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Biofortification and Human Health

Iyabo Christianah Oladipo* and Olatayo Shamsudeen Ishola

Department of Science Laboratory Technology,
Ladoke Akintola University of Technology, Ogbomoso 210214, Oyo State, Nigeria

**Corresponding author*

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A B S T R A C T

This review has focused on how biofortification can rescue the global micronutrient malnutrition. Various methods have been adopted and perhaps still in use to provide the body with nutrients that are not readily available in diet. Examples include, Food supplements and Diet alteration which involves eating different plant based food to provide these essential micronutrients to the body. Micronutrient deficiencies is usually referred to “hidden hunger” and it is the leading cause of many diseases in sub-Sahara Africa especially amongst the low income earners that cannot afford the food supplements that are readily available in the city. Biofortification is a process of improving nutritional profile of plant-based foods through *agronomic interventions*, *genetic engineering*, and *plant breeding*. This has proven effective in Biofortified Golden rice, Wheat, Cassava and Maize etc. In health, biofortified food/crops has no well documented adverse effect and as helped to ensure bioavailability of micronutrients such as Zinc, Iodine, Iron, Selenium, Carotenoids and Vitamin A which are essential for healthy living and if not present would have severe adverse effect. This review has explored different advantages of biofortification and provided wealth of knowledge that can be of immense benefits for farmers in crop cultivation using biofortification techniques and to encourage the consumption of biofortified food to end malnutrition globally. Biofortification is a technology with grave advantage to reduce or eradicate micronutrient deficiencies globally. Proper orientation and awareness should be administered to farmers and the masses to encourage the use of this technological advancement to help malnourished people globally. Also government policies should be such that to accommodate the use of biofortified crops and foster development in Agriculture sector. However, further research should encourage detecting and affirming any adverse health implications and environmental hazard.

Introduction

The world population that has micronutrient deficiencies can be estimated to be over 3billion. This is common among women, infant, and children mostly in the third world countries (Mason and Garcia, 1993).

Micronutrient deficiency is known as “hidden hunger” and affect one in three people worldwide (FAO, 2013). Micronutrient deficiencies may lead to serious illnesses. For example, it could lead to poor growth, intellectual impairments, prenatal complications, and risk of morbidity and mortality (Bailey *et al.,* 2015). Also, they aggravate infectious diseases including osteoporosis osteomalacia, thyroid deficiency, colorectal cancer, and cardiovascular diseases and thus greatly impact quality of life (Tulchinsky, 2010).

Deficiencies of Iron (Fe), Zinc (Zn), Folic acid, and β-carotene are global issues, but they are predominant in Asian, African, and Latin American countries (Tulchinsky 2010; Darnton-Hill *et al.*, 2006).

Micronutrient deficiency affect women globally, potentially leading to intrauterine growth restriction, low birth weight, protein malnutrition, and chronic energy deficit (Ahmed *et al.,* 2012). Deficiencies of Fe, I, Zn, and vitamin A, are common in Asia, Africa and Latin America which are responsible for about 12% of deaths globally among children under 5 years of age (Ahmed *et al.,* 2012).

Enriched or fortified food crops could address micronutrient deficiencies and thus provide a sustainable solution to global malnutrition issues and health conditions caused by malnutrition (Welch, 2002). Peas (*Pisum sativum L*.), chickpeas (*Cicer arietinum L*.), lentils (*Lens culinaris Medik*.), common beans (*Phaseolus vulgaris L.),* mung beans (*Vigna radiate L*.) and Rice (*Orizae sativa*) are examples of pulse crops grown globally (Duranti, 2006).

They are great sources of dietary proteins, complex carbohydrates, vitamins, and minerals required for human nutrition (Patterson *et al.,* 2009; Roy *et al.,* 2010; Ray *et al.,* 2014; Diapari *et al.,* 2014; Diapari *et al.,* 2015; Jha *et al.,* 2015). Pulse crops are common in everyday diets of people in many parts of the world since they are rich in proteins and amino acid carbohydrates (Duranti, 2006; Patterson *et al.,* 2009; Messina, 1999).

Biofortification is a process of breeding nutrient into to crops to improve their nutritional contents. This procedure is cost-effective and sustainable in delivering micronutrients into crops. With the rise in malnourished people around the world especially in the third world countries, there is need to foster biofortification technology to meet the daily demands of nutrients. Many industrial fortified foods and food supplements that are readily available in developed countries are out reach for people in third world countries especially amongst low income people. Biofortified foods cannot deliver as high level of minerals and vitamins per day as food supplements or industrially fortified foods, but they can help to ensure bioavailability of micronutrients which is essential for healthy living (Bouis *et al.,* 2011).

Micronutrients

These are essential nutrient that should be present in the every diet. These nutrients, although required in small amount are needed in the body to build immunity, Energy production, clotting and other functions. Some examples include: Zinc, Iron, Iodine, Selenium, Carotenoid and Vitamin A etc to mention a few.

Function of micronutrients

Iron (Fe)

Iron (Fe) is an indispensable nutrients and vital for various metabolic processes such as electron transport and deoxyribonucleic acid synthesis (Abbaspour *et al.,* 2014). In humans, Fe is an essential part of hemoglobin; oxygen transport and enzymes involved in electron transfer and oxidation-reductions (Hurrell, 1997; McDowell, 2003). Iron serves as a carrier in the hemoglobin of oxygen (Oxygenated Hemoglobin) to deficient cells and tissues. Iron deficiency is predominant amongst micronutrient deficiencies and it is the major contributor of anemia that affect more than two billion people globally (WHO, 2001; 2008). It can cause weakness due to loss of energy, drowsiness, and poor pregnancy; premature births, low birth weight of babies, slow growth and development in infants, and poor cognitive skills (Bailey *et al.,* 2015; Allen 2000; Lozof *et al.,* 2008).

Zinc (Zn)

Zinc (Zn) is also an important mineral required by humans. It is involved in many biological functions, such as wound healing through its involvement in membrane signaling systems in cell growth and proliferation (Prasad, 1996; MacDonald, 2000), protecting cells from damage by quenching reactive oxygen species (Rostan, 2002; Prasad *et al.,* 2004), and reducing risk of various cancerous diseases such as prostate and pancreatic cancer (Costello *et al.,* 2017). Deficiency of Zn can lead to weak immune system, continuous infections, mental illness, retarded growth rate and fertility (Roohani *et al.,* 2013).

Selenium (Se)

Selenium is an essential micronutrient which is required for growth and development. It protects the human body against infection, stress, and progressive cancer (Jansson, 1980; Rayman, 2005; Tinggi, 2008; Zeng, 2008). In humans, Se deficiency is associated with diseases, such as Keshan, Keshin-Beck, and myxedematous cretinism (Coppinger, 2001).

Iodine (I)

Iodine is the major constituent of the thyroid hormone. In humans, it is produced by the thyroid gland which is found around the neck region. The thyroid hormone secretes thyroxin and triodothyronine both which are essential for growth and metabolism in humans.

Deficiency of iodine causes hypothyroidism, goiter, cretinism, mental retardation, and retarded fertility and is accountable for prenatal death and infant mortality (Delange, 1994; WHO, 2007). Deficiency of iodine during pregnancy can impair brain development in offspring (Skeaf, 2011; Pearce *et al.,* 2016). Deficiency of iodine is a global issues affecting both developed and under developed countries (Pearce *et al.,* 2013; Cakmak *et al.,* 2017; Gonzali *et al.,* 2017). This could be as a result of low concentration of iron in the soils and cereal-based foods (Cakmak *et al.,* 2017).

Carotenoids

Carotenoids are pigments produced by plants. They give the plant color. Crop foods are sources of carotenoids because humans and animals cannot synthesize carotenoids (Fraser and Bramley, 2004). There are different types of carotenoids that are of benefit to humans. Example include, Lutein and zeaxanthin which prevent age-related degeneration (Fraser and Bramley, 2004; Olmedilla *et al.,* 2001). Lutein reduces the risk of cataracts and prevents cardiovascular disease (Moeller *et al.,* 2000; Alves-Rodrigues, 2004). Vitamin A is important for sharp vision, bone developments, and cell division in mammals (Stephens *et al.,* 1996). β-Cryptoxanthin initiates osteoblastic bone formation and inhibits osteoclastic bone resorption (Yamaguchi and Uchiyama, 2004), which makes an essential nutrient for bone formation. Carotenoids also have strong cancer-fighting properties (Tanaka *et al.,* 2012) and protect cellular organelles from oxidative damage by scavenging free radicals generated during various metabolic processes (Iannone *et al.,* 1998; Sujak *et al.,* 1999). Carotenoids are considered as Fe absorption promoters and hence improve bioavailability of Fe from plant-based foods (Welch, 2002).

Folates

Folates are B9 vitamins and are cofactors in various metabolic functions such which includes nucleotide biosynthesis and amino acid metabolism in the human body (Bailey and Gregory, 1999; Scott *et al.,* 2000), and are therefore required for human growth and development. In plants, folates are essential for biosynthesis of molecules including lignin, alkaloids, and chlorophyll (Hanson and Roje, 2001). Humans depend on plant and/or animal-based food as their sources folates (Scott *et al.,* 2000; Basset *et al.,* 2005). Deficiency of folates is connected to various chronic diseases, such as neural tube defects (Geisel, 2003), impaired cognitive function (Ramos *et al.,* 2005), Alzheimer's disease (Seshadri *et al.,* 2002), cardiovascular diseases (McCully, 2007), and certain types of cancers (Choi and Friso, 2005). Diets rich in folates are highly recommended during pregnancy as it reduces the risk of neural tube defects in newborns (Pitkin, 2007). Inadequate folate intake during pregnancy increases the risk of pre-term delivery and delay in fetal growth (Scholl and Johnsin, 2000).

Different approach to improve availability of micronutrients in diets

Food supplements

There are consumed inform of pills or solutions that contains different micronutrients. They are used when there are dietary deficiencies in the daily food consumed. Food supplements can be used as a short-term method to improve nutritional health and may be unsustainable for large populations. For example, folate levels in diets were achieved by the use of folic acid supplements (Blancquaert *et al.,* 2013; Shohag *et al.,* 2012; Hefni *et al.,* 2010). Also, this method was successful with vitamin A and zinc supplementation (Black *et al.,* 2008). Folic acid, iron, and zinc supplements have been helpful for children and pregnant women. However, this method is not cost-effective, especially for low-income consumers (Bailey *et al.,* 2015; Wiltgren *et al.,* 2015).

Food fortification

This is a process of adding essential nutrients, minerals and Vitamins into food to improve nutritional qualities and availability to low income consumers. This is done to selectively achieve nutrient availability with little or no health risk.

Food fortification with iron, ferrous sulfate, ferrous fumarate, ferric pyrophosphate, is usually accomplished through electrolytic iron powder compounds (WHO, 2006). Similarly, food folates level can be improved in diet with folic acid (Blancquaert *et al.,* 2013; Hefni *et al.,* 2010). Salt iodization was successfully achieved to reduce the occurence of goiter (Gómez-Galera *et al.,* 2010).

Types of food fortification

Mass fortification

This is the process of adding essential nutrient directly to consumables i.e Adding nutrient directly to food such as milk, cereals, oils and vegetable fats, milk, sugar, and condiments.

Targeted fortification

This is the process of adding sufficient amounts of essential micronutrients to provide large proportions of the daily needs through foods such as complementary foods for infants, foods for institutional programs such as those aimed at pre-school and school-aged children, and foods used under emergency situations.

Market driven fortification

This is a process by food manufacturing industries to increase the nutrient content and added value of a highly processed product with the purpose of attracting consumers and increasing sales.

Approach for food fortification

Mandatory and voluntary fortification

Mandatory fortification

Mandatory fortification occur when governments legally oblige food producers to fortify particular foods or categories of foods with specified micronutrients. Mandatory fortification, especially when supported by a properly resourced enforcement and information dissemination system, delivers a high level of certainty that the selected food(s) will be appropriately fortified and in constant supply.

Globally, mandatory regulations are most often applied to the fortification of food with micronutrients such as iodine, iron, vitamin A, and increasingly folic acid. Of these, the iodization of salt is probably the most widely adopted form of mandatory mass fortification (Allen *et al.*, 2006).

Voluntary food fortification

Fortification is described as voluntary when a food manufacturer freely chooses to fortify particular foods in response to permission given in food law, or under special circumstances, is encouraged by government to do so.

Some fortified nutrients

Iron fortification

Iron fortification is important because iron is one of the essential micronutrients to human. In plants, there is an iron storage protein called ferritin (Theil, 1987) which is a large protein with 24-subunits, with increased ferroxidase activities and is capable of storing up to 4500 iron atoms in a non-toxic complex form (Andrews *et al.*, 1992; Theil, 2003).

In soybean, the two types of ferritin proteins that are present are encoded by SoyferH1 and SoyferH2 ferritin genes (Kok, 2018). In human intestine absorption of iron from the soybean ferritin iron complex is achieved easily which is the reason soybean ferritin gene was considered to be the right gene for iron biofortification in rice (Theil, 2011).

Rice with high iron value is developed from molecular breeding and could be used as donor material in subsequent interbreeding programs for high iron local rice variety development. Vasconcelos *et al.,* (2003) successful achieved high iron IR68144 rice variety by expressing soybean ferritin gene, which increased iron concentration in polished rice (Vasconcelos *et al.*, 2003). Such interbreeding projects have a positive impact in developing countries which are one of the most consumers of rice grains to increase high iron rice varieties and help fight against micronutrient deficiencies.

Zinc fortification

Zinc deficiency can be alleviated by increasing dietary Zn intakes through supplements or by zinc biofortification of edible crops (White and Broadley, 2009). Crops can undergo biofortification through the application of Zn-fertilizers in the soil, which are then taken up by the plant. Alternatively, crop varieties have been developed which acquire more Zn from the soil and then collect it in the edible portions.

High concentrations of zinc can be achieved in roots and leaves with soil fertilizers and even with foliar zinc-fertilizers (Wei, 2012). However, zinc concentrations in fruits, seeds, and tubers are generally significantly lower. Plants generated through biotechnology can translocate zinc through the phloem and thus increase zinc concentrations to the edible portions of plant tissues.

Iodine fortification

There have been vast studies recorded on various methods such as foliar fertilization and application of salt in soil through irrigation water for biofortification of crops with iodine. The consumption of foods with low iodine concentration; grains, cereals is the major cause of iodine deficiency in humans (Gonzali *et al.,* 2003; Cakmak *et al.,* 2017; Fuge and Johnson, 2015). Compared to grain, biofortification of leafy vegetables can be easily achieved through translocation of the majority of iodine to xylem tissues, which is why majority of research is focused on iodine biofortification of vegetables instead of grains (Gonzali *et al.,* 2003; Mackowiak and Grossl, 1999; Medrano-Macias *et al.,* 2017).

Folic acid fortification

Folic acid is a monoglutamate synthetic compound, it is added to food to derive more chemically stable form than the natural vitamins (Blakley, 1969). Folic acid has been linked to many diseases including congenital abnormalities, which is why preventing folic acid deficiency is paramount. This can be achieved following 3 steps to improve folate status among target populations: pharmacological supplementation; which requires taking of folic acid tablets, fortification of staple foods with folic acid and the advice to increase intakes of natural folate food sources. Over the years, folic acid supplements have been generally accepted and it is use up till today, however, this drug is out of reach for rural dwellers with little income that are unlettered which is why folic acid fortification is considered to be the best approach to solving its deficiency.

Diet diversification/diet varieties

This is mostly carried out by household or by individuals to make available required nutrients for the body. It involves consuming different plant based food such as vegetables, fruits and whole grains. Dietary diversification also uses strategies at the household level, such as preparation of food that involves soaking, fermentation, and germination, as these enhance micronutrient content and bioavailability (Gibson and Hotz, 2001).

Fruits and Vegetable rich in nutrient promoters like; β- carotenoids, ascorbate when consumed would improves mineral uptake. For example, for iron improvement, foods rich in ascorbic acid is encouraged (Hurrell, 2002; WHO, 2004).

Microorganisms as growth enhancers

Several microorganisms that enable the growth and developments of plant is achieved through symbiotic relationships. They help in ensuring bioavailability of essential nutrients to plant and help in nutrient uptake. Examples includes: *Rhizobia*, *mycorrhizal fungi*, *actinomycetes*, and *diazotrophic* bacteria (FAO, 2019). Although these microbes are naturally present in the soil, their populations can be increased by seed inoculation or through agricultural management practices. Various plant growth-promoting microbes present in the soil including *Enterobacter*, *Bacillus*, and *Pseudomonas* can be used to increase the phytoavailability of micronutrients through the production of growth hormones, antibiotics, chitinases, and siderophores (Mahafee and Kloepper, 1994). Plant growth promoting microorganisms chelate iron through the production of siderophore compounds, solubilize phosphorus, and inhibit growth of pathogens (Panhwar *et al.*, 2012; Sreevidya *et al.*, 2016), thus playing a significant role in soil fertility and iron fortification. Plant growth promoting microbes are usually present in soil compost and decomposing organic materials and provide an economical and harmless method for increasing crop production and improve environmental and soil health (Gopalakrishnan *et al.,* 2016). Numerous studies have shown increased concentrations of iron, selenium, and zinc using microorganism inoculants through mycorrhizal associations (Rengel *et al.,* 1999; Smith and Read, 2008; Cavagnaro, 2008).

Enhancement of nitrogen fixation, plant growth, and grain yield have been reported in legumes including chickpeas, soybeans and peas by colonization of *Pseudomonas sp*., *Brevibacterium sp*., *Bacillus sp*., *Enterobacter sp*., and *Acinetobacter sp.* in their roots and nodules (Tokala *et al.*, 2002; Valverde *et al.*, 2006; Minorsky, 2008; Soe *et al.*, 2010; Gopalakrishnan *et al.,* 2015).

Biofortification process

Biofortification is a process of improving nutritional profile of plant-based foods through agronomic interventions, genetic engineering, and plant breeding.

Agronomic approaches

Biofortification through agronomic approaches is achieved through direct application mineral fertilizers to the soil, foliar fertilization (White and Broadley, 2009), and soil bio-inoculation of beneficial microorganisms.

Fertilizer

These are inorganic substances containing essential minerals that are applied to the soil to improve or to increase the micronutrient in the soil and thus plant quality. The availability of minerals in the soil is often low which could be due to soil leeching or erosion; hence, to improve the concentration of beneficial minerals in food crops, the application of mineral fertilizers with high solubility and mobility of the minerals is required (White and Broadley, 2009). This method has been used by farmers to fortify plants with mineral elements, but not organic nutrients, such as vitamins, which are synthesized by the plant itself.

This method has been used to introduce Selenium, Iodine, and Zinc, due to their high mobility in the soil as well as in the plant tissues (White and Broadley, 2009; 2005; Dai *et al.,* 2004; Hartikainen, 2005). For example, application of inorganic fertilizers containing sodium selenate increased Selenium concentration in various food items, fruits, vegetables, cereals, meat, dairy products, eggs, and fish in Finland (Eurola *et al.,* 1989; 1991).

Also, application of fertilizers with sodium selenate proved to be an effective way to increase Selenium intake in the human population (Alfthan *et al.,* 2015). This method has been used to enrich soil with Iodine and Zinc in China and Thailand (Winkler, 2011). However, Fe fertilization was not successful due to a low mobility of Fe in soil (Grusak, 1999).

The concentration of Zinc was increased in pea grains fields by soil application of Zinc fertilizer alone or combined form with foliar treatments. This method can be adopted for the biofortification of peas grains (Poblaciones *et al.,* 2016). The fertilization approach for biofortification typically requires frequent applications, and this could be harmful to the environment because it would increase the availability of other minerals to soil (White and Broadley, 2009; Winkler, 2011; Hirschi, 2009). Furthermore, soil composition is location bound, mineral mobility, bioavailability are also constraints in execute this strategy (Frossard *et al.*, 2000; Ismail *et al.,* 2007).

Genetic engineering

Biofortification through genetic engineering is another alternative when variation in the desired traits is not available naturally in the available germ plasm. A specific micronutrient does not naturally exist in crops, and modifications cannot be achieved through conventional breeding (Mayer *et al.*, 2008; Perez-Massot *et al.*, 2013). Along with increasing the concentration of micronutrients, Genetic engineering can also be targeted simultaneously for removal of anti-nutrients or inclusion of promoters that enhances the bioavailability of micronutrients (White 2009; Garg, *et al.,* 2018; Carvalho, 2013). This approach utilizes genes associated with various metabolic pathways operated in plants, and also genes from bacteria and other organisms (Christou and Twyman, 2004; Newell-McGlo, 2008).

Development of transgenic crops requires huge capital at the initial stage, but these transgenic crops through genetic modification can be a sustainable approach as a potential to target large populations, especially in developing countries (White, 2005; Hirschi, 2009; Heferon, 2016). Significant breakthrough has been recorded using this biofortification technique. For instance, enhanced accumulation of iron was noted in rice through expression of the iron-storage protein, ferritin (Goto *et al.,* 2000; Vasconcelos *et al.,* 2003). Genetically modified rice (golden rice) was developed to produce β-carotene (pro-vitamin-A) to combat vitamin-A deficiency (Paine *et al.*, 2005). Recently, transgenic multivitamin corn was produced by simultaneous modification of three distinct metabolic pathways to increase the levels of three vitamins, i.e., β-carotene (169-fold), ascorbate (6-fold), and folate (2-fold), in the endosperm, and this could open the door to developing nutritionally complete cereals (Naqvi *et al.*, 2009). Metabolic engineering was used to increase the folate concentration in tomato and rice (Blancquaert *et al.*, 2013; 2014). Recently, targeted gene editing technologies using artificial nucleases, zinc finger nucleases (ZFNs), transcription nucleases (TALENs), and the clustered regularly interspaced short palindromic repeat (CRISPR)/CRISPR-associated protein 9 (Cas9) systems open the door to the possibility of precisely modifying genes of interest, and thus can be applied for crop improvement (Bortesi and Fischer, 2015; Jaganathan *et al.*, 2018).

Plant breeding

In an attempt to provide micronutrients to plant based food, the use of fertilizers hasn't given the most desired result in a long term. Its effectiveness, and sustainability which isn't cost effective has given scientist the chance to explore the used of genetic engineering to produce genetic modified plants (GMO).

Genetically modified plants have desired traits; nutrients, and even in some cases traits to withstand adverse weather conditions without affecting outputs. This can be a technological approach for crop improvement; however, political views to GMOs in many countries, legal frame work to accept the commercialization of transgenic crops, along with expensive and extensive regulatory processes are the major hindrance of this method (Winkler, 2011; Inaba and Macer, 2004; Watanabe *et al.,* 2005). For example, golden rice has been available since the early 2000s which has the potential to deliver required vitamin A needed for low income people, but unfortunately it has not been commercially introduced in any country to date due to risk factors involved in the approval processes (Wesseler *et al.,* 2014; Bouis and Saltzman, 2017).

Some biofortified crops

Biofortified golden rice

Golden Rice, which is named due to its golden colour and its high β-carotene content, was generated using biotechnology to proffer viable solution to the deficiency of Vitamin A. This transgenic crop was engineered with two genes from different organisms (daffodil and the bacterium *Erwinia uredovoia*) which reconstitute the carotenoid biosynthetic pathway within the rice genome (Tang *et al.*, 2009). The Golden Rice technology, known as GR2, utilizes genes from two distinct pro-vitamin A pathways, including the substitution of the phytoene synthesis gene from maize for the analogous daffodil gene used in GR1 rice (Tang *et al.*, 2012; Shumskaya and Wurtzel, 2013).

Golden rice can produce β-carotene that would be up to 35 µg/g of dry rice (Tanumihardjo *et al.*, 2010). In an experiment to determine the nutritional benefits and bioavailability potentials of GR2, 130–200 g of deuterium-labeled Golden rice grown hydroponically in heavy water expressing 0.99–1.53 mg β-carotene and was fed to human volunteers.

Blood samples were taken at 36 days and exhibited 0.34–0.94 µg retinol, indicating that β-carotene derived from Golden rice is effectively converted to vitamin A at a rate of 500–800 µg retinol per 100 g uncooked Golden rice, which is close to the recommended daily allowance for children (Tanumihardjo *et al.*, 2010).

The vitamin A value of Golden rice, nontransformed spinach and β-carotene provided in oil to children were also compared, and the results of this study showed that the β carotene derived from Golden rice was just as effective as pure β-carotene and in fact more effective than β-carotene provided from spinach in providing vitamin A to children (Haskell, 2012). Together, these results suggest that Golden rice could be used to alleviate Vitamin A deficiency amongst rice-consuming populations (Xudong *et al.*, 2000). Golden Rice could be considered the first genetically engineered crop designed to combat malnutrition.

The advantage of a biofortified crop such as Golden Rice is that it could readily reach remote rural populations which have no access to food supplements (Van Loo-Bouwman *et al.*, 2014; Murray-Kolb *et al.*, 2002; De Steur *et al.*, 2012). Genetic modified rice that expresses essential amino acids such as free lysine has also been developed using RNAi silencing-based technologies. De Steur *et al.*, (2012) demonstrated that transgenic biofortified rice could be cost-effective in reducing folate deficiencies instead of investing in conventional supplementation programs. One of the short comings of biofortified rice is the presence of Phytic Acid.

This is known inhibitor of zinc absorption and other essential micronutrients like iron. It binds with zinc and iron to form an insoluble complex in the gastrointestinal walls that prevents mineral absorption. The presence of phytic acid in cereals such as wheat, corn and rice could have serious nutritional consequences (Brnić *et al.*, 2014; Gao *et al.*, 2013; Ali *et al.*, 2013).

The application of recombinant microbial phytase helps to reduce the level of phytic acid in grain (Li *et al.*, 2010). Several methods have been developed to lower the presence of phytic acid in rice and since microbial phytase has proven effective in lowering it and hence increase mineral availability and uptake.

Transgenic corn expressing phytase has been derived using *Aspergillus niger*. These transgenic varieties were found to be as efficient at lowering phytic acid levels as conventional corn that was supplemented with commercially used phytases (Muzhingi *et al.,* 2011).

Recently, cereal mutants exhibiting a low phytic acid (lpa) phenotype have also been developed in rice, wheat and maize (Howe and Tanumihardjo, 2006).

Biofortified maize and cassava

Maize has also been genetically modified to provide essential micronutrients needed for a healthy life. Li *et al.,* (2010) measured the triglycerol-rich lipoprotein proportion in blood from North American female volunteers who consumed biofortified maize porridge. In this case, the authors found a vitamin A equivalence value of β-carotene in biofortified maize to be 3.1-fold higher than in conventional white porridge maize (Mugode *et al.,* 2014). A similar study using Zimbabwean men found biofortified yellow maize porridge provides an equivalence of 40%–50% of the US recommended Dietary Allowance of vitamin A (Jeong *et al.,* 2008). Another study using Mongolian gerbils who were fed biofortified maize containing β-cryptoxanthin resulted in a more efficient bioconversion than the use of a β-carotene supplement (Jeong *et al.,* 2008). These results shows that biofortification of maize has increased the needed micronutrients through the use of biotechnology as an effective approach to solve micronutrient deficiencies. A vitamin fortified maize which expresses high amounts of β-carotene, ascorbate, and folate has been developed in the endosperm through metabolic engineering (Mugode *et al.,* 2014). The transgenic kernels contained 169-fold the normal amount of β-carotene, 6-fold the normal amount of ascorbate, and double the normal amount of folate as conventionally-bred crops. Crops such as these can offer far more nutritionally complete meals for malnutrition in Africa (Jeong *et al.,* 2008).

Biofortified cassava

Several projects have been enacted to enrich cassava to increase it functionality and usage. Cassava with high levels of β-carotene has been produced and fed to healthy volunteers in the form of porridge (Naqvi *et al.,* 2009). Blood samples taken from these volunteers demonstrated that biofortified cassava increases β-carotene and retinyl palmitate TRL plasma concentrations (Naqvi *et al.,* 2009). These indicate that, biofortified cassava can effectively combat the micronutrient deficiencies in sub-Saharan Africa. Cassava roots have show reduced level of proteins and minerals. By reducing levels of the toxin cyanogens in roots, iron root uptake and protein accumulation in cassava could be enhanced (Sayre *et al.,* 2011).

Biofortified wheat

Wheat has been genetically modified to increase its level of lysine, and essential amino acid. Biofortified wheat provides a better option for the fraction of populations who are gluten intolerant, and can also provide higher levels of micronutrients, such as iron and zinc, to those in developing countries who use wheat as a staple food (Gil-Humanes *et al.,* 2014; Borrill *et al.,* 2014; Hotz, 2009). Recently, wheat has been under studied to improve the presence of Zinc to help countries or communities that largely consume grain crops such as wheat. Zinc is known to be the leading causes of diseases in low-income countries. However, due to insufficient Zinc in the soil, Nitrogen management has enhanced the availability of

Zinc in soil and also increased its uptake by plant roots. Radiolabelled ^{65}Zn has been shown to be taken up by plant roots, translocated to shoots and to accumulate in the wheat grain (Grillet *et al.,* 2014; Cakmak, 2009). Erenoglu *et al.,* (2011) demonstrated that by increasing the nitrogen content in soil would stimulate the root-to-shoot translocation of Zinc and enhance its accumulation in wheat grain, possibly by increasing the abundance of transporter proteins in the presence of nitrogen (Cakmak *et al.,* 2010).

Health implications of biofortification

There have been numerous concerns about the consumption of biofortified crops majority due to misinformation or inadequate awareness. While Biofortified crops which have been nutritionally enhanced through biotechnology could clearly play a role in eradicating malnutrition for developing countries, a number of issues must still be addressed (Schubert, 2008). Prior to marketing they require the same regulatory approval, including an assessment of their safety, as is needed for single transformation events (Christer *et al.,* 2011). In the European Union (EU), Genetically Modified (GM) maize and oilseed rape stacked events have already been evaluated with respect to their risks factor in the environment and for human or animal health (Siró *et al.,* 2008). At least about three countries in Africa (South Africa, Burkina Faso and Sudan) have commercialized GM cotton and maize with great success, and several other African countries are undergoing field trials and taking steps toward commercializing GM foods. New GM crops that could help poor African farmers, such as insect resistant cowpea, are also under research and development (De Schrijvera *et al.,* 2007). So far, the health implications of biofortified foods have been of grave importance. They have been able to replenish deficiencies of micronutrients in malnourished populace in sub-Sahara Africa. For example, the development and introduction of the biofortified orange sweet potato with β-carotene increased vitamin A intake among children and women in Mozambique (Hotz *et al.,* 2012) and Uganda (Hotz *et al.,* 2012), also maize biofortified with pro-vitamin A increased the concentration of vitamin A in children between the ages of 5-7years in Zambia who consumed it for three months (Gannon *et al.,* 2014). Similarly, serum ferritin and total body iron were improved in iron-deficient adolescent boys and girls from Maharashtra, India, who consumed biofortified pearl millet flat bread with iron for four months (Finkelstein *et al.,* 2015). The vast majority of crops which have been approved for commercialization are pest resistance and herbicide tolerance crops (FAO, 2015). In the industrialized world, plants with improved fatty acid content, such as omega-3-Fatty Acid are now available (Butell *et al.,* 2008).

Biofortification and the future

Biofortified crops have gained publicity in sub-Saharan Africa, example includes Orange Fleshed Sweet Potatoes, Cassava and Maize rich in carotenes as well as high-iron pearl millet beans (HarvestPlus, 2011). All crops were developed in the context of the HarvestPlus Challenge Program of the Consultative Group for International Agricultural Research (HarvestPlus, 2011). Also, there are over 150 biofortified varieties of crops which have been released in 30 countries, and are consumed by more than 20 million people in developing countries (Bouis *et al.,* 2017).

Increased micronutrient density and high yields are prerequisites for effective biofortification, and these crops must be adopted by farmers and accepted by the target population (Bouis *et al.,* 2011). There are some major challenges facing the distribution and general acceptability of biofortified crops. They are: Building consumer capacity, introducing biofortified traits into public plant breeding programs and policies (Bouis *et al.,* 2017).

Factors such as genetic diversity, the reduction of antinutrients (especially phytate and polyphenols), and increasing the concentration of promoters such as cysteine, lysine, methionine and ascorbic acid which enhance the absorption of essential minerals, are essential for the success of biofortification strategies (White and Broadley, 2009; Bouis, 2003).

Genetic variation in the plant gene pool, development time for desired trait, and the dependence on the phyto availability of the mineral nutrients in the soil are limitations for conventional breeding approach (Carvalho and Vasconcelo, 2013).

To make biofortification effective in solving malnutrition in Africa and beyond, focus should be driven to bioavailability of micronutrients to humans. This can be achieved by increasing the concentration of promoters that stimulate the absorption of minerals and by reducing the concentrations of antinutrients that interfere with absorption in humans (White and Broadley, 2009; Bouis, 2003). Some examples of such promoters include Vitamin E, vitamin D, vitamin C, choline, niacine, and provitamin A and stimulate the absorption of Selenium, Calcium Phosphorus, Iron, Zinc, methionine, and tryptophan (Brinch-Pedersen *et al.,* 2007). Certain antinutrients including phytate and some polyphenols reduce the bioavailability of micronutrients in crops (White and Broadley, 2009; Bouis, 2003). Phytate is form of phosphorus stored in seed, is not digested by humans or monogastric animals (Warkentin *et al.,* 2012). During digestion, it has the ability to bind to iron and zinc and thus restrict their absorption bracket (Liu *et al.,* 2015). The concentration of phytate can be controlled by identifying low phytate lines by germplasm screening (Shewry and Ward, 2012), manipulating the biosynthesis of phytate via mutation of a myo-inositol kinase (MIK) gene (Shi *et al.,* 2005), and over expressing phytase, a phytate degrading enzyme (Brinch-Pedersen *et al.,* 2002).

Polyphenols is secondary metabolites which include flavonoids and proanthocyanidins (Vermeris *et al.,* 2006) provides protection against various fungal pathogens (Lattanzio *et al.,* 2006). They are natural sources of antioxidants in the human diet and are present in fruits, vegetables, cereals, and legumes (Manach *et al.,* 2004; Scalbert *et al.,* 2005).

Postharvest processing can play an important role in utilizing biofortified crops, as a significant amount of minerals from the diet can be lost by milling or polishing (Gregorio *et al.,* 2000) and cooking. Therefore biofortified crops should be made in such a way to retain the micronutrient concentration in edible seeds and their absorption by the consumer after processing and cooking (Haas *et al.,* 2005). Iodization of salt was not enough to overcome iodine deficiency due to several factors such as the unavailability of iodized salt for all households, the volatilization of iodine during cooking, and low consumption rate due to health issues (Cakmak *et al.,* 2017; White and Broadley, 2009; 2000; Winger and Konig, 2008). Hence, further research is needed to identify traits that control uptake, mobilization, and retention of iodine in the plant, and these can be manipulated in plant breeding or using a genetic engineering approach during biofortification (Gonzali *et al.,* 2017).

Micronutrients deficiencies is the causes of many diseases in Africa, it is popularly referred to as hidden hunger. Several interventions have been applied to curb the extent of this malnutrition. Biofortification through plant breeding have proven to be very effective in combating micronutrient deficiencies and it is generally accepted. Biofortification through genetic modification is another effective approach but health concerns by regulatory bodies have hindered the commercialization and public acceptance of this technology. Biofortification is also a cost effective approach for bioavailability of nutrients because it is one time investment as plant seedlings can be reproduced across the years for farmers during planting season. Also farmers sensitization, awareness, orientation and reorientation for acceptance for both farmers and the populace should be adopted as biofortification as proven to be very effective in making available micronutrients at all times.

Furthermore, research should be extended to determining the bio-safety, bio-hazard to human health and environments. Government policies should be adjusted to accommodate the research, developments and usage of Biofortified crops, through plant breeding and genetic engineering.

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