frontiers | Frontiers in Genome Editing

TYPE Review
PUBLISHED 21 June 2023
DOI 10.3389/fgeed.2023.1200987

OPEN ACCESS

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RECEIVED 05 April 2023
ACCEPTED 09 June 2023
PUBLISHED 21 June 2023

CITATION
Kumari R, Suman K, Karmakar S, Mishra V, Lakra SG, Saurav GK and Mahto BK (2023), Regulation and safety measures for nanotechnology-based agri-products. *Front. Genome Ed.* 5:1200987. doi: 10.3389/fgeed.2023.1200987

Regulation and safety measures for nanotechnology-based agri-products

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There is a wide range of application for nanotechnology in agriculture, including fertilizers, aquaculture, irrigation, water filtration, animal feed, animal vaccines, food processing, and packaging. In recent decades, nanotechnology emerged as a prospective and promising approach for the advancement of Agri-sector such as pest/disease prevention, fertilizers, agrochemicals, biofertilizers, bio-stimulants, post-harvest storage, pheromones-, and nutrient-delivery, and genetic manipulation in plants for crop improvement by using nanomaterial as a carrier system. Exponential increase in global population has enhanced food demand, so to fulfil the demand markets already included nano-based product likewise nano-encapsulated nutrients/agrochemicals, antimicrobial and packaging of food. For the approval of nano-based product, applicants for a marketing approval must show that such novel items can be used safely without endangering the consumer and environment. Several nations throughout the world have been actively looking at whether their regulatory frameworks are suitable for handling nanotechnologies. As a result, many techniques to regulate nano-based products in agriculture, feed, and food have been used. Here, we have contextualized different regulatory measures of several countries for nano-based products in agriculture, from feed to food, including guidance and legislation for safety assessment worldwide.

KEYWORDS

nanotechnology, regulation, safety measures, agri-product, nanocarrier, peptidecarrier

Introduction

The security of food, nutrition, and energy has come under intense strain due to the climate problem, population growth, a scarcity of arable land, diminishing crop yields, and growing crop use as raw materials for industry (Rosenzweig et al., 2020). According to United Nations 2019, the demand for food will increase as the world population increases by 34% by 2050 (www.un.org). The developed crops with enhance phenotypes through conventional plant breeding methods (classical and mutational) will not be enough to meet the immediate availability of food and fodder globally. However, these methods were unable to introduce features that are not currently present in many plant species (Arya et al., 2020). Despite of setbacks, there is time to choose modern, scientific and technical advancement to redress the agricultural insufficiencies. To meet the demand, several crops were successfully improved/enhanced against biotic and abiotic stresses through plant genetic engineering via the genetic modification or genetic alteration of plants by using advanced biotechnological technique like RNA interference (siRNA and miRNA) and genome editing (CRISPR/Cas: Clustered Regularly Interspaces Palindromic Repeats/CRISPR associated protein). Nanobiotechnology has the potential to revolutionize the field of plant genetic engineering, specifically by leveraging nanocarriers to transport biomolecules into plant cells (Arya et al., 2021a). Recently, nanotechnology emerged as an advance technique for the improvement of agricultural products and play a significant impact on the world's economy and industries (Haris et al., 2023).

Although seeds were set for this field's research about 50 years ago, history reveals that applications of nanotechnology to agriculture have only just begun to appear (Mukhopadhyay, 2014; Chhipa, 2019; Sashidhar et al., 2019; Pramanik et al., 2020; Usman et al., 2020). In last decade, for the sustainable agriculture, several nanotechnology-based mechanisms were developed for the improvement of crops using nanomaterials (NMs) or engineered nanomaterials (ENMs) against various biotic and abiotic stresses such as nanopesticides, nanobiofertilizers, nanobiosensor and soil decontamination (Usman et al., 2020; Sonawane et al., 2021; An et al., 2022). As a result, recent years have seen a considerable increase in interest in studies pertaining to uses of nanotechnology in agriculture and, the use of nanomaterials is necessary to enhance the fertilization process, raise yields through nutrient optimization and reduce the need for plant protection agents (Huang et al., 2015; Parisi et al., 2015; Kah et al., 2019). For the delivery of nanomaterials and engineered nanomaterials in to the plant cells, the cell wall act as a physical barrier to delivering functional biomolecules due to its size exclusion limit (5–20 nm) (Zhang H. et al., 2019; Arya et al., 2021b). Conventional biomolecule approaches in plants have significant limitations such as low transgenes efficiency, a small species spectrum for application, a small variety of cargo types, and tissue injury. Cunningham et al. (2018), suggested that the advancement in nanotechnology have made it possible to get beyond constraints in traditional methods: Nanoparticles (NPs) show promise for the passive transfer of DNA, RNA, and proteins across species by enhance genetic engineering (GE) via targeted and an efficient delivery. The constraints of designing an ideal NC with a broad host range, high cargo loading capacity, and efficiency are thus the subject of great attention, to access plant cells and the potential to move inside a plant's system without the need for external mechanical aid (Jinek et al., 2012; Burlaka et al., 2015; Cunningham et al., 2018; Demirer et al., 2019).

Nano carrier based genetically modified crops has been successfully introduced in several plants such as rice, tobacco, rapeseed, maize, wheat, onion, cotton, cowpea, spinach and arugula (Demirer et al., 2019). These nano-based agri-products need to be addressed with different disciplines and strategies to meet or evaluate any kind of hazardous (physico-chemical parameters) or negative effects in humans, animals and environment. Various countries including the United States of America, Europe, India, China, Canada, Australia, and others have developed regulatory frameworks to address genetically engineered agricultural products using nanocarriers. These regulations focus on overseeing nano-based products in the field of plant genetic engineering on a global scale. So, in the current review discussed about different regulatory measures of several countries for NC-based products in agriculture including their guidance and legislation for safety assessment throughout the world.

Advanced approaches for biomolecules delivery

Methods based on nanotechnology have been suggested as low-cost, simple, and reliable ways to transfer genes or other compounds into plants with great efficacy and minimal harm (Chandrasekaran et al., 2020). Biomolecules and chemicals have been successfully delivered into cells in both plant and mammalian cell systems using nanotechnology-based techniques (Ahmar et al., 2021). Genetic engineering was frequently employed in plant improvement to increase productivity and crop fitness, including yield enhancement, nutritional quality enhancement, herbicide tolerance, drought resistance, insect resistance, and viral resistance (Altman and Hasegawa, 2011; Chang et al., 2013; Wang et al., 2014; Mahakham et al., 2017; Fortuni et al., 2019; Mahto et al., 2020). According to the base material, NPs for gene delivery can be categorized as carbon nanotube-based (DNA and RNA), silicon-based (DNA and protein), metallic-based NPs (only deliver DNA as genetic cargo), or polymer-based NPs (encapsulated RNA, DNA and proteins) (Silva et al., 2010; Bates and Kostarelos, 2013; Moon et al., 2014; Kafshgari et al., 2015; Karimi et al., 2016; Zhao et al., 2017; Zhou et al., 2018; Su et al., 2019; Sashidhar et al., 2021) (Supplementary Table S1; Figure 1). The size, concentration and types of nanomaterials plays a crucial role to decide the level of toxicity. The increased surface area of the nanomaterials with decreased size shows a positive correlation with the uptake efficiency by the plants which might be responsible for the adverse effects in the system (Nel et al., 2006). It has been reported that size less than 5 nm and 20 nm can easily translocate through the pores of cell wall and plasmodesmata, respectively. This reflects that, the decreased size of nanoparticles can easily be taken up by the plant system which ultimately leads to the toxicity in the plants after accumulation (Ma et al., 2010; Rico et al., 2011; Sashidhar et al., 2021). Besides size and concentration, nanomaterials should possess few properties for its positive outcome and interaction with the plant system such as reactivity and light confinement, etc. Due to these properties, composition of nanomaterials maybe categorized as carbon nanomaterial, metal-based nanomaterial, quantum dots and nano polymers (Sun et al., 2019; Yan et al., 2021). The toxicity level of such nanomaterials can be assessed during the germination period and growth period in which the carbon nanomaterials (fullerene, carboxyfullerene, graphene oxide, etc.) and metal-based nanomaterials (Cerium, titanium, zinc oxide, etc.) had showed the desirable results in the plant system by reducing the level of toxicity as well as the negative effect. Its effects had been recorded in *Arabidopsis*, *Nicotiana*, bean, flax, etc. (Liu et al., 2010; 2013; Clement et al., 2013; Anjum et al., 2014; Cunningham et al., 2018). Another strategy to make a superior plant which is capable to cope up with the biotic as well as abiotic stress, is possible through the nano-priming technology. This technique involves the treatment of desired seeds with the

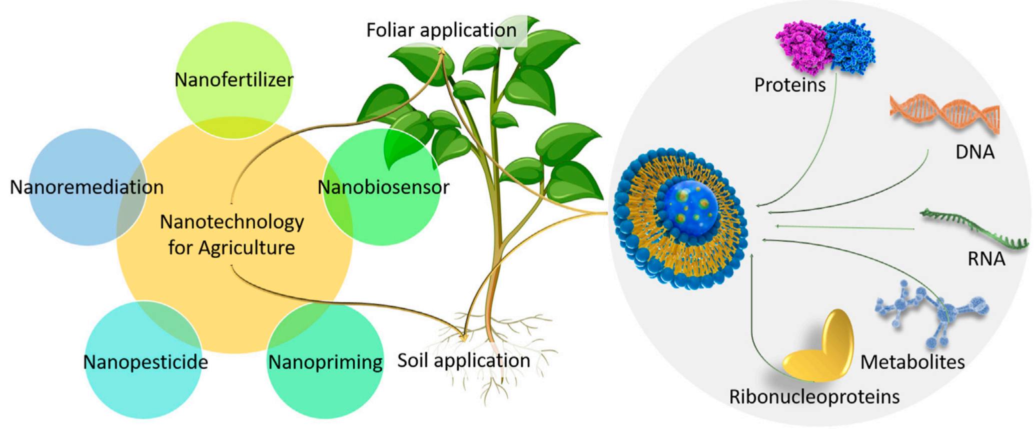

FIGURE 1
Various approaches for the delivery of biomolecules, DNA, RNA and protein using nano-/peptide-carrier. This figure was drawn by using BioRender (https://www.biorender.com).

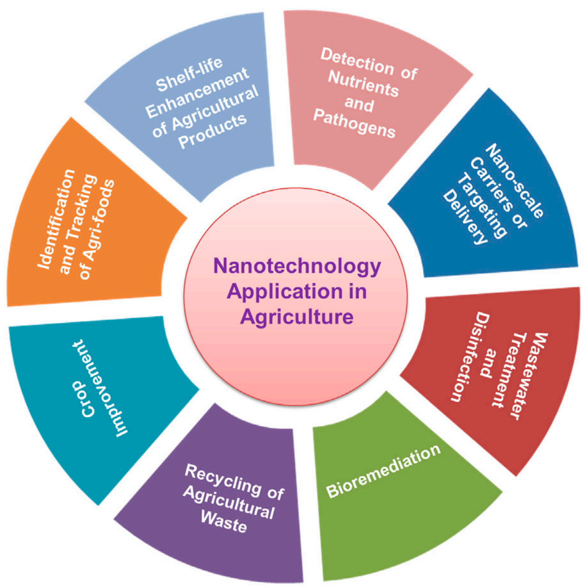

FIGURE 2
Several applications of nanotechnology in agri-food sector.

nanoparticles and priming is done in nanoparticles solution. The resultant nanoprimed seeds then produces a nanoprimed plants such as *Zea mays*, *Oryza sativa* and *Triticum aestivum* with the enhanced properties at molecular, chemical and physiological level (Wang Z. et al., 2019; Afzal et al., 2021; Shah et al., 2021; Imtiaz et al., 2023). Overall, NPs should have the ability to crossing the cell wall and localise to organelles.

Nanotechnology-based agriculture product

In recent years, various tools and devices created by nanotechnology, such as nanodevices and nanocapsules have been utilized to improve, diagnose and treat plant diseases, transport active ingredients to specific target areas, purify waste water, and improve plant nutrient absorption. With the increasing global population, climate change and burden on pests and diseases of agricultural crops, food security is a major concern especially in the developing nations. Nano-based agriculture products are designed and developed with aim of enhancing food security around the world. Nanotechnology is being used for synthesizing and delivering; fertilizers, pesticides, plant growth regulator, transgenic plants with disease resistance, high yield and more nutritional values (Oliveira et al., 2015; He et al., 2019) (Figure 2).

Nanofertilizers

Conventional fertilizers are being used indiscriminately in agriculture to keep pace with ever increasing demand of food for increasing population as conventional chemical fertilizers have lower nutrient uptake capacity and suffer high losses. Nanofertilizers (<100 nm in size) are outstanding alternative to overcome negative impact of conventional fertilizers because they reduce nutrient loss from fertilizers and application rate of fertilizers (Dimkpa and Bindraban, 2017; Babu et al., 2022). Research and development of nanofertilizers is skewed towards plant micronutirents like iron, zinc, manganese, copper, Nickel and molybdenum (Supplementary Table S2) (Dimkpa and Bindraban, 2017; Sashidhar et al., 2020; Al-Mamun et al., 2021; Arya et al., 2022; Soni et al., 2023). Nano-carbons (Biochars), carbon nano-onions and Chitosan NPs have reported to boost growth and quality of agricultural crops (Saxena et al., 2014; Tripathi et al., 2017; Khalifa and Hasaneen, 2018; Arya et al., 2022). When tomato plants were treated with Cu NPs at 250 mg L^{-1} resulted in significant increase in fruit quality and bioactive compound, whereas treatment at 500 mg L^{-1} had negative effect on bioactive compound of tomato fruits (López-Vargas et al., 2018). Joint application of silica nanoparticles (SiNPs) at 250 mg L^{-1} and 600 mg L^{-1} through soil and foliage respectively, resulted in enhancement of flowering characteristics, growth and flowering period in marigold, *Tagetes erecta* L. (Attia and Elhawat, 2021). ZnO NPs at 100–200 mg/kg improves photosynthesis of cilantro (*Coriandrum sativus*), though at 400 mg/kg affected the nutritional components of the cilantro. ZnO NPs also showed less toxicity than bilk and ionic counterparts (Pullagurala et al., 2018). CuO and ZnO NPs can traverse through many chemical and biochemical processes which could damage plant cells, affect soil biota and nitrogen fixation and even could result in critical health problem (Rajput et al., 2020). Thus, nanofertilizers have the ability to transform the agriculture, but nanoparticle related toxicity at high concentration, their accumulative effect and biosafety related comprehensive study must be done before commercialization nanofertilizers (Tripathi et al., 2017; Khalifa and Hasaneen, 2018; He et al., 2019).

Nanopesticides

Different types of pesticides has been used indiscriminately worldwide, owing to the growing demand of agriculture-based food product. This indiscriminate use of different pesticides, has been associated with unprecedented environmental damage due to contamination of soil, water and food, leading to harmful effect on non-target pest species and humans (Guillette et al., 2012; Oliveira et al., 2015). Thus, it is important to develop a novel technique to minimize harmful effect of pesticides, without lowering production of agricultural crops.

Nanopesticides (nanometer size range) provide a solution with its three characteristic features; to increase solubility, slow/targeted release and protection against premature degradation (Kah et al., 2013). Nanopesticides can be based on nanoemulsion, nanodispersion, solid liquid nanoparticles and nano metals (Supplementary Table S2). Silica Nanoparticles (SiO_2-NPs, 2 g/kg of stored grain) showed 100% mortality against four stored product insects; *Rhizopertha dominica, Tribolium castaneum, Sitophilus oryzae,* and *Orizaephilus surinamenisis* (El-Naggar et al., 2020). Temperature-responsive mixed micelle (MMs–Pys–7) of pyrethrins exhibited higher larvicidal activity against *Culex pipiens pallens* at 26 °C (Zhang Y. et al., 2019). Carboxymethyl chitosan (CMCS) modified mesoporous silica nanoparticles (MSN), when loaded with azoxystrobin results in better fungicidal effect against tomato late blight *Phytophthora infestans* (Xu et al., 2018). Nanopermethrin based on nanoemulsion are more potent larvicidal than bulk permethrin (Anjali et al., 2010). Nanometal based imidacloprid has shown significantly high toxicity against *Martianus dermestoides* than aqueous formulation (Guan et al., 2008). Thus, nanopesticides are better alternative of pesticides as they more potent and required in low dosages than traditional pesticides with high toxicity against target organism and low toxicity in aquatic medium.

Nano-based plant growth regulators

Plant growth hormones like auxins, cytokinins, gibberellins, nitric oxide, abscisic acid, and ethylene (either synthetic or natural) are used in various ways in agriculture to improve crop production (Pereira et al., 2017). Various nanoparticles system is used for control release of plant growth hormones for most efficient and justified use as these result in sustained release of active agent as well in protecting against degradation processes (Supplementary Table S2). Nitric oxide (NO)-releasing chitosan nanoparticles (CS NPs) containing the NO donor S-nitroso-mercaptosuccinic acid (S-nitroso-MSA) allow a sustained NO release resulting in increase of NO bioactivity under salt stress in maize plants (Oliveira et al., 2016). It has been observed that when tomato plants are grown on multi-walled carbon nanotubes (CNTs) supplemented soil, they bear twice flower and fruit as compared with control plants thus CNTs acted as plant growth regulators (Khodakovskaya et al., 2013). In another study, poly (γ-glutamic acid) (γ-PGA) and chitosan (CS) polymers nanoparticles encapsulated gibberellic acid (GA3) showed increase biological activity, rate of seed germination and leaf area in *Phaseolus vulgaris* as compared to free GA3 (Pereira et al., 2017).

Nanosensors

Nanosensers has many beneficial aspects in agriculture such as real time monitoring of environmental conditions and stress, crop growth and diseases, pest attack and nutrient efficiency (Supplementary Table S3) (Chen and Yada, 2011; He et al., 2019). Development and advancement in the nanosensers technology had great contribution towards sustainable agriculture by real time monitoring of fertilizers and pesticides in the field, thereby reducing their excess use. Many different nanomaterials haven been used for development of nanosensors for pesticides detection; various nano composites with polymers, Carbon nanotubes (CNT), gold nanoparticles (Au NP) and quantum dots (QD). Nanosensors based on enzymes acetylcholinesterase (AChE) and/or choline oxidase (ChOx) enzyme as biological receptors for detection of organophosphorus and carbamate pesticides in smaller amount and are very sensitive in these pesticides detection (Zheng et al., 2011; Cesarino et al., 2012; Liu et al., 2012; Talarico et al., 2016; Telarico and Georgiev, 2016). Soil nutrients like nitrate have been successfully detected in lower concentration in the direct filed setting using Cysteamine modified gold nanoparticles and graphine oxide based nanosensors (Mura et al., 2015; Pan et al., 2016). Graphene-based nano-antenna integrated carbon nano-tubes sensed volatile organic compound (VOCs) emitted by plant during insect attack, hence can be used for insect attack monitoring (Afsharinejad et al., 2016). Nanosensors have been utilized for detection of water tension of soil in real time, soil pH and nutrient, prediction of nitrogen intake and detection of pathogen in soil (Bellingham, 2011; Fraceto et al., 2016).

Nanotechnology in transgenic plant development

For sustainable agriculture, plant genetic engineering is crucial for enhancing crop output, quality, and resilience to abiotic/biotic stressors (Shaheen and Abed, 2018). Plant genetic engineering frequently makes use of Agrobacterium, biolistic bombardment, electroporation, and poly (ethylene glycol) (PEG)-mediated genetic-transformation systems. These methods do, however, have drawbacks, such as species dependence, loss of plant tissues, ineffective transformation, and high cost (Fiaz et al., 2021). Methods of gene delivery based on nanotechnology have recently been developed for plant genetic modification (Altpeter et al., 2016; Wang J. W. et al., 2019; Zhang Y. et al., 2019). Excellent transformation efficiency, strong biocompatibility, acceptable exogenous nucleic acid protection, and the potential for plant regeneration are all demonstrated by this Nano strategy. Yet, the gene-delivery mechanism in plants that is mediated by nanomaterials is still in its infancy, and there are several obstacles to its widespread usage. The traditional methods of genetic modification applied to plants. The advancement of the development of gene delivery methods based on nanomaterials is then taken into consideration. The use of plant nanotechnology in conjunction with CRISPR-Cas-mediated genome editing is being addressed (Puchta et al., 1993; Wright et al., 2005; Christian et al., 2010). The conceptual advancements, techniques, and real-world applications of nanomaterial-mediated genetic transformation will help advance plant genetic engineering in contemporary agriculture.

Several nanoparticle-mediated transgenic delivery techniques and the plant biotechnology industry's crowded field of existing methods. Together with a mix of the many newly created technologies, some other intriguing approaches, such the CRISPR technology, might be used in the processes of changing crops. Unfortunately, a number of significant problems still need to be fixed (Supplementary Table S4). The majority of these problems might be resolved by combining several approaches for the efficient delivery of various genomes, the design and production of contemporary hybrid NMs, and the advancement of pollen magnetofection and CRISPR techniques (Watson et al., 2018; Ahmar et al., 2021). In conclusion, while nanotechnology applications may take some time to join the area, sustained support for and knowledge of these challenges will guarantee that the field is not negatively impacted in the future.

Safety and regulations for nanotechnology based agri-products around the world

Nanotechnology has been increasingly used in the agricultural sector for various purposes, such as enhancing crop growth, improving soil quality, and developing more efficient and targeted pesticide delivery systems (Prasad et al., 2014; Prasad et al., 2017; Hassani et al., 2020; Singh et al., 2021). However, the use of nanotechnology in agri-products raises apprehensions about the possible environmental and health risk factors related to their use (Khot et al., 2020; Mishra and Singh, 2021).

To address these concerns, regulatory bodies around the world have developed guidelines and regulations to ensure the safe use of nanotechnology in agri-products. Here are some of the key regulations and guidelines related to nanotechnology-based agri-products.

1. Regulatory Oversight: Each country has its own regulatory framework for using nanotechnology in agriculture. In the United States, Pesticides are governed by the Environmental Protection Agency (EPA), while agricultural biotechnology products are governed by the U.S. Department of Agriculture (USDA). Nanotechnology in foods and pesticides are governed by the European Chemicals Agency (ECHA) and the European Food Safety Authority (EFSA) in the European Union.
2. Risk Assessment: Regulatory bodies require risk assessment before approval of any nanotechnology-based agri-product. This includes evaluating the toxicity of the nanomaterials used, the potential for environmental release, and the impact on human health.
3. Labeling: Regulatory bodies require labeling of agri-products that contain nanomaterials. This helps consumers make informed decisions about the products they purchase and use.
4. International Standards: International standards have been developed to assure the safety and quality of nanotechnology-based agri-products. The International Organization for Standardization (ISO) has developed several standards related to nanotechnology, including ISO/TS 80004-1, which provides terminology and definitions for nanomaterials.
5. Research and Development: Regulatory bodies encourage research and development of nanotechnology-based agri-products to ensure that the products are safe for human health and the environment. Overall, the safe use of nanotechnology in agri-products requires a collaborative effort between researchers, manufacturers, regulatory bodies, and consumers. It is important to continue to monitor and assess the risks associated with nanotechnology-based agri-products to ensure their safety and effectiveness (Arya et al., 2021a). Some examples of nanomaterials that have been studied and defined by United States regulatory bodies on parameters such as safety, risk assessment, and effectiveness (Supplementary Table S5).

Different countries have established various regulations and guidelines to ensure the safe use and development of nanotechnology-based agri-products (Supplementary Table S6). Here are some examples:

> ***United States of America***: Nanotechnology-based agricultural products in the United States are regulated by a number of governmental organisations, including the Food and Drug Administration (FDA), the Environmental Protection Agency (EPA), and the United States Department of Agriculture (USDA). There are nanomaterials that have been approved by the US-FDA for use in food applications. The following are some examples:

1. Titanium dioxide: This is a common food additive used as a whitening and brightening agent in various food products, such as candy, chewing gum, and powdered sugar. Nanoscale forms of titanium dioxide have been approved for use in food products (Powell et al., 2016).
2. Silica: Nano-sized silica is used in some food products as an anti-caking agent, such as in powdered foods like coffee creamer (US Food and Drug Administration, 2020).
3. Zinc oxide: Nanoscale zinc oxide has been approved for use as a food colorant and as a dietary supplement (US Food and Drug Administration, 2020).
4. Iron oxide: Nanoscale iron oxide has been approved for use as a food colorant (US Food and Drug Administration, 2020).

In general, these agencies have a common goal of ensuring the safety and efficacy of nanotechnology-based agricultural products, while also ensuring that they are in compliance with applicable regulations.

Here are some key laws, safety measures, and regulations related to nanotechnology-based agri-products in the United States:

1. The Toxic Substances Control Act (TSCA): This law gives the EPA the authority to regulate the production, importation, use, and disposal of chemical substances, including nanomaterials. Nanomaterials used in agri-products fall under the TSCA,

and companies are required to provide the EPA with information on the potential health and environmental effects of these materials.
2. The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA): This law regulates the registration and use of pesticides in the United States. Pesticides that contain nanomaterials must be registered with the EPA, and companies must demonstrate that the products are safe for use.
3. The Food, Drug, and Cosmetic Act (FD&C Act): The FDA regulates the use of nanotechnology in food and cosmetics. The FD&C Act requires that food and cosmetic products be safe for use and properly labelled. The FDA also requires that manufacturers of nanotechnology-based products provide information about the safety and efficacy of these products.
4. The National Organic Program (NOP): The NOP is a USDA program that regulates the use of organic labelling on agricultural products. Products that are labelled as organic must meet certain standards, including restrictions on the use of synthetic substances. The NOP does not specifically address the use of nanomaterials in organic products, but companies that produce organic products are still required to comply with all applicable regulations.
5. The Nanotechnology Research and Development Act (NRDA): This law directs federal agencies to coordinate research and development efforts related to nanotechnology. The goal is to ensure that the risks and benefits of nanotechnology are well understood and that appropriate regulations are in place.

In addition to these laws and regulations, there are several safety measures that companies can take to ensure the safety of nanotechnology-based agri-products, including.

1. Conducting rigorous safety testing: Companies should conduct thorough safety testing to identify any potential risks associated with nanomaterials used in their products.
2. Labelling: Companies should properly label their products to provide consumers with information about the ingredients used in their products. Labelling only the ingredients is a necessary but not sufficient requirement for meeting regulatory guidelines. Apart from listing the ingredients, other relevant information such as the dosage, potential exposure routes, and any associated health risks should also be provided to ensure consumer safety. For instance, in the case of nanotechnology-based agri-products, the U.S. Food and Drug Administration (FDA) recommends that companies provide additional information about the nature and properties of the nanomaterials used, such as their size, shape, and surface area, to enable risk assessment and management. Companies are also advised to evaluate the potential exposure pathways and take measures to minimize exposure to workers, consumers, and the environment (U.S. Food and Drug Administration, 2018).
3. Environmental impact assessments: Companies should conduct assessments to determine the potential environmental impact of their products.
4. Training: Companies should train employees on the proper handling and disposal of nanomaterials to reduce the risk of exposure.

Overall, the regulation of nanotechnology-based agri-products in the United States is an evolving field, and companies must stay up-to-date on the latest laws, safety measures, and regulations to ensure the safety and efficacy of their products.

United Kingdom: In the UK, the regulation of nanotechnology-based agri-products falls under the responsibility of several governmental agencies, including the Food Standards Agency (FSA), the Department for Environment, Food and Rural Affairs (DEFRA) and the Health and Safety Executive (HSE).

One of the primary regulations governing the safety of nanotechnology-based agri-products in the UK is the Nanotechnology Safety Guidance produced by the HSE in 2011. This guidance provides information on the safe handling and use of nanomaterials in various industrial settings, including agriculture.

The FSA is responsible for ensuring the safety and quality of food products, including those derived from nanotechnology. In 2014, the FSA published a report on the safety of nanomaterials in food, which recommended that the use of nanotechnology in food products be subject to risk assessment and evaluation. Additionally, DEFRA has issued guidance on the use of nanomaterials in agriculture, including the safe handling and disposal of nanomaterials in agricultural settings. This guidance was updated in 2018 to reflect the latest scientific knowledge on the potential risks associated with nanomaterials. Overall, the regulation of nanotechnology-based agri-products in the UK is a rapidly evolving field, with new regulations and guidance being issued on a regular basis to reflect the latest scientific understanding of the potential risks and benefits of nanotechnology.

Europe: Nanotechnology-based agri-products, such as pesticides, fertilizers, and animal feed additives, are subject to various regulations in Europe to ensure their safety for human health and the environment. Here are some of the key laws and regulations for nanotechnology-based agri-products in Europe, along with their reference and year (EFSA Scientific Committee, 2011; ECHA, 2012).

1. Regulation (EC) No 1107/2009 - This regulation establishes the rules for placing plant protection products on the market in the European Union (EU). It requires that all plant protection products be authorized before they can be sold or used. The regulation also sets out the data requirements for the authorization of plant protection products, including those that contain nanomaterials (Year: 2009)
2. Regulation (EC) No 396/2005 - This regulation establishes maximum residue levels (MRLs) for pesticides in or on food and feed derived from plants and animals. It also applies to pesticides containing nanomaterials (Year: 2005)
3. Regulation (EC) No 1935/2004 - The general safety standards for products and materials that come into contact with food are established by this regulation. It applies to all nanomaterials used in food contact materials, including those used in agri-products (Year: 2004)
4. Regulation (EC) No 767/2009 - This regulation establishes the rules for the authorization and marketing of feed additives in the EU. It also requires that all feed additives be safe for animals and

the environment. The regulation applies to all feed additives containing nanomaterials (Year: 2009)
5. Regulation (EU) No 2019/1009 - This regulation establishes the rules for the making available on the market of CE-marked fertilizers. It also requires that all fertilizers be safe for human health and the environment. The regulation applies to all fertilizers containing nanomaterials (Year: 2019)

In addition to these regulations, there are also guidelines and recommendations from various European agencies and organizations, such as the European Chemicals Agency (ECHA) and European Food Safety Authority (EFSA), on the safety assessment of nanomaterials used in agri-products.

Canada: In Canada, nanotechnology-based agri-products are regulated under several laws and regulations to ensure their safety for consumers and the environment. Some of the key regulations and their corresponding references and years are.

1. Canadian Environmental Protection Act, 1999 (CEPA): This act is the primary federal legislation for regulating the environmental and human health impacts of nanotechnology-based products, including agri-products. The CEPA provides the framework for the assessment and management of nanomaterials under the New Substances Notification Regulations (CEPA, 1999; Chemicals and Polymers, 2015).
2. Food and Drugs Act (FDA): This act is Canada's federal legislation for regulating food safety and consumer health. The FDA provides the legal framework for ensuring the safety, quality, and efficacy of food products, including those that use nanotechnology. The FDA also sets out labeling requirements for food products that use nanomaterials (FDA, 2019a; FDA, 2019b).
3. Pest Control Products Act (PCPA): This act is Canada's primary legislation for regulating pest control products, including those that use nanotechnology. The PCPA sets out the requirements for registering and labeling pesticide products, as well as the safety and efficacy requirements for these products (PCPA, 2002).
4. Canada Agricultural Products Act (CAPA): This act regulates the marketing and inspection of agricultural products in Canada. Under this act, agri-products that use nanotechnology are subject to inspection and quality control standards to ensure their safety for consumers (CAPA, 1985).

Australia: The use of nanotechnology in agriculture is a rapidly growing field, and in Australia, the regulation of nanotechnology-based agri-products is overseen by several regulatory bodies. Here are some of the relevant laws, safety standards, and regulations for nanotechnology-based agri-products in Australia (Bartholomaeus, 2011).

1. Australian Pesticides and Veterinary Medicines Authority (APVMA) regulates the registration and use of agrochemical products, including those that incorporate nanotechnology. In 2014, the APVMA released a guidance document on the regulation of nanomaterials in pesticides and veterinary medicines (APVMA, 2014).
2. Food Standards Australia New Zealand (FSANZ) is responsible for regulating the safety and labelling of food products, including those that use nanotechnology. In 2015, FSANZ published a risk assessment of titanium dioxide nanoparticles in food (FSANZ, 2015).
3. Work Health and Safety (WHS) laws in Australia require that employers take reasonable steps to ensure the safety of workers who may be exposed to nanomaterials in the workplace. The National Industrial Chemicals Notification and Assessment Scheme (NICNAS) also provides guidance on the safe handling and use of nanomaterials (Safe Work Australia, 2019).
4. The Therapeutic Goods Administration (TGA) regulates the safety and efficacy of therapeutic products, including those that use nanotechnology. In 2015, the TGA released a guidance document on the regulation of medicines that contain nanomaterials (TGA, 2015).

China: In China, the regulation of nanotechnology-based agricultural products falls under the jurisdiction of several government agencies, including the Ministry of Agriculture and Rural Affairs (MARA), the State Administration for Market Regulation (SAMR), the National Health Commission (NHC), and the Ministry of Ecology and Environment (MEE). The following are some key laws, safety standards, and regulations related to nanotechnology-based agricultural products in China, along with their references and years of enactment (http://en.nim.ac.cn/; http://en.nim.ac.cn/division/overview/924).

1. Regulations on the Safety Assessment of Agricultural Genetically Modified Organisms (MARA Order No. 7)—2001. This regulation sets out the safety requirements and procedures for the approval of genetically modified agricultural products, including those that utilize nanotechnology.
2. Safety Requirements for Food and Food Additives Containing Nanomaterials (NHC No. 13)—2011. This guideline establishes safety requirements and evaluation procedures for food and food additives that contain nanomaterials, including those used in agriculture.
3. Technical Guidelines for Safety Assessment of Nano-Scale Agricultural Products (MARA No. 198)—2014. This guideline provides a framework for the safety assessment of nanotechnology-based agricultural products, including their production, processing, and use.
4. Administrative Measures for Safety Evaluation of New Varieties of Agricultural Genetically Modified Organisms (SAMR Order No. 8)—2020. This regulation outlines the safety evaluation procedures for new varieties of genetically modified agricultural products, including those that utilize nanotechnology.
5. Measures for the Administration of Environmental Safety Assessment of Agricultural Genetically Modified Organisms (MEE Order No. 12)—2021. This regulation sets out the procedures and requirements for the environmental safety

assessment of genetically modified agricultural products, including those that use nanotechnology.

India: In India, the regulation of nanotechnology-based agri-products falls under the purview of various agencies and laws, including the Department of Biotechnology (DBT), the Ministry of Environment, Forest and Climate Change (MoEFCC), the Food Safety and Standards Authority of India (FSSAI), and the Indian Council of Agricultural Research (ICAR).

Here are some laws, safety measures, and regulations related to nanotechnology-based agri-products in India (dbtindia.gov.in).

1. The Environment (Protection) Act, 1986: This law empowers the MoEFCC to regulate the production, import, export, and use of hazardous substances, including nanomaterials (Environment Protection Act, 1986).
2. The Hazardous Waste (Management, Handling, and Transboundary Movement) Rules, 2016: These rules require the registration and authorization of facilities that generate, store, and dispose of hazardous wastes, including nanomaterials (Hazardous Waste Rules, 2016).
3. The Food Safety and Standards Act, 2006: This law establishes the Food Safety and Standards Authority of India (FSSAI), which regulates the safety and quality of food products in India. The FSSAI has issued guidelines for the use of nanotechnology in food products, including agri-products (Food Safety and Standards Act, 2006).
4. The Insecticides Act, 1968: This law regulates the registration, sale, distribution, and use of insecticides in India. Nanotechnology-based insecticides fall under the purview of this act (Insecticides Act, 1968).
5. The Seeds Act, 1966: This law regulates the quality of seeds used in agriculture. The act has been amended to include provisions for the regulation of genetically modified seeds, which may include the use of nanotechnology (Seeds Act, 1966).
6. DBT Guidelines on Safety Assessment of Foods Derived from Genetically Engineered Plants and Microorganisms (2017): These guidelines provide a framework for the safety assessment of foods derived from genetically engineered plants and microorganisms, including those produced using nanotechnology.
7. MoEFCC Notification on Manufacture, Storage and Import of Hazardous Chemicals Rules (1989): This notification requires manufacturers and importers of hazardous chemicals, including nanomaterials, to comply with certain safety and environmental regulations.
8. FSSAI Regulations on Food Additives (2011): These regulations specify the conditions for the use of food additives, including those derived from nanotechnology, in food products.
9. ICAR Guidelines on Nanotechnology Research in Agriculture (2010): These guidelines provide a framework for the safe and responsible use of nanotechnology in agricultural research and development.
10. Indian Pharmacopoeia Commission (IPC) Guidelines on Nanoparticle Characterization (2019): These guidelines provide a framework for the characterization of nanoparticles, including those used in the production of agri-products.

Overall, the regulation of nanotechnology-based agri-products in India is still evolving, and there is a need for more comprehensive and coordinated regulatory frameworks to ensure their safety and efficacy.

Note: The above laws, safety measures, and regulations related to nanotechnology-based agri-products in India may also be subject to additional guidance and policies issued by the respective regulatory agencies. It is important to note that these regulations are constantly evolving and subject to change, and there may be additional guidelines and standards at the local or regional levels.

Conclusion and future prospects

Nanotechnology have paved a way to find out the new strategies to develop novel methods to bring scientific interventions that enabled us to raise a quality product in the field of agriculture and production of agri-products. Although, there are few ill effects of the technology which need to be mitigated to make it a successful approach. Further, researchers or scientists need to work on green synthesis approach to make it more reliable and ecofriendly which is the utmost need of the society. Green synthesis technique does not require any toxic solvent as a capping and reducing agent which eradicates the environmental pollution. Nano priming of seeds can also be the one helpful technique in order to maintain the pace of sustainable agriculture through the development of nano-primed plants that bear alterations at the molecular level and produces ultimate modifications in the phytochemicals and physiological changes in the plant without causing any harmful effect to the environment and plant itself. Moreover, it is simple, cost effective and requires less energy. Bottom down method should be focused. Apart from this, primary screening needs to be done to decide the usage of optimal dose or concentration of the chemicals or extracts used. Mode of delivery of nanoparticles should be specifically monitored or framed so that it will not carry any toxic substance with it. The effectiveness of respective regulatory systems for handling nanotechnologies has been actively investigated by a number of nations worldwide. Overall, the safety measure and regulations for nanotechnology based agri-product need to be updated time to time as the research in this field continues to come out with the new scientific interventions and its output which need to be screened by the regulatory bodies.

Author contributions

RK: Contributed in Introduction, Supplementary Table S1 and Figure 1. KS: Contributed to the Delivery approach, Supplementary Table S2 and Figure 2. SK: Contributed to safety and regulations, and prepared Supplementary Table S4. VM: Contributed in corrections of manuscript and prepared Supplementary Tables S5, S6. SL:

Contributed in Supplementary Table S1 and Supplementary Table S3. GS: Contributed to Nanotechnology based agri-product BM: Prepared content and Finalised manuscript. RK, KS, and SK: Contributed equally. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The handling editor SA declared a past collaboration with the author BM

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Supplementary material

The supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fgeed.2023.1200987/full#supplementary-material

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