Review

Nanobiotechnology for Agriculture: Smart Technology for Combating Nutrient Deficiencies with Nanotoxicity Challenges

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Abstract: Nanobiotechnology in agriculture is a driver for modern-day smart, efficient agricultural practices. Nanoparticles have been shown to stimulate plant growth and disease resistance. The goal of sustainable farming can be accomplished by developing and sustainably exploiting the fruits of nanobiotechnology to balance the advantages nanotechnology provides in tackling environmental challenges. This review aims to advance our understanding of nanobiotechnology in relevant areas, encourage interactions within the research community for broader application, and benefit society through innovation to realize sustainable agricultural practices. This review critically evaluates what is and is not known in the domain of nano-enabled agriculture. It provides a holistic view of the role of nanobiotechnology in multiple facets of agriculture, from the synthesis of nanoparticles to controlled and targeted delivery, uptake, translocation, recognition, interaction with plant cells, and the toxicity potential of nanoparticle complexes when presented to plant cells.

Keywords: nanofertilizer; smart delivery systems; nanoparticle–plant interaction; in situ tracking; toxicity studies

1. Introduction

The ever-growing population coupled with shrinking cultivable agricultural areas has created an immediate and increasing demand for new technologies and processes to improve agricultural production. The concurrent demand for food calls for an increase in the production and protection of crops worldwide [1]. Despite fertilizer consumption increasing worldwide in the past few decades, the nutrient removal from soil is much higher than the nutrient additions through fertilization (N, P, and K). This has created a net negative soil nutrient balance of about 10 million tons and significantly threatened soil health, which has translated into widespread economic losses for farmers [2]. The subsequent leaching losses reduce productivity and cause associated environmental problems [3]. Thus, appropriate uses for and doses of fertilizer products need to be determined to keep the ecological impact at a minimum.

Nanobiotechnology is a revolutionary technology of the 21st century. Nanoparticles (NPs) are defined as natural or engineered small particles with a size between 1 and 100 nm which, compared to their bulk counterparts, exhibit significantly different physical and chemical properties. NPs have unique properties—including shape, size, large surface area, crystallinity, surface functionalization, porosity, zeta potential, hydrophobicity, or hydrophilicity—that allow the targeted controlled release kinetics of NPs to be used as smart delivery systems [2]. Nanoparticles offer state-of-the-art solutions for precision farming; the targeted/controlled delivery of inputs; improved soil and plant health; and, importantly, the need-based application of agricultural inputs for improved productivity, efficiency, and economic benefits. Furthermore, improved methods for the biological synthesis of agriculturally important metal NPs have come to light with the advancement

and awareness of nanotechnology. Highly targeted, improved nano fertilizer formulations with a high use efficiency for plants are needed to ensure the minimal loss of nutrients [2]. This review provides a deeper understanding of the advances in nanobiotechnology in the field of agriculture, particularly biotechnological advances in nano formulation, delivery, and the fate of nano fertilizer, and encourages interactions within the scientific community for their more extensive application through innovation for sustainable agro-practices.

Nanoparticles—as a result of their small size (<100 nm), shape, atomic arrangement, and structure—have complex interactions with different biomolecules, ionic particulates, and colloids. These uncertain and complex properties of NPs make it difficult to determine their compatibility and fate in the soil–plant system. Moreover, plant–NP interaction studies are lacking due to technological gaps and efficiencies of techniques used. Comprehensive risk assessment and biocompatibility studies (cyto- and phytotoxicity) are needed for NP acceptance and to identify the fate of NPs in the soil–plant system.

The application of nanotechnology in agriculture relies on successful implementation of regulations from all stakeholders. Budding young researchers and scientists from R&D institutes, academia, and industry from across the globe need to come together to discuss the current practices and future scope of nanotechnologies to promote innovation and knowledge transfer for agriculture. The use of agrochemicals is essential in present-day agriculture; however, there have been few advances in the fields of nanopesticides and nanofertilizers, relative to other sectors, such as food handling, storing, and packaging. Deliberations and discussions would not only promote future collaborations for accelerated product development for agricultural application but will also be captured to prepare policies that will signify the need to prioritize future research in nanotechnology, identify scope for innovation, and highlight how nano-enabled systems can address contemporary issues in agriculture for the efficient delivery of fertilizers and nutrients (Figure 1).
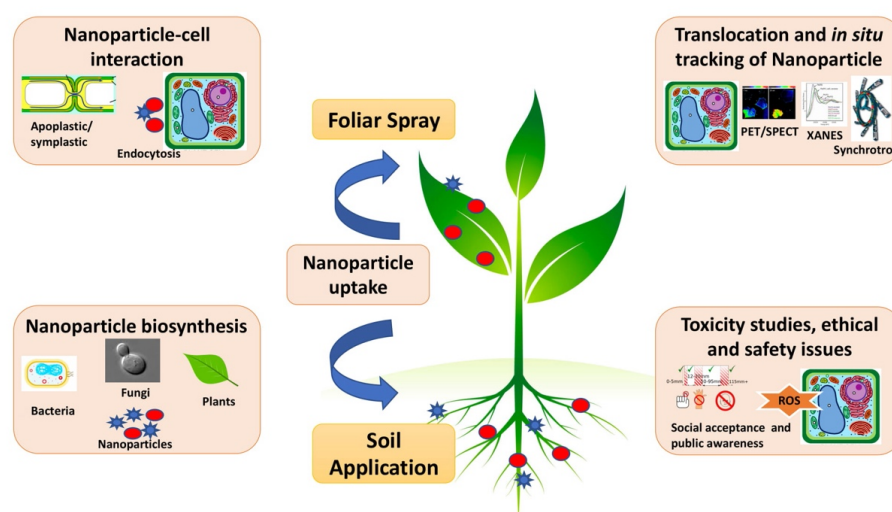
Figure 1. Nanobiotechnology in agriculture for combating nutrient deficiencies with nanotoxicity challenges.

2. Nutrient Deficiency—Causes and Implication

Nutrient deficiency is widespread in soils, adversely affecting soil health, decreasing the nutritional quality of farm produce, and incurring economic losses for the farmer. Fertilizers are applied in large quantities to enhance crop productivity, but most macronutrients are not readily available for plant use; thus, crops typically use less than half of the fertilizer applied. Additionally, most macronutrients are insoluble in the soil, and thus are unavailable for utilization by plants [4]. The remaining unused fractions of applied fertilizer are either leached or run off, contributing to soil, air, and water pollution. Hence, applying chemical fertilizers to enhance productivity may result in short-term economic gains but has a long-term harmful effect on the agroecosystem. The excessive use of chemi-

cal fertilizers damages soil health and microflora and disturbs belowground food webs, leading to genetic mutations and changes in ecosystem ecology [2]. Numerous factors such as nutrient immobilization, leaching, surface run-off, the excessive use of pesticides and herbicides, soil erosion, poor soil fertility, temperature, and moisture influence the general nutritional status of the plant [5]. The addition of macronutrients such as N, P, and K and various micronutrients is gradually hindering plant growth and development in agricultural fields worldwide [6].

Hence, sustainable alternatives to chemical fertilizers need to be developed that scaffold fundamental science and apply innovation to improve the functional value of crops and their related biota for better and more efficient nutrient use, value-adding, and environmental remediation [7]. Nanotechnology can systematically overcome the obstacle of different agricultural domains, including food security and productivity [8]. Micronutrients and macronutrients assume critical roles in the protection of plants against disease. Using NPs, the nutritional status of plants can be enhanced to improve yields, tolerate stress, and withstand attack from pathogens [9]. This raises a need for nanotechnological interventions that are highly targeted, site-specific, and release the carrier material (nutrient) in a controlled manner to effectively address nutrient deficiency in agricultural soils.

3. Traditional Chemical vs. Nanofertilizers

Chemical fertilizers are applied to plants by broadcasting or spraying without considering the nutritional state of the plant and/or soil, especially in developing countries. Due to the non-targeted approach of conventional fertilizer application, the amount of nutrients reaching the plant (use efficiency) is less than that through leaching and seepage from agricultural fields to the water bodies and soil underneath; such wastage incurs economic and environmental losses [10]. The repeated excessive application of fertilizers renders the soil unusable due to the over-accumulation of nutrients, which disrupts the whole-plant nutrient homeostasis and has other soil-degrading outcomes, such as reduced N fixation, increased numbers of pathogens and pests affecting soil flora and fauna, and mineral homeostasis [11].

Around 75% of urea (principal N fertilizer) is lost upon its application due to volatilization and leaching [12]. The inefficiency in the delivery of fertilizer is related to groundwater contamination and water bodies being over-burdened with nitrates, extending the dead zones in water bodies and the release of nitrous oxide into the environment. Nitrous oxide is the third-most copious ozone-depleting substance (greenhouse gas, GHG), with a higher global warming potential than any other GHG, including carbon dioxide and methane [13]. Our reliance on chemically manufactured N fertilizer has significantly expanded anthropogenic impedance with the N cycle, which is key for the production of proteins for all living things. Nanoparticle fertilizers enable the slow and controlled on-demand release of nutrient/s, in turn preventing premature losses [6].

Nanotechnology can be used to explore nanoscale materials for carrying fertilizers and/or as vectors for enabling controlled-release kinetics in the design of smart nanofertilizers [13]. Metal NPs' synthesis and use in nanofertilizers is a sustainable alternative method to the existing, expensive, environmentally destructive conventional chemical fertilization techniques, with long-term applicability and acceptability, and is considered to be a 'Nano-Bio Revolution' in the field of nano-enabled NP synthesis technologies. Moreover, using the biological system to develop such NPs is an added advantage of nano-biofertilizers by virtue of its targeted needs-based release and minimal wastage of fertilizer [14]. Besides their small size, large surface area, high solubility, and mobility, NPs also have a high surface tension, which helps to control their release of the encapsulated fertilizer [15]. NPs can quickly translocate in plants [16], advancing the release of nutrients through nanofertilizer and providing better protection through nanoproducts for agricultural use such as nanopesticides, nanofertilizers, and nanoherbicides [8,17]. A summary of the effect of the type and amount of NPs and their application methods on different plant species is presented in Table 1.

Table 1. Nanotechnological interventions in agriculture.

Nutrient	Nanoparticles	Plant Species	Application Method	Concentration	Effect on Plant	References
Titanium	TiO$_2$	*Oryza sativa* (rice)	Root	750 mg kg^{-1}	Increased P in root, shoot and grain, amino acids, fatty acids	[18]
		Solanum lycopersicum (tomato)	Root	20 mg L^{-1}	Increased amino acids, total phenolics, antioxidant capacity	[19]
		Hordeum vulgare (barley)	Root	500 mg kg^{-1}	Increased P, Ca, Mg, Zn, Mn, amino acids	[20]
		Mentha piperita (peppermint)	Foliar	150 mg L^{-1}	Increased N, chlorophyll, menthol, menthone	[21]
		Solanum lycopersicum (tomato)	Root and foliar	100 mg kg^{-1}	Increased lycopene	[22]
Cerium	CeO$_2$	*Oryza sativa* (rice)	Root	500 mg kg^{-1}	Increased K, Ca, Na, protein albumin, total sugars	[23]
		Hordeum vulgare (barley)	Root	500 mg kg^{-1}	Increased P, K, Ca, Mg, S, Cu, Fe, Zn, Mn, amino acids, fatty acids	[24]
		Triticum aestivum (wheat)	Root	400 mg kg^{-1}	Increased P, K, Fe, amino acids, fatty acids, total sugars	[25,26]
		Cucumis sativus (cucumber)	Root	750 mg kg^{-1} 400 mg kg^{-1}	Increased K, Ca, Mg, S, P, Fe, Mn, Zn, total sugars, starches, proteins	[27,28]
		Coriandrum sativum (cilantro)	Root	125 mg kg^{-1}	Increased Ce, catalase, and ascorbate peroxidase activities	[29]
Zinc	ZnO	*Pisum sativum* (pea)	Root	250 mg kg^{-1}	Increased P, Fe, Zn, Mn, total sugars	[30]
		Cucumis sativus (cucumber)	Root	400 mg kg^{-1}	Increased K, Mg, Fe, Mn, Zn, S, prolamin, globulin, glutelin	[28]
		Zea mays (maize)	Foliar	100 mg L^{-1}	Increased Zn, germination, growth, yield	[31]
		Solanum lycopersicum (tomato)	Root and Foliar	10 mg L^{-1}	Increased lycopene	[32]
		Arachis hypogaea (peanut)	Foliar	1000 mg L^{-1}	Increased Zn, chlorophyll, root biomass, yield	[33]
	Zn-amino acid nano complex	*Ocimum basilicum* (sweet basil)	Foliar	1500 mg L^{-1}	Increased catechin, hesperetin	[34]
Copper	Cu	*Solanum lycopersicum* (tomato)	Root and Foliar	250 mg L^{-1}	Increased K, total proteins, vitamin C, total phenols, flavonoids, lycopene, antioxidant capacity	[35,36]
		Cucumis sativus (cucumber)	Root	400 mg kg^{-1}	Increased Cu, Fe, sugars, organic acids, amino acids, fatty acids	[37,38]
Iron	Fe$_2$O$_3$	*Arachis hypogaea* (peanut)	Root	1000 mg kg^{-1}	Increased Zn, growth, biomass	[39]
		Glycine max (soybean)	Foliar	750 mg L^{-1}		[40]
Calcium	CaO CaCO$_3$	*Arachis hypogaea* (peanut)	Foliar	500 mg L^{-1}	Increased Ca, root development	[41]
		Vigna mungo (Black gram)	Seed	750 mg L^{-1}	Increased root and shoot growth, biomass	[42]
Magnesium	Mg	*Vigna unguiculata* (cowpea)	Foliar	500 mg L^{-1}	Increased photosynthesis, growth, yield	[43]
Silver	Ag	*Cucumis sativus* (cucumber)	Foliar	3000 mg L^{-1}	Increased growth, fruit yield, biomass, total soluble solids in fruit	[44]
		Solanum lycopersicum (tomato)	Root	1000 mg L^{-1}	Increased superoxide dismutase activity	[45]
		Lactuca sativa (lettuce)	Foliar	100 mg kg^{-1}	Increased Ag content	[46]
Gold	Au	*Arabidopsis thaliana* (thale cress)	Root	10 mg L^{-1}	Increased seed germination, growth, yield	[47]
		Brassica juncea (brown mustard)	Foliar	10 mg L^{-1}	Increased germination, yield, protection from oxidative damage	[48]

4. Advanced Use of Nanotechnology to Develop Nanofertilizers

Nanobiotechnology is a valuable tool with extensive application in ecological sustainability and has emerged as an integrated 'toolbox' for agro-economy and ecosystem service providers. The synthesis of NPs using living organisms—such as bacteria, fungi, and plant extracts, and their metabolites—is termed the biosynthesis of NPs. Biologically synthesized NPs or biogenic NPs are a green alternative to the existing chemical methods of NP synthesis, which are toxic and energy-intensive with hazardous byproducts that damage the environment [49,50]. Biosynthesized NPs are biocompatible, are highly reproducible, have a low polydispersity, and are easy to upscale. The biological method of NP synthesis is comparable to other existing physical or chemical methods [51]. Microorganisms, with their inherent properties to remediate and reduce heavy metals using numerous reductase enzymes, have potential as the workhorses of nanobio factories for synthesizing metallic bio-NPs [50]. Over the years, interest has moved from inorganic to biogenic NPs (e.g., nanocomposites). Nano-agrochemicals that utilize biogenic delivery frameworks compete well in terms of environmental sustainability but often do not compete economically with other agrochemicals. Investigations to determine whether nanoproducts can contend with existing chemical formulations in terms of performance and cost are required [52,53].

The synthesis of NPs by biological means can be broadly classified into two categories—intracellular and extracellular synthesis. Intracellular synthesis occurs within the biomass/cells of plants, fungi, bacteria, etc., while extracellular synthesis occurs outside the organism in question, which is aided by several biomolecules and extracellular metabolites (such as peptides) [54]. The challenges of intracellular synthesis, including the high extraction cost and complex downstream processing, can be overcome by extracellular synthesis, which ultimately improves the efficiency of downstream applicability. In the face of bioremediation, intracellular synthesis is preferred, as it is easier to remove the microbes containing the contaminant (intracellularly or extracellularly through adsorption) [55]. For all NP synthesis methodologies, a good monodispersity can be achieved by controlling critical parameters—for example, metal salt concentration, incubation time, pH, and temperature. The biological synthesis of NPs helps in providing characteristic natural capping to NPs, thus providing additional stability which can enhance the efficacy of biological nanoparticles [50]. Several organisms known to synthesize NPs by both extracellular and intracellular strategies have been selected for intensified NP productivity due to the simple upscaling, higher surface area of reactivity, and amount of proteins produced and excreted by organisms for effective downstream handling [49].

In a study conducted in an inert growth medium, the application of hydroxyapatite NPs stabilized by carboxy methylcellulose increased the growth rate and seed yield of soybean by 33% and 18%, respectively [56]. However, changes in grain production due to the application of hydroxyapatite NPs were not reported in the study and no significant statistical differences were observed when comparing the application of traditional phosphorus fertilizer and hydroxyapatite NPs. It must also be considered that the results expected from real soil conditions can be different from those observed in controlled lab conditions. Recently, a nanofertilizer form of nitrogen was synthesized wherein hydroxyapatite NPs were covered with urea, leading to a slow release of nitrogen to plants. Additionally, research in rice plants has indicated that urea nanohybrids (i.e., modified hydroxyapatite) can deliver nitrogen multiple times over a period of time, much slower than synthetic urea with an enhanced yield of the grain at just half the rate utilized with synthetic urea [57]. In another study, phosphorus NPs applied as a seed treatment in a suspension of water and phosphorite increased the growth rates in nine test plants (wheat, rye, pea, barley, corn, buckwheat, tomato, radish, and cucumber) by about two-fold [58]. Similarly, the high solubility of phosphate due to the use of ammonium zeolites increased the uptake of phosphorus in plants [59]. The fungal-mediated biosynthesis of phosphorus NPs was carried out employing *Aspergillius tubingensis* using tri-calcium phosphate as a precursor salt [60]. The further application of biosynthesized phosphorus NPs was not reported in the study. A slow potassium release formulation of nano-potassium fertilizer

was developed and found to reduce potassium losses in the soil while supporting the long-term sustained supply of potassium to plants [61]. Likewise, the foliar application of nano-potassium fertilizer improved the biomass, growth, and yield of parchment pumpkin (*Cucurbita pepo*) [62]. In another study, Zinc NPs improved the Zn content in grains and enhanced the growth and yield of maize growing in Zn-deficient soil [31]. However, the study was performed in sandy clay loam with a low organic matter content, and different results could be observed if the organic matter content percentage was increased even in the same soil. In another study, the use of ZnO NPs increased the lycopene content by 113% in tomato [32]. Similarly, the use of Fe NPs in various crops [39,63] improved enzyme function (heme proteins responsible for cytochromes) and overall agronomic traits, including Fe biofortification, nutritional quality, biomass, and N and P metabolism. In another study, the use of ZnO NP in Clusterbean (*Cyamopsis tetragonoloba*) increased the P uptake by 11%, as the Zn helps to mobilize P for plant use [32,64]. The application of ZnO NPs increased the cotton biomass and yield and increased the activity of antioxidant enzymes and other regulatory and functional proteins in soil [32,65]. Similarly, P mobilization occurred with the use of magnetite NPs (Fe_3O_4) in lettuce [63]. Thus, along with serving the primary role of a nano nutrient, NPs have multi-dynamic and systemic effects, with an active role in mobilizing and increasing the availability of other nutrients and improving the overall nutritional quality of farm produce [66].

The use of nanotechnology in plant sciences is gaining interest, particularly for the use of NPs as vehicles of biomolecules of agronomic importance/agrochemicals in plants [67]. The NPs encapsulate nutrients in a nano-thin protective film or nanoemulsion, which ensures a stronghold of nutrients on the plant surface due to the higher surface tension of the nanocoating [68] and has great potential for improving crop efficiency [69]. Nanozeolites [70] and nanoclays [71] are used as soil improvement products to aid in the efficient release and retention of water and nutrients. These zeolite NPs have characteristic well-defined pore networks that ensure the slow release of the agrochemical/nutrient in question [70]. Similarly, NPs such as nanowires (including microbial nanowires) [72] and nanofibers [73] help in the development of nanosensors and related diagnostic devices for the detection of pesticides/fertilizers [74]. Hence, nanobiotechnology is a key enabling technology that could revolutionize modern agriculture.

Various factors come into play during the uptake and translocation of NPs inside the plant system, from physiological plant factors—such as age, the plant species itself, and its biotransformation pathways—to the biophysicochemical factors of NPs, which define the functionalization of NP when presented to plant cells and have a cumulative effect on the fate of NPs [22]. The most commonly used method for providing nutrient supplements is the soil application of organic and chemical fertilizers. Soil is a dynamic and heterogeneous amalgamation of several biotic and abiotic factors (living or dead) that poses several challenges with respect to various soil properties such as texture and pH which govern the fate and longevity of fertilizer in the soil. Ion exchange capacity also plays a vital role in nutrient mobilization in the soil–plant system. Another method uses liquid fertilizers sprayed directly onto aerial plant parts, mainly leaves. This minimizes the loss of nutrients and is readily available for plant use, circumventing soil issues that render them less available to plants. Despite its clear advantages, this method requires rigorous optimization considering the role stomata and epidermal cells play in nutrient uptake, bearing in mind their diurnal physiological responses [75,76]. Another critical aspect to be taken into consideration is the size of the nutrient formulation that should not interfere or hinder the normal stomatal function by blocking the stomatal pores in case of nutrient supplied is larger than the size of the stomatal pore or if it is provided in an excess concentration.

Similarly, for NPs nano agrochemicals are generally delivered to plants via three methods: seed treatment, soil application, or foliar application. In general, the possible modes of entry of NPs in aerial parts of the plants include the passive uptake of NPs that occurs through plant openings with specific size exclusion (nano/micro)—e.g., stomata,

bark, hydathodes [77]. However, other physiological and anatomical perspectives should be considered to better understand how NPs and plants interact. Other viable routes for NP uptake include wound and injury on plant surfaces [78]. Lateral root junctions in the rhizodermis, especially near the root tip, provide easy access to NPs at the root level [79]. In general, the presence of microbes (symbiotic/parasitic), organic matter, and exudates, among others, in the soil complicates the dynamics of NP uptake relative to that in aboveground plant parts. Additionally, when NPs are applied to soil, rather than in a foliar spray, the high exposure of these NPs may influence soil microbial communities and agglomerate NPs due to various soil physicochemical properties that could confine NP uptake by plants [66,80,81]. It is evident from the literature that NP delivery by foliar application is advantageous for nano-nutrient uptake [22,82]. Furthermore, laboratory-scale tests have revealed that aerosol spray helps to produce monodisperse particles that do not agglomerate when applied through foliar application [66].

Different NP properties, such as size, shape, area of curvature, and radius, facilitate NP uptake by cells up to a threshold limit deviating from which decreases the cellular uptake (Figure 2). This might account for the difference in several contact sites in NPs of different sizes and shapes used for interaction between the NP and the cell membrane, thus affecting the free energy accessible for the NP to interact with the cell [83].
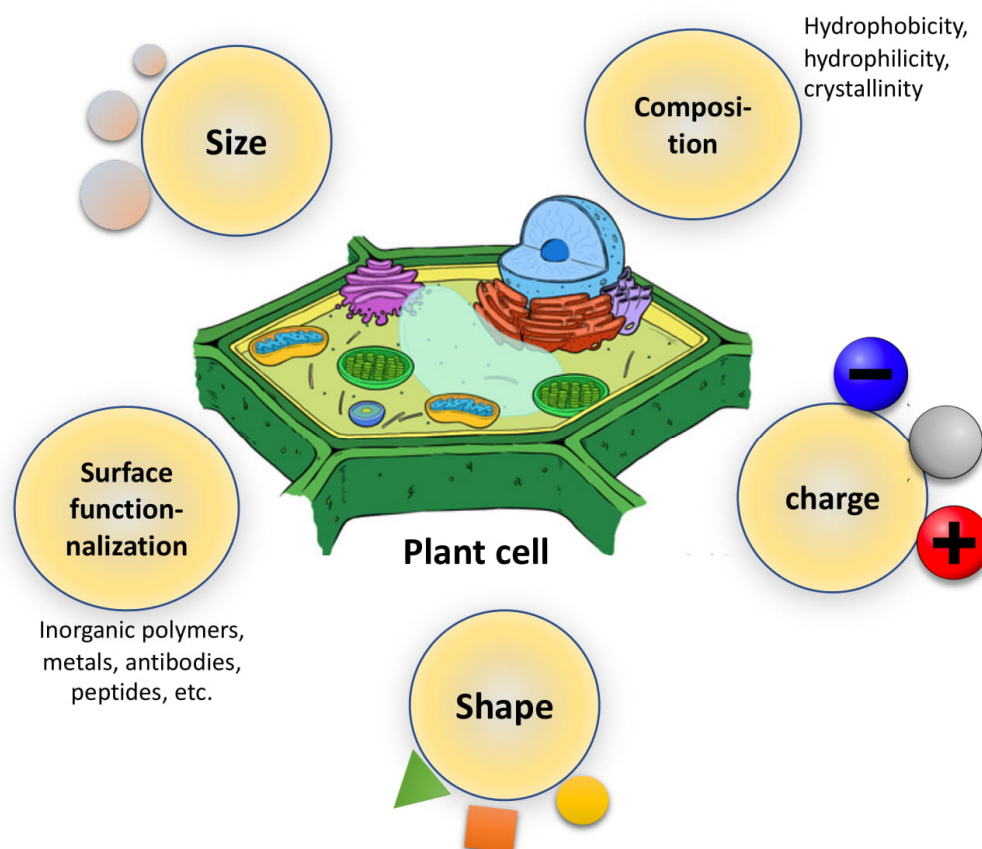

Figure 2. Physicochemical factors of nanoparticles (NPs) affecting NPs–plant cell interaction.

5. Nano-Nutrient Uptake and Regulation in Plants

The presence of nutrients in a bioavailable form is a prerequisite for their easy uptake by plants; however, their nature, amount, and association with other nutrients in the soil also define the amount available for plant use. The dynamic capacity of the soil–plant system and interface—comprising nutrient release and transformation from a solid state to the solution, translocation from soil to plant, and assimilation by the plant—also determines the relationship between nutrient supply and use [84]. Various edaphic factors,

such as moisture, texture, pH, water-holding capacity, redox potential, cation-exchange capacity, and biotic factors (including organic biomass and microbiome), regulate the concentration of nutrients in the soil. Excess amounts of minerals present in the soil limit plant growth and regulation processes—metals accumulate in the soil, which in turn affect water availability and plant growth. Roots are an integral point of contact between plants and soil, facilitating the uptake of nutrient minerals, water, and other biologically relevant entities (endo/ectomycorrhiza, etc.). Root development depends on the aeration, nutrient availability, pH, and texture of the soil, all of which affect nutrient availability to plants [85]. The uptake and transfer of nutrients from the soil through roots to shoots mainly occurs by a) diffusion and b) bulk (mass) flow. Diffusion is the movement of nutrients by concentration gradient due to the action of individual molecules down the gradient (also termed the short-distance or lateral flow of nutrients—i.e., from cell to cell) [86]. Bulk or mass flow is the movement of solutes and water together (through xylem and phloem at the whole-plant level) by the pressure gradient and is dependent on the transpiration rate and nutrient availability in soils [87].

The uptake of NPs is unpredictable and depends on various factors within the NP (size, net charge, surface coating, surface functionalization, stability), application route (aerial, root, seed), interacting environmental components (soil surface, water accessibility, microbiota), cell wall rigidity, and the physiology, anatomy, and biochemistry of the individual plant species. After entering the plant's external defensive layers, NPs have two routes of mobilization: the apoplastic and symplastic pathways. Apoplastic transport advances radial movement, which tends to move NPs toward the central cylinder of the root and vascular tissues, and an upward trend toward aerial parts [88,89]. Apoplastic translocation is vital for applications that require systemic delivery of NPs. The Casparian strip prevents the radial movement of NPs in the root endodermis, which can be overcome by switching from the apoplastic to a symplastic pathway. The symplastic pathway is a more regulated and organized pathway for the movement of NPs in the plant system [90,91].

Further, NPs can enter cells by different processes, including phagocytosis, pinocytosis, or endocytosis, and can accumulate in the cytoplasm, vacuoles, or lysosomes [92]. The receptor-bound endocytosis is a significant interfacial phenomenon between NP-bound protein epitopes/ligands and integral receptors bound with the cell membrane, which determine NP contact with cells and engulfment at particular (generally specific) adhesion sites [93]. In addition, the direct cell passage of NPs that does not hamper cell integrity can be achieved by using amphipathic CPPs (cell-penetrating peptides)—the cationic groups of the CPPs communicate with membrane-bound anionic groups on one side leaving their hydrophobic surface to reach the hydrophobic insides of the film easily, subsequently overcoming the hydrophobic barrier presented by cell membranes [94]. Cationic strength over dosage can hamper the integrity of the cell layer, consequently prompting cytotoxicity and eventually cell lysis [95].

Once the NP is in the cytoplasm, cell-to-cell movement occurs with the help of plasmodesmata [96,97]. Some studies have revealed that metal NPs can infiltrate seeds and translocate into seedlings, with no significant effect on germination rate or viability, suggesting the effective use of functional NPs for stimulating plant growth using seed priming [69,98].

6. In Situ Visualization and Tracking of NPs

NPs should be thoroughly characterized for future applications and NP biosafety analysis. Physicochemical characterization is essential for understanding the material's properties, qualities, and functionalities, such as solvency, dispersibility, and stability [99]. The recent interest in metal NPs has made it important to develop methods for studying their uptake, transformation, and environmental fate, hence raising the need to design tools for the real-time tracking and visualization of ENPs in the soil–plant system and advanced microscopic and tracer techniques.

Some studies have used micro X-ray fluorescence (µ-XRF) and micro X-ray absorption spectroscopy (µ-XAS) to study the translocation and accumulation of NPs in plants [88]. The characterization and particle size distribution of NPs in leaves can be investigated using single-particle inductively coupled plasma mass spectrometry (sp-ICP-MS) [100,101], and the spatial distribution of metals in leaf tissues can be analyzed using X-ray fluorescence microscopy (XFM) [102]. Metal speciation can be assessed with X-ray absorption near-edge spectroscopy (XANES), without damaging the samples. In situ analyses of metal speciation in plant tissues can be done using synchrotron-based X-ray absorption spectroscopy [100], which can reveal the underlying mechanisms around nutrient bioavailability, mobility, and behavior [103]. Translocation of TiO_2 NPs in cucumber (from roots to fruit) has been analyzed using synchrotron µ-XRF and µ-XANES [27].

For tracer techniques, NPs are tagged with suitable probes (radiotracers) for analysis using positron emission tomography (PET) or single-photon emission computed tomography (SPECT) to visualize inside plant tissues [104,105]. The labeling of metal NPs with radioactive isotopes (extrinsic or intrinsic) is a valuable tool for the sensitive and specific localization of NPs in a system. Labelled NPs have a similar surface and chemical composition as unlabelled NPs and thus reflect the actual intended behaviour of NPs, which is lost in other fluorescence labelling techniques due to the surface modifications required for such techniques [106]. Moreover, intrinsic radiolabelling has more advantages than extrinsic radiolabelling because the exogenous radiotracer in exogenous labelling is prone to breaking away from the metal core of the NP, such that it does not represent the actual behaviour of the metal NP and is a misfit for in vivo studies [107,108]. In situ tracking and imaging can be well achieved with intrinsic radioactive isotope-labelled NPs using nuclear imaging techniques (PET or SPECT) [109,110]. These advanced microscopic and tracer techniques can be used to help understand the adsorption, translocation, transformation, and assimilation of NPs in the soil–plant system and advance the knowledge on the cellular uptake of NPs and parameters controlling nanocellular interactions.

7. Smart Target Delivery System (Based on Environmental Triggers and Biological Demands)

Technological advancements can improve the commercial production of physiologically and agronomically important metal core NPs for fertilizer formulations to curb nutrient losses and increase plant use-efficiency, and thus qualify as 'smart delivery systems' [111]. The NPs can be applied to the plant or soil as nano fertilizer to enhance and improve fertilizer uptake and performance [112]. While nano fertilizers are promising for agribusiness, the use of nanotechnology for nutrient supply is sparse [13]. Multifunctional characters define a smart delivery system with a highly controlled, specific, remotely coordinated, and targeted approach that avoids biological barriers [113]. Likewise, nano fertilizers can be discharged at much slower rates, which may assist with soil fertility and nutritional balance by reducing run-off into groundwater and minimizing the dangers of toxicity caused by over-application [112]. Zeolites, having nano-porous properties, exhibit high selectivity towards plant nutrients and high specific surface area, which might be released in a slow and controlled manner for uptake by the plant as per the need (triggered by various factors) and hence ensure minimized nutrient loss and ecological risk and improving their viability [68]. Nano fertilizers designed for slow release and targeted delivery using urea-coated hydroxyapatite NP significantly enhanced rice crop yields, even with half the amount of urea compared to conventional fertilizer [57]. Specific natural polymers, such as chitosan NPs, have been used for the controlled release of N, P, and K by foliar uptake in wheat [114].

In biologically synthesized NPs, the protein corona (PC), which is a highly dynamic and complex biomolecular (primarily protein) coating that forms around NPs in physiological environments, dictates events such as the specific binding of the NP to the cell surface, its internalization, and its subsequent transport [115]. Protein binding on the NP surface changes its size and surface charge, which ultimately affects NP uptake and bio-distribution inside the cell. These proteins control cellular receptors, which aid the

protein–NP complex for cellular internalization [116] and subsequent transport and assimilation. Such protein coatings can facilitate the internalization of NPs coated with specific proteins for a target cell type or tissue, and/or can be masked (PEGylation) to prevent recognition by the immune system ensuring prolonged circulation in host cells without being recognized as a potential threat [117,118]. This might provide broader avenues for developing NP-based targeted action with minimized non-specific uptake [119]. How proteins are adsorbed and arranged on the NP surface influence the movement and bioactivity of the NP at the cellular level [120]. The protein–NP complexation modifies the hydrodynamic, plasmonic, and electrokinetic properties of the NP [121]. Various studies have revealed significant connections between PC composition and NP physicochemical properties, giving biological character and identity to the NP [122,123]. Protein-coating the NP can achieve the targeted delivery of NPs in a plant model. Recently, gold NPs coated with antibodies for α-1,5-arabinan (found on guard cells of stomata) were accurately targeted to stomata in *Vicia faba* and gold NPs coated with bovine serum albumin (BSA) protein had a specific affinity to trichomes [124].

In a biological system, various biophysicochemical properties, such as ionic strength, temperature [125], pH, and density of PC impact the functioning of NPs [126], critically characterize the physiological interactions between NP and the cell, and provide suitable modifications of cellular functions in the plant system [127]. In addition, various factors come into play that affect the formation of PC surrounding the NP. The protein adsorption on NP is a multifactorial procedure, which relies on the amount of accessible protein, the surface/area accessible on NP to communicate, and the protein affinity to the NP. This is a competitive process of protein adsorption on the NP surface and is subject to its affinity, duration of contact, and abundance, and is known as the 'Vroman effect' [128,129]. The Vroman effect oversees how the NPs disseminate and the PC develops inside cells during bio-dispersion and translocation to different locations within cells. Such time-based protein kinetic studies assume a significant role in unravelling the key protein players comprising the hard and soft corona with their residence time and association-disassociation rates [130,131]. The surface charge impacts the density of protein adsorbed, but does not change the profile of the proteins adsorbed [132,133]. Any communication driven electrostatically between NP and protein is a functional component of distinct local charge districts on the surface of the protein, but not the mass isoelectric point of the protein moiety itself [121]. Protein binding to the NP in a unique orientation is reversible and free of modification in the protein surface charge [134]. Several studies have shown that PC composition is characterized by the size of the NP; larger NPs tend to adsorb proteins of higher molecular weight than smaller NPs. Likewise, the size of the NP–PC complex fluctuates with the suspending media [122]. The NP surface curvature assumes a significant role in the adsorption of proteins, administering the structure and composition of the PC. Several studies have shown that fewer changes occur in the structure of the proteins adsorbed on curved surfaces of NP than level surfaces [135,136]. The PC profile changes both quantitatively and qualitatively with exposure/incubation time [137]; an increase in the concentration of proteins adsorbed can impact NP uptake and its interaction with cells [138]. The PC is very dynamic for an initial couple of minutes/hours upon interaction with NP in a biological medium. The underlying period of 'soft corona' development might be a rapid but gradual formation of 'hard' corona is a drawn-out procedure which changes the physiological reaction of the NP-PC complex, relying on the phase of evolution and structure of PC at that very moment [129,139].

It is conceived that PC surrounding NP provides stability against broad homo-aggregation which is additionally governed by media composition and chemistry of the NP surface. Hence, in biological media, the surface properties of NPs deviate from their initial design and should be engineered with this in mind to enable communication with cell membranes and receptors while checking for the impact of proteins bound to NPs for their uptake, circulation, and assimilation in bio-systems [139–141].

8. Toxicity Studies Related to NPs Uptake by Plants

The successful commercial utilization of NPs pre-necessitates risk assessment and nano-toxicological evaluations, which will shape the future development of safe NPs. Nanostructure (form) is regarded as more toxic than its non-nano form, but this needs further examination upheld by toxicological evidence [142]. There is a need to create rational science-based approaches to manage the toxicological effects of NP interactions with the environment and biological systems [143]. It is clear that NP interactions with living systems or cells are mediated and regulated by the PC surrounding the NP surface, which possibly triggers the cytotoxic, genotoxic, and pathophysiological [144] impacts if NP–PC interaction with the cell is not compatible [145]. On the biocompatibility front, the PC is a positive or negative player depending on the various factors influencing the interaction, such as type of protein forming PC, hydrodynamic size and charge associated with protein, which can induce an increase or decrease in NP toxicity [117,146].

The phytotoxic impacts of NPs are evident on the morphological and physiological front, with reduced root length, injured root tips, decreased biomass, chlorophyll degeneration, and other formative changes due to oxidative damage. However, this is not the case for all NPs. For example, TiO_2 NPs in *Cucumis sativus* and ZnO NPs in *Cyamopsis tetragonoloba* enhanced chlorophyll content [147,148], while ZnO NPs in *Pisum sativum* and Ag NPs in *Solanum lycopersicum* reduced chlorophyll content [45,149]. Reactive oxygen species (ROS) are commonly produced in biological systems in response to NP penetration, which can disrupt typical biophysicochemical and abiotic stress-related functions [150] and the regulation of genes associated with combating stress, leading to NP-specific genotoxic effects [151,152]. In response to NP penetration, ROS induces other toxic effects. such as ion leakage and cell death, which are primarily due to oxidative stress and abnormalities in cell membranes due to ROS-induced lipid degeneration. The CeO_2 NPs in *Zea mays* caused lipid peroxidation due to ion leakage in cells, but no such effect was observed in *Oryza sativa* at the same NP concentration (0–500 mg/L) [153]. Plant–NP interactions can adversely affect secondary plant metabolism, hormonal homeostasis, growth and development of the plant. A recent analysis of transcriptomes in *Arabidopsis thaliana* uncovered that NP exposure suppressed the expression of specific genes associated with phosphate loss, pathogens, and stress response, with possible negative impacts on plant defense mechanisms and root development [69].

NPs can also disrupt nutrient distribution, which affects optimum growth and development. The N_2-fixing ability of rhizobacteria for use by soybean plant was hampered by CeO_2 NPs [154], reducing the availability of N in the plant and affecting its normal development and function [155]. In contrast, TiO_2 NPs in *Cucumis sativus* improved the accessibility of P and K. Plants treated with 500 mg kg^{-1} had 35% more K and 34% more P [27]. Additionally, several nanomaterials such as TiO_2 are obstinate and, with prolonged use, the metals component can tend to accumulate in the environment. Additionally, nutrients such as Cu, under constant application ultimately ends in the soil in excess which can be deleterious for plants. Potential mechanisms for NP stress mitigation include the upregulation of antioxidant compounds and downregulation of genes responsible for metal transport to hinder further metal uptake [156]. A recent study that included omics information in a systems biology approach in plant varieties such as rice, tobacco, and wheat showed that a generalized stress response is incited by metal NPs, primarily the oxidative stress response [157]. This suggests that even if no toxic effect is observed at the phenotypic level, high-throughput examinations of genetic and metabolic reactions, activated by NP exposure, are needed to reveal aspects of NP phytotoxicity [158].

It is not known whether or not nanotoxicity is specifically dependent on the NP type and its interaction, or whether the detoxification mechanisms that are activated in reaction to NP stress are proficient at balancing the stress at the biomolecular level. Before exploring their impact in the plant system, it is important to understand the properties of synthesized NPs to avoid any risks (human and environmental) associated with the use and applications of these NPs [8]. Identifying protein markers (signatures) through

proteomic investigations will provide insight into toxicities induced by NPs at the proteome level. Thorough in vitro and in vivo phytological testing is needed to ensure efficient use of nutrients with minimum or no associated toxicity before any nano agriproducts are commercialized [8].

9. Ethical and Safety Issues Surrounding the Use of Nanoparticles for Enhanced Plant Productivity

Ethical and safety issues surrounding the use of NPs for agronomic applications must be considered and carefully evaluated. Considering possible nanoproducts in the food and agribusiness domains, there is a broadly acknowledged fact that sparse dependable information is available concerning the safe use of NPs in light of the lack of safety assessment regulations [52,53].

A robust life cycle assessment (LCA) is essential to thoroughly assess the environmental impact of nano fertilizers and to design suitable fertilizer products and appropriate dosages for their effective use [3]. Toxicity and risk assessment studies will identify the risks associated with the spread and bioaccumulation of NPs in the food chain and will enable us to make sound policy decisions for their broader commercialization [11], directly influencing consumer decisions. Biocompatibility studies are needed for the successful commercial applications of NPs. Biocompatibility is primarily attributed to the protein coating surrounding the NP that interacts with the cellular components and machinery of the test organism. In addition to the role of the protein coating, the metal core subjected to metal homeostasis in the cell can explain the specificity and elicit cellular reactions in response to NP invasion [159]. The high surface area of NPs interacts with cells and governs NP uptake and intracellular localization [160]. The agglomeration of NPs can alter some surface properties; lead to different cell interactions, change the surface area available for protein adsorption; and induce a conformational change in the proteins, triggering a differential uptake and localization pattern [161]. Thus, controlling agglomeration is important for enhanced bioavailability to limit spread and improve safety [162]. In addition to the surface area and protein coating, the net change in amino acid residues determines the preferential active uptake of NPs [163]. Thus, successful commercial application of NPs requires nano-toxicological and risk assessment studies, which form the baseline for the development of safe NPs. It is generally perceived that nanoform is more toxic than its bulk form counterpart, but this needs thorough investigation backed by toxicological evidence [142]. Exposure and risk assessments depend on examinations related to the environmental fate of a compound. Few studies have examined nano-agrochemicals regarding their implications for the environment [164], with the results insufficient for a reliable evaluation of the risks related to their use. Comprehensive risk assessment and biocompatibility studies (cyto- and phytotoxicity) need to be prioritized [165] for NP acceptance and to identify the fate of NPs in the soil–plant system for successful application and acceptability in the field of agriculture.

Expanding regulatory pressure, joint efforts across fields (e.g., industry, research, and regulators), and the integration of scientific disciplines with social development and law will ensure the development of practical legal frameworks and consumer and public acceptance [53]. A transdisciplinary approach underpinned by the One Health concept is needed to support the sustainable development of these technologies and the safe use of nanotechnology [166]. This concept is endorsed by several organizations, including the World Health Organization (WHO) and the Food and Agriculture Organization (FAO), and is defined by the FAO as "The One Health vision is a unifying force to safeguard human and animal health, to reduce disease threats and to ensure a safe food supply through effective and responsible management of natural resources" [167]. Hence, the use of nanobiotechnology in agriculture requires a deliberate effort to overcome the difficulties presented by regulations and policies that have not yet been put in place or are not fit for purpose [168].

10. Conclusions and Perspective

The application of nanotechnology in agriculture is in its infancy. The lower profit margins in agriculture compared with other sectors, such as medicine, have resulted in fewer sound investments and research ventures that support nanotechnology in agriculture, both for producers and consumers. Joint efforts between disciplines at each phase of the development and assessment of agrochemicals (e.g., plant material, formulations, and ecological researchers) will advance nano agriproducts by overcoming numerous limitations in the agrochemical sector and will likely add value to existing products.

On the research front, inconsistent results on the mechanism of NP biosynthesis, its cellular uptake and mobilization in the plant system, and factorial analyses of their connection with biological systems has increased the need for comprehensive understanding in this area to design safe and effective NPs. It is critical to recognize and fill the knowledge gap concerning the fate and effect of NPs as it relates to precise and effective exposure and risk assessment for a sustainable environment. A fair and reasonable evaluation of nano-agricultural inputs should focus on assessing both the challenges and opportunities related to their use, relative to current solutions (Figure 3).
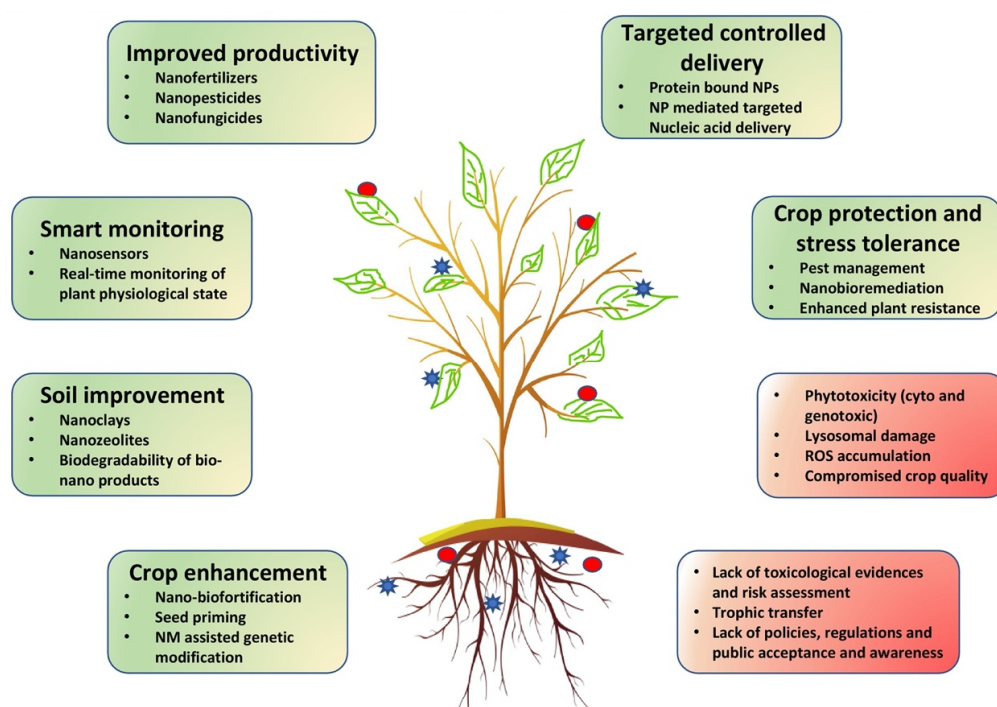

Figure 3. Opportunities (in green) and challenges (in red) for nanobiotechnology in agriculture.

It is essential to understand that NPs and their PCs and other related biophysicochemical characteristics, not NPs alone, characterize the ecological and biological effects of NPs. Using computational strategies for a point-by-point analysis of the NP–protein–cell interface is critical for understanding the structure and composition of PCs formed under specific physiological conditions and NPs' compatibility with the biological system. Further investigations are required on the direct and indirect impact of the biophysicochemical attributes encompassing NP–protein–cell interactions on cell signaling and cellular toxicity. The mechanisms involved in the protein–NP interaction and its fate in biological systems need to be investigated using in vivo frameworks.

Comprehensive proteomic and metabolomic tools need to be developed to better understand NP stress in biological systems that induce biomolecular and physiological responses. Systems in particular domains, such as the soil–plant framework in agriculture, which is commonly viewed as the sink for NP accumulation, should form the model framework for studies on toxicity and risk assessment, as the water–soil–plant interface

identifies with the sustainable food chain and ecosystem functioning. Novel science-based tools are needed to assess nano-formulations in light of the risks and advantages over the whole life cycle of developed or existing products.

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Abbreviations

NP(s), nanoparticle(s); PC, protein corona; ENP(s), engineered nanoparticle(s); N, nitrogen; P, phosphorus; K, potassium; R&D, research and development; GHG(s), greenhouse gas(es).

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