Review article

Biofortification as a solution for addressing nutrient deficiencies and malnutrition

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ABSTRACT

Malnutrition, defined as both undernutrition and overnutrition, is a major global health concern affecting millions of people. One possible way to address nutrient deficiency and combat malnutrition is through biofortification. A comprehensive review of the literature was conducted to explore the current state of biofortification research, including techniques, applications, effectiveness and challenges. Biofortification is a promising strategy for enhancing the nutritional condition of at-risk populations. Biofortified varieties of basic crops, including rice, wheat, maize and beans, with elevated amounts of vital micronutrients, such as iron, zinc, vitamin A and vitamin C, have been successfully developed using conventional and advanced technologies. Additionally, the ability to specifically modify crop genomes to improve their nutritional profiles has been made possible by recent developments in genetic engineering, such as CRISPR-Cas9 technology. The health conditions of people have been shown to improve and nutrient deficiencies were reduced when biofortified crops were grown. Particularly in environments with limited resources, biofortification showed considerable promise as a long-term and economical solution to nutrient shortages and malnutrition. To fully exploit the potential of biofortified crops to enhance public health and global nutrition, issues such as consumer acceptance, regulatory permitting and production and distribution scaling up need to be resolved. Collaboration among governments, researchers, non-governmental organizations and the private sector is essential to overcome these challenges and promote the widespread adoption of biofortification as a key part of global food security and nutrition strategies.

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1. Introduction

Malnutrition in mothers and children causes 45 percent of all deaths in children under five years of age in low- and middle-income (LMIC) nations [1]. Hidden hunger is one of the most pervasive issues in LMICs, characterized by a persistent lack of essential nutrients, such as vitamins and minerals, in the diet [2]. Millions of people are affected by micronutrient deficiencies such as vitamin A, iron and zinc. Vitamin A and iron deficiencies account for 7.3 percent of the global illness burden, ranking among the top 15 causes [3,4]. According to World Health Organization (WHO) data, approximately 40 percent of children and pregnant women worldwide are anemic [5]. The four main strategies adopted by the United Nations Food and Agriculture Organization (FAO) and WHO to boost dietary consumption are food micronutrient supplementation, fortification, disease management measures and nutrition education. In recent years, it has been demonstrated that dietary diversity can be increased, and micronutrient deficiencies can be successfully reduced by fortifying staple foods [6].

Different fortification techniques have emerged as measures to enhance nutritional quality and advocate public health by minimizing the possibility of negative health effects. Methods such as agricultural practices, conventional plant breeding and contemporary biotechnology are well-known for fortification. Compared to conventional fortification, biofortification aims to increase the nutritional status of crops during plant development rather than agricultural processing [7,8]. There has been progressive development in the techniques applied for biofortification since 2001. Conventional breeding methods include applying mineral fertilizers through soil or foliar sprays, using microbes to increase nutrient uptake and conventionally crossing plants to obtain the correct gene combination for balanced bioavailability and nutrient uptake [7,8]. On the other hand, the discovery of new breeding techniques (NBTs, such as Transgenic breeding, RNA interference (RNAi) and genome editing) involves the development of balanced nutritional profiles in mutant plants by gene transfer, over expression of gene, gene editing and silencing from other species [8]. With advancements in targeted gene editing technologies, it is now possible to precisely modify the gene of interest. It uses artificial nucleases, zinc finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs) and the clustered regularly interspaced short palindromic repeat (CRISPR)/CRISPR-associated protein 9 (Cas9) system (CRISPR/Cas9) to modify the gene of interest [9,10].

Despite such advancements in biofortification techniques, there are still several obstacles, including inadequate public-private collaborations, laws and regulations. Genetic and agronomic biofortification is a practical method for enhancing dietary nutritional content. The advantages of genetic biofortification (ZIP transporters) are constrained by their time-consuming processes and the limited variety of targeted crop gene pools. Large-sized inorganic fertilizers suffer from volatilization and leaching losses, whereas organic fertilizers in agronomic biofortification confront the challenge of longer periods of nutrient release and lower mineral content [11,12]. To overcome these limitations, nanotechnology has emerged. Khan et al. assessed the potential of nanotechnology and Rasheed et al. used nano-based nutrients and nanoparticles to stimulate plant growth. Nano-based approaches were proved successful in addressing climate change and abiotic stress resilience [12,13]. Researchers have used several machine learning algorithms and omics tools to further enhance the efficiency of genetically modified crops [14]. This review explores primary techniques, from conventional breeding methods to the most contemporary CRISPR-Cas9 technology, which is used to improve the nutritional content of staple crops. It discusses how these technologies are helpful in enriching micronutrients in fruits, vegetables, cereals and oil seeds in battle with hidden hunger. Therefore, biofortification might be a good choice for addressing populations in which supplementary and
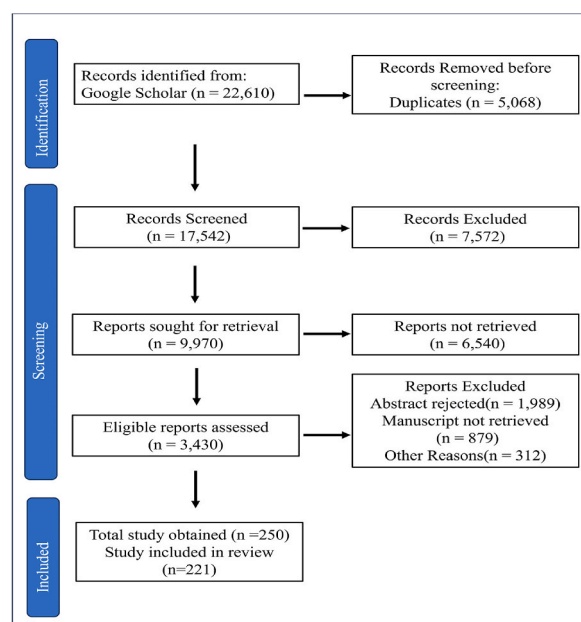

Fig. 1. Approaches for data collection.

traditional fortification approaches are challenging to apply or are limited.

2. Approaches for data collection

For data collection, a systematic review was conducted using Google Scholar. The initial search was based on various keywords, resulting in a total of 22,613 papers. A total of 13,600 articles were obtained using the keywords ("Nutrient deficiency" and "Malnutrition"). The data was further refined using more specific keywords such as ("Nutrient deficiency" and "Malnutrition" and "Biofortification"), ("Nutrient deficiency" and "Malnutrition" and "Biofortification" and "health"), ("Nutrient deficiency" and "Malnutrition" and "health"), ("Nutrient deficiency" and "Malnutrition" and "health" and "Biofortification" and "Agriculture") and ("Nutrient deficiency" and "Malnutrition" and "health" and "Biofortification" and "Agriculture" and "Genetic Engineering") which resulted in 945, 914, 7010, 840 and 303 articles respectively. A detailed overview of the screening process is shown in Fig. 1.

3. Techniques of biofortification

3.1. Agronomical biofortification

The micronutrient profiles of edible crops can be improved through agronomic biofortification. The goal of this study was to increase the nutritional content of the edible parts of crops by applying strategies such as zinc (foliar using ZnSO4), iodine (using iodate or iodide in soil) and selenium (as selenite) applications. Foliar feeding is a quick and simple way to improve nutrient uptake and strengthen micronutrients in plants, like copper (Cu), zinc (Zn) and iron (Fe). Numerous studies have revealed that higher concentrations of zinc (Zn), copper (Cu), iron (Fe) and selenium (Se) in agricultural plants are a result of mycorrhizal relationships. It has been noted that arbuscular mycorrhizal (AM) fungi improve the uptake and efficiency of micronutrients like Fe, Cu and Zn. Onions have also been shown to contain more sulfur owing to the sulfur-oxidizing bacteria [15].

3.2. Classical breeding approach

The practice of improving, expanding, or generating plants with desired qualities through genetic changes that are advantageous to humans is referred to as plant breeding. To achieve this, ideal parent plants were chosen and successful mating between them was performed. The resulting progeny were weeded out to choose only those who had mastered the required traits [16]. Traditionally, this strategy has been used to increase the micronutrient content of provitamin A, iron and zinc to satisfy the daily demands of pregnant women and children [17]. The provitamin target concentrations for sweet potatoes and maize were 32 ppm and 15 ppm, respectively, as part of the Harvest Plus breeding program. Whereas the Zn targets for rice and maize were established at 28 ppm and 37 ppm, respectively, the target Fe for beans and pearl millet were set at 94 ppm and 77 ppm, respectively. The stand ard for high uptake of micronutrient content and successful crop breeding is the sum of micronutrient content and their combination for each crop [18]. Through the creation of an interdisciplinary network of cooperating institutions, Harvest Plus is still working to produce a range of crops with enhanced levels of Zn, Fe and provitamin A [18]. The World Health Organization (WHO) and Consultative Group on International Agricultural Research (CGIAR) are two well-known international organizations that have been actively working to create biofortified plant types with higher nutritional values. Developing crops with higher yields and improved nutritional values is their main goal [19]. Biofortification has not yielded fruitful results because the intake and excretion of nutrients in the edible portion of the crop are controlled by polygenes, which have very little impact [20].

3.3. Metabolic engineering

Nutraceuticals and micronutrients perform key functions in human health to regulate different metabolic pathways and provide immunity, but unfortunately, they are not present in sufficient amounts in staple crops [21]. Conventional germplasm breeding lacks significant outcomes in the improvement of crop nutrient content; thus, researchers have focused on new approaches called metabolic engineering. Metabolic engineering has introduced alternative and successful methods to produce biofortified crops by simply changing genes or gene products [22]. This implies that gene modulation or gene networks improve the expression level and target compound production under *in-vivo* conditions [23]. Some integrated approaches involve a combination of metabolic engineering and synthetic biology for the creation and development of new biosynthetic cycles or pathways to induce the production of new compounds in the organism [24], called synthetic metabolic engineering [25]. Therefore, by using metabolic engineering along with other integrated approaches, the metabolic levels in crops can be increased [26]. Some examples of biofortified crops using metabolic engineering are the β–carotene-enriched 'Golden Rice' [27], the 'Purple Tomatoes 'enriched with anthocyanin [28] and the 'STAR rice' enriched with astaxanthin [29]. Algal genes bhy (β-carotene hydroxylase) and Crbkt (β-carotene ketolase) are widely used in plant metabolic engineering to produce astaxanthin. To enable astaxanthin production in tobacco plants. Li et al. explored the insertion of the HpCrtO gene, a β-carotene ketolase derived from *H. pluvialis*. In a related study, chloroplast metabolic engineering was used to express two genes of similar interest, CrtZ and CrtW, in tobacco leaves. Using this method, they collected approximately 5.45 mg/g dry weight of astaxanthin [30].

In a ground-breaking study, it was discovered that tomato plants produce 16.1 mg/g dry weight of astaxanthin. Co-expression of Hpbhy from *H. pluvialis* and Crbkt from *Chlamydomonas reinhardtii* resulted in this successful outcome [31]. Maize is a major staple cereal crop worldwide and provides a cost-effective foundation for astaxanthin seed production. Farré et al. found that transgenic

maize with *Crbkt* and *BrCrtZ* yielded 16.77 mg/kg dry weight astaxanthin inside its endosperm after being transformed using a particle delivery technique [32]. After four synthetic genes relevant to carotene production were inserted into aSTARice, the rice endosperm accumulated 16.23 mg/kg DW of astaxanthin [29]. The rice variety, also known as "Golden Rice," was developed to biosynthesize the precursor of vitamin A and β-carotene. This novel biofortified rice shows promise for the treatment of vitamin A deficiency, a major global public health concern. It is expected that Golden Rice will play a much bigger role in preventing vitamin A deficiency because it contains considerably more β-carotene. One of the two genes utilized to create Golden Rice, the daffodil gene encoding phytoene synthase (psy), is thought to represent the limiting step in β-carotene accumulation [33]. After carrying out comprehensive experiments on diverse plant phytoene synthase (psy) genes, Paine et al. discovered a maize psy gene that significantly increased carotenoid deposition in a model plant system [34]. Following this, "Golden Rice 2″ was produced by combining this gene with the *Erwinia redovora* carotene desaturase (crtI) utilized in the initial production of Golden Rice [35]. Compared with the original Golden Rice, the modified enhanced variety had a 23-fold increase in total carotenoids and preferential accumulation of β-carotene [36].

Anthocyanins form a class of flavonoids that are present in vegetables and fruits, have significant antioxidant properties and play an important role in human health [37]. The biosynthetic pathway of anthocyanins is well studied and understood. The information gained from the study of this biosynthetic pathway can be utilized for the biofortification of crops with anthocyanin and flavonoids using metabolic engineering.

Carotenoids also form an important phytonutrient required by humans to promote good health. For instance, astaxanthin, one of the strongest antioxidants found in fruits and vegetables, is present in very small quantities in cereal grains and β-carotene is a biosynthetic precursor of vitamins [38]. Therefore, it is necessary to fortify cereal grains using these carotenoids.

Like flavonoids, the carotenoid biosynthetic pathway well studied and understood, their level can also be increased in crop grains using metabolic engineering as has been done in 'Golden Rice' [39]. Similarly, crops are also biofortified with other micronutrients like omega 3, vitamins, iron and zinc.

3.4. Genetic engineering

Genetic engineering (GE) is an innovative approach to reduce the time for crop improvement compared to traditional approaches and produces high-yielding crops within 2–3 years [16]. In this approach, foreign genetic material is integrated into the targeted host cell body to produce chimeric DNA, termed transgenic, bioengineered, or genetically modified (GM) products [40]. The development of transgenic crops has been possible through the injection of new genes, overexpression of already expressed genes, reduction in the level of a gene's expression, or disruption of inhibitor gene production pathways. Therefore, GE has the potential to boost the phytonutrient content in the food supply, minimizing the risk of numerous chronic diseases [41]. In the nutraceutical food industry, fortifying staple foods with vital antioxidant components, such as vitamins E and C and supplementing leisure foods with health-promoting antioxidants, such as flavonoids, merge two disparate ecosystems. This combination of functional and recreational food industries promotes health and nutrition benefits [42]. Engineering initiatives to increase the availability of organic antioxidants, including carotenoids, tocochromanols, ascorbic acid and flavonoids, include altering endogenous plant metabolism [43]. A variety of tactics can be used to accomplish this by following the strategies, including (a) modifying the activity of one or more important enzymes or numerous enzymes involved in rate-limiting steps in target processes; (b) upstream precursors can increase the flow through the pathway by overexpressing the enzyme that catalyzes the first committed step of the target pathway; (c) blocking and relieving feedback inhibition at route branch points via RNA interference or antisense; and (d) increasing the number of sink compartments available for storing target chemicals [44].

"Golden Rice" is the most well-known example of biofortification by genetic mutation, as well as the most advanced. Ye et al. documented the development of transgenic rice that produced both the daffodil phytoene synthase (Psy) gene and the bacterial phytoene desaturase (CrtI) gene under the control of a rice glutelin promoter unique to the endosperm [45]. The development and field testing of PVA-biofortified transgenic Cavendish bananas took place in Australia to achieve an objective level of 20 g/g dry weight (dw)-carotene equivalent (CE). When the phytoene synthase 2a (MtPsy2a) gene from the Fe'i banana was produced, PVA levels were higher than the desired amount, with one line reaching 55 g/g dw-CE. Although many lines had undesired traits, 'Golden Rice 2′ was made by overexpressing the maize phytoene synthase 1 (ZmPsy1) gene, which led to higher fruit PVA levels [46].

3.5. Clustered regularly interspaced short palindromic repeats (CRISPR) technology

A genome-editing method called CRISPR uses editing effectiveness to alter the nutrient make-up of crops. In recent years, CRISPR has been the most focused technology that involves gene editing with desirable expression products [47]. In this technique, gene editing is performed at a specific location or gene locus to alter the gene expression product without inherited errors in the next generation. Modification of the genetic material can be performed simply by deletions, insertions, large fragment substitutions, or single nucleotide substitutions. The guide RNA (gRNA) forms CRISPR RNA (crRNA), which has a spacer sequence of 20 nt fragments complementary to the target genes, serially arranged with PAM (Protospacer Adjacent Motif) in the gene of interest. Furthermore, Cas9 nuclease generates transactivating crRNA (trancrRNA) formation and double-strand breaks (DSBs) under the guidance of gRNA at three base pairs upstream of the protospacer adjacent motif (PAM). These DSBs can be repaired by two mechanisms: Non-Homologous End Joining (NHEJ), which generally results in the introduction of indels adjacent to the cleavage site, or by Homologous Directed Recombination (HDR), which carries out the repair of breaks either by using homologous flanking sequences or by employing exogenous repair templates, resulting in large inserts or replacement of fragments [48]. Hence, HDR can be stimulated by the introduction of an exogenous DNA repair template, which leads to the addition of the repair exogenous template into the region of the

targeted genome. Large-scale studies on the biofortification of Indica and Japonica rice varieties with significant amounts of Fe, Zn and carotenoids with a low level of phytate have been conducted [49]. Several crops have been engineered using this approach for disease resistance, drought, salinity and temperature tolerance traits [50]. It has also been used to generate climate-ready crops and enhance the nutritional profile of agricultural products [47]. The CRIPSR-based genome editing approach has been employed to create golden crops by editing carotenes [51]. The most common example of this category is the Golden Rice cutoff, which was generated by editing a 5.3 kb carotenogenesis cassette made up of Crtl andPSY genes [52]. Vitamin E content has been increased through targeted over-expression of *Hordeum vulgare* homogenisate geranylgeranyl transferase (HvHGGT) and *H. vulgare* homogenisate phytyltransferase (HvHPT) [53]. Iron enrichment in crops can be achieved by disrupting inositol pentakisphosphate-2-kinase 1 (PK1) [54]. Zn biofortification has been achieved by disrupting *Triticum aestivum* Inositol Pentakisphosphate 2-kinase 1 (TaIPK1), which reduces phytic acid content and finally increases Zn accumulation in wheat. Genetically modified plants with lower cytokinin levels enhance the enrichment of Zn, Cu, Mn, Ca, S, P and Fe in crops. By using an RNA-guided Cas9 method to knock out CKX genes, it was possible to improve the grain output of barley. This resulted in the creation of mutant lines for the HvCKX1 and HvCKX3 genes [55]. Fig. 2 illustrates the scientific methodologies employed in the practice of biofortification.

3.6. Organisms used in biofortification

3.6.1. Bacteria

In conventional agricultural practices, organic and chemical fertilizers are used to improve crop quality and yield. However, all of them have certain drawbacks, including toxicity, environmental risks from excessive use, difficulty in choosing acceptable germplasms for breeding and challenges associated with the introduction of transgenic crops due to public acceptance and safety concerns [56]. Therefore, using microorganisms for biofortification is more environmentally friendly than other methods to ensure sustainable agriculture [57]. Several microbiome species, like fungi, bacteria and cyanobacteria can be considered for effective plant growth by obtaining significantly higher levels of nutrient concentrations in crops through genetics-based biofortification that is genetic and agronomic-based. However, microbiological agents that promote plant growth have been thoroughly studied for the biofortified approach; they need to be included in the natural biofortification agent category to grow bio-enriched crops [58].

Microorganisms play a crucial role in the biofortification of Zn, Fe, Mn and Se in various crops [58]. Both rhizosphere and endophytic microorganisms have important effects on the bioavailability of trace elements in plants. However, endophytic microbes are thought to be more advantageous because they can indirectly influence the regulation of metal transporters [59]. Microorganisms use an approach to solubilize zinc (Zn) and other nutrients by producing various organic acids. Fungi and Bacteria have been shown to increase Zn solubility in the rhizosphere. Among the identified bacterial genera considered as Zn solubilizers are *Gluconobacter, Azospirillum, Pseudomonas, Azotobacter* and *Bacillus* [60]. *Bacillus* strains have been shown to dissolve inaccessible forms of Zn via the secretion of vitamins, proton extrusion, vitamins, amino acids, phytohormones, oxidoreductase systems and organic acids [61]. Shakeel et al. reported the cooperation of *Bacillus* (*Bacillus* sp. SH-10 and *B. cereus* SH-17) as powerful determinants of cultivating Zn-fortified rice grains with an approximate Zn translocation index value of 1.6–1.7 [62]. *Arthrobacter* sp. (DS-179) and *Bacillus subtilis* (DS-178) were found to increase the Zn content by 75 percent (on average) compared to controls in soils with Zn deficiency [63]. The use of the plant growth-promoting rhizobacterium (PGPR) *Pseudomonas fluorescens* was adequate for the biofortification of Zn in wheat
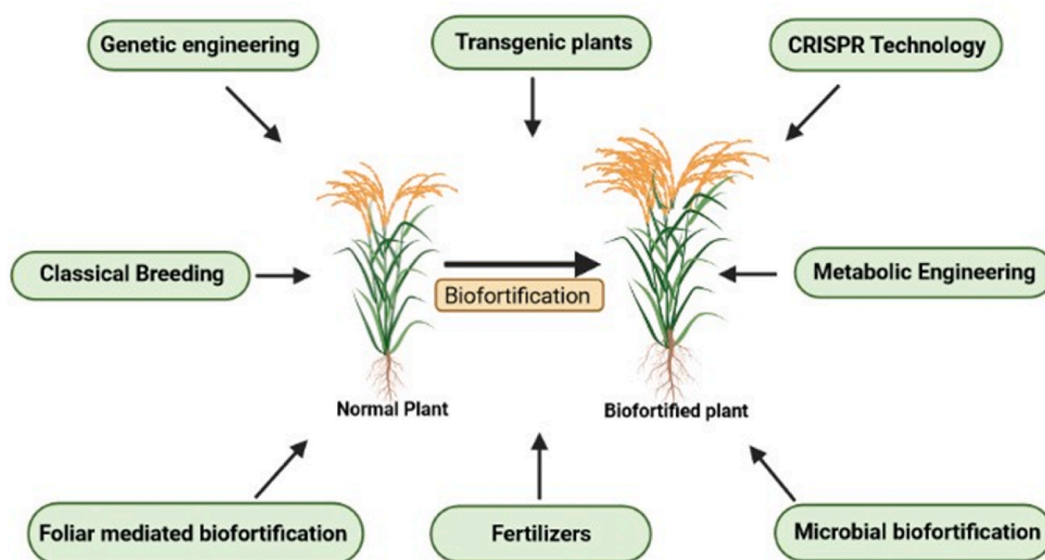
Fig. 2. The important methods used in biofortification of agriculture produces.

grains [64]. When *Anabaena oscillaiodes, Brevundimonas diminuta* and *Ochrobactum* anthropic were used for biofortification, the yield of rice increased by 21.2 percent when compared to chemical fertilizers [65]. *P. fluorescens* enhances saponin and Zn levels in the same crop [66].

Plants absorb Fe via. various mechanisms from bacterial siderophores, such as chelate and iron secretion, direct absorption of siderophore-iron complexes and ligand exchange reactions [67]. When siderophore-producing bacteria attach to plants, iron absorption is improved, particularly in cases of iron deficiency. This interaction helps iron in plants, effectively addressing iron deficits [67]. As suggested by various researchers [14,15,57,58,63] microorganisms have been used as a tool for biofortification to increase the Fe content in crops. Microorganisms capable of producing siderophores may have good potential for biofortification, as they provide additional access to Fe for plants. Several PGP bacteria, including *P. putida, Enterobacteria* sp. and strains of other bacteria, increase the Fe content of rice grains twice, with greater Fe-transport efficiency from root to stem and grains, indicating the development of a potent application of PGP bacteria for iron biofortification [68].

Fungi and bacteria are essential microbes producing siderophores. The most important bacteria are *Mycobacterium* sp., *Klebsiella pneumoniae, Aerobacter aerogenes, E. coli, Yersinia* sp. and *Vibrio cholera.* The use of *Pseudomonas* sp. and *Azospirillum* sp. as PGP bacteria can increase the iron content of rice [68].

Azospirillum, Agrobacterium, Pseudomonas and *Erwinia* all produce IAA, which increases the length, number of root hairs, number of root branches and surface area of seedling roots, whereas *Rhizobium* strains that also produce IAA exhibit improved lateral root development, increased nodulation and delayed nodule senescence [69]. Under Fe-limited conditions, siderophore-producing *Pseudomonas* strain GRP3 inoculated with mung bean plants showed fewer chlorotic symptoms and enhanced chlorophyll content than untreated plants [70]. Increased Fe content has been reported in *Brassica juncea* with the application of bacteria, such as *Lysinibacillus fusiformis, Rhodococcus hoagii, Bacillus toyonensis* and *Lysinibacillus mangiferihumi* [71]. When using *P. plecoglossicida,* a rhizosporic bacterium, the Fe content was improved in pigeon peas and chickpeas [72]. Concerning Fe availability in wheat grains, comparable findings were obtained using *Enterococcus hirae* (DS-163) and *Arthrobacter sulfonivorans* (DS-68) [63]. According to Rana et al. inoculation with *Providencia* sp. PW5 increased the Fe content of wheat grains [73].

Three endophytic bacterial strains, *Bacillus, Acinetobacter* and *Klebsiella,* may be used for the biofortification of Se in wheat plants [74]. Different studies have shown that a group of endophytic selenobacteria and the AM fungus *Rhizophagus-intraradices* boosted the selenium level of lettuce plants and their resilience to abiotic stress [75]. The amount of selenium in wheat grains increased noticeably after injection with *Bacillus* spp. R12 and *Pseudomonas* spp. R8 [76]. There was a remarkable improvement in Se content in wheat inoculated with *P. jessenii* R62 and *P. synxantha* [77].

Certain rhizobacteria, such as *Geobacter, Pseudomonas* and *Bacillus,* convert oxidized Mn^{4+} to Mn^{2+}, which is beneficial for plant metabolism [78]. Tang et al. recently reported Mn accumulation and plant growth enhancement in *Myriophyllum verticillatum* by injecting Mn-resistant *Bacillus cereus* WSE01 [79]. In pigeon peas and chickpeas, *E. ludwigii* SRI-229 and *E. ludwigii* SRI-211 increased the concentration of Mn by 2–39 percent [72].

3.6.2. Fungi

Trichoderma and arbuscular mycorrhizae are two types of fungi that can dissolve zinc in soil [80,81]. Fungi have been found to significantly affect plant development, biomass and micronutrient absorption [82]. The endophytic bacteria isolated from *Sedum alfredii H.* were able to colonize rice roots and increase zinc availability in the rhizospheric soil. This colonization improved root structure and overall plant development was observed. In addition, it led to higher grain yields and higher Zn concentrations in the grains [83]. Arbuscular mycorrhizal (AM) fungi, such as *Funneliformis mosscae* have increased the content of Zn, protein and Fe in chickpeas [84]. Similarly, the AM fungus *Rhizopus irregularis* improved the production of onion biomass and the concentration of organic acids [85]. In greenhouse settings, *P. indica,* an endophytic fungus with an additional concentration of 10 mg/L Zn, significantly increased the Zn content in lettuce plants (7.6 times) with high chlorophyll content. This verified the presence of *P. indica* in biofortification [86].

Inoculation with *Trichoderma asperellum* markedly enhanced the concentration of Fe in wheat plants in a calcareous medium deficient in Fe and demonstrated the effectiveness of this fungal strain on the concentration of iron in wheat plants [87]. A similar finding of improvement in selenium levels has also been reported with arbuscular mycorrhizal fungi such as *Glomus clarideum* [76]. Thus, among all the fungi, Mucor, *Saccharomyces cerevisiae, Rhizopus, Penicillium chrysogenum* and *Aspergillus nidulans* are important for Fe biofortification [88].

4. Nutrients used in biofortification

Under various agroclimatic conditions, numerous microorganisms have been used to supply macro-and micronutrients to a variety of agricultural plants. However, few microorganisms can mobilize essential microelements such as Zn/Fe and other microelements such as phosphate and potassium. Although the nitrogen-fixing abilities of some nitrogen-fixing bacteria are biological processes, inoculation leads to increased nitrogen intake by linked plants. Researchers have isolated, identified and reported some powerful microflora that can solubilize micro- and macro-elements from rhizospheric soils [89,90].

4.1. Micronutrients

4.1.1. Zinc

Biofortification is a collection of strategies employed to elevate the bioavailability of essential nutrients in common food items,

including maize, rice, pearl millet, wheat and other grains [91]. The efficiency of several bacterial strains, viz. *P. plecoglossicida* SRI-156, *Enterobacter ludwigii* SRI-211, *Brevibacterium antiquum* SRI-158, *P. monteilii* SRI-360, *B. altitudinis* SRI-178, *Acinetobacter tand oii* SRI-305 and *E. ludwigii* SRI-229 as potential biofortifying agents was demonstrated by Gopalakrishnan et al. [72]. They reported a rise in the amount of mineral content like Fe (12 and 18 %), Zn (5 and 23 %), Cu (8 and 19 %), Mn (39 and 2 %) and Ca (11 and 22 %) in pigeon pea and chickpea plants, correspondingly, when compared to uninoculated plots The effectiveness of zinc-utilizing microorganisms in increasing the zinc content of wheat crops has been documented by Kamran et al. [60]. They reported that roots treated with EPS 13 (*P. agglomerans*) and shoots treated with PBS 2 (*E. cloacae*) had the highest zinc concentrations, surpassing zinc-supplemented control plants. A similar study conducted by Naz et al. demonstrated the role of zinc-solubilizing bacteria, such *Azospirillum, Pseudomonas* and *Rhizobium* in increasing zinc concentrations in different parts of wheat plants at different growth stages via inoculation. Plant growth was greatly enhanced by inoculation compared to the control treatments [92].

Furthermore, solubilization of Zn by *B. aryabhattai* strains has been reported by Vidyashree et al. [93]. The researchers found improved growth in wheat and soybean plants, along with enhanced biofortification of zinc in both crops, compared with non-treated plants grown in vertisols, a clayey soil with low organic matter, in the central Indian region. They identified *P. protegens* RY2 as a Zn-solubilizing bacterium, whose inoculation along with ZnO resulted in higher chickpea (*Cicer arietinum* L) growth, as well as higher zinc content in both the shoots and seeds [94]. Bhatt and Maheshwari [95], reported that *B. megaterium* strain CDK25 not only solubilized ZnO and $ZnCO_3$ but also demonstrated phosphate solubilization potential [95] Inoculation of *Capsicum annuum* L. with CDK25 strain resulted in the highest Zn content in fruit (0.25 mg/100 g) under pot culture assay. Bhakat et al. highlighted that As-tolerant, ZN-solubilizing *Burkholderia* spp. could be a promising candidate for mobilizing zinc in the soil [96]. These researchers used Zn-solubilizing *Burkholderia* spp in rice crops to obtain biofortified rice grains. It also helps in reducing the rate of inorganicZn-nourishment in agronomic soils.

4.1.2. Iron

Many reports have suggested that microbes play a significant role in iron (Fe) mobilization from the soil. Mobilized Fe is utilized by microbes facing a deficiency in Fe metal, but excess metal is transported to the plant root system, which fulfills the plant's iron deficiency. Lurthy et al. reported the role of three distinct ferripyoverdines (Fe-pvds) produced by *Pseudomonas* sp. in two pea cultivars [97]. Priming of pea cultivar seeds with siderophore-producing *Pseudomonas* sp. resulted in an enhanced amount of Fe in the roots, shoots and seeds. Kong et al. studied the role of the rhizobacterium *Rahnella aquatilis* JZ-GX, which produces volatile organic compounds (VOCs) and bacterial volatile organic compounds (2-undecanone and 3-methyl-1-butanol), resulting in enhanced uptake of Fe by *Arabidopsis thaliana* [98]. Harbort et al. conducted studies on iron uptake in *A. thaliana*, specifically investigating the role of root-associated microbiota and secretion of plant-derived coumarins [99]. Singh and Prasanna stated that the seed priming of fluorescent *Pseudomonas*, which produces siderophores, was efficient in improving the quantity of iron (Fe) in chickpea grains [58]. Similarly, a field experiment study revealed that inoculation of wheat crops with siderophore-forming bacterial endophytes *Enterococcus hirae* and *Arthrobacter sulfonivorans* improved the iron content in wheat grains of high- and low-Fe accruing wheat genotypes by 46 and 67 %, respectively, compared to the non-inoculated ones [63]. Iron mobilization by siderophore-producing rhizospheric bacteria (*P. fluorescens*) was also reported by Yazdi et al. [100]. Of the 25 isolates, three were efficient in mobilizing Fe from soil to corn plants in Khorasan Razavi Province, Iran. Additionally, studies on inoculated bacteria have shown increased fresh and dried root weights, as well as improved plant growth. The endophytic strain *B. altitudinis* WR10 led to an increase in Fe content in wheat cotyledons, but other macronutrients such as N, P and K were also mobilized by endophytic bacteria in the root and stem [101]. *Pantoea dispersa* MPJ9 and *P. putida* MPJ6 were observed to be efficient Fe-chelating rhizobacteria that biofortified mung bean crops with enhanced iron content in shoots and grains [102].

4.1.3. Selenium

Selenium (Se) is an important mineral for human health, mainly due to its immune-boosting and oxidative stress reduction properties and plays a significant role in enzyme activity. Selenium is mainly obtained from selenium-rich crops such as wheat, cowpea and turnip potato [103–106]. Thus, the improvement of public health by biofortifying crops with Se using agronomic [103] and microbial approaches is a sustainable practice [104–106]. The accumulation of selenium in plants mainly depends on the amount and biological availability of soil selenium. The microbiome may alter the elemental configuration and bioavailability of Se. Microbial augmentation of Se biofortification involves the following steps.

(1) Efficient microbes change soil characteristics and influence Se redox chemistry to increase its bioavailability in the soil.
(2) Furthermore, valuable microorganisms synchronize root morphology and encourage plant development through their exudates, expediting Se plant uptake and metabolism.
(3) Efficient microbe inoculation causes plants to produce specific metabolites, resulting in Se captivation [106]. Similarly, several studies have demonstrated iodine (I) biofortification in plants using an agronomical approach [107].

4.1.4. Amino acids

There are various reports suggesting that researchers have employed various approaches to enhance the amount of amino acids in crop plants. Cereal crops are the primary nutritional source in underdeveloped nations and harbor significant amino acid contents, such as lysine, thereby suggesting biofortification to emphasize the need for targeted enrichment [108]. *Oryza sativa* L. (rice), the most important crop worldwide, has inadequate levels of lysine [109]. Parray et al. improved the accumulation of sesame 2S albumin-boosted cysteine and methionine levels in genetically manipulated rice seeds [110]. Dai et al. biofortified soybeans with

glycine [111], Yang et al. [112] reported enhanced free lysine content in rice seeds, Dueñas et al. reported increased accumulation of tryptophan transgenic rice seeds [113] and Tiong et al. overexpressed aspartate aminotransferase genes in rice, resulting in induced amino acid content in rice seeds [114]. Yang et al. used a combination of transgenic events to develop two pyramid transgenic lines (High Free Lysine; HFL1 and HFL2) with more than 20-fold higher free lysine levels in rice seeds than in the wild type [115]. Furthermore, Yang et al. biofortified rice with lysine by regulating the feedback inhibition of two key regulatory enzymes, aspartate kinase and dihydrodipicolinate synthase [112]. Using this method, researchers were able to enhance the lysine levels of rice by up to 58.5-fold higher than that of the wild variety. Moreover, agronomical functioning analysis showed that rice transgenic lines showed customary plant development, growth and seed exterior, similar to wild-type plants. Moving on similar lines, Lee et al. fortified rice with lysine using mutant-derived lines. Lee et al. were able to increase the amount of lysine in a rice mutant variety to 3.86 mg/g, which is almost five times greater than that of the parent line [116]. Mohammadipour and Souri used a conventional approach to enhance the amino acid glycine in coriander plant [117]. They applied various concentrations of glycine 0, 5, 10, 20, or 40 mg/L via. Hoagland 's nutrient solution to coriander plants. All glycine levels, except 40 mg/L, enhanced the leaf glycine content and overall plant growth.

After rice, maize is the main cereal and the crop has a plentiful supply of carbohydrates, which is commonly consumed in many regions of the world but has very few other nutrients, such as amino acids, tryptophan and lysine [118]. Researchers have been working on the biofortification of the amino acid profile in maize using diverse techniques over the last 20 years. Mondal et al. exploited the expression of sb401, which enhances lysine levels in maize seeds [119]. Similarly, Yang et al. increased lysine content in corn by modulating lysine biosynthesis and catabolic pathways [120]. Huang et al. improved tryptophan and lysine contents in transgenic maize by reducing both multigene family proteins and 19- and 22-kD alpha-zeins [121]. However, Khulbe et al. enhanced methionine content in maize seeds using the mRNA stability technique [122].

4.1.5. Vitamins

The second most essential group of micronutrients necessary for human growth and development are vitamins. Vitamin levels in cereals are low; therefore, vitamin deficits affect up to 50 percent of the world's inhabitants [123]. The uptake of vitamin A from dietary sources is necessary for complete nourishment to avoid several acute diseases involving cancer. It is essential for immune system functions and disease resistance. It has been reported that approximately 30 percent of children less than five years of age have a Vitamin A deficiency [124]. Therefore, it is the most prominent cause of avoidable childhood blindness. Harvest Plus has collaborated with international organizations such as Centro Internacional de Mejoramiento de Maíz y Trigo (CIMMYT), Empresa Brasileira de Pesquisa Agropecuária (EMBRAPA) and the International Institute of Tropical Agriculture (IITA) to improve highly profitable maize cultivars in terms of yield, consumer acceptability and abundance of provitamin A carotenoids. Numerous vegetal derivatives contain β-carotene, which is an antecedent of provitamin A. In plants, it is the most common provitamin A carotenoid studied by researchers to raise the standard of food. Cereal biofortification with provitamin A resulted in "golden" harvests [125]. The breeding focus for maize was 15 μg/g of β-carotene. This was important to deliver an added 50 percent of Vitamin A in predictable normal amounts in maize-consuming territories. Maize crops developed with targeted levels of β-carotene could be a source of Vitamin A deficiency reduction.

An improved build-up of lutein, violaxanthin and β-carotene was demonstrated via. overexpression of the CrtB gene in potato crops [126]. Furthermore, the overexpression of phytoene PSY from the daffodil incorporated with the bacterial daffodil LCYB gene and/or crtI gene in rice endosperm produced a whole carotenoid matter of 1.6 μg/g dry weight [45]. In another work on the biofortification of vitamin A, Welsch and Li (2022) described a total carotenoid content of more than 35 μg/g in 'Golden rice 2,' where the daffodil gene was swapped out with the maize gene PSY1 [127]. The transgenic approach provides a viable strategy to fulfill this purpose, but to date, it has been limited to augmenting individual vitamins, such as vitamin A, although some success has been achieved with other vitamins [22]. This approach plays a notable role in cereals, where the metabolic pathways for vitamins are inhibited, lacking, or truncated in the endosperm [128]. The creation of "Golden Rice" [129] and sorghum crops [17] with an enhanced amount of pro-vitamin A are typical examples of transgenic-created biological fortification technology.

Wurtzal et al. suggested that in food crops, the amount of provitamins can be enhanced by readdressing the metabolic flux in the direction of carotenoids using the gene-quieting approach [130]. Another possible approach to address vitamin A deficiency is to change the gene by combining overexpression (the push approach) with gene quieting (the block strategy). To address vitamin A deficiency Zeng et al. have suggested (push approach) with gene quieting (block strategy), which improve metabolic flux: boosting (CrtB) and blocking (carotenoid hydroxylase) [131]. They have developed transgenic wheat plants with the ability to accumulate as much as 5.06 μg/g β-carotene. This concentration is thought to be sufficient to treat vitamin A deficiency completely. Plants with a higher vitamin C content may produce foods high in this important nutrient, which is necessary for tissue growth, repair, development and possibly even longer postharvest shelf-life. Furthermore, increased vitamin C levels may improve the ability of plants to withstand a variety of stressors, which is an essential component of sustainable agriculture.

4.2. Macronutrients

4.2.1. Phosphate

Many researchers have also demonstrated the role of phosphate/potassium (K) solubilization by microbes and the uptake of sol-ubilized nutrients in the development and growth of plants. Otieno et al. described the capability of gluconic acid (GA)-producing endophytic bacteria to solubilize insoluble phosphate, which promoted the growth of pea (*Pisum sativum* L) plants in pots under greenhouse conditions. Moving on the same lines, Saadouli et al. reported the efficacy of the phosphate-solubilizing rhizospheric

bacterium *Pantoea agglomerans* in enhancing the phosphate content in jute plants along with higher overall growth distinct to uninoculated plants [132].

Cozzolino et al. described the roles of *Bacillus amyloliquefaciens* and *Pseudomonas* spp., either alone or in combination with humic acid (HA) extracted from green compost and phosphate-mobilizing AM fungi [133]. The inoculation of microbes resulted in higher growth of maize plants and increased uptake of phosphate from the soil compared to untreated plants. Ahmad et al. described the combined use of Zn-solubilizing *Bacillus* sp. (IA16) and *P*-solubilizing *Bacillus subtilis* (IA6) to enhance cotton plant growth and nutrient acquisition [134].

4.2.2. Potassium

Potassium is another significant macronutrient essential for plant development and growth and the only known inorganic fertilizer
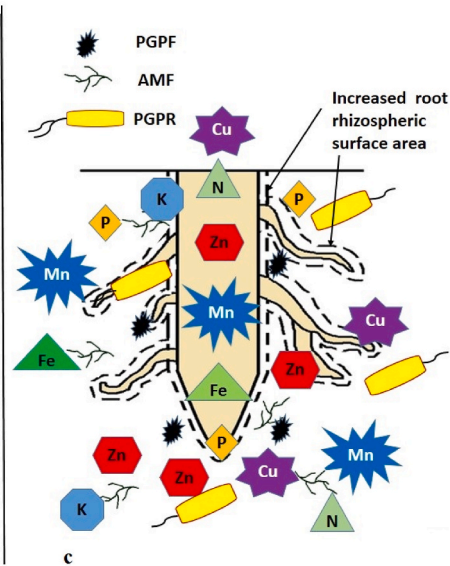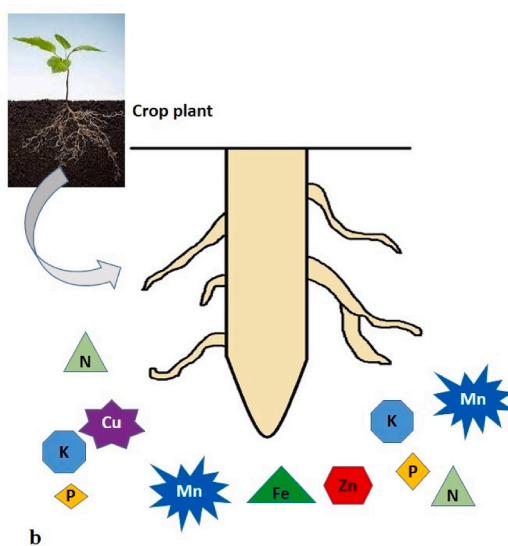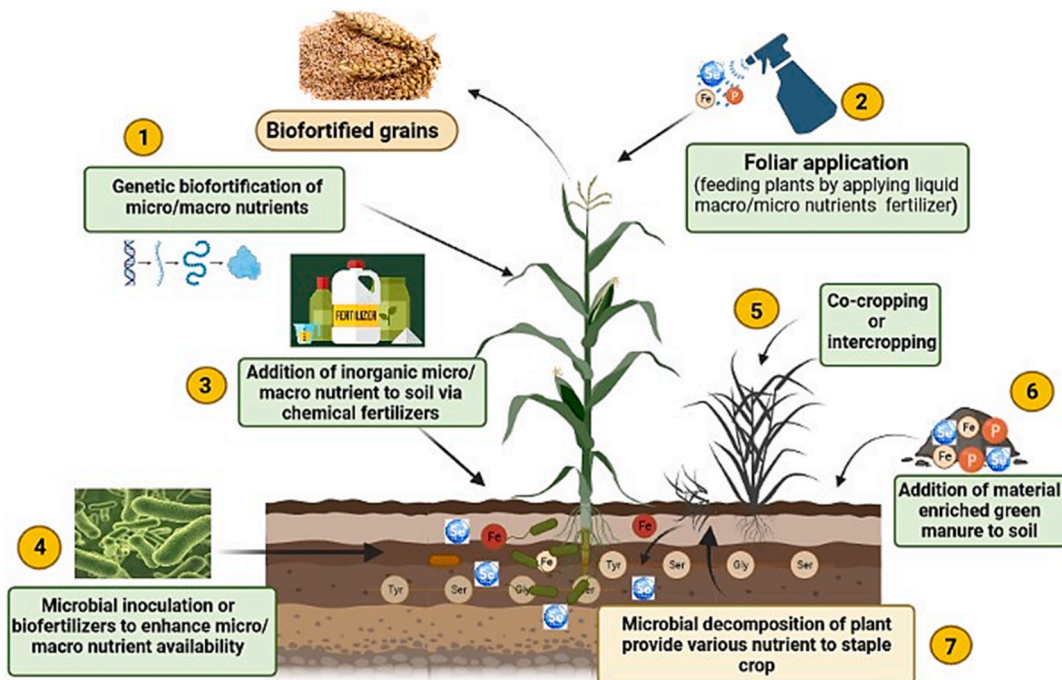

Fig. 3. (a)Depicts various methods to implement nutrient biofortification; (b–c) shows the various means of biofortification/uptake of micro and macronutrients by plant roots assisted by the competent microbiome.

employed in the agro-ecosystem is muriate of potash (MoP). The exploitation of potassium-solubilizing microbes (KSM) as bio-inoculants could be an important part of managing K in cultivable soils. Pramanik et al. inoculated tea seedlings in soil from north-eastern India treated with mica debris using a native strain of Bacillus pseudomycoides, which can solubilize potassium. By increasing the accessibility of K in the soil, this inoculation improved the ability of seedlings to utilize it [135]. Sun et al. isolated potassium-solubilizing *Burkholderia* sp. from *Mikania micrantha* rhizospheric soil having significant potassium-solubilizing ability (1.75 mg/L) from Mikania micrantha rhizospheric soil [136]. Inoculation of *Burkholderia* sp. into *Mikania micrantha* plants not only enhanced K uptake but also P content when tested against non-inoculated plants. Khanghahi et al. investigated the effects of three potassium-solubilizing bacteria, *Rahnella aquatilis*, *Pseudomonas orientalis* and *Pantoea agglomerans* on K, P and N uptake in *Oryza sativa* plants [137]. The results of the experiment demonstrated the importance of bioinoculation with bacterial species isolated from paddy soil as an applicable way to enhance N, P and K uptake by rice plants under flooded irrigation environments. Similarly, Raji et al. reported the inoculative effects of K-solubilizing bacteria (*B. cereus, Burkholderia cenocepacia, B. cereus* and *B. licheniformis*) on tomato plants [138]. Under greenhouse conditions, inoculated bacterial cultures enhanced the plant tissue K content in sterilized and un-sterilized Vertisol and Alfisol soils. Consequently, several researchers have reported the beneficial effects of K-solubilizing bacteria on various crop plants under different agro-climatic conditions. Baba et al. reported that psychrotolerant *Mesorhizobium* sp. has a K-solubilizing ability of 23.38 μg/L and produces multiple phytohormones [139]. Rallos et al. described K solubilization by *Pseudomonas umsongensis* MG774425, *Bacillus aryabhattai* MG774424, *P. frederiksbergensis* MG774426, *P. mandelii* MG774428 and *Burkholderia sabiae* MG774427, leading to enhanced K uptake in *Brassica rapa*. L, under field conditions [140]. Fig. 3 (a) depicts various methods to implement nutrient biofortification; (b) shows the various means of biofortification/uptake of micro-and macronutrients by plant roots assisted by the competent microbiome.

Biofortification, the process of enhancing the nutritional value of food using agricultural practices, is an important asset in fighting hidden hunger, primarily caused by vitamin and mineral deficiencies. Several technological advances have led to recent breakthroughs.

4.3. Regulation of L-galactose/D-mannose pathway

Numerous genes of the L-galactose/D-mannose pathways have resulted in diverse crops to increase ascorbic acid content, but the results were not satisfactory [141,142]. It has been shown that the countenance of GGP, which characterizes the blockage of ascorbic acid biosynthesis [143], is a beautiful approach to biofortify vitamin C [144]. For example, in *Arabidopsis*, transient overexpression of the GGP gene results in an increase in ascorbic acid content up to 2.5 times, however; increased expression of the extra genes implicated in the same biosynthetic pathway does not result in significant changes in ascorbic acid content [145]. Comparable outcomes were observed in rice plants, where the maximum vitamin C amount was obtained in regions where the GGP gene was over-expressed when compared to other genes based on the same line [146]. Further innovative approaches for the improvement of ascorbic acid content in different plants were achieved through overexpression of the GGP gene isolated from the Kiwi plant in three crops, resulting in the augmentation of ascorbic acid twice in strawberries, three times in potatoes and six times in tomatoes. However, in the case of tomatoes, overexpression of GGP results in seed loss, which is a type of fruit morphological alteration [146,147].

4.4. Other biosynthetic pathways manipulation

In terms of the augmentation of ascorbic acid in various crops, genes related to the maintenance of alternate biosynthetic pathways have shown favorable outcomes. Concerning the glucose pathway, encouraging findings have been reported with the demonstration of rat cDNA encoding GulLO, an enzyme involved in the last phase of the animal ascorbic acid biosynthesis pathway [145,148]. This gene was consistently expressed in lettuce and tobacco plants, which also displayed increased ascorbic acid levels of 7 and 4, respectively [30]. The same gene was overexpressed in transgenic potato plants, improving ascorbic acid accumulation in tubers and abiotic stress tolerance [149]. Stimulating findings have been reported by maneuvering the galacturonate pathway. Overcountenance of the strawberry FaGalUR gene in potatoes resulted in a two-fold enhancement in ascorbic acid content; moreover, this increment resulted in abiotic stress tolerance in transgenic lines [150]. Comparable progressive findings have also been described in the case of tomatoes; although a reasonable increment in ascorbic acid amount was observed, total antioxidants were reported to increase, which was connected to the regulation of the redox state [151] and overexpression of the FaGalUR gene in tomato plants was reported to be more resistant to abiotic pressures [143].

4.5. Recycling genes manipulation

The vitamin C content can be increased in a variety of crops by regulating the genes that code for MDHAR and DHAR, which are responsible for the reduction of MDHA and DHA. Numerous studies have shown that regeneration of ASC by DHAR overexpression could be an effective approach for ascorbic acid biofortification in a variety of plant species, including blueberry [152], corn [153] and tomato [143]. Cytosolic DHAR from the *Liriodendron chinensea* plant was overexpressed in *Arabidopsis*, resulting in enhanced growth under stress, as well as an increase in vitamin C [154].

5. Bio-fortified agro-products

As discussed earlier, biofortification is a common method for boosting the amounts of micronutrients (iron, zinc, selenium, vitamin

Table 1
Biofortification of major agriculture produces.

S·NO.	Agriculture produces	Technique used	Genes incorporated	Type of fortification	Health benefits	Reference
Fruits						
1	Banana	Genetic engineering	PSY gene (*PSY2a*)	beta carotene	To alleviate vitamin A deficiency	[155]
		In vitro Polyploidization	–	Vitamin A	Prevent night blindness, vision improvement	[155, 156]
		Genetic engineering	*Apsy2a* gene	pro-vitamin A carotenoids (pVAC)	Overcome vitamin A deficiency	[155]
2	Strawberry	Agronomic	–	Selenium	Antioxidant properties	[157]
		Microbial approach	–	Selenium	Antioxidant properties	[158]
		Agronomic	–	Silicon	Nutraceutical qualities of the fruits	[159]
3	Apple	Agronomic	–	Selenium	Antioxidant properties	[160]
		Genetic engineering	*stilbene* synthase	Stilbenes	Antioxidant and nutraceutical properties	[161]
4	Tomato	Genetic engineering	mutation of *SlAPX4* gene	Vitamin C	More nutraceutical value and antioxidant	[162]
		Agronomic	–	Selenium	Antioxidant properties	[163]
		Agronomic root treatment	–	Iodine	Regulate the production of thyroid hormones	[164]
		Metabolic engineering	CHI, expression of two transcription factors, Rosea 1 and Delila, transcriptional activators AtMYB75	Anthocyanin	Protection against cardiovascular risk factors and type 2 diabetes	[22]
		Transcriptional regulation	3-hydroxymethylglutaryl CoA	Tocopherol	Antioxidant, reduction in arterial clotting	[165]
		CRISPR-Cas9	Deletion of SlGAD2 and SlGAD3	Increased GABA		[166]
5	Plum	Agronomic	–	Anthocyanin	Protection against cardiovascular risk factors and type 2 diabetes	[167]
6	Apple, pear	Agronomic	–	Iodine	Regulate the production of thyroid hormones	[168]
Cereals						
7	Golden Rice	Genetic engineering	PSY and carotene desaturase	provitamin A (beta-carotene	Eye health, good vision	[22]
8	Biofortified rice	Metabolic engineering	Aminodeoxy- chorismate synthase and Arabidopsis GTP-cyclohydrolase I (GTPCHI)	Folate (vitamin B9) in biofortified rice	Help in the management of Alzheimer's, megaloblastic anemia, cardiovascular, coronary diseases, neural tube defects (NTDs) and several types of malignancy	[169]
9	Biofortified rice	genetic engineering/ molecular breeding/Plant breeding	For Fe: iron transporter OsIRT1, nicotianamine aminotransferase, nicotianamine synthase 1 (OsNAS1) and 2 (OsNAS2) For Zn: OsIRT1, mugineic acid synthesis genes from barley [HvNAS1, HvNAS1, HvNAAT-A, HvNAAT-B, IDS3	Fe and Zn rich rice	Fe Prevents Anemia, Zn promotes physical growth, sensory functions, functioning of the immune system, neurobehavioral development and reproductive health	[49]
10	Resistant starch-rich rice	Genetic engineering, breeding	expression of antisense RNA inhibition of starch-branching enzymes (SBE) and antisense waxy genes	RS1, RS2, RS3, RS4 and RS5	Enhancing the colon's fermentable qualities and bacterial activity, lowering the risk of colon cancer, preventing gallstone formation, promoting mineral absorption and enhancing gut health	[170]
11	Fortified wheat	conventional breeding or transgenic methods	–	Fe, Zn	Prevent Fe and Zn malnutrition	[171]
12	Low PA- level wheat	RNAi Technology, CRISPR/Cas9	expression of the phytochrome gene [phyA, silencing of wheat ABCC13 transporter	Lowering phytic acid content,	Increase in Bioavailability of Fe, Zn and other micronutrients	[172, 173]
13	Anthocyanin rich wheat	conventional breeding,	regulatory genes (*C1, B-peru*)	High Anthocyanin content	Antioxidant, nutraceutical properties anti-inflammatory activities	[174]

Table 1 (*continued*)

S·NO.	Agriculture produces	Technique used	Genes incorporated	Type of fortification	Health benefits	Reference
14	High amylose-rich wheat	RNAi Technology	Silencing gene encoding SBE [*SBEIIa*]	Amylose	improves metabolic and digestive health	[175]
15	High amylose-rich wheat	CRISPR-Cas9	Targeted mutagenesis in *SBEI* and *SBEIIb*	High amylose content	improves metabolic and digestive health	[176]
16	Biofortified Maize	Breeding genetic engineering	expressing multiple carotenogenic genes and bacterial *crtB*	Pro-vitamin A	Reduce Vitamin A deficiency	[177]
17	Quality Protein Maize	Breeding, bifunctional expression/ silencing transgene cassette	expression of *sb401* from antisense dsRNA targeting alpha-zeins from potato	Lysine and Tryptophan	Good quality proteins	[178]
18	Zn and Se-rich maize	PGPRS, Cyanobacteria	–	Zn, Se	Health benefits	[179]
19	Phytase, ferin-rich maize	Genetic engineering	ferritin and *Aspergillus niger* phyA 2,	Phytase, ferin	Increase bioavailability	[180]
20	Barley	Agronomic biofortification, mutagenesis, genetic engineering	overexpression of zinc transporter	Zn, Se, Fe	Prevent anemia, boasts immunity	[181]
		Genetic engineering	phytase gene [*HvPAPhy_a*]	Increase Phytase activity	Bioavailability of Zn and Fe	[182]
		Genetic engineering	cellulose synthase-like gene [*HvCslF*]	β-glucan expression	Reduced risk of CHD and type II Diabetes	[183]
		RNAi Technology	Masking all SBE-coding genes [*SBE I, SBE IIa, SBE IIb*]	Resistant starch-amylose	improves metabolic and digestive health	[184]
		Genetic engineering-expressing Δ6 –desaturase	expressing Δ6 -desaturase [*D6D*]	stearidonic acid and γ-linolenic acid	Maintain brain function, skeletal health, reproductive health and metabolism.	[185]
Legumes						
21	Soybean	Genetic engineering/ metabolic engineering	PSY gene, PSY (*crtB, crtW, bkt1*), carotene desaturase	increased oleic acid, provitamin A (beta-carotene) and seed protein contents	Nutraceuticals	[186]
			sulfur assimilatory enzyme, O-acetylserine sulfhydrylase, maize zein protein	cysteine and methionine	Essential amino acids	[187]
		Antisense RNA technology, siRNA-mediated gene silencing	reticence of Δ^{12} oleate desaturase [*GmFAD2-1b*] expression	decreasing linolenic acid levels	Increase soybean quality with health benefits	[22]
		Metabolic engineering		Enhanced Isoflavone content	Reduced menopausal symptoms, decreased risk of cardiovascular disease and decreased risk of some hormone-related malignancies	[188]
22	PUF rich soybean	Genetic engineering		Linoleic acid γ-Linolenic Acid + stearidonic acid	nutraceutical and pharmaceutical potential	[22]
Vegetables						
23	Sweet Potato	Breeding and agronomic biofortification, genetic engineering		Beta-carotene, Antioxidants	Eye health and cancer	[189]
24	Potato	Genetic engineering	Lycopene β-cyclase, phytoene desaturase and *PSY*	Beta-carotene Zeaxanthin	Anticancer property	[22,190]
		Genetic engineering	*GalUR*	Vitamin C	Antioxidant property	[220
		Genetic engineering-Antisense inhibition threonine synthase	cystathionine γ-synthase (*CgSΔ^{90}*)	Methionine	Protein-rich	[191, 192]
		Genetic engineering	cyclodextrin glycosyltransferases	High-value carbohydrate	multipurpose dietary fiber cyclodextrins	[193]

(continued on next page)

Table 1 (*continued*)

S·NO.	Agriculture produces	Technique used	Genes incorporated	Type of fortification	Health benefits	Reference
		CRISPR-Cas9	Starch branching enzyme (*Sbe*)	Mutation in Sbe genes to increase amylose and long amylopectin chains		[194]
25	Cassava	Genetic engineering	*nptII, crtB and DXS*	Beta-carotene	Anticancer property	[195]
26	Linseed	Genetic engineering	fatty acyl-desaturases and elongases	Very long chain unsaturated fatty acids: DHA C22:5 n-3 (docosahaenoic acid), EPA C20:5 n-3 (eicosapentaenoic acid) and arachidonic acid (C20:4 n-6)	cholesterol-lowering agent	[196]
27	Canola	Genetic engineering	expression of PSY, phytoene desaturase and lycopene cyclase genes, *crtE, crtI, crtZ crtW, idi, crtB* and *crtY*	Elevated β-carotenoid content	Nutraceutical	[197]
			lycopene ε-cyclase and DET1 - RNAi silencing	Higher beta-carotene concentration, as well as xanthophylls and lutein levels	Nutraceutical	[22]
			dihydrodipicolinic acid synthase and aspartokinase (AK)	Lysine	Essential amino acid	[198]
			expression of Δ^6 or Δ^{12} desaturases genes	GLA	Nutraceutical	[199]

A and other micronutrients) utilized by plants and passing them to consumers. The following are some of the most valued agricultural products. Table 1 shows the biofortification methods used to agriculture produces with health benefits.

5.1. Bio-fortified grain

Over 50 percent of the world's population is malnourished or has inadequate micronutrients, which is one of the most serious concerns of humanity. Modern plant breeding and agronomic modifications have focused on increasing agronomic yields rather than nutritional quality. However, alternative initiatives, which are quite expensive for the average person, are growing to address these issues through industrial fortification or pharmaceutical supplementation. Preschoolers, mothers and adolescent girls frequently experience micronutrient malnutrition, which is also known as hidden hunger. This condition is mostly caused by the inadequate dietary intake of certain elements, particularly Zn and Fe. Biofortification can be defined as the process of increasing the level of nutrients in food crops such as rice, maize and wheat, employing fertilizers, genetic modification, or selective breeding [200].

5.1.1. Biofortification of rice

In developing countries, such as India, the Green Revolution greatly increased agricultural productivity and reduced concerns about food security, but it did not sufficiently address the nutritional diversity that exists in industrialized countries. Nearly half of the world's population still lacks crucial micronutrients, such as zinc (Zn), iron (Fe) and vitamin A, which can result in xerophthalmia, iron deficiency anemia and weakened immune systems. Diversifying one's diet is advised to help balance micronutrient deficiencies, although adoption is limited by financial resources. The process of biofortifying staple crops, specifically rice and wheat, has significant potential to address nutrient shortages and should be further investigated [201].

5.1.1.1. Bio fortification of enhancing vitamin A (Golden rice).
Dietary carotenoids have several positive health effects, *viz.* as a lower risk of cancer and eye illness. Numerous carotenoids, including β-carotene, lycopene, lutein and zeaxanthin, have been examined for their potential to improve human health, glycoprotein synthesis, growth, bone development and cell differentiation [202]. Beta-carotene may have additional benefits as it can be converted to vitamin A. A rice genome with enhanced provitamin A (β-carotene) content is a genetically engineered food crop. Professor Peter Beyer and Ingo Potrycus are inventors of golden rice fortified with β-carotene. To alter the genetic makeup, they employed daffodil and *crtl* genes from a soil bacterium (*Agrobacterium tumifascience*). However, breeding does not produce golden rice. Golden Rice is available in two grades: Golden Rice 1 (SGR1) and Golden Rice 2, formed by substituting the maize gene for the daffodil Pys gene to produce 31 g of β-carotene per gram of rice. In addition, BRRI dhan 29 in Bangladesh, IR 36, IR 64 (mega-varieties with broad Asian coverage), PSB Rc 82 in the Philippines and Swarna in India are a few popular rice varieties that have been enhanced with beta-carotene.

5.1.1.2. Biofortification for enhancing Fe content.
Iron is a mineral that is required for human health (Fe). Processing after harvest reduces the amount of Fe in rice more than any other mineral. Iron content in paddy (raw rice) is 38 ppm; after processing, it becomes 8.8 ppm in brown rice and 4.1 ppm in milled rice [203]. Another study found that polishing brown rice lowered the iron content from 19 parts per million to approximately 4 parts per million (4.75-fold reduction) [204]. The problem that led to the development of Fe

biofortification, specifically for milled rice, is the apparent decrease in edible rice grains.

5.1.1.3. Biofortification to boost Zn content. For the treatment of iron deficiency anemia (IDA), sufficient zinc is needed in addition to iron [205]. Zn is also essential for physical development, immune system performance, reproductive health, sensory perception and neurobehavioral progression. A rice variety with Zn biofortification created by conventional breeding in Bangladesh was distributed using CGIAR-Harvest Plus in 2013. Eight types of Zn-biofortified rice are currently accepted by 1.5 million agricultural households, who have been growing them ever since. An IET23832 (DRRDhan45) biofortified semi-dwarf, medium-duration (125 days), non-lodging plant variety with a Zn content of 22.6–24.00 ppm was created by the Indian Institute of Rice Research (IIRR), Hyderabad [206].

5.1.2. Wheat biofortification

A significant agronomic crop used around the world, wheat (*Triticum aestivum* L.) is a long-day, self-pollinating plant of the Poaceae family that thrives in arid and semi-arid climates [207]. It has long been a major staple food, providing more than 30 percent of all food consumed worldwide [208].

5.1.2.1. Biofortification for increased Fe and Zn contents. Every person needs vital minerals and micronutrients to support their metabolism, which comes from food. Critical micronutrients, particularly iron and zinc, are present in wheat at unsatisfactory levels, similar to many other types of staple cereals. Hidden hunger is a serious problem in most developing countries as it is becoming more common in communities with limited resources. Micronutrient deficiencies, especially in zinc and iron, are particularly harmful to women because they can cause growth retardation, impaired immunity, decreased productivity and stunted development. Therefore, this problem should be addressed as soon as possible. Its inadequacies result in malnutrition, abnormal growth, lowered immunity, increased susceptibility to infections and illnesses and other severe risks to human health [209]. Through direct (nutrition-specific) interventions, such as post-harvest food fortification, dietary diversification and nutrient supplementation, as well as indirect (nutrition-sensitive) interventions, such as biofortification, wheat's capacity to reduce micronutrient-related malnutrition can be increased [210]. Although wheat crops are often fortified during processing, biofortification, which requires the creation of new wheat varieties with naturally greater zinc and iron concentrations in their grains, is an efficient and sustainable alternative [211]. Garg et al. demonstrated two typical ways of biofortification: economical for dietary difficulties and genetic biofortification, such as plant breeding and agronomic biofortification, including fertilizer use [22].

5.1.3. Biofortification of maize

Maize is one of Asia's top three cereal crops and a significant contributor to economic growth and food security in Latin America, sub-Saharan Africa (SSA) and the Caribbean. Tryptophan and lysine are two essential amino acids that function as neurotransmitters and protein-building components. Lysine should be consumed in amounts of 35 mg/kg in children and 30 mg/kg in adults each day. According to WHO/FAO/UNU [212], the daily needs for tryptophan are 4.8 and 4 mg/kg body weight for children and adults, respectively. These amino acid deficiencies result in decreased hunger, delayed growth, poor skeletal development and abnormal behavior [213]. Due to this, a variety of Quality Protein Maize (QPM) have been developed with tryptophan and lysine contents approximately twice as high as those of ordinary maize cultivars (lysine: 0.15–0.20 percent in flour; tryptophan: 0.07–0.08 percent in flour), resulting in much higher nutritional quality [214].

5.2. Biofortified vegetables

Vegetable crops are an essential part of an average individual's diet. Therefore, biofortifying vegetables can help alleviate micronutrient deficiencies. The biofortification of vegetables for health benefits is a relatively new phenomenon that has been emphasized by the effort and funding dedicated to addressing human nutritional inadequacies. Biofortification of vegetables is in development in many parts of the world. However, this is a relatively new concept in India [201]. To boost mineral concentrations in edible crops, two complementary techniques can be used.

5.2.1. Techniques for producing biofortified vegetables

5.2.1.1. Conventional breeding. Since yield quality and resistance breeding have received much attention in traditional breeding over the past four decades, the nutrient status of the current varieties has deteriorated. Minerals such as Cu, Mg, Fe and Zn are examples of minerals whose mean concentrations in dry matter have decreased in a variety of plant-based diets. The fortification of vital vitamins, antioxidants and micronutrients has become increasingly crucial owing to recent advancements in traditional plant breeding. Cultivars must have adequate genetic variation in iron, carotene, carotenoids, zinc and other mineral concentrations to select nutrient-appropriate breeding materials to boost the micronutrient profile of staple foods through traditional breeding [22].

5.2.1.2. Genetic engineering. Genetic engineering (GE) is frequently cited as a technology critical for fulfilling future food, feed and energy demands. The quantity of land utilized for biotech crops increased to 179.7 million hectares in 2015 which was more than 100 times that of 1996. In 2013, an all-time high of 175.2 million hectares of transgenic crops was planted worldwide, showing a 3 percent yearly growth rate since the initial large-scale release of the Flavr-Saver tomato in 1996 [215]. The adoption of biotech crops has been

the fastest in recent memory, growing approximately 100 times between 1996 and 2013 [216]. Transgenic or genetically engineered crops enable breeders to introduce beneficial genes into superior cultivars that were previously unavailable, thereby increasing their value. This breakthrough is a revolutionary development in agricultural research because it presents unmatched opportunities for improving the nutritional content, and health benefits and managing infections, pests and viruses.

5.2.1.3. Tomato antioxidants. Fruits and vegetables possess a high content of antioxidants, such as carotenoids (β-carotene and lycopene) and anthocyanins, as well as vitamins C and E. Giovinazzo et al. observed an increased concentration of ascorbate and glutathione, which are soluble antioxidants in primary metabolism, along with an overall enhancement in antioxidant activity in transgenic fruit that accumulates *trans*-resveratrol [217].

5.2.1.4. Tomatoes high in carotenoid. Strong antioxidant lycopene can protect against epithelial cancer and enhance human health. Therefore, increasing the carotenoid content in tomato fruits through genetic modification and enhancing the nutritional quality of the crop is of great interest. Constitutive expression of the Psy-1 gene was performed to increase carotenoid content in tomatoes. This gene is responsible for increasing the conversion of GGPP (geranylgeranyl diphosphate) to phytoene in the first step of the carotenoid synthesis pathway [218].

5.2.1.5. Tomatoes high in flavanols. Transgenic tomato lines that exhibited a significant increase in flavonoid concentrations in the fruit peel were produced by introducing Petunia chi-a, which encodes chalcone isomerase, into tomatoes. These levels increased up to 78 times, mostly because of the significant accumulation of rutin [219]. Ectopic expression of chalcone isomerase, a single biosynthetic enzyme, leads to a 78-fold increase in total fruit flavanols [220].

5.2.1.6. Tomatoes high in folate. According to Díaz et al. even a slight increase in pteridine synthesis can dramatically improve the amount of folate in food crops and increasing the availability of PABA can provide auxiliary advantages [221]. Vine-ripened tomato fruit had more than 20 times the folate content when pteridine-overproduction and transgenic PABA characteristics were crossed together [222]. The expression of the yeast S-adenosylmethionine decarboxylase gene (ySAMdc; Spe 2) linked with a ripening-inducible E8 promoter raises the levels of the polyamines spermidine and spermine in tomato fruit specifically during ripening. Lycopene levels rose as a result and the quality of the fruit juice was improved.

5.3. Bio-fortified egg with increased xanthophyll density and yolk pigmentation

Corn cultivars with high carotene content have been produced through plant breeding [223]. Humans who consume carotenoids through their diet have been found to improve eye health in humans and most importantly, prevent age-related macular degeneration. It may help boost the dietary supply of macular carotenoids in the typical American diet to use high-carotenoid orange maize in poultry diets to increase macular carotenoid concentrations in egg yolks. Three different diets were provided to 360 Novogen White laying hens for thirty-one days. Six groups of 20 chickens each were kept in regular colony cages and fed a particular diet. White, yellow and orange corn were the three different varieties tested and the only difference between the diets was the type of corn used to test its effect on yolk color, egg production and carotenoid deposition. In this study, eggs from the feeding trial and 43 boxes of 12 eggs sourced from various production settings, such as cage-free, free-range/pasture organic, conventional cage, cage-free organic and free-range/pasture systems, were analyzed. Carotenoid densities and yolk color were assessed using a portable colorimeter, high-performance liquid chromatography (HPLC) and DSM Yolk Fan. In comparison with egg yolks from hens fed the yellow diet (5–6 DSM and 12.3–17.7 mg/g xanthophylls) and the white diet (1–2 DSM and 2.5–3.0 mg/g xanthophylls), those from hens fed the orange corn diet showed higher DSM yolk color (6–10) and total xanthophyll content (23.5–35.3 mg/g of egg yolk). After 12 days of treatment, the orange-corn diet (35.3 mg/g of egg yolk) caused the highest level of xanthophyll deposition in egg yolks, which then remained constant. The results of the evaluation of commercial egg brands revealed that egg yolks from the orange-corn diet had greater amounts of xanthophyll (30–61 percent). This indicates that adding carotenoid-rich orange corn to hen diets can effectively increase xanthophyll density of eggs [224].

Biofortification techniques have been investigated for meat production to boost the concentration of vitamin D, an essential nutrient that affects the functioning of the immune system, bone health and general well-being. There are several ways to biofortify meat with vitamin D, such as feeding livestock feed additives rich in vitamin D or exposing them to ultraviolet (UV) light. These methods increase the amount of vitamin D synthesized and accumulated in animal tissues, which increases the concentration of vitamin D in meat products. According to previous studies, biofortification can effectively increase the amount of vitamin D in meat, providing customers with a dietary supply of this essential mineral [225]. The choice of vitamin type (e.g., vitamin D2 or D3) is important for improving the natural vitamin D concentration in meat through biofortification. The maximum amount of vitamin D that can be included in European bovine diets is 4000 IU of vitamin D2 or D3 per kilogram of complete nutrition, as stated in Article 9t (b) of Council Directive 70/524/EEC. Furthermore, under the same directive, the European Food Safety Authority's regulation on the addition of vitamin D to poultry and swine feeds specifies the maximum inclusion rate for both vitamin D3 and D2 combined as 2000 IU and 3000 IU vitamin D per kilogram of feed, respectively. For swine and poultry nutrition, commercially available 25-OH-D3 is recommended for inclusion at 75 and 50 g/kg of feed, respectively. However, it is important to note that 25-OH-D3 is not permitted in cattle diet. This compound exhibits five-fold the biological vitamin D activity of vitamin D3, making its addition to pig and poultry diets significant. Notably, 25-OH-D3 bypasses the first hydroxylation stage in the liver because of its higher polarity, enabling rapid

absorption from the proximal jejunum into the portal vein [226]. Thus, it is concluded that biofortification is also a method for increasing the amount of vitamin D in meat, which will enhance nutritional quality and may solve the issue of vitamin D deficiency in the public.

6. Conclusion

In summary, biofortification appears to be a viable approach for addressing dietary deficiencies and preventing malnutrition. Biofortification provides a sustainable and economical means of boosting the nutritional value of staple crops through selective genetic modification, innovative breeding methods and suitable mineral fertilization. The efficacy of biofortification programs in providing vital micronutrients such as iron, zinc, selenium and provitamin A to susceptible groups underscores their capacity to mitigate the health consequences associated with malnutrition, especially in poor countries. Furthermore, the combined efforts of interdisciplinary research teams and national and international organizations highlight the shared commitment to promoting biofortification as a crucial part of global food security and nutrition initiatives.

Biofortification has great potential to treat global hunger and enhance future public health outcomes. Advances in biotechnology, such as CRISPR-Cas9, a gene-editing technique, have intriguing prospects for creating biofortified crops with improved nutritional profiles. To scale up biofortification activities globally, cooperation among governments, research institutions, non-governmental organizations and the commercial sector is essential. To maximize the impact, biofortification solutions must be tailored to address specific nutrient shortages that are common in certain populations and areas. For biofortified foods to be widely accepted, it is crucial to address consumer concerns about genetic manipulation and educate consumers about the health advantages of these foods. The adoption of biofortification is facilitated by policy support and investment from governments, which include the implementation of regulatory frameworks that support the practice and allocation of funds for research and development. Incorporating biofortification into more comprehensive food security plans is essential to achieve sustainable development objectives for health and nutrition. By adopting these opportunities and addressing current issues, biofortification can maintain its status as a potent instrument for enhancing global food security and waging a widespread war against malnutrition.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

Data will be made available on request.

CRediT authorship contribution statement

Bindu Naik: Writing – review & editing, Writing – original draft, Visualization, Validation, Conceptualization. **Vijay Kumar:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Investigation, Formal analysis, Conceptualization. **Sheikh Rizwanuddin:** Writing – review & editing, Writing – original draft. **Sadhna Mishra:** Writing – review & editing, Writing – original draft. **Vivek Kumar:** Writing – review & editing, Writing – original draft. **Per Erik Joakim Saris:** Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization. **Naresh Khanduri:** Writing – review & editing, Writing – original draft. **Akhilesh Kumar:** Writing – review & editing, Writing – original draft. **Piyush Pandey:** Writing – review & editing, Writing – original draft. **Arun Kumar Gupta:** Writing – review & editing, Writing – original draft. **Javed Masood Khan:** Writing – review & editing, Writing – original draft. **Sarvesh Rustagi:** Writing – review & editing, Writing – original draft.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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