Bio-fortification and Its Impact on Global Health

Abstract

Biofortification, the process of increasing the density of vitamins and minerals in a crop through plant breeding, agronomic practices, or biotechnology, is being increasingly recognized as a cost-effective and sustainable strategy to address micronutrient malnutrition globally. This comprehensive review provides an in-depth analysis of the role of biofortification in improving global health, with a particular focus on its impact on micronutrient deficiencies, public health, and socioeconomic aspects, along with the challenges and opportunities it presents. The review is timely and relevant, given the persistent challenge of micronutrient malnutrition and the growing interest in sustainable nutrition strategies. It addresses gaps in the current understanding by synthesizing the latest research on various aspects of biofortification and providing insights into its potential and challenges. Biofortification encompasses various methods, from traditional breeding to modern biotechnological approaches. Numerous successful examples of biofortified crops, like Golden Rice and High Iron Beans, underscore its potential. These crops have been demonstrated to contribute significantly to reducing deficiencies of essential micronutrients like iron, vitamin A, and zinc, thereby positively influencing public health outcomes. The review also explores the wider impact of biofortification, including its economic benefits and influence on food security and farmer livelihoods. Acceptance by farmers and consumers and the sociocultural context are highlighted as crucial factors for the successful implementation of biofortification initiatives. Biofortification faces several challenges, ranging from technical issues in the biofortification process, including genetic limitations and bioavailability concerns, to political and regulatory hurdles. Additionally, the environmental impact and sustainability of biofortified crops are critical considerations. Despite these challenges, opportunities exist for future research and development, such as expanding the scope of biofortification, harnessing advanced breeding techniques, and integrating biofortification with other nutrition strategies.

Keywords: *Biofortification, Malnutrition, Biotechnology, Sustainability, Micronutrients*

Introduction

Global health refers to health issues that transcend national borders and governments and call for actions on the global forces that determine the health of people [1]. It incorporates various fields, aiming to achieve equity in health for all people worldwide and emphasizing transnational health issues, determinants, and solutions [2]. As per the World Health Organization, global health issues are characterized by a universal susceptibility to adverse health conditions, including malnutrition [3]. Malnutrition a broad term for a range of conditions affecting people who do not get the right amount or type of nutrients remains a serious global health problem [4]. It exists in various forms, the most common being undernutrition (including wasting, stunting, and underweight), micronutrient-related malnutrition (a lack or excess of essential vitamins and minerals), and overweight or obesity [5]. The Food and Agriculture Organization of the United Nations (FAO) estimates that nearly 690 million people, about 8.9% of the world's population, were hungry in 2019, with the vast majority living in low and middle-income countries [6]. In particular, micronutrient malnutrition or 'hidden hunger,' a chronic lack of vitamins and minerals, afflicts over two billion individuals globally, causing long-term, severe health consequences and socio-economic challenges [7]. Biofortification enhancing the nutritional value of crops through conventional plant breeding, agronomic practices, or biotechnology considered a promising solution to the malnutrition problem [8]. Biofortification is cost-effective and sustainable, targeting rural populations that might be difficult to reach through other nutritional interventions [9]. It involves the enhancement of a crop's genetic potential to synthesize or accumulate specific nutrients to improve human health significantly [10]. This approach contrasts with conventional fortification, which occurs post-harvest and can be more expensive and logistically challenging in resource-poor settings [11]. Biofortified crops have been developed for several nutrients, including vitamin A, iron, and zinc, which are often lacking in the diets of people at risk of malnutrition [12]. This review aims to comprehensively examine the biofortification concept, its application, and its impact on global health. We begin with an exploration of the biofortification process, its methods, and techniques. Then, we delve into the measurable impact of biofortification on global health, examining case studies and specific examples. We also touch upon the socio-economic impacts of biofortification and discuss the associated challenges and opportunities. Finally, we discuss policy implications and recommendations, focusing on the integration of biofortification into broader health and agricultural policies. The purpose of this review is threefold: to provide an overview of the existing literature on biofortification and its role in global health. to highlight the successful applications and potential challenges in implementing biofortification strategies and to suggest ways forward for researchers, policymakers, and practitioners in the field.

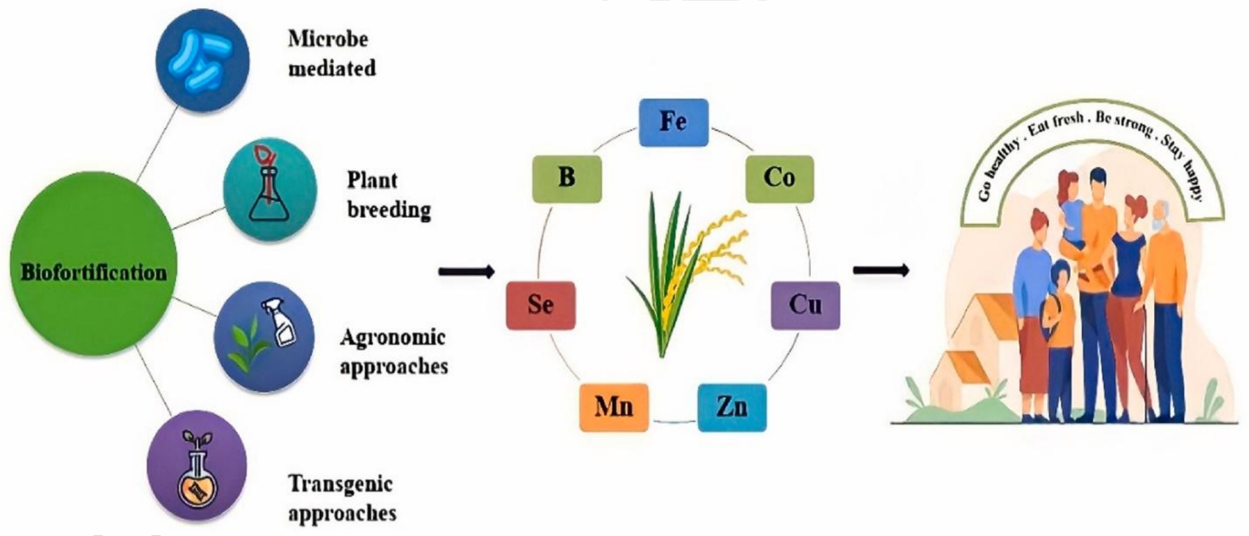

Image 1: Biofortification in human health (Source: https://www.sciencedirect.com/)

Conceptual Framework

Biofortification is a sustainable agricultural strategy aimed at increasing the nutrient levels in staple food crops through plant breeding, genetic modification, or agronomic practices [13]. The term was first coined by Bouis and Welch to define the process of conventionally breeding crops to increase their nutritional value, particularly in terms of essential micronutrients. These essential micronutrients include iron, zinc, and vitamin A, deficiencies of which contribute significantly to the global burden of disease [14]. Biofortification is distinguished from conventional fortification because it focuses on plant foods only, and the aim is to increase nutrient levels in crops during plant growth rather than through manual means during food processing [15]. It is a unique and promising approach to enhance nutrient intakes across populations, including the rural poor, who often have limited access to commercially fortified foods and diverse diets [16]. There are three main types of biofortification: conventional breeding, agronomic, and transgenic. Conventional breeding involves cross-breeding two varieties of a crop to combine desirable traits from each into a single, high-yielding variety [17]. For example, plant breeders can cross a high-iron variety with a high-yielding variety to create a new variety that is both high-yielding and high in iron [18]. Agronomic biofortification involves the application of nutrients to the crop or soil, often through fertilizer, to increase the nutrient content of the harvested part of the crop [19]. This method has been especially successful in increasing the selenium and iodine content of crops [20]. Transgenic biofortification is the introduction of a new gene into a crop to increase its nutrient content. The most well-known example is "Golden Rice," a genetically modified crop that contains a gene from corn, allowing it to produce beta-carotene, a precursor of vitamin A [21].

Biofortification in Agricultural and Food Systems

Biofortification plays a crucial role in agricultural and food systems as it has the potential to increase the nutritional quality of food crops and thus improve public health. It is a practical approach to delivering micronutrients to populations that may have limited access to diverse diets or other micronutrient interventions [22]. Additionally, biofortification is considered a highly cost-effective strategy for addressing micronutrient malnutrition on a global scale, particularly in comparison with other interventions such as dietary diversification or micronutrient supplementation [23]. By enhancing the nutritional quality of food crops, biofortification can also contribute to food security, which is defined as access to sufficient, safe, and nutritious food by all people at all times [24]. Biofortification can make a significant contribution towards achieving several of the United Nations Sustainable Development Goals, including ending hunger, achieving food security, improving nutrition and promoting sustainable agriculture [25]. Biofortification also benefits farmers. By focusing on staple crops that are already widely grown and consumed, biofortification can be integrated into existing agricultural systems, making it a sustainable strategy [26]. Because biofortified crops do not require any special treatment or cost more than other crops, farmers can adopt them without changing their farming practices or incurring additional costs [27].

Nutritional Deficiencies Worldwide

Nutritional deficiencies, often referred to as 'hidden hunger' due to the lack of visible warning signs, have severe health and economic implications and can impede national development efforts [28]. Micronutrient deficiencies affect over two billion individuals globally [29]. Iron, vitamin A, and zinc deficiencies are among the most prevalent and contribute significantly to the global burden of disease [30]. Iron deficiency is the most common and widespread nutritional disorder in the world, affecting a significant proportion of the population in both developing and developed countries [31]. The World Health Organization estimates that over 30% of the world's population is iron deficient, causing widespread adverse health effects, including impaired physical and cognitive development, increased maternal and child mortality, and decreased physical performance [32]. Vitamin A deficiency is a public health problem in more than half of all countries, especially in Africa and Southeast Asia, hitting hardest at young children and pregnant women in low-income countries [33]. Severe deficiencies can have harmful consequences, including blindness and increased mortality due to infections. Zinc deficiency affects around 17% of the global population and is particularly prevalent in Sub-Saharan Africa and South Asia. Zinc is necessary for growth and development, immune response, neurological function, and reproduction, and its deficiency can lead to numerous health issues, including stunted growth, diarrhoea, and increased susceptibility to infection.

Methods and Techniques in Biofortification

Biofortification employs both traditional plant breeding and modern biotechnological methods to improve the nutrient content of food crops. This section discusses these methods and provides examples of successful biofortified crops. Traditional breeding methods have been the cornerstone of biofortification. These methods use the natural genetic diversity of crops to select and breed varieties with higher micronutrient content [34]. The process typically involves cross-breeding varieties with high nutrient content and high yield potential [35]. The offspring are then selected for further breeding, with an emphasis on those that retain the desired traits, such as high yield and nutrient content, disease resistance, and adaptability to local growing conditions [36]. This iterative process continues until a variety with the desired characteristics is developed. The traditional breeding process is laborious, and it may take several years to develop a biofortified variety [37]. However, once developed, these biofortified varieties are usually well adapted to local growing conditions and consumer preferences [38]. Also, traditional breeding methods do not introduce new genes into the crops, thus reducing regulatory and acceptance issues that often accompany genetically modified crops [39]. Modern biotechnological methods, including genetic modification and gene editing, offer opportunities to improve nutrient content in crops beyond what is possible through traditional breeding. Genetic modification (GM) involves introducing one or more genes from another organism into a crop's genome. This method has been used to develop biofortified crops when conventional breeding is challenging. For example, the most notable GM biofortified crop is Golden Rice, which has been genetically engineered to produce beta-carotene in the endosperm, the part of the rice grain that is consumed [40]. This was possible because rice naturally lacks the pathway to produce beta-carotene in the endosperm. Gene editing, a newer technology, allows for precise modifications in a crop's existing genes without introducing foreign genes. This method has potential applications in biofortification, for instance, to knock out genes that inhibit nutrient bioavailability. The most common gene editing technology is CRISPR/Cas9, which has been used to improve iron, zinc, and provitamin A content in rice [41]. While these technologies offer significant potential, it is important to note that GM and gene-edited crops are subject to regulatory approval, and public acceptance varies across regions [42]. Also, they require considerable technical expertise and resources, which may limit their use in resource-poor settings [43].

Examples of Successful Biofortified Crops

Several biofortified crops have been developed and disseminated around the world. These include, but are not limited to:

C.1 Golden Rice: As previously mentioned, Golden Rice is a GM crop that produces beta-carotene in the endosperm. The beta-carotene is converted into vitamin A in the human body. Golden Rice was developed as a strategy to combat vitamin A deficiency, which is prevalent in many regions where rice is a staple food [44].

C.2 High Iron Beans: High Iron Beans have been developed using traditional breeding methods to help combat iron deficiency. These beans have almost twice the iron content of regular beans and have been released in several countries, including Rwanda and DR Congo, showing promising results in improving iron status among consumers [45].

C.3 Zinc Wheat: Zinc wheat was developed using traditional breeding methods to improve zinc content. Field trials have shown that zinc wheat can provide 20-40% more zinc than regular wheat, contributing significantly to daily zinc requirements [46].

Biofortification on Global Health

Biofortification is a key strategy to combat the pervasive global problem of micronutrient deficiencies. By incorporating biofortified crops into their regular diets, populations worldwide can consume more essential nutrients, consequently leading to improved overall health. Iron deficiency is a leading cause of anaemia, a condition characterized by a decrease in the number of red blood cells or the amount of haemoglobin in the blood, which impedes the ability to transport oxygen effectively [47]. Biofortification has shown promising results in combating this widespread issue. Vitamin A deficiency is a major public health problem in many low-income countries, leading to impaired immune function, blindness, and even death [48]. Biofortified crops rich in beta-carotene, a precursor of vitamin A, have demonstrated efficacy in combating this deficiency. Golden Rice, for instance, has been genetically engineered to produce beta-carotene, which the human body can convert into vitamin A. A study in the Philippines showed that consumption of Golden Rice improved the vitamin A status of children [49]. Hence, biofortified crops like Golden Rice could significantly contribute to reducing the burden of vitamin A deficiency. Zinc deficiency is widespread, causing growth retardation, loss of appetite, and impaired immune function [50]. Zinc biofortified wheat has been developed to combat this deficiency. The impact of biofortified crops extends beyond just reducing micronutrient deficiencies. By improving nutritional status, biofortification can reduce morbidity and mortality rates. For instance, improved iron status from consuming biofortified crops can reduce the risk of maternal mortality by preventing severe anaemia during pregnancy [51]. Likewise, enhancing vitamin A status through biofortified crops can reduce child mortality by improving immune function and reducing the severity of infections. Therefore, biofortification can play a crucial role in improving public health outcomes, particularly in resource-poor settings where micronutrient deficiencies are rampant and diet diversification is challenging.

Socioeconomic Impacts of Biofortification

Biofortification, along with its nutritional and health impacts, also has profound socioeconomic implications. This section explores the economic benefits of biofortification, its influence on food security and the livelihoods of farmers, and its sociocultural acceptance. The cost-effectiveness of biofortification in combatting micronutrient deficiencies is increasingly recognized. Traditional supplementation and fortification approaches often require repeated interventions and continuous funding, whereas biofortification is a one-time investment with a lasting impact [52]. Once farmers start growing and consumers start eating biofortified crops, the benefits continue as long as the crop is grown and consumed. Studies have shown that biofortification can be a highly cost-effective strategy. The return on investment in biofortification is significant considering its health and economic impacts. An ex-ante analysis of the potential impact of biofortified crops on vitamin A, iron, and zinc deficiencies estimated that every dollar invested in biofortification could benefit 15 to 20 people. Furthermore, a study by Straeten *et al.* [53] found that the ROI of biofortification, considering health and economic benefits, could be quite substantial, with benefits exceeding costs by a considerable margin. Therefore, from an economic standpoint, biofortification offers a strong investment case. Biofortification can also have significant impacts on food security and the livelihoods of farmers. Biofortified crops not only provide enhanced nutritional value but can also contribute to food security. Since these crops are bred to be high-yielding and adaptable to local growing conditions, they can contribute to increased agricultural productivity and thus improve food availability [54]. Furthermore, by improving nutritional status, biofortified crops can enhance the ability of individuals to lead active and productive lives, thus improving food utilization, another pillar of food security. Farmers who adopt biofortified crops can benefit from increased yields and improved crop characteristics, such as disease resistance, which can lead to enhanced income and livelihood security. For example, high-iron beans released in Rwanda have shown yield advantages over local varieties, leading to increased income for farmers. Moreover, since biofortified crops are bred to be adaptable to local growing conditions, they are often more resilient to environmental stresses such as drought and disease, providing further benefits to farmers [55]. While biofortification has numerous potential benefits, its success heavily depends on its sociocultural acceptance. Consumers' acceptance of biofortified crops can be influenced by several factors, including taste, appearance, cooking characteristics, and cultural beliefs. For instance, in Uganda, the introduction of orange-fleshed sweet potatoes, which are biofortified with vitamin A, was initially met with resistance due to their unfamiliar colour. However, through community-based promotional activities, the consumption of these sweet potatoes increased substantially. Farmers' acceptance of biofortified crops, on the other hand, can be influenced by factors such as yield potential, disease resistance, and marketability. Ensuring that biofortified crops meet these criteria, along with their nutritional enhancements, is crucial for successful adoption by farmers.

Challenges and Opportunities in Biofortification

While biofortification offers immense potential in addressing micronutrient deficiencies, there exist several challenges, ranging from technical issues in the biofortification process to political and regulatory hurdles. In the face of these challenges, however, there also exist opportunities for future research and development, which could drive advancements in the field. Biofortification relies on the existence of genetic variation in the nutrient content of crops. In cases where such variation is limited, enhancing the nutrient levels becomes challenging. Moreover, breeding for higher nutrient content can sometimes result in trade-offs with other desirable traits, such as yield or disease resistance [56]. However, with advancements in breeding techniques and a better understanding of the genetic basis of nutrient content, these challenges could potentially be overcome. The impact of biofortified crops on nutrition status is also affected by the bioavailability of the nutrients, i.e., the proportion of the nutrient that is absorbed and utilized by the body. The bioavailability of certain nutrients, such as iron and zinc, can be influenced by various factors, including the presence of other dietary components. Research is ongoing to address these challenges by identifying ways to enhance nutrient bioavailability in biofortified crops. One of the key challenges to the advancement of biofortification is the lack of political will and adequate funding. While the cost-effectiveness of biofortification is well recognized, it often competes with other public health priorities for funding [57]. Advocacy and evidence generation are needed to garner political commitment and financial support for biofortification initiatives. For biofortified crops developed using biotechnological methods, such as genetic modification, there exist considerable regulatory challenges. The process of getting approval for genetically modified organisms (GMOs) is lengthy and complex, often requiring rigorous safety assessments. These regulatory hurdles can delay the introduction of biofortified crops and add to their development costs. While biofortified crops can contribute to improving nutrition, their environmental impact is also a concern. The cultivation of biofortified crops, like any other agricultural practice, can have implications for soil health, water use, and biodiversity [58]. It is important to ensure that biofortification efforts are integrated with sustainable farming practices to minimize their environmental footprint. Another concern with biofortified crops is their sustainability, particularly to their acceptance by farmers and consumers. If farmers do not adopt biofortified varieties or if consumers do not prefer them, the sustainability of biofortification initiatives can be compromised. Efforts are needed to ensure that biofortified crops are not only nutritionally superior but also agronomically desirable and culturally acceptable. Despite the challenges, biofortification offers numerous opportunities for future research and development. While current biofortification efforts have primarily focused on a few key nutrients, such as vitamin A, iron, and zinc, there is potential to expand the scope of biofortification to other important nutrients. For instance, research is ongoing to develop crops biofortified with essential amino acids, vitamins, and other micronutrients [59]. Advanced breeding techniques, such as marker-assisted selection and gene editing, offer exciting opportunities to enhance the efficiency and precision of the biofortification process. These techniques could allow breeders to simultaneously improve multiple traits, such as nutrient content, yield, and disease resistance, thus overcoming some of the breeding challenges associated with biofortification. Biofortification can be effectively integrated with other nutrition strategies, such as dietary diversification and supplementation, to maximize its impact. For instance, combining biofortification with nutrition education can enhance dietary diversity and improve overall nutrition status [60].

Conclusion

Biofortification represents a significant opportunity to address global micronutrient malnutrition. It combines advancements in agricultural sciences with public health initiatives, offering a sustainable approach to improving global health. While challenges such as technical limitations, political, and regulatory issues, and environmental concerns exist, they can be surmounted with continuous research, supportive policies, and advanced technologies. Importantly, the expansion of biofortification to a wider range of nutrients and integration with other nutrition strategies can further enhance its impact. Therefore, biofortification should be given due consideration in global strategies aimed at improving nutrition and health outcomes.

References:

1. Kickbusch, I., & Berger, C. (2010). Global health diplomacy. In *Routledge Handbook of Global Public Health* (pp. 275-281). Routledge.

2. Jogerst, K., Callender, B., Adams, V., Evert, J., Fields, E., Hall, T., ... & Wilson, L. L. (2015). Identifying interprofessional global health competencies for 21st-century health professionals. *Annals of global health*, *81*(2), 239-247.

3. World Health Organization. (2017). *Integrating neglected tropical diseases into global health and development: fourth WHO report on neglected tropical diseases*. World Health Organization.

4. Cederholm, T., Bosaeus, I., Barazzoni, R., Bauer, J., Van Gossum, A., Klek, S., ... & Singer, P. (2015). Diagnostic criteria for malnutrition–an ESPEN consensus statement. *Clinical nutrition*, *34*(3), 335-340.

5. Ntenda, P. A. M. (2019). Association of low birth weight with undernutrition in preschool-aged children in Malawi. *Nutrition journal*, *18*(1), 1-15.

6. Arora, N. K., & Mishra, I. (2022). Current scenario and future directions for sustainable development goal 2: A roadmap to zero hunger. *Environmental Sustainability*, *5*(2), 129-133.

7. Muthayya, S., Rah, J. H., Sugimoto, J. D., Roos, F. F., Kraemer, K., & Black, R. E. (2013). The global hidden hunger indices and maps: an advocacy tool for action. *PloS one*, *8*(6), e67860.

8. Saltzman, A., Birol, E., Oparinde, A., Andersson, M. S., Asare- Marfo, D., Diressie, M. T., ... & Zeller, M. (2017). Availability, production, and consumption of crops biofortified by plant breeding: current evidence and future potential. *Annals of the New York Academy of Sciences*, *1390*(1), 104-114.

9. Mayer, J. E., Pfeiffer, W. H., & Beyer, P. (2008). Biofortified crops to alleviate micronutrient malnutrition. *Current opinion in plant biology*, *11*(2), 166-170.

10. DellaPenna, D. (1999). Nutritional genomics: manipulating plant micronutrients to improve human health. *Science*, *285*(5426), 375-379.

11. Pazhanisamy, S. 10. Digital Farming: Prospects and Obstacles in India. *Eco-friendly Pest Management Strategies for Major Vegetable Crops*, 22.

12. Majumder, S., Datta, K., & Datta, S. K. (2019). Rice biofortification: high iron, zinc, and vitamin-A to fight against “hidden hunger”. *Agronomy*, *9*(12), 803.

13. Saltzman, A., Birol, E., Oparinde, A., Andersson, M. S., Asare‐ Marfo, D., Diressie, M. T., ... & Zeller, M. (2017). Availability, production, and consumption of crops biofortified by plant breeding: current evidence and future potential. *Annals of the New York Academy of Sciences*, *1390*(1), 104-114.

14. Simpson, J. L., Bailey, L. B., Pietrzik, K., Shane, B., & Holzgreve, W. (2011). Micronutrients and women of reproductive potential: required dietary intake and consequences of dietary deficienty or excess. Part II-Vitamin D, Vitamin A, Iron, Zinc, Iodine, Essential Fatty Acids. *The Journal of Maternal-Fetal & Neonatal Medicine*, *24*(1), 1-24.

15. Yadav, D. N., Bansal, S., Tushir, S., Kaur, J., & Sharma, K. (2020). Advantage of biofortification over fortification technologies. In *Wheat and barley grain biofortification* (pp. 257-273). Woodhead Publishing.

16. García-Bañuelos, M. L., Sida-Arreola, J. P., & Sánchez, E. (2014). Biofortification-promising approach to increasing the content of iron and zinc in staple food crops. *Journal of Elementology*, *19*(3).

17. Oladosu, Y., Rafii, M. Y., Abdullah, N., Hussin, G., Ramli, A., Rahim, H. A., ... & Usman, M. (2016). Principle and application of plant mutagenesis in crop improvement: a review. *Biotechnology & Biotechnological Equipment*, *30*(1), 1-16.

18. Younas, A., Sadaqat, H. A., Kashif, M., Ahmed, N., & Farooq, M. (2020). Combining ability and heterosis for grain iron biofortification in bread wheat. *Journal of the Science of Food and Agriculture*, *100*(4), 1570-1576.

19. De Valença, A. W., Bake, A., Brouwer, I. D., & Giller, K. E. (2017). Agronomic biofortification of crops to fight hidden hunger in sub-Saharan Africa. *Global food security*, *12*, 8-14.

20. Gonzali, S., Kiferle, C., & Perata, P. (2017). Iodine biofortification of crops: agronomic biofortification, metabolic engineering and iodine bioavailability. *Current opinion in biotechnology*, *44*, 16-26.

21. Greedy, D. (2018). Golden Rice is safe to eat, says FDA. *Nat. Biotechnol*, *36*(7), 559.

22. Langyan, S., Yadava, P., Khan, F. N., Bhardwaj, R., Tripathi, K., Bhardwaj, V., ... & Kumar, A. (2022). Nutritional and food composition survey of major pulses toward healthy, sustainable, and biofortified diets. *Frontiers in Sustainable Food Systems*, *6*, 878269.

23. Wakeel, A., Farooq, M., Bashir, K., & Ozturk, L. (2018). Micronutrient malnutrition and biofortification: recent advances and future perspectives. *Plant micronutrient use efficiency*, 225-243.

24. Simkin, A. J. (2019). Genetic engineering for global food security: Photosynthesis and biofortification. *Plants*, *8*(12), 586.

25. Rehman, A. U., Masood, S., Khan, N. U., Abbasi, M. E., Hussain, Z., & Ali, I. (2021). Molecular basis of Iron Biofortification in crop plants; A step towards sustainability. *Plant Breeding*, *140*(1), 12-22.

26. Qaim, M., Stein, A. J., & Meenakshi, J. V. (2007). Economics of biofortification. *Agricultural Economics*, *37*, 119-133.

27. Mayer, J. E., Pfeiffer, W. H., & Beyer, P. (2008). Biofortified crops to alleviate micronutrient malnutrition. *Current opinion in plant biology*, *11*(2), 166-170.

28. Titcomb, T. J., & Tanumihardjo, S. A. (2019). Global concerns with B vitamin statuses: biofortification, fortification, hidden hunger, interactions, and toxicity. *Comprehensive Reviews in Food Science and Food Safety*, *18*(6), 1968-1984.

29. Black, R. (2003). Micronutrient deficiency: an underlying cause of morbidity and mortality. *Bulletin of the World Health Organization*, *81*(2), 79-79.

30. Caulfield, L. E., & Black, R. E. (2004). Zinc deficiency. *Comparative quantification of health risks: global and regional burden of disease attributable to selected major risk factors*, *1*, 257-280.

31. Baltussen, R., Knai, C., & Sharan, M. (2004). Iron fortification and iron supplementation are cost-effective interventions to reduce iron deficiency in four subregions of the world. *The Journal of nutrition*, *134*(10), 2678-2684.

32. Pasricha, S. R., Drakesmith, H., Black, J., Hipgrave, D., & Biggs, B. A. (2013). Control of iron deficiency anemia in low-and middle-income countries. *Blood, the Journal of the American Society of Hematology*, *121*(14), 2607-2617.

33. Pasricha, S. R., & Biggs, B. A. (2010). Undernutrition among children in south and south- east Asia. *Journal of paediatrics and child health*, *46*(9), 497-503.

34. Sakellariou, M., & Mylona, P. V. (2020). New uses for traditional crops: the case of barley biofortification. *Agronomy*, *10*(12), 1964.

35. Oladosu, Y., Rafii, M. Y., Abdullah, N., Hussin, G., Ramli, A., Rahim, H. A., ... & Usman, M. (2016). Principle and application of plant mutagenesis in crop improvement: a review. *Biotechnology & Biotechnological Equipment*, *30*(1), 1-16.

36. Oltenacu, P. A., & Broom, D. M. (2010). The impact of genetic selection for increased milk yield on the welfare of dairy cows. *Animal welfare*, *19*(S1), 39-49.

37. Ortiz-Monasterio, J. I., Palacios-Rojas, N., Meng, E., Pixley, K., Trethowan, R., & Pena, R. J. (2007). Enhancing the mineral and vitamin content of wheat and maize through plant breeding. *Journal of Cereal Science*, *46*(3), 293-307.

38. Chowdhury, S., Meenakshi, J. V., Tomlins, K. I., & Owori, C. (2011). Are consumers in developing countries willing to pay more for micronutrient- dense biofortified foods? Evidence from a field experiment in Uganda. *American Journal of Agricultural Economics*, *93*(1), 83-97.

39. Lassoued, R., Macall, D. M., Hesseln, H., Phillips, P. W., & Smyth, S. J. (2019). Benefits of genome-edited crops: expert opinion. *Transgenic research*, *28*(2), 247-256.

40. Kumar, K., Gambhir, G., Dass, A., Tripathi, A. K., Singh, A., Jha, A. K., ... & Rakshit, S. (2020). Genetically modified crops: current status and future prospects. *Planta*, *251*, 1-27.

41. Fiaz, S., Ahmad, S., Noor, M. A., Wang, X., Younas, A., Riaz, A., ... & Ali, F. (2019). Applications of the CRISPR/Cas9 system for rice grain quality improvement: perspectives and opportunities. *International journal of molecular sciences*, *20*(4), 888.

42. Dahlstrom, M. F., Wang, Z., Lindberg, S., Opfer, K., & Cummings, C. L. (2022). The media's taste for gene-edited food: Comparing media portrayals within US and European regulatory environments. *Science, Technology, & Human Values*, 01622439221108537.

43. Turnbull, C., Lillemo, M., & Hvoslef-Eide, T. A. (2021). Global regulation of genetically modified crops amid the gene edited crop boom–a review. *Frontiers in Plant Science*, *12*, 630396.

44. Buu, M. (2003). Golden Rice: Genetically Modified to Reduce Vitamin A Deficiency, Benefit or Hazard?. *Nutrition Bytes*, *9*(2).

45. Junqueira-Franco, M. V. M., de Oliveira, J. E. D., Nutti, M. R., Pereira, H. S., de Carvalho, J. L. V., Abrams, S. A., ... & Marchini, J. S. (2018). Iron absorption from beans with different contents of iron, evaluated by stable isotopes. *Clinical nutrition ESPEN*, *25*, 121-125.

46. Balk, J., Connorton, J. M., Wan, Y., Lovegrove, A., Moore, K. L., Uauy, C., ... & Shewry, P. R. (2019). Improving wheat as a source of iron and zinc for global nutrition. *Nutrition Bulletin*, *44*(1), 53-59.

47. Tatala, S., Svanberg, U., & Mduma, B. (1998). Low dietary iron availability is a major cause of anemia: a nutrition survey in the Lindi District of Tanzania. *The American journal of clinical nutrition*, *68*(1), 171-178.

48. Tanumihardjo, S. A., Palacios, N., & Pixley, K. V. (2010). Provitamin A carotenoid bioavailability: what really matters?. *International Journal for Vitamin and Nutrition Research*, *80*(4), 336.

49. Zimmermann, R., & Qaim, M. (2004). Potential health benefits of Golden Rice: a Philippine case study. *Food Policy*, *29*(2), 147-168.

50. Prasad, A. S. (2012). Discovery of human zinc deficiency: 50 years later. *Journal of Trace Elements in Medicine and Biology*, *26*(2-3), 66-69.

51. Stoltzfus, R. J. (2011). Iron interventions for women and children in low-income countries. *The Journal of nutrition*, *141*(4), 756S-762S.

52. Gupta, S., Brazier, A. K. M., & Lowe, N. M. (2020). Zinc deficiency in low- and middle- income countries: prevalence and approaches for mitigation. *Journal of Human Nutrition and Dietetics*, *33*(5), 624-643.

53. Van Der Straeten, D., Bhullar, N. K., De Steur, H., Gruissem, W., MacKenzie, D., Pfeiffer, W., ... & Bouis, H. (2020). Multiplying the efficiency and impact of biofortification through metabolic engineering. *Nature Communications*, *11*(1), 5203.

54. Murphy, K., Lammer, D., Lyon, S., Carter, B., & Jones, S. S. (2005). Breeding for organic and low-input farming systems: An evolutionary–participatory breeding method for inbred cereal grains. *Renewable Agriculture and Food Systems*, *20*(1), 48-55.

55. Shiferaw, B., Prasanna, B. M., Hellin, J., & Bänziger, M. (2011). Crops that feed the world 6. Past successes and future challenges to the role played by maize in global food security. *Food security*, *3*, 307-327.

56. Snell- Rood, E., Cothran, R., Espeset, A., Jeyasingh, P., Hobbie, S., & Morehouse, N. I. (2015). Life- history evolution in the anthropocene: Effects of increasing nutrients on traits and trade- offs. *Evolutionary applications*, *8*(7), 635-649.

57. De Steur, H., Gellynck, X., Blancquaert, D., Lambert, W., Van Der Straeten, D., & Qaim, M. (2012). Potential impact and cost-effectiveness of multi-biofortified rice in China. *New Biotechnology*, *29*(3), 432-442.

58. Bertola, M., Ferrarini, A., & Visioli, G. (2021). Improvement of soil microbial diversity through sustainable agricultural practices and its evaluation by-omics approaches: A perspective for the environment, food quality and human safety. *Microorganisms*, *9*(7), 1400.

59. Garcia- Casal, M. N., Peña- Rosas, J. P., Giyose, B., & Consultation Working Groups. (2017). Staple crops biofortified with increased vitamins and minerals: considerations for a public health strategy. *Annals of the New York Academy of Sciences*, *1390*(1), 3-13.

60. Sharma, P., Aggarwal, P., & Kaur, A. (2017). Biofortification: A new approach to eradicate hidden hunger. *Food Reviews International*, *33*(1), 1-21.