to the fact these soils are sandy in nature and have poor Zn holding capacity (Pendies and Pendies, 1992). Conversely, soils produced from the sedimentary rock are clay in nature and have higher Zn content owing to better cation exchange capacity (CEC) (Alloway, 2008; Pendies and Pendies, 1992).

Soil pH: Soil pH greatly affects the Zn availability from the soil solution and soils with higher pH has lower Zn availability compared to soil with lower pH (Sadeghzadeh, 2013). Globally, most soils have pH above 7 and solubility of Zn from the soil-solution decreases with increasing the soil pH. The upsurge in pH of soil ranging from 5-8 substantially decreases the Zn concentration from 10^{-4}-10^{-10} M in soil solution. The higher pH also decreased the Zn availability owing to the rapid fixation of Zn with soil particles, aluminum and iron oxide (Imtiaz, 1999).

Restricted root zone: The modernized agriculture substantially improved crop production; however, modern practices have many disadvantages. Likewise, the soil compaction owing to the utilization of weighty machines is also a main reason for the lower Zn accessibility for roots to plant. The soil compactions also reduced the penetration of roots and thus reduced the Zn uptake which in turn negatively affect the crop production and quality (Parlak and Parlak, 2011).

Soil organic matter: The organic matter (OM) considerably affect Zn availability and soils with low OM have Zn deficiency, whereas the soil with higher OM has the better Zn availability and solubility (Ahmad *et al*., 2012). Most stable constituents in soil OM are the humic substance, and these substances have a great attraction for the metal's ions including Zn (Kiekins, 1995). Nonetheless, soils with too much OM like peat soils also face Zn deficiency owing fixation of Zn on humic substance (Katyal and Randhawa, 1983).

Soil texture: The soil texture also has a remarkable impact on the Zn availability from soil to plant roots. The soils with calcareous nature have lower Zn availability owing rapid Zn fixation with soil-particles which therefore, reduced the Zn accessibility. Similarly, soils with course textures like sandy soils also has reduced Zn availability due to lower CEC and reactive sites (Hafeez *et al*., 2013). Conversely, fine textural soils like clay soils have higher CEC and reaction sites and therefore, they have higher Zn retaining capability (Singh *et al*., 2005). Thus, Zn scarcity is frequently arise in course textural soils as compared to fine texture soils (Singh *et al*., 2005).

Soil flooding: Soil flooding is also a major reason for Zn deficiency. Generally, Zn deficiency in flooded soils occurs owing to reactions of Zn with free sulphides (Mikkelsen and Shiou, 1977). Moreover, in flooded soil, Zn is also changed into sesquioxide precipitates, and theses sesquioxid binds the major part of applied Zn and therefore, reduce Zn availability (Singh and Abrol, 1986). The soil flooding also changed soil pH which also affects the Zn availability. The soil pH usually increased in flooded conditions which in turn reduced the Zn solubility (Renkou *et al*., 2003). The flooded conditions also reduced the Zn uptake due to participation of Zn with Fe and Al in soil solution (Moraghan and Mascagni, 1991; Rehman *et al*., 2012).

Soil temperature: The lower soil temperature (ST) also leads toward Zn scarcity in plants (Moraghan and

Mascagni, 1991). The microbial activities considerably reduced at low temperature which in turn reduced the release of Zn from OM. Moreover, lower temperature also reduced the rate of mineralization which also favors the Zn deficiency (Sadeghzadeh, 2013).

Zn interaction with other nutrients: The other soil nutrients also affect the rate of absorption, availability and utilization of Zn in plants. The interaction of Zn with P and nitrogen (N) are the most-wide spread problem which reduced the Zn availability. The interaction of Zn with P is the main cause of Zn paucity in crops. The phosphorus (P) fertilization affects the Zn availability from soils and P induces the Zn deficiency in plants (Singh *et al*., 1986). The higher P contents in soils either inherently or from the heavy doses of P application causes Zn deficiency (Alloway, 2008). The overdose of P also reduced the uptake of Zn owing to physiological imbalances caused in plants (Singh *et al*., 1986; Soltangheisi *et al*., 2014; Xie and Tang, 2019). The P induces the Zn deficiency occurs due to interaction of Zn with P, reduction in rate of Zn translocation from root to shoot, and imbalance between the P and Zn that causes metabolic disorder in plants (Olsen, 1972). The higher P concentration in soil owing to inherent P or heavy P application reduced the Zn translocation and availability to plants. Moreover, in soils Zn and P also co-precipitate as the $ZnO_3(PO_4)^2$ that decreases the soil Zn contents thus affect the Zn availability to plants (Brown *et al*., 1970). The increase in P application reduces the grain, Zn contents owing to the reduction in Zn uptake (Yang *et al*., 2011).

The N addition to the soil can increase/decrease Zn deficiency. The Zn and N have synergetic interactions, as the application of N improved the crop growth. However, N application in the soils deficient in Zn further enhanced the Zn deficiency owing to the absorption of Zn due to changes in pH of the soil (Sadeghzadeh, 2013). The interactions of macro-nutrients, like, Ca, Mg and K with Zn also inhibit the Zn absorption (Hafeez *et al*., 2013). Copper also affects the Zn availability, as Zn greatly inhibit the Cu absorption, whereas Cu affects the Zn re-distribution in plants (Loneragan and Webb, 1993). Increase in the Zn application reduces the Fe uptake and accumulation in plant parts, whereas increase in Fe concentration has a depressive impact on the Zn contents in plant parts (Norvell and Welch, 1993).

The possible strategies for combating Zn deficiency in humans

Supplementation: In this method, nutrients are given to the human being as a clinical treatment (Bouis and Welch, 2010). The Zn and Fe supplementations can be a quick solution during the times of higher Zn susceptibility (Gibson *et al*., 1998). Moreover, this practice is usually suggested in the time periods of acute Zn deficiency especially in pregnancy and in early childhoods (Stein *et al*., 2007; Allen, 1998). However, Zn supplementation is very costly and only suggested when we require a rapid response (Stein *et al*., 2007).

Fortification: The fortification involves the addition of minerals during the processing of foods to increase the nutrient contents to fulfil human needs. This strategy is recommended when Zn deficiency becomes endemic to target the particular areas (Maria *et al*., 2002). However, fortification is un-economical and typically restricted to only urban areas (Bouis and Welch, 2010; White and Broadley, 2005).

Food diversification/modification: This strategy is related to the changes in the selection of foods and making food plans more differentiated (White and Broadley, 2005). Moreover, this technique is applicable to those areas where the people have a good diversity of foods, however, this technique is not useable in developing countries where most of people live in rural areas (Bouis and Welch, 2010).

Bio-fortification: Bio-fortification is a promising Figure 3 to overcome the problem of micro-nutrition deficiency (Bouis and Welch, 2010). This technique involves the utilization of agronomic as well as breeding techniques to increase the quantity of desired nutrients in food crops (Bouis and Welch, 2010). It is an economical approach and can effortlessly target rural areas (FAO/WHO, 1998; White and Broadley, 2005). Additionally, it also substantially improved crop production in Zn deficit conditions (Bouis and Welch, 2010), and this approach is considered to be an permanent solution to solve the deficiency of Zn.

Genetic bio-fortification

This technique focused on development of genotypes with higher Zn and lower PA contents by using the breeding techniques. In breeding approach, architecture of plants changed to ensure the maximum accretion of micro-nutrients including the Fe and Zn in cereals (Bouis, 2003). Moreover, breeding techniques help the plants to absorb and accumulate desirable nutrients (Bouis, 2003). This is the best way to cope with Zn deficiency problem by exploring the natural variations amid the genotypes and by bringing the changes in genetic makeup of plants to enhance the quantity and bio-availability of desirable micro-nutrients in crops (Pfeiffer and McClafferty, 2007).

In past, most important objective of breeding programs was to increase the wheat production by improving biomass, harvest indexes, and shorting the plant height (Ortiz *et al*., 2007; Trethowan, 2007). Similarly, grain protein contents and composition of micro-nutrients were equally imperative, however, often ignored. Internation maize and wheat improvement center (CIMMYT) started research on wheat crop and discovered the largest variations among the genotypes for the Zn contents, disease resistance and distribute varieties with higher Zn and Fe contents (Cakmak, 2008). Previously, it was documented that Zn and Fe are an inherited traits (Trethowan *et al*., 2005; Trethowan, 2007). The modern, as well as wild germplasms showed that Zn and Fe have the a positive association, which indicates that physiological as well as the genetic factors are involved in the Zn and Fe decomposition in seeds (Cakmak *et al*., 2004; Gomez-Becerra *et al*., 2010). CIMMYT focused the breeding programs on the transformation of genes involved in increasing the grain Zn contents from *Triticum aestivum* ssp. spelta and *T. turgidum* ssp. Dicoccon.

The transgenic approach can be the best solution to improve the grain Zn contents (Cakmak, 2008). It has been documented that ZIP family proteins and Fe transport proteins improve the concentraion of micro-nutrients in grains (Schachtman and Barker, 1999; Eide, 2006). Moreover, these proteins, appreciably increased the uptake as well as the translocation of nutrients in the plant cells. Previously different authors reported that ferritin proteins effectively improved the uptake and Zn accretion in grains. Similarly, transformation of ferritin genes for soybean (*Glycine max*) to rice increased the Fe contents (Goto *et al*., 1999; Qu *et al*., 2005). Moreover, increase in the expression of ferritin proteins increased Fe and Zn contents in transgenic plants (Drakakaki *et al*., 2005). The multiplexing genes in rice significantly improved Zn and Fe uptake by modifying the different pathways of uptake. The NAM-B1 transcription factors that are present in rice and wheat and different other members of the poaceae family gives point of entrance to improve the protein, Fe and Zn contents. The greater understanding of targets of NAM-B1 and transportation steps are the vital points that can help to engineer the pattern of expression down-streaming targets in order to improve the grain Zn contents (Distelfeld *et al*., 2012). Modern technologies have helped us to develop the lines with NAM-B1 which helps to regulate the Zn and Fe uptakes (Cantu *et al*., 2011). Recently it was documented that Gpc-B1 locus from *Triticum diccocoides* encodes NAC transcriptions factor (NAM-B1) that appreciably improves the grain Zn by remobilizing Zn from plant leaves to grains (Uauy *et al*., 2006). However, the decrease in NAM genes expression declined the Fe and Zn accumulation in grains (Uauy *et al*., 2006).

The use of molecular markers is also a promising approach for the identifications of plants with higher Zn and Fe concentrations. Some authors identified that quantitative trait loci (QTL) associated with Zn in cereal crops and revealed that wild emmer wheat has the higher allelic diversities for the Fe and Zn (Xie and Nevo, 2008). Peleg *et al*. (2009) did the mapping of 82 QTLs for the ten diverse nutrients and they noticed that most of positive alleles are donated by wild emmer wheat. Moreover, TtNAM-B1 genes, originated from *T. dicoccoides* have been cloned and they substantially affected the Zn and Fe contents (Distelfeld *et al*., 2007). In diploid wheat, one QTL for Zn on chromosome A7 and two QTLs for Fe on chromosome on A2 have been identified (Tiwari *et al*., 2009). Similarly, a QTL in wheat (*T. monococum*) on chromosome 5B linked with Zn, Fe, Mn abd Cu has been also identified (Ozkan *et al*., 2006) and four QTLs for the grain Zn have been also identified in double haploid wheat for the grain Zn (Genc *et al*., 2009).

Constrains to genetic bio-fortification: There is no doubt that breeding practices are a sustainable and long-term approach to adress the problems of Zn deficiency. Nonetheless, this technique is time taking and substantially needs large resources as well as breeding activities (Cakmak, 2008). Moreover, success of any newly produced genotype largely depends upon the availability of Zn pools in the soil. Additionally, high pool of Zn should be maintained in soils for having the desirable grain Zn (Cakmak, 2008). The Zn deficiency is well-known problem around the globe and it has been documented more than 50% of soils used for the growing of cereals are Zn deficient and have low Zn availability (Cakmak, 2002). The Zn availability in soils depends upon soil pH and increase in pH (5.5-7.0) resulting in a reduction of more than 30-45 folds in Zn availability (Marschner, 1995).

Similarly, soil OM also affects the stability of newly produced genotypes. The OM play a considerable role in Zn Figure 4 and solubility from soil to the roots of plant (Obrador *et al*., 2003). The low OM in soil resulting in Zn deficiency, whereas the higher OM substantially improved the Zn availability (Hafeez *et al*., 2013). Most of soil used around the globe have lower OM which induced Zn deficiency in cereals (White and Zasoski, 1999; Alloway, 2004) and resulting in production of grains with poor Zn content. Therefore, genetic capabilities of newly evolved genotypes to absorb the required quantity of Zn from the soil to accumulate it in grains cannot be fully expressed in soils with lower Zn availability (Cakmak, 2008).

The transportation of Zn from the soil to roots occurs due to diffusion, therefore, soil moisture plays a crucial role in Zn diffusion from soil solution to roots (Cakmak, 2008). The drought stres adversely affects Zn nutrition in plants especially in those areas where the top soil is mostly dried in later parts of the growing period (Cakmak, 2008). Thus, in the aforementioned circumstances; agronomic bio-fortification can offer a rapid solution to cope with the problem of Zn deficiency (Bouis *et al*., 2011).

Agronomic bio-fortification

The fertilizers application susbtantially increased the grain Zn contents and it can be quick solution to combat the problem of Zn deficiency. Additionally, this approch also improves the Zn availability, crop growth, and grain yield and grain Zn concentration (Yadav *et al*., 2011).

Forms of Zn fertilizers: Zinc can be applied to crops in organic and as well as in inorganic form (Cakmak, 2008). The variable Zn fertilizers are using around the globe to alleviate Zn deficiency and to increase the grain Zn (Shahid *et al*., 2010). $ZnSO_4$ is mostly using Zn fertilizer owing to its higher solubility and lower cost (Shahid *et al*., 2010). Moreover, Zn can also be used in the forms of ZnO, ZnEDTA and Zn-oxysulfate. The agronomic efficiencies of Zn fertilizer with Zn-EDTA are quite higher, however, their higher cost mostly restricts their use for cereals production (Cakmak, 2008).

Methods of Zn application: The variable methods of Zn application are used globally, however, sucess of any application method largely depend upon the soil and socio-economic factors (Cakmak, 2009). Most of the farmers do not use the Zn for cereals production owing to economic problems in developing countries (Shahid *et al*., 2010). Moreover, poor information, financial constraints and un-availability of Zn products are the major causes for slower adaptation towards the Zn application (Bell and Dell, 2008). The methods of Zn application have a significant impact on the production and grain Zn contents. Therefore, method of application must be farmer friendly and economical (Shahid *et al*., 2010).

Seed priming: Seed priming (SP) refers to soaking of seeds in water prior to sowing until processes related to germinations start, but radical does not emerge (Farooq *et al*., 2009). The SP with Zn fertilizers significantly increased the wheat production and Zn uptake by the seeds (Kang and Okoro, 1976). Moreover, SP with $ZnSO_4$ (0.4%) effectively met the Zn needs of wheat and substantially increased the grain yield by more than 21% compared to no SP (Harris *et al*., 2007). Additionally, SP with Zn also improved seed Zn by more than 12% in wheat 29% in chickpea (Harris *et al*., 2007). Likewise, in another study, on rice, it was reported Zn priming was more economical and it led to a considerable increase in production and grain Zn (Slaton *et al*., 2005). Moreover, Yilmaz *et al*. (1997) noticed that SP with Zn effectively increased the wheat yield in Zn deficient soil, however, it had no impact on grain Zn. The SP with Zn is cost-effective, environment friendly and it resulting in a significant increase in the yield, and in rare cases, SP proved to a non-beneficial method (Farooq *et al*., 2012).

Soil application of Zn: The deficiency of Zn causes a considerable reduction in crop production and grain Zn contents nonetheless, Zn deficiency can be alleviated by Zn application. The soil application of nutrients is considered as the best method for the continuous nutrients supply when nutrients are needed in larger quantities. The high Zn application is mostly recommended for those crops which are quite sensitive against the Zn deficient conditions (Martens and wester, 1991). The banding placement of Zn requires 3 times less Zn requirements compared to broadcasting (Sarwar *et al*., 2017). Moreover, in soil application it is quite difficult to uniformly distribute the Zn on the soil which resulting in loss of nutrients and increases the cost of production (Savithri *et al*., 1999).

In an investigation, Cakmak *et al*. (2010) noticed that soil applied Zn was beneficial to increase the yield, however, soil application was less effective to improve the grain Zn compared to foliar application owing to low fertilizer use efficiency (FUE). Soil applied Zn also effectively improved the grain Zn contents, however, owing to lower FUE this method requires higher application of fertilizers (Singh, 2007). Zou *et al*. (2012) performed investigations in different countries and noticed that soil applied appreciable increased the grain yield, however, foliar feeding was superior for increasing the grain Zn compared to soil application. In another study, Chattha *et al*. (2017b) also claimed soil+foliar application was more effective to increase the grain production and Zn contents, compared to alone soil and foliar application.

Foliar application of Zn: The foliar feeding of micro-nutrients effectively improves the grain Zn owing to the fact in this application method the loss of nutrients is very low and nutrients are directly absorbed by plants (Johnson *et al*., 2005). The foliar-applied Zn is very effective in increasing the grain Zn and Zn bio-availability (Hussain *et al*., 2012; Zhang *et al*., 2012). Zinc is immobile in plants and Zn application in higher concentrations is also toxic for plants therefore, Zn should be used as repeated sprays to overcome Zn deficiency. The foliar applied Zn at the later growth stages significantly increased the grain Zn contents (Yilmaz *et al*., 1997). The Zn application in the form of SP and foliar feeding appreciable increased the grain Zn contents and the increase in grain Zn reduced the PA contents which in turn increases the Zn bio-availability (Cakmak, 2008).

The foliage feeding is most important and curative method for combating the Zn deficiency in cereals. Moreover, in arid as well as the semi-arid areas the foliar application is considered as a special application method due to increase in direct Zn absorption (Chapagan and Wiesman, 2004). The foliar feeding is considered as an economical method, however, sometimes it becomes un-economical owing to the repetition of spray during the crops growing period. The foliar feeding of Zn alone or in combination with other micronutrients improved yield traits, grain production and grain quality (Maralian, 2009).

The foliar feeding is more effective in increasing the Zn contents in grain and flour than the soil application, even though a small quantity of Zn is used in foliar feeding equated to soil applied Zn (Cakmak *et al*., 2010). Moreover, soil application is less effective due lower mobility of Zn and its quick fixation with soil particularly in alkaline and calcareous soils (Alloway, 2008). The soil application has another problem; the roots of wheat and applied Zn have diverse distributions in soil profile which declines the Zn uptake by roots of the plant (Holloway *et al*., 2010). Additionally, in field top soil layer is dry during later growth stages (reproductive stages) and root activity also declined during these stages owing to less allocation of photosynthates. Thus, Zn uptake from soil substantially decreased during this stage which in turn reduced the Zn accumulation in grains (Zhang *et al*. 2010). The foliar feeding of Zn during the later growth stages maintain the higher pool of Zn and contributes appreciably towards the bio-fortification of wheat crop (Cakmak, 2008; Cakmak *et al*., 2010).

Benefits of agronomic bio-fortification: The fertilization strategy is a quick and economical solution for combating the Zn deficiency (Bouis and Welch, 2010). The exogenously applied Zn not only increases the grain production and grain Zn but also resulting in Figure 5. The Zn application effectively reduced P uptake as well as the accretion in seeds (Soltangheisi *et al*., 2014). The PA is an important component that limit the Zn bio-availability (Gibson, 2007; Hotz and Gibson, 2007) and it has been documented that 60-85% P present in the form PA in seeds which limits the Zn bio-availability (Gibson, 2006). Thus, Zn application reduced the accretion of PA in seeds which in turns increases Zn bio-availability in humans (Cakmak, 2008).

The exogenous applied Zn increased the stand establishment (Yilmaz *et al*., 1997) and no Zn application resulting in poor stand establishment, vigor and poor final grain production (Yilmaz *et al*., 1998). Additionally, sowing of seeds with higher Zn concentration, improves the seed viability, seed vigor, and grain production and reduces seed rates for sowing of crops (Rengel and Graham, 1995; Cakmak, 2008). Moreover, high Zn contents, also protect the plants from pathogens and abiotic stresses owing to fact Zn protect the cell membrane and increase the activities of the anti-oxidant system (Cabot *et al*., 2019; Rehman *et al*., 2012).

Table 1: *Zn requirements for human beings.*

Age	Daily Zn requirement (mg/kg)
Infants of three months to 3 years children	3
4-7 years children	5
9-13 years children	8
Adult humans	15
Pregnant females	13
Females in lactation period	14

FAO/WHO, 2002; Hotz and Brown, 2004.

The success stories of agronomic bio-fortification in different countries during the recent years

The concentrating of Zn in wheat ranged from 5 to 12 mg/kg in Zn deficient soils (Erdal *et al*., 2002). Moreover, on the basis of different studies, it was reported that average Zn contents in wheat grain vary from 20 to 35 mg/kg (Rengel *et al*., 1999; Graham *et al*., 2007; Fardet *et al*., 2008; Cakmak *et al*., 2010; Cakmak and Kutman, 2018). These Zn concentrations are not sufficient to meet daily needs of people particularly for those people who consume a large quantity of cereals-based products. Thus, for having desirable effects on human health, agronomic bio-fortification should increase the grain Zn contents by more the 40-50 mg/kg (Cakmak, 2008; Zhao *et al*., 2009). The agronomic bio-fortification is widely using in different regions of the world and this strategy significantly increasing the grain Zn contents. The findings of different authors are described in the Table 2, which is indicating the success of this strategy. Moreover, in all discussed studies agronomic bio-fortification considerably increased the grain Zn contents to meet the needs of humans.

Concluding remarks and future prospects

The deficiency of Zn in humans causes many health problems, including stunted growth, lower IQ level, birth problem, poor sexual maturation and reduction in efficiency of the immune system. The use of cereal-based products lower in the Zn are main cause of Zn deficiency, particularly in developing countries. The bio-fortification strategies including breeding and fertilizer application can be a viable solution to combat the Zn deficiency in humans. Breeding techniques are long term process, not economical and require larger resources. Conversely, agronomic bio-fortification of wheat is a promising approach which appreciably enhanced the grain production and grain Zn up to the desired level to meet the human needs. The application of Zn fertilizers as seed priming, soil and foliar application and as well as soil+foliar application effectively enhanced the grain production and grain Zn contents. Various abiotic stresses negatively affect the growth and productivity of wheat crop, and these stresses also change the nutritional profiles of wheat grains. The seeds enriched with Zn contents can with stand the adverse conditions and show improved adaption and production under stress conditions. Moreover, in future more studies are direly needed to discover the efficient methods of Zn application for increasing the uptake and accumulation of Zn in wheat grains to meet human needs. Additionally, more studies should be focused on to increase the Zn concentration and bio-availability which can be accomplished by increasing the grain Zn contents and reducing the grain phytic acid contents.

Table 2: *The success stories of agronomic bio-fortification.*

Country	Year	Methods of Zn application					Reference
		Control	Seed priming	Soil application	Foliar application	Soil+Foliar application	
China	2012	37.1	NDA	38.9	46.01	NDA	(Yue *et al*., 2012)
China	2019	31.4	NDA	NDA	60.35	NDA	(Ning *et al*., 2019)
India	2010	24.9	NDA	52.0	64.8	65.3	(Zou *et al*., 2012)
India	2013	24.23	NDA	21.93	NDA	36.75	(Bharti *et al*., 2013)
Kazakhstan	2010	20.0	NDA	26.0	73.0	91.0	(Zou *et al*., 2012)
Pakistan	2017	33.7	39.45	46	60.15	62.7	(Chattha *et al*. 2017b)
Pakistan	2019	35.3	40.92	49.7	60.92	NDA	(Hassan et., 2019)
Turkey	2010	30.1	NDA	30.6	43.0	44.8	(Zou *et al*., 2012)
Turkey	2010	12	NDA	18	NDA	35	(Cakmak *et al*., 2010)
Zambia	2010	23.0	NDA	24.0	NDA	43.0	(Zou *et al*., 2012)

NDA: No data available.

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Novelty Statement

Zinc deficiency is wide spread problem in humans and plants. Therefore, in this review we discussed role of breeding and agronomic approaches to increase wheat grain Zn contents in order to reduce the Zn deficiency in crops and humans. Additionally, we also recommended future suggestions to improve the grain Zn contents of wheat for combating Zn deficiency.

Author's Contribution

Muhammad Umair Hassan: Conceived the idea and write original draft.
Muhammad Aamer, Muhammad Nawaz, Abdul Rehman, Talha Aslam and Ubaid Afzal: Writing, review and editing.
Bilal Ahmad Shahzad, Muhammad Ahsin Ayub and Faryal Ahmed: Review and editing.
Ma Qiaoying and Su Qitao: Writing, review and editing and literature collection.
Huang Guoqin: Conceived the idea and funding acquisition.

Conflict of interest
The authors have declared no conflict of interest.

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