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Nano-biofortification of different crops to immune against COVID-19: A review

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ABSTRACT

Human health and its improvement are the main target of several studies related to medical, agricultural and industrial sciences. The human health is the primary conclusion of many studies. The improving of human health may include supplying the people with enough and safe nutrients against malnutrition to fight against multiple diseases like COVID-19. Biofortification is a process by which the edible plants can be enriched with essential nutrients for human health against malnutrition. After the great success of biofortification approach in the human struggle against malnutrition, a new biotechnological tool in enriching the crops with essential nutrients in the form of nanoparticles to supplement human diet with balanced diet is called nano-biofortification. Nano biofortification can be achieved by applying the nano particles of essential nutrients (e.g., Cu, Fe, Se and Zn) foliar or their nano-fertilizers in soils or waters. Not all essential nutrients for human nutrition can be biofortified in the nano-form using all edible plants but there are several obstacles prevent this approach. These stumbling blocks are increased due to COVID-19 and its problems including the global trade, global breakdown between countries, and global crisis of food production. The main target of this review was to evaluate the nano-biofortification process and its using against malnutrition as a new approach in the era of COVID-19. This review also opens many questions, which are needed to be answered like is nano-biofortification a promising solution against malnutrition? Is COVID-19 will increase the global crisis of malnutrition? What is the best method of applied nano-nutrients to achieve nano-biofortification? What are the challenges of nano-biofortification during and post of the COVID-19?

1. Introduction

Human health is of a great global issue, which was and still is the

main objective of nearly all people all over the world. The human health is directly and indirectly linked with all environmental elements (e.g., soil, edible plants, drinking water and air) with absolute sharing of

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microbes in the agroecosystem (van Bruggen et al., 2019). The supplying of nutrients to edible plants through fertilization or other approaches is called biofortification, which is a vital process for human health (Tiozon et al., 2021). The most important biofortified food crops include rice (de Lima Lessa et al., 2020), wheat (Shi et al., 2020), maize (Cheah et al., 2020), cassava (Okwuonu et al., 2021) and sweet potato (Siwela et al., 2020) or horticultural crops like pear (Pessoa et al., 2021) and strawberry (Budke et al., 2020) or pulse crops (Jha and Warkentin, 2020). The major nutrients, which could be used in biofortification may include boron (Hussain et al., 2020), copper (Grujic et al., 2021), iron (Okwuonu et al., 2021), iodine (Dobosy et al., 2020), calcium (Pessoa et al., 2021), selenium (González-García et al., 2021) and zinc (Pal et al., 2021). Not only nutrients could be biofortified in edible crops, but also some vitamins also can be applied like vitamin B1 (thiamine), B2 (riboflavin), B3 (e.g., niacin), B5 (pantothenate), B6 (e.g., pyridoxine), B7 (biotin), B9 (e.g., folates and their derivatives) and B12 (cobalamin) or vitamin C (ascorbate) or vitamin E (tocopherol) or carotenoids (Jiang et al., 2021; Tiozon et al., 2021).

The nano-biofortification is a new approach which helps to enrich the crops with essential nutrients to supplement human diet with balanced diet using -nutrients against malnutrition. This new approach has several advantages and disadvantages like nano-fertilizers or nanoparticles-based nutrients (El-Ramady et al., 2020a, 2020b, 2020c). These nano-nutrients like other nanomaterials have positive and negative impacts on the natural ecosystem and human health (Malakar et al., 2021; Silva et al., 2021). The positive sides may include promoting crop production and the nano-remediation of soils and water, whereas the main negative impacts may include the toxicity and nano-pollution (Martínez et al., 2021; Rizwan et al., 2021). The green synthesis of nanoparticles (NPs) could be achieved using plant extracts (i.e., leaves, roots, flowers and seeds), microbes (e.g., bacteria, yeast, fungi and algae) and biomolecules (enzymes, proteins, and carbohydrates), which represent biological substrates instead of chemical as solvents and stabilizing agents to reduce the harmful nature of the product (Bandeira et al., 2020; Abinaya et al., 2021). The biogenic synthesis of nanoparticles is "a boon" to human health, more convenient, economical and environmentally-friendly process compared to physical and chemical methods (Stephen et al., 2021). Many studies reported about the green synthesis of nanoparticles using plant extracts such as production of S-NPs using leaves of *Ocimum basilicum* (Ragab and Saad-Allah, 2020), iron-NPs by green tea and black tea leaves (Mareedu et al., 2021), Copper-NPs from *Eucalyptus globulus* and mint leaves (Iliger et al., 2021), zinc oxide -NPs from *Nilgiantusciliantus* leaf (Resmi et al., 2021), nickel oxide-NPs from fennel (*Nigella sativa*) seeds (Boudiaf et al., 2021) and magnesium oxide-NPs from different plant extracts (Abinaya et al., 2021). These nano-nutrients also can support the struggle of humanity against many diseases particularly COVID-19 like nano-selenium (He et al., 2021), and ZnO-NPs (Gatadi et al., 2021). On the other hand, nanotechnology has distinguished opportunities tools and approaches to treat COVID-19 including the promising use of nano-nutrients as anti-Covid-19 nanoparticles (Taleblian and Conde, 2020; Gatadi et al., 2021), or nanomedicine for COVID-19 (Medhi et al., 2020; Vahedifard and Chakravarthy, 2021).

Therefore, this review is an attempt to highlight nano-biofortification and human health in the era of COVID-19, and the links between nano-biofortification and human health. What are the expected environmental impacts of COVID-19 on biofortification process? Is there any direct or indirect relationship between COVID-19 pandemic and nano-biofortification?

2. Nutrients based nanoparticles in edible plants for human health

Starting from 2008, the US Environmental Protection Agency focused on the environmental implications of engineered nanoparticles (NPs) or nanomaterials (ENMs) and their hazard assessment at cellular

and molecular level of human beside the toxicity of ENMs to terrestrial and marine organisms, transport, fate, and life cycle assessment (Gomez et al., 2021). However, the specific effects of NPs on human health are still missing, which resulted from the consumption of edible plants that exposed to -agro-chemicals (Gomez et al., 2021). Beside the agricultural sector, distinguished applications of technology in biomedical sciences like neurotoxicity, neurological diseases, drug delivery, cancer diagnosis, and treatment of viral infections in particular corona virus infection (Mao et al., 2021). There are potential risks could be noticed resulted from excess consumption of dietary mineral nutrients contained in plants such as Ca (kidney stones), K (heart abnormalities), Fe, (gastric upset), Mg (muscle spasms), Mn (affects central nervous system), and Mo (Gut-like symptoms), whereas the daily required amount of common nutrient for human is 1200 mg Ca, 20 mg of B, 8–18 mg Fe, 1400–2600 mg K, 310–320 mg Mg, 1.8–2.3 mg Mn, 45 µg Mo and 8–11 mg Zn mg per day (Gomez et al., 2021).

Nutrients-based nanoparticles or nano-nutrients are an important source for supply cultivated plants with the enough and proper nutrients for plant nutrition, which are represent main source for human health. The engineered-NPs could be directly applied for human as food additives or food industry (Deng et al., 2021) like colorants, emulsifiers, flavor enhancers, artificial sweeteners, foaming and anti-foaming agents (Medina-Reyes et al., 2020). The nanoparticles also in form of silver (Ag), titanium oxide (TiO₂) and zinc oxide (e.g., Ag-NPs, TiO₂-NPs and ZnO-NPs) could be utilized in packaging of foods as antimicrobial agents (C. Deng et al., 2020; J. Deng et al., 2020). Although many nanoparticles have been applied as nano-fertilizers or nano-pesticides, which promote crop productivity, but might cause some problems in soil-plant interfaces particularly the over-doses (Ragab and Saad-Allah, 2020). Several studies have depicted applied engineered-NPs as nano-fertilizers (e.g., Guo et al., 2018; Farshchi et al., 2021; Madzokere et al., 2021) to improve crop productivity under many stresses (Ye et al., 2019; Landa, 2021) like drought (Sreelakshmi et al., 2020; Ahmed et al., 2021; Ali et al., 2021), salinity (Manzoor et al., 2021; Zulfiqar and Ashraf, 2021), pollution of heavy metals (Noman et al., 2020; Xin et al., 2020; Manzoor et al., 2021), and biotic stress (Tauseef et al., 2021a, 2021b). These nanoparticles can enhance cultivated plants under stress through many mechanisms such as improving antioxidant defense system, promoting photosynthesis, increasing water, nutrient and phytohormones (Zulfiqar and Ashraf, 2021). The main positive effects of engineered nanoparticles on cultivated plants may include the applications as potential agents in agriculture (e.g., nanofertilizers, nano-pesticides and nano-growth enhancers), protecting plants from environmental stresses (e.g., salinity, water deficit and drought) and decreasing the accumulation and toxicity of heavy metals (Landa, 2021). However, many negative environmental impacts of higher concentrations of these NPs were reported, which may cause the toxicity for all environmental compartments (i.e., plants, microorganisms, animals and human) (Landa, 2021). The possible mechanisms of the engineered-NPs toxicity may include the induced cytotoxicity, genotoxicity, and cell death and many nanoparticles at higher concentrations also can damage the lungs, DNA of cell, oxidative damage, and the cell viability of human hepatoma (Jaswal and Gupta, 2021). The positive mechanism effects of NPs may include (1) promoting some plant enzymes (e.g., nitrate reductase, phosphatase, amylase, and phytase), which are involved in the nutrient metabolism and its acquisition, (2) stimulating the biosynthesis of chlorophyll and photosynthetic activities, (3) enhancing the opening of stomata and assimilation rate of CO₂, and (4) modulating the oxidative stress through stimulating of enzymatic antioxidants like catalase, superoxide dismutase, and peroxidases (Landa, 2021). On the other hand, the negative mechanism effects of NPs may include reported the phytotoxic effects of NPs on plants, which induced the damage of chloroplast via inducing the oxidative stress conditions that ultimately obstructed photosynthesis process by disturbing photosystem I activity particularly under higher concentrations of these nanoparticles (Rastogi et al., 2019; Zulfiqar and Ashraf, 2021).

On the other hand, natural nanoparticles in fossil or coal and mineral fuel sectors have serious impacts on human health and still need more studies about their mining and behavior, which could acquire through inhalation, oral ingestion and dermal absorption causing damage or diseases on heart, lung, kidney and brain particularly through inhalation (Silva et al., 2021). Due to the accumulation of the nanoparticles and its unsafe discharge in the environment especially soil-plant systems, human exposure becomes inevitable through direct touching or via edible plant tissues causing hazardous health impacts (Rajput et al., 2020). The fate and behavior of nanoparticles in different environmental compartments was and still one of the most important issue, which totally linked to the human health like aquatic systems (Turan et al., 2019; Parsai and Kumar, 2021), which need a remediation (Ebrahimbabaie et al., 2020). Although, the engineered NPs could be used in remediation the polluted soil, water and air environments, the excess amounts of these NPs might cause serious hazards for the ecosystem and should be removed by proper remediation tools. This means NPs is double-edged sword (Srivastav et al., 2018; Zhang et al., 2019; Romeh and Saber, 2020; Gong et al., 2021; Ganie et al., 2021). Common case studies are published about removing many heavy metals using NPs from contaminated media (i.e., water, soil and sediments) such as arsenic (Alka et al., 2021; Maity et al., 2021), cadmium (Gong et al., 2021), chromium (Azeez et al., 2021), copper (Yin et al., 2020), lead (Lian et al., 2021), mercury (Kumari et al., 2020), and zinc (Fajardo et al., 2020).

Green-synthesized nanoparticles have been used successfully in human health issues, which included many approaches like solving, treatment and preventing these problems (Nkanga and Steinmetz, 2021; Paiva-Santos et al., 2021). The green metal-NPs have several applications as antimicrobial agents (Banasiuk et al., 2020), in cellular imaging, as catalysts (Modak et al., 2020), for remediation of environmental pollutants (Bhavaya et al., 2021; Orooji et al., 2021), as alternative energy source, as sensors (Zamarchi and Vieira, 2021) and as anti-microfouling agents (Rana et al., 2020). Many green synthesis

nanoparticles have been applied for multifaceted applications for human health such as antimicrobial agents (Sharma et al., 2021) as reported for nanoparticles of MgO-NPs (Vidhya et al., 2021), Zn-NPs and Ag-NPs (Munir et al., 2020), and ZnO-NPs (Umavathi et al., 2021).

3. Nano-biofortification for human health

The humanity faces several problems related to human health especially malnutrition and hidden hunger. These problems are representing in deficiency of minerals and vitamins even in individuals who are attaining healthy levels of calories (Tiozon et al., 2021). This deficiency of minerals and vitamins could overcome through the biofortification. It could be defined as “biofortification is a process that enhances the bioavailable concentrations of enriched vitamins or minerals in staple diet like rice achieved through three different approaches, namely (a) agronomic biofortification, (b) conventional breeding or (c) transgenic and gene editing approaches” (Tiozon et al., 2021). The applied nutrients in form of nanoparticles to enrich the edible plants for human health is called nano-biofortification as reported in many studies on Cu, Fe, Mn, and Zn oxide-NPs (Liu et al., 2016), on ZnO-NPs (Abdel Latef et al., 2017; Thunugunta et al., 2018), and nano-selenium (e.g., El-Ramady et al., 2020a, 2020b, 2020c; Seleiman et al., 2021).

Copper-based NPs, iron-based-NPs, selenium-based-NPs and zinc oxide-NPs for biofortification have discussed in details in Tables 1–4. These Tables included different cases of nano-biofortification, which contain the applied nano-dose of each nano-nutrient, in which form applied and prepared these nutrients, the used growth media and most important findings of these studies. The data in Tables 1–4 confirmed that the main factors controlling the using of nano-nutrients (i.e., Cu, Fe, Se and Zn) may include:

1. Applied nano-dose: where the higher applied dose may cause the toxicity for cultivated plants and consequently toxicity for human

Table 1

Details about some published studies on applied Cu-based NPs biofortification.

Targeted plant (scientific name)	Applied nano-dose	Nutrient forms (preparing type)	Growth media (applied method)	Main findings	References
Bell pepper (<i>Capsicum annuum</i> L.), var. Kitrino	Cu-NPs at 100 and 500 mg L ⁻¹	Cu-NPs (50 nm, chemical)	Bags contained mixture peat and perlite in (1:1)	Cu-NPs increased the content of fruit bioactive compounds (flavonoids, carotene, carotenoids) under saline stress	González-García et al. (2021)
Alfalfa (<i>Medicago sativa</i> L.)	80 and 280 mg Cu kg ⁻¹ soil	Cu(OH) ₂ and Nano-Cu (OH) ₂ (chemical)	Pot experiment	Nano-Cu is considered nano-fertilizer improving physiology of alfalfa	Cota-Ruiz et al. (2020)
Rosie and green bok choy (<i>Brassica rapa</i>)	75, 150, 300, and 600 mg Cu kg ⁻¹ soil	Bulk CuO and CuO-PNs (chemical)	Pot experiment filled with soil	Cu-distribution patterns depends on size in parenchyma and leaf midrib	J. Deng et al. (2020); C. Deng et al. (2020)
Wheat (<i>Triticum aestivum</i> L.) var. Galaxy	From 25 to 100 mg kg ⁻¹ soil	Cu-NPs (17–38 nm biological)	Pot experiment filled with soil	Green Cu-NPs-based tool is sustainable way to grow wheat in metal-polluted soils	Noman et al. (2020)
Lettuce (<i>Lactuca sativa</i> L.)	From 0.2 to 300 mg L ⁻¹	CuO-NPs (~6.6 nm, biological)	Petri dishes	Low concentrations (≤20 mg L ⁻¹) of CuO-NPs enhanced plant growth	Pelegrino et al. (2020)
Maize (<i>Zea mays</i> L.)	From 10 to 1000 mg L ⁻¹ Cu	Cu(OH) ₂ and Nano-Cu (OH) ₂ (chemical)	Petri dishes	At 10 ppm nano-Cu can enhance defense system of maize	Valdes et al. (2020)
Soybean (<i>G. max</i> L. Merr.)	From 50 to 500 mg kg ⁻¹ soil	CuCl ₂ and CuO-NPs, at 25–250 nm (sol-gel method)	Field experiment	CuO-NPs (25 nm) can improve seed nutritional Cu value	Yusefi-Tanha et al. (2020a)
Green onion (<i>Allium fistulosum</i> L.)	75–600 mg kg ⁻¹	CuO and CuO-NPs (chemical)	Pot experiment (soil application)	CuO-NPs improved content allicin, Ca, Fe, Mg, Mn	Wang et al. (2020)
Soybean (<i>G. max</i> L. var. Stonewall)	1 mg Cu kg ⁻¹	CuO and CuO-NPs (40 nm, chemical)	Pots contain soil	Nano-Cu enhanced residual soil N (80%) and Zn (42%)	Dimkpa et al. (2019a)
Tomato (<i>Solanum lycopersicum</i> L.), saladette “El Cid F1	From 10 to 250 mg L ⁻¹	Cu NPs (42 nm, chemical)	Bags filled with peat moss and perlite (1:1)	Cu-NPs at 50 mg L ⁻¹ improved quality of fruits and antioxidant system	Hernández-Hernández et al. (2019)
Tomato (<i>S. lycopersicum</i> L.), saladette El Cid F1	From 10 to 50 mg L ⁻¹	Cu-NPs (40 nm, chemical)	Bags filled with peat moss and perlite (1:1)	Cu-NPs at 50 mg L ⁻¹ enhanced antioxidant system at biotic stress fungal pathogen	Quiterio-Gutiérrez et al. (2019)
Lettuce (<i>Lactuca sativa</i> L.) var. ramosa Hort.	From 200 to 400 mg Cu kg ⁻¹ soil	CuO and CuO-NPs (10–100 nm, chemical)	Pot spiked soil	CuO-NPs enhanced photosynthesis and transpiration rate	Wang et al. (2019b)
Wheat (<i>Triticum aestivum</i> L.)	50 and 500 mg CuO kg ⁻¹ soil	CuO-NPs (14.85 nm, chemical)	Pot experiment (soil: sand in 3:1 (v/v) ratio)	High dose CuO-NPs reduced some essential amino acids in wheat grains	Wang et al. (2019a)

Table 2
Details about some published studies on applied Fe-based NPs biofortification.

Targeted plant (scientific name)	Applied nano-dose	Nutrient forms (preparing type)	Growth media & applied method	Main findings	References
Rice (<i>Oryza sativa</i> L. cv. Gobindobhog)	From 10 to 80 mg l ⁻¹	Nano-scale zero valent iron (20 nm, chemical)	Field trial (seed priming)	Nano-ZVI is considered a 'pro-fertilizer' boosting plant growth and its yield	Guha et al. (2021)
Wheat (<i>Triticum aestivum</i> L.)	From 25 to 100 mg kg ⁻¹ soil	FeO-NPs (19–40 nm, biological)	Pot spiked soil	FeO-NPs increased biomass, antioxidants, photosynthetic pigments under Cd and salinity stresses	Manzoor et al. (2021)
Wheat (<i>T. aestivum</i>) cv. Cumphuriyet-75	500 mg L ⁻¹	Fe ₂ O ₃ -NPs (20–40 nm)	Hydroponic system	NPs served as Fe-source in supporting chlorophyll synthesis	Al-Amri et al. (2020)
Evening primrose (<i>Oenothera biennis</i> L.)	From 0.2, 0.5 and 1.0 g l ⁻¹	α-Fe ₂ O ₃ and Fe ₂ O ₃ NPs (40 nm, chemical)	Suspension for 28 days	Germination stimulated in 0.2 g l ⁻¹ of seeds	Asadi-Kavan et al. (2020)
Paddy rice (<i>Oryza sativa</i> L.)	2.5 g L ⁻¹	Nano chelated iron fertilizer	Field trial	Nano increased yield by 27% and protein content by 13% but decreased hollow grain number by 254%	Fakharzadeh et al. (2020)
Sunflower (<i>Helianthus annuus</i>)	Concentration 1.0 or 2.0%	Fe-0 NPs (35–45 nm, chemical)	Soil spiked with NPs	NPs improved growth plants under Cr toxicity	Mohammadi et al. (2020)
Soybean (<i>Glycine max</i> L.)	From 15 to 60 mg pot ⁻¹	Fulvic acid-coated Fe ₂ O ₃ -NPs, Fe ₂ O ₃ -NPs (5 nm, chemical)	Pot experiment (soil; foliar)	Plants responded better to the foliar of nano-Fe ₂ O ₃ -FA than nano-Fe ₂ O ₃ alone	Yang et al. (2020)
Wheat (<i>Triticum aestivum</i> L.)	From 5 to 20 mg L ⁻¹	Fe-NPs (50 – 100 nm, chemical)	Seed priming in potted soil	Fe-NPs increased chlorophyll and gas exchange attributes under Cd stress	Rizwan et al. (2019)
Wheat (<i>Triticum aestivum</i> L.)	50 and 500 mg Fe ₂ O ₃ kg ⁻¹ soil	Fe ₂ O ₃ -NPs (20 nm, chemical)	Pot experiment, soil: sand in 3:1 (v/v) ratio	Fe ₂ O ₃ -NPs increased cysteine and tyrosine grains	Wang et al. (2019a)
Soybean (<i>G. max</i> , cv: DM4670RR)	56 ± 3 mg kg ⁻¹	FeSO ₄ and FeSO ₄ -NPs (chemical)	Field trial	Soybean is ill-suited for agronomic biofortification due to their inherently high Fe and protein content and tight genetic constraints	Knijnenburg et al. (2018)
Cumin (<i>Cuminum cyminum</i> L.)	500 and 1000 mg l ⁻¹ nano-chelated Fe	Fe-EDDHA and Fe-NP-chelated	Field experiment (foliar)	1000 mg l ⁻¹ NPs was the most effective	Sabet and Mortazaiezhad (2018)

Table 3
Details about some published studies on applied Se-based NPs biofortification.

Targeted plant (scientific name)	Applied nano-dose	Nutrient forms (preparing type)	Growth media (applied method)	Main findings	References
Cucumber (<i>Cucumis sativus</i> L.)	25 mg L ⁻¹	Nano-Se (biological)	Protected cultivation (foliar)	Improved growth under heat and salinity stress	Shalaby et al. (2021)
Bell pepper (<i>Capsicum annuum</i> L.), variety Kitrino	Se-NPs at 10 and 50 mg L ⁻¹	Se-NPs (2–20 nm, chemical)	Bags contained mixture peat and perlite in (1:1)	Cu-NPs increased the content of bioactive compounds in fruits (flavonoids, carotene, yellow carotenoids) under saline stress	González-García et al. (2021)
Chicory (<i>Cichorium intybus</i> L.)	Nano-Se (4 and 40 mg l ⁻¹)	Se-NPs (10–45 nm, chemical)	Pots contained peat and perlite (1:1)	Applied Se-NPs increased ascorbate concentration (31.5%) but reduced glutathione (35%)	Abedi et al. (2021)
Paddy rice (<i>Oryza sativa</i> L.)	25–100 μmol L ⁻¹ Se NPs	Nano-Se (chemical)	Pot experiment (foliar)	50 μmol L ⁻¹ Se NPs is the best to ameliorate polluted soil (3.0, 300 mg kg ⁻¹ Cd and Pb)	Wang et al. (2021)
Bitter melon (<i>Momordica charantia</i> L.)	From 1 to 50 mg L ⁻¹	Na ₂ SeO ₄ and Se-NPs (10–45 nm, chemical)	<i>In vitro</i> experiment	Se treatments at low dose enhanced the activity of leaf nitrate reductase (52%)	Rajae Behbahani et al. (2020)
Strawberry (<i>Fragaria × ananassa</i> Duch.)	Se/SiO ₂ -NPs (50 and 100 mg L ⁻¹)	Se-NPs (25 mg L ⁻¹ , 60 nm, chemical)	Pots filled with mixture of ratio (1:1:2) sand: animal manure: topsoil	Applied Se/SiO ₂ at 100 mg L ⁻¹ can manage harmful impacts of soil drought stress via higher level of osmolytes like proline and carbohydrate	Zahedi et al. (2020)
Tomato (<i>S. lycopersicum</i> L.), saladette "El Cid F1	From 10 to 20 mg L ⁻¹	Se-NPs (2–20 nm, chemical)	Bags filled with peat moss and perlite (1:1)	Se-NPs at 10 mg L ⁻¹ recorded the highest yield and improved quality of fruits	Hernández-Hernández et al. (2019)
Tomato (<i>S. lycopersicum</i> L.), saladette El Cid F1	From 10 to 20 mg L ⁻¹	Se-NPs (2–20 nm, chemical)	Bags filled with peat moss and perlite (1:1)	Se-NPs at 20 mg L ⁻¹ promoted antioxidant system under biotic stress of fungal pathogen (<i>Alternaria solani</i>)	Quiterio-Gutiérrez et al. (2019)
Groundnut (<i>Arachis hypogaea</i> L.)	20 and 40 mg l ⁻¹	Se-NPs (10–30 nm, chemical)	Pot experiment (foliar)	Improved yield components and oil production of seeds	Hussein et al. (2019b)
Groundnut (<i>Arachis hypogaea</i> L.)	20 and 40 mg l ⁻¹	Se-NPs (10 – 30 nm, chemical)	Pot experiment (foliar)	Stimulator enhanced plant antioxidant defense system	Hussein et al. (2019a)
Tomato (<i>S. lycopersicum</i> L.), saladette El Cid F1	From 5 to 20 mg L ⁻¹	Se-NPs (2–20 nm, chemical)	Bags filled with peat moss and perlite (1:1)	Se-NPs generated a positive impact against salinity stress and bioactive compounds in fruits for human health	Morales-Espinoza et al. (2019)
Pomegranate: <i>Punica granatum</i> L. cv. Malase Saveh	5 L per tree at 1 or 2 μM	Na ₂ SeO ₄ and Se-NPs (10–45 nm, chemical)	Field trial (foliar)	NPs enhanced the maturity index; decreased cracking of fruits	Zahedi et al. (2019b)
Strawberry (<i>Fragaria ananassa</i> Duch.), cv. Kurdistan	10 and 20 mg L ⁻¹	Se-NPs (10–45 nm, chemical)	Pots filled with perlite, coco peat and sand (5:7:23) as foliar applied	Se-NPs at 20 mg L ⁻¹ mitigated soil salinity stress and improved plant tolerance to salinity	Zahedi et al. (2019a)

Table 4
Details about some published studies on applied ZnO-NPs biofortification.

Targeted plant (scientific name)	Applied nano-dose	Nutrient forms (preparing type)	Growth media, applied method	Main findings	References
Wheat (<i>Triticum aestivum</i> L.)	From 40 to 120 mg L ⁻¹	ZnNO ₃ and ZnO-NPs (biogenic)	Sandy loam soil in pots	ZnO-NPs at dose of 80 ppm showed the best results and caused maximum increase in height, seed weight, yield and biomass	Sheoran et al. (2021)
Eggplant (<i>Solanum melongena</i> L.)	50, and 100 mg kg L ⁻¹	ZnO-NPs (chemical)	Foliar applied to field (loamy sand soil)	Foliar ZnO-NPs alleviated drought stress (60% of ETc) under saline soil (7.33 dS m ⁻¹)	Semida et al. (2021)
Sesame (<i>Sesamum indicum</i> L.)	From 3 to 10 mg l ⁻¹	ZnO-NPs (10 nm, biological)	Pot experiment (soaking seeds)	NPs has been improved the germination and vegetative growth of sesame	Umavathi et al. (2021)
Wheat (<i>T. aestivum</i> cv. Shield)	From 7.5 to 750 mg L ⁻¹	Zn-EDTA, ZnCl ₂ and ZnO-NPs (45 nm, chemical)	Hydroponic glasshouse	ZnO-NPs foliar fertilizer is translocated to wheat grains	Doolette et al. (2020)
Wheat (<i>T. aestivum</i> L. var. Dyna-Gro9522)	3.5 and 1.7 mg Zn kg ⁻¹ for bulk and ZnO-NPs	ZnO (>1000 nm) ZnO-NPs (18 nm, chemical)	Pot experiment	Drought could be modulated by ZnO-NPs	Dimkpa et al. (2020b)
Wheat (<i>T. aestivum</i> L. var. Dyna-Gro9522)	2.17 and 4.34 mg kg ⁻¹ ZnO-NPs and ZnO	ZnO (>1000 nm) ZnO-NPs (18 nm, chemical)	Pot experiment	ZnO-NPs may improve production under drought	Dimkpa et al. (2020a)
Soybean (<i>Glycine max</i> cv. Kowsar)	From 40 to 400 mg Zn kg ⁻¹ soil	ZnCl ₂ and ZnO-NPs (38 nm, sol-gel method)	Pot experiment (soil mixed)	ZnO-NPs may serve as a novel nano-fertilizer for enriching Zn-deficit soil with Zn	Yusefi-Tanha et al. (2020b)
Green pea (<i>Pisum sativum</i> L.)	100 mg L ⁻¹	ZnSO ₄ ·7H ₂ O, ZnO-NPs (50 nm, chemical)	Hydroponic study	ZnO-NPs forms affected heavy metals transfer	Skiba et al. (2020)
Sorghum (<i>S. bicolor</i> var. 251)	1, 3, and 5 mg Zn kg ⁻¹	ZnO-NPs (18 nm, chemical)	Pot experiment	ZnO-NP may alleviate drought	Dimkpa et al. (2019b)
Soybean (<i>G. max</i> L. var. Stonewall)	2 mg Zn kg ⁻¹	ZnO and ZnO-NPs (18 nm, chemical)	Pot experiment	ZnO-NPs stimulated P uptake by 14%, promoted grain yield and modulated nutrient uptake	Dimkpa et al. (2019a)
Wheat (<i>Triticum aestivum</i> L.)	From 20 to 1000 mg L ⁻¹	ZnSO ₄ and ZnO-NPs (<100 nm, chemical)	Soil in pots	ZnO-NPs increased Zn in grain than in leaf compared to than ZnSO ₄	Du et al. (2019)
Wheat (<i>Triticum aestivum</i> L.)	From 25 to 100 mg L ⁻¹	ZnO NPs (20–30 nm, chemical)	Seed priming in potted soil	ZnO-NPs increased chlorophyll and gas exchange attributes under Cd stress	Rizwan et al. (2019)
Common bean (<i>Phaseolus vulgaris</i>)	From 10 to 40 mg l ⁻¹	ZnO-NPs (≈20 nm, chemical)	Field trial (foliar)	ZnO-NPs at 30 ppm recorded the highest yield of seeds (2.41–2.48 Mg ha ⁻¹)	Salama et al. (2019)

when these plants will be consumed by him. That means the proper applied dose of nutrient must be identified before biofortification.

- The applied and prepared method of nutrients: it is well known that foliar application of nano-nutrients is better than soil application particularly when the used soil has problems like high or low pH, salinity and other. The prepared method of nutrients especially the biological ones are preferable due to its low toxicity and eco-friendly.
- The used growth media: growing media may represent a crucial factor controlling the efficiency of biofortification process, where normal soil is preferable at large scale of production but hydroponics and in vitro are most suitable under small scale.
- There are many methods for biofortification like seed priming using engineered nanomaterials, which may consider a good pathway to alleviate malnutrition (Kah et al., 2019; De La Torre-Roche et al., 2020; Acharya et al., 2020). Beside seed priming, biofortification could be achieved by soil and foliar application or cultivated plant in soil rich in candidate nutrient.
- Controlled or slow-release nano-fertilizers are promising approach (Guo et al., 2018; Yu et al., 2021), whereas nano-encapsulated conventional fertilizers may help in slow and sustained release of nutrients over an extended period of time (Madzokere et al., 2021).
- Agricultural sustainability could be promoted using coated fertilizers, which might enhance the nutrient utilization efficiency and decrease environmental problems like sulfur coated urea (Zhang et al., 2021). Many materials could be used as green bio-based coating materials (e.g., chitin, cellulose, keratin, poly-amino acid and starch), which are considered low-cost, renewable and have the ability to control-release of nutrients in fertilizers. It could be also used nano-silica and organosilicon as modified superhydrophobic bio-based polymer, which are considered promising tools in improving the poor release properties of bio-materials (Zhang et al., 2021).

4. Challenges of biofortification in the era of COVID-19

No one deny that COVID-19 is classified as one of the most critical global health crises, which faced the humanity in the 21st century. This virus has caused a lot of troubles in different sectors of our life as reported by our previous reports (i.e., El-Ramady et al., 2020c, 2020b, 2020a, 2021a, 2021b). This disease increases the difficulties and life burdens on the humanity beside the global malnutrition and hidden hunger. It is reported that all forms of malnutrition not might only increase drastically due to the COVID-19 pandemic but the potential of the double burden of malnutrition epidemic, of particular concern, will be also increased (Littlejohn and Finlay, 2021). Therefore, some studies recently published about the production of biofortified crops enriched in some nutrients like Zn, which has the ability to improve the respiratory disorders and pneumonia beside the susceptibility to the outbreak of COVID-19 (El-Ramady et al., 2021a; Gastélum-Estrada et al., 2021; Okwuonu et al., 2021). There are new dimensions and challenges have been created during and post-COVID-19 pandemic, which threaten human health. With aggravation of the previous problems in different countries, the instant impact of COVID-19 on the food security and food supply systems has been reported (Heck et al., 2020). This impact included several obstacles that restricted the movement of goods and people among the countries, restricted internal movement, border closure, preventing the access to markets, services and foods particularly in the agricultural sector (Ilesanmi et al., 2021). What could be expected in the future due to COVID-19 is the drop in the global demand, a great loss in markets and employment as well as growing concerns about international cooperation (Wolfe and Patel, 2021). Therefore, all countries need different strategies to protect foods and nutrition security of the world's poor through focus on the prioritization of diversification for production and markets (Heck et al., 2020). The mitigation strategies for COVID-19 as a global risk should be linked with climate change as a global problem because both climate change and COVID-19 already rapidly expanded to all over the world (Rasul, 2021).

Under the theme of COVID-19 and nano-nutrients, many challenges

mainly related to the parts of nano-biofortification process: which nano-nutrients are essential for human health? Which crops are needed to be biofortified and how? Are all nutrients could be converted into nano-form? Is that possible to achieve this process and what about its costs? All previous questions are representing serious challenges especially in developing countries and may control by the global status under COVID-19. More issues could be summarized in the following points:

- (1) Is there any possibility for nano-nutrients like selenium to combat COVID-19? Selenium is essential nutrients for human health and its nano-form has distinguished properties like low toxicity, good candidate for the treatment of many viral diseases, cancers, Huntington's disease and Se has a direct association with COVID-19 (He et al., 2021).
- (2) Using the nano-phyto-therapy like nano-curcumin against COVID-19: this phytotherapy is an anti-inflammatory herbal based agent, which modulates the high rate of inflammatory cytokines particularly IL-6 and IL-1 β mRNA expression and the secretion of cytokine in COVID-19 patients causing an enhancement in clinical manifestation and overall recovery (Valizadeh et al., 2020). There are new promising phyto-anti-inflammatory like the mixture of green tea, guava and rose extracts, which could be used for the treatment of COVID-19 (Shin et al., 2021). The phytomedicine or herbal immune-boosters may have substantial warriors of pandemic Covid-19 battle and more concerns are needed (Khanna et al., 2020).
- (3) Production of nanoparticles-based drugs has great attentions nowadays, which might create a new alternative and safer therapeutic agents (i.e., alternative antiviral and antimicrobial agents). Nanoparticle-based drugs (e.g., Ag-NPs, Cu-NPs, Co-NPs, and ZnO-NPs) have attractive physio-chemical properties including the shape, size, surface charge, and its area, aggregation, crystallinity, agglomeration and chemical composition (Gatadi et al., 2021). These NP-based drugs can inhibit the impacts of viral infection like coronavirus (anti-COVID-19 nanoparticles) in many ways such as by halting viral replication and proliferation, blocking receptor cell entry and through direct inactivation (Gatadi et al., 2021). Is there any chance for repurposed vaccines and drugs for possible treatment of COVID-19 (De et al., 2021)? Or are nanoparticle-based drugs the best solution for treating microbial and viral infections like COVID-19?

5. Conclusions and future recommendations

Nano-biofortification approach may consider a promising tool against malnutrition. This approach has several advantages like nano-fertilizers including the efficiency and lower amount particularly the biological nano-form. Till now, this approach still in the infancy period and needs more effects to be applied on the global level. For nano-biofortification under COVID-19, there are several open questions that are needed to be answered such as how can the world overcome the expected crises in the global food security? How can developing countries fight malnutrition and food insecurity particularly under crisis of food production during and post-COVID-19? How can different countries build resilient food system amidst COVID-19? To what extent different countries can overcome the food losses in the agriculture during the COVID-19 pandemic? What is the expected role of nano-technology in saving the treatment against COVID-19? Can nano-biofortification be the solution to fight the global malnutrition? Can we use nano-selenium and other nano-nutrients to combat COVID-19? Which elements beside Se can fight against different viruses especially COVID-19? Is there any possibility for nano-nutrients to be part of the solution of vaccine against COVID-19?

CRedit authorship contribution statement

The idea of the review article and write up of the 1st draft was contributed by Hassan El-Ramady and Neama Abdalla. They also contributed in revising the MS and made constructive changes during revision of the MS. The data collection and draft write up of the manuscript was contributed by Heba Elbasiouny, Fathy Elbehiry, Tamer Elsakhawy, Alaa El-Dein Omara, Megahed Amer, Yousry Bayoumi, Tarek A. Shalaby, Yahya Eid. The final edits and finalizing of the data were made by Muhammad Zia-ur-Rehman. Moreover, he took the responsibility to submit the article. He also has made the corrections during revision process and resubmitted the article.

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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