



Review Article

Nanotech drug delivery system: The perfect physio-Chemical deal for biological command

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ABSTRACT

The application of nanotechnology in drug delivery is offering several exhilarating possibilities not only in healthcare but also in agriculture. Nanoparticles combined with the therapeutic agents have a proven edge over problems associated with conventional therapy; however, some issues like side effects and toxicity are still under debate and are of prime concern in utilization in biological systems. Herein, we discuss the role of nanotech drug delivery system mostly in animal and plants- highlighting the comparative accounts of the key techniques for designing of drug in animals and plants, the challenges therein, the important nanoparticles being used in both the area and prospects of the field in the near future.

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1. Introduction

Although nanoscience and nanotechnology are being mentioned for the last one and a half decades, but unknowingly the right nanotechnology has been used since very ancient times. Since the enunciation of the term “nanotechnology” by Norio Taniguchi, a researcher at the University of Tokyo, Japan in 1974, the wider utility and possibilities of these particles are being explored in every field of science. Due to the many potential applications of this technology in revolutionizing healthcare and crop production, it is becoming an area of great interest among medical and agricultural researchers. In this direction, till the first decade of 2000, most of the work in medicine and agriculture through nanotechnology was at the research stage, with very few products and processes available to the public use, but the prospects were quite clear, and they are constantly being explored. It has been expanded and

now its potent biological activity is quite apparent. Through, this review, we intend to serve as a quick summary of the major aspects of nanotechnology in healthcare and crop production.

2. Key Characters of Nanocarriers Used for Drug Delivery System

The problems associated with the use of synthetic materials in drug delivery such as large size, poor bioavailability, in vivo instability, meagre solubility and poor absorption in the body poses major challenges. Probable side effects, low efficacy, toxicity, issues with target-specific delivery are also of prime concern. As nanoparticles embrace materials designed at the atomic or molecular level, they are usually small sized nanospheres and can move more freely in the human body as compared to bigger materials.¹ Hence nanoparticles have the potential to address these critical issues of synthetic materials and hence could be an option to solve these grumbles more effectively.

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Nanoparticles, more precisely known as nanocarriers exhibit unique structural, mechanical, electrical, chemical, magnetic, and biological properties and have been investigated as efficient tools for the delivery of bioactive species in plants as well as animals since last one and half decades. It is quite fascinating to know that how a nanoscale particle can effectively do this miracle. In fact, reflexive targeting is achieved by integrating the therapeutic agent into a nanoparticle. Drugs either encapsulated in or coupled to nanoparticles passively reach the target organism. To be an ideal nanocarrier, nanoparticles must have certain technical features for biomedical and agricultural purposes. Most importantly, nanocarriers should not cause any side effects or produce toxic response in the recipient organism. Besides, bio compatibility, chemical stability over time and encapsulation efficiencies are essentially sought properties. Unique behaviour of nanocarriers makes them precise in terms of colloidal stability and absorbance in physiological media inside any biological system. The technical structures including their conjugation with other molecules and suitable design for efficient nanocarriers of bioactive molecules largely affect the delivery of bioactive species. The nanocarrier should be carefully selected so that they must meet the technical criteria to address mandatory regulations of the target prior to being commercialized.

3. Nanotools and Nanotechnologies in Pharmaceutical Systems

In healthcare field, nanotechnologies make their most significant contribution in diagnosis of a disease. Owing to lack of specificity regarding the target cells, mostly the current drug administration systems demand high doses. On the other hand, and associated risks of side effects of toxic drugs necessitate low concentrations to minimize adverse side-effects. In this scenario, targeted drug delivery can execute the intention of achieving the intake of desirable and accurately low quantities to be harmless for the patient but in contrast, precisely lethal enough for the infectious agent. One of the foremost advances in current decades has been the lessening in the size of drug carriers to the dimensions below 100 nm and consequently at this scale, the carriers are capable of being internalized very efficiently by living cells. These particles having size below 100 nm are called nanotools, display superior properties for attaining increased efficacy, better patient compliance, improved biodistribution and site-specific drug delivery. Among the various types of potential nanotools, the important are polymeric nanoparticles, solid lipid nanoparticle, liposomes, carbon nanotubes, dendritic polymers, and DNA cages. These nanotools are attractive therapeutic agents in pharmaceutical systems and can be functionalized with a plethora of roles in drug delivery, bioimaging, tissue engineering and therapeutic applications.

3.1. Classes of nanotools

There exists primarily two main categories of nanotools, i.e., nanomaterials and nanodevices. Nanomaterials can be further considered on the basis of three basic parameters including structure, dimension, and phase composition. According to phase composition, these nanomaterials can be categorized in three groups. Nanodevices are subdivided in three groups, including microelectromechanical systems/nanoelectromechanical system (MEMS/NEMS), microarrays, and respirocytes. These structures and devices can be fabricated with a high degree of functional properties for use in medicine to interact with cells at a molecular level, thus allowing an extent of integration between biological systems and the latest technology that was not achievable previously. Nanodevices are nanotools, specifically created for the purpose of interacting with cells and tissues to perform very specific tasks. These tools have become quite common for disease diagnosis and being widely used during surgeries. The most common and popular nanodevices are the imaging tools. These tools contain miniature cameras and can be taken as oral pills. These cameras reach deep inside the body and able to provide high-resolution pictures of cells and tissues as small as 1 μm in width. This makes them very useful in getting deep insight the roots of diseases.

3.2. Nanotechnological applications in pharmaceutical systems

Ideally, disease diagnoses are desired to be fast and accurate. Nanotechnology mediated in vivo imaging is a technique that identifies signs or symptoms within a patient's live tissues, without undergoing surgery. The medical imaging modalities include magnetic resonance imaging, optical imaging, photoacoustic imaging, computed tomography, positron emission tomography, single photon emission computerized tomography and ultrasound. Besides, various cancer therapeutic methods are also included, like photothermal therapy, chemotherapy, photodynamic therapy, immunotherapy along with recent advances in multimodality imaging, image-guided therapy and combination therapy. Additionally, these nanoparticles can hold therapeutic agent for the tumor to provide the necessary concentrations of it via external molecular stimuli.² Chitosan, a biopolymer possesses characteristic properties with biocompatibility, is applied for the coating of a variety of types of nanoparticles so as to produce different particles with manifold functions for their uses in the detection and diagnosis of various diseases.³ Another potential example is Gadolinium that is used as a carrier for IL-13 liposome to sidestep the blood-brain barrier. Gadolinium uses the interleukin-13 receptor as a targeting moiety for glioma detection.⁴ The medical imaging contrast agents being used widely these days are mainly the small

Table 1: The key examples with their applications of nanoparticles agents in the biomedical field

Sub types	Examples	Application
Polymeric	Drug conjugates	Increase potency, tolerability and activity of drugs and deliver cytotoxic agents
	Micelles	Extremely small structure Increase aqueous solubility of drugs
	Dendrimers	Photodynamic therapy, boron neutron capture therapy Potent anticancer agents,
Nonpolymeric	Quantum dots	Luminescent nanoprobes Improved efficacy and bioavailability Reduced side effects
	Carbon nanotubes	Increase drug solubility and stability Targeted drug delivery Combination therapy
	Metallic nanoparticles	Contrast agents Provide controlled, targeted delivery
	Silica nanoparticles	Improved pharmacokinetic profile Enhanced bioavailability Cornell dots
	Spheres, clusters (fullerene)	Production of nanoparticles Functionalization of nanoparticles by dendritic structures
	Fibers, wires, rods	Increase stability Use in nanodevices, fibrils of nanodimensions, fabrication of polymer nanocomposites
	Films, plates, networks	Used in sensing, electronics and optoelectronics
Sub types	Examples	Application
NEMS/MEMS		Microscopic devices with length more than 100 nm but less than 1 mm, possess combined electrical and mechanical components Used for optical activities, electronic or biological applications and micro machines
Microarrays		Mapping of biological pathways, analysis of bio molecular interactions, assay development for compound screening, delivery of protein and peptides
Respirocytes		Artificial nanospherical robotic erythrocytes with internal pressure 1000 atm of combined oxygen and carbon dioxide. Preserve living tissues, treat anemia, asphyxia, and other respiratory problems

molecules that demonstrate swift metabolism with non specific distribution and hence produce detrimental side effects.⁵ Potential drug toxicity can be reduced with the possibility of monitoring the distribution of drugs around the body and by releasing the drug as required.⁶ Gold nanoshells (a heavy metal nanoparticle encapsulated in gold shells) are also one of the most effective materials in optical imaging of cancers.⁷ Gold nanoshells are considered very efficient being cost-effective and safe due to its non-invasive property. It has capability of providing high resolution imaging also. The key examples of nanoparticles agents in the biomedical field have been summarised in Table 1.

4. Nanotools: Manufacturing Approaches

The main parameters of nanoparticles are their size, shape and external structure. Nanoparticles exist primarily as

an aerosol as mostly solid or liquid particles in the air, a suspension or an emulsion. In the presence of chemical surfactants, the surface and interfacial properties of nanoparticles can be modified. Indirectly, such chemical factors prevent nanoparticles from aggregating together by preserving the charge of the nanoparticle or by modifying their top layer. Nanoparticles, in the process of conversion into nanotools, combine with chemical agents to form very complex structures, often with a very different or opposite nature from the original materials. In addition, the surface chemical nature of nanoparticles varies greatly. For example, the physical properties such as electronic and optical properties and chemical reactivity of small nanoscale clusters of a substance are completely different from these properties of the bulk or extended surfaces of the same material. The dissolution rate and bioavailability increase with the reduction in the particle size to nanoscale range because of the increase in surface area.⁸ These altered

physical and chemical properties at the nanoscale have been used in a variety of techniques in pharmaceutical systems, including adhesion, lubrication, and stabilization specifically for the formulation of poorly water soluble drugs.

There are two types of concepts for the synthesis of nanometer sized particles. These concepts are categorized into bottom up techniques, top down techniques, and the combination of both the bottom up and top down techniques. Under Bottom up techniques, the core concept is to build a complex structure by integrating tiny microscopic components. In this, matter and equipments are made from molecular components, which are based on the chemical principle of self-assembling through the molecules. The major techniques that follow bottom up approach for synthesis of nanometer sized particles encompass inverse micelles based liquid phase techniques, sol-gel processing, chemical vapor deposition, and molecular self-assembly. In the recent past, molecular recognition elements have been artificially created at the nanoscale, as an alternative to naturally occurring molecular recognition elements in the body, such as the conjugation of synthetic fluorescent nanomaterials. These nanomaterials can generate synthetic macromolecular structures or complex molecular structures that serve as optical protein recognition and synthetic antibodies. As another example, an instrument called an atomic force microscope can be used as a "right head" on a nanometer for the dip pen nanolithography process. In top down techniques, materials are transformed into nanoscale materials by means of successive cutting carving, and molding of larger materials. This technology was first ever started with the manufacture of solid devices but later modified to make microprocessor devices. The key examples comprise milling, hydrodermal technique electroplating, and physical vapor deposition. In addition, currently the most commonly used area of the top-down concept is photolithography. For the past few years it has been used to manufacture computer chips and to fabricate structures smaller than 100 nanometers. Typically, a 1 μm thick photoresistive layer is coated around the oxidized silicon (Si) wafer. After exposure to ultraviolet light, the photoresistive layer undergoes a chemical reaction, causing the polymer chains to disintegrate and break. Thus a 3-D structure is formed by washing the deformed oxidized silicon (Si) wafer in solution.

5. Nanoscale Effects

The importance of nanotechnology has begun to be realized in various scientific disciplines including physics, such as chemistry, biology and engineering. This promising acceptance is mainly due to two reasons. First, nanoscale materials have novel functionalities and hence there are many possibilities for the use of nanoscale materials in various technical applications. Secondly, the knowledge

about the evolution of shape-dependent physical properties has not yet been put into practice, and in this direction, with the development of various physical properties, there exists lot of potential for their practical application. The nanoscale effect can be understood from the following points.

1. The nano scale at which quantum effects dominate the properties of a substance: When particles of a solid material with dimensions of about 1–100 nanometers are created, the properties of those materials change significantly at this level. It is the size scale where a particular quantum effect governs the behavior and properties of particles. Thus, when the particle size is transformed to the nanoscale level, a range of particle's properties such as melting point, fluorescence, electrical conductivity, magnetic permeability and chemical reactivity change.
2. The nano scale at which many biological processes take place: Many processes occur naturally at the nanoscale within cells. For example, the diameter of hemoglobin protein that transports oxygen to different parts of the body is 5.5 nanometers. A strand of DNA, is just 2 nanometers in diameter. Owing to the activation of biological elements on the nanoscale, many types of therapeutic tools are being designed in the field of medical science with the help of nanoparticles, which are more accurate and useful comparable to traditional techniques. The popular use of bio-barcodes to detect disease-specific biomarkers in blood at relatively low cost is a good example of this.
3. Surface and intersurface properties at the nanoscale play a major role in determining the physical properties and interactions of matter: At the nanoscale, the surface area of a substance increases manifold, and due to this increased area, nanoparticles are exponentially more useful than large-sized substances.

5.1. Applications of Nanotechnology in Pharmaceutical Systems

1. Disease detection and diagnosis: The study and exploration of complex nanostructures requires highly sophisticated experimental, theoretical and modelling tools. In particular, the molecular level or even smaller sizes require sophisticated imaging and quantitative techniques. Since earlier too, in situ diagnostic devices, such as capsule endoscopy cameras, have shown to be successful in the clinical stage. For various purposes in nanotechnology mediated pharmaceutical systems, there are mainly two classes of tools are used, namely analytical tools and nanoimaging tools. Nanoparticles as analytical tools are specifically designed and used as biomedical devices, for diagnostics, nutrient delivery and research specifically targeting the cancer cells,

whereas nanoimaging tools are primarily used for imaging, analysis, and documentation with the help of molecular transmission electron microscopy (TEM). Being of size 10–100 nm, nano particles offer a perfect medium to perform molecular level modifications such as the site-specific imaging and targeting in cancer cells.⁹ Some latest advancement in the imaging techniques includes radionuclide imaging, quantum dots, biosensor and magnetic nanoparticles.

2. Treatment and prevention of diseases: Nanomedicines are the most effective and appreciated applied areas of nanotechnology. Nanoparticle-based drug delivery systems have earned the confidence of medical professionals for being the most suitable option in dealing with the deliverance drawbacks attached with conventional drug formulations along with augmenting the therapeutic efficacy of drugs. The major Nanoparticle-based drug delivery systems include liposomes, dendrimers, solid lipid nanoparticles, and solid metal-containing NPs. Specific drug targeting strategies involve physio-chemical and biological conjugation of drug molecules with the specific target receptors. By this method, particular protein expression can be adequately regulated and monitored. Conjugation of lectin with nanocarriers showed increased transport across the intestinal mucosa, while, grafting of vitamin B12 on the surface of some nanocarriers resulted into specific cell targeting.¹⁰ Some prominent examples of nanoparticles applied in the pharmaceutical fields are presented in Table 2.
3. Nutraceutical delivery: Nutraceuticals are health supplements generally consumed to various allopathic treatments to have immunities against several chronic illnesses.¹¹ They provide anti-inflammatory, antioxidative, antiapoptotic, and antiangiogenic effects. Like any other drugs, the bioavailability of orally consumed nutraceuticals is largely affected by food metabolism, aqueous solubility, and epithelial permeability.¹² Nanoparticles coated with nutraceuticals offers an effective option of intake to ensure their bioavailability. A good and extensively investigated example of nutraceuticals is curcumin (diferuloylmethane). Despite proven health effects, being water insoluble it has very poor bioavailability, thus a range of approaches such as liposomes, phospholipid vesicles, and polymer-based nano-formulation have been adopted to address this problem. Higher oral bioavailability of curcumin was observed to an extent of nine fold when compared to curcumin co-administered with piperine as absorption enhancer.¹³

Table 2: Examples of nanoparticles in the pharmaceutical fields

Nano particles	Application
Gold particles	X-ray / CT scan.
Gold particles (core shell structure)	Ultrasound
FeO (Iron oxide)	Detection/Imaging of tumours
Perfluoro Carbon	Detection of blood clots and cancer metastases, Imaging of angiogenesis
Gadolinium complexes	CT imaging of thrombi as a contrast agent
Fullerenes	Magnetic Resonance Imaging
Quantum dots	Specific Cellular Imaging
Silicon particles	Enhancement of MRI contrast

6. Mechanism of Drug Delivery Through Nanoparticles

6.1. Drug loading

A successful nanoparticle based drug delivery system must have a potential drug-loading capacity, Drug loading can be accomplished by two methods. One of the methods is passive (incorporation) that requires the drug to be incorporated at the time of nanoparticle formulation. The drug delivery is achieved by incorporating the therapeutic agent into a macromolecule or nanoparticle that indirectly reaches the target site by affinity or binding influenced by properties like pH, temperature, molecular site and shape. Another one is self-delivery method (adsorption/absorption) that calls for absorption of the drug after nanoparticle formation; in this method, the timing of release is crucial as the drug will not reach the target site and it gets dissociated from the carrier very quickly. This method requires the therapeutic agents in the form of moieties, such as antibodies and peptides to be achieved by conjugating the therapeutic agent or carrier system to a tissue or cell-specific ligand. For small molecules, studies show the use of ionic interaction between the drug and matrix materials can be very effective in increasing drug-loading.¹⁴

6.2. Drug release

It is important to consider both drug release and polymer biodegradation when developing nanoparticulate delivery system. In general, the drug release rate depends drug solubility, desorption of the surface-bound or adsorbed drug, drug diffusion through the nanoparticle matrix, nanoparticle matrix erosion or degradation, and the combination of erosion and diffusion processes. In the case of nanospheres, where the drug component is homogeneously distributed, release occurs by diffusion of the matrix. The rapid or 'burst release' is chiefly attributed to weakly adhered or adsorbed drug to the relatively large nanoparticles surface.

If the drug is loaded by the passive method, then the system has a relatively small burst effect and sustained release characteristics. In case of polymer coated nanoparticle, the release controlled by diffusion of the drug from the polymeric membrane.¹⁵

7. Nanotechnology and Agricultural Applications

Traditionally, in farming, major inputs like seeds, water, fertilizers and pesticides etc. have been used in a disproportionate manner, some part of these inputs are not used in crop production and gets mixed with land, water and air causes pollution. Owing to such anomalous agricultural practices, eventually there is a danger of extinction of water resources, soil quality and uneven distribution of rainfall. Nanotechnology can play an important role in addressing these anomalies associated with agricultural operations. It is thus recognized that the deployment of nano-based agricultural technologies is essential in the farming systems of the near future. The specific role of nanotechnology in agricultural applications focuses on (i) ensuring a controlled distribution system of fertilizers, insecticides and weedicides as needed and (ii) using field-sensing systems to monitor the actual crop status and environmental stress at the field level. Nanotech based smart chemical and micronutrients delivery system is also exploited in plant disease control system. An ideal nano-carrier of plant nutrients or other protective chemicals should have certain technical and economical characteristics for agricultural purposes Table 3. The nanomaterials used as carriers should not cause any adverse response in the recipient organism nor should the complex material be bio compatible. The mechanical properties of the polymer must give protection for prolonged time to its cargo allowing chemical stability over time. In addition, The encapsulation efficiency, and stability must be technologically feasible. The materials to act as nano-carriers should be carefully selected so as to meet the technical criteria to address mandatory regulations prior to being commercialized.

Table 3: Characteristics of an ideal nano-carrier for Agricultural purposes

Fabrication conditions	Encapsulation properties	Release profile
Mild conditions	Stable	Controlled
Scalable	No early cargo release/leakage	Targeted
Low-cost	Non-toxic	Stimuli sensitive (pH, light, temperature)
Reproducible	Biodegradable	
Low batch-to batch	Eco-compatible Water soluble	

7.1. Nanofertilizers

Fertilizers coated in nanomaterials hold plants more firmly than conventional surfaces due to the higher surface tension of nanoparticles. The stability of the nanocoating lessens the rate of fertilizer dissolution and allows for a measured and sustained release of the coated fertilizer that is more efficiently absorbed by the plant's roots. Thus the use of nano-fertilizers minimizes the toxicity of soil and the possible adverse effects of excessive chemical fertilizer use. Research study showed that the use of nano-zinc increased the production efficiency of wheat as well as reduced the adverse effects of fertilizer use.¹⁶ The most important quality of these fertilizers is that they contain one or more medium and micronutrients that can be used in minimal amounts with environment friendly approach. Nano fertilizers may contain nano zinc, silica, iron and titanium dioxide, cadmium, selenium, zinc sulfate, gold nanorods, etc. The absorption, translocation and accumulation of nanoparticles primarily depend on the plant species, age and developmental stage. These processes are also influenced by the distribution, physical properties of nanoparticles, their reactivity, and stability. According to a study, some nanoparticles such as ZnO^{2+} , Cu^{2+} , Al^{3+} , Ag^{2+} and Fe_3O_4 are absorbed by the root system of plants of almost all species and reach the leaves, whereas nanoparticles such as Cu, ZnO, Al and Ag directly through the leaves and $Ni(OH)_2$ is absorbed and stored by the stems. The CeO_2 nanoparticles are equally absorbed and stored by the stems and leaves. The absorption of various nanoparticles and the site of interaction in plants are shown in Table 4.

Table 4: Absorption and interactions between different nanoparticles in plants Four categories of nano fertilizers are mainly defined in terms of application:

Nanoparticles	Site of interaction in plants
Fe_3O_4	Cambium
ZnO	Endodermis, Metaxylem
CeO_2	Cortex
Al	Metaxylem, Cortex
Ag	Metaxylem, Cortex
Cu	Metaxylem, Cortex , Cambium
TiO_2	Cortex
$Ni(OH)_2$	Metaxylem

1. Nano scale fertilizers (i.e. nanoparticles containing nutrients): In chemical fertilizers, nutrients that are more used per unit area (such as in kilogram units) are converted to nano scale (parts per million).
2. Nanoscale Compound Fertilizers (i.e. a mixture of nanoscale additives with conventional fertilizers): Nanoscale compound fertilizers are prepared by

mixing nanoscale nutrients with chemical fertilizers. Plants are able to utilize more of the phosphorus mineral by increasing the rate of its solubility when used in combination. Similarly, the use of urea chips conjugated to zeolites slows and controls the release of nitrogen.^{1,17}

3. Nanoscale coating (i.e. nanoparticle coated conventional fertilizer): The use of nanoparticle coating or encapsulation on fertilizer particles is in vogue these days to increase the utilization efficiency of nutrients in conventional chemical fertilizers. Nutrients can be coated with a thin protective film, or delivered as an emulsion or nanoparticles and thus aids in the controlled release of nutrients. Coating urea with nitrous inhibitors (nano scales) has been shown to reduce nitrous oxide emissions by up to 75 percent.¹⁸
4. Nutrient-rich synthesized nanoparticles (i.e., the synthesis of nutrient-derived nanoparticles): The extracts of biological factors such as micro-organisms and plants can be used as protection agents for the manufacture of metal nanoparticles. In these extracts, the ability to reduce various biomolecules such as amino acids, vitamins, proteins, enzymes and combinations of polysaccharides can be found, which are environmentally benign yet chemically complex.

7.2. Nanopesticides

The nanoparticle itself, in most of the claimed applications of nanopesticides, is not the active agent, but acts as an adjuvant compound to stabilize the active agent or enhance its controlled release. Nanopesticides can be of several types depending on the applications. Nanoparticles are often used as carriers of the active ingredient available in emulsions, capsules, gels, fibers and particles. Nanoparticles can also act independently as nanopesticides (eg copper).

(1) Plant nanobionics: Recently, the basic idea of conjugating nanomaterials with living plants to enhance plant efficiency has been propounded. This concept is known as plant nanobionics. Single-walled carbon nanotubes, located between plant chloroplasts and the outer lipid envelope, are able to perform photosynthesis at a rate three times higher than normal.¹⁹

(2) Nano biosensors: The sensitivity and performance potential of the biosensor can be harnessed for the development of new varieties through signal transduction technologies in plants using nano scale materials.

8. Conclusion and Future Prospects

Nanotechnology offers substantial prospects for the development of innovative products and applications in many pharmaceutical and agricultural sectors. Under pharmaceutical sectors, they have remarkably facilitated healthcare procedures, from diagnosis to therapeutic interventions and follow up monitoring. It is necessary

to give a consistent push to develop novel nanotools to progress disease diagnosis approach with the eventual intention of making medical access more efficient and economical. In agriculture, need based and target-specific nutrient delivery and approaches for nanotech enabled farming are the areas of prime importance. Expected benefits of both the sectors include increased efficacy of pharmaceutical, agrochemicals through nano-encapsulation, enhanced bioavailability of nutrients or more secure packaging material through microbial nanoparticles. The vision of nanotechnology lies within using the judicious nanoparticles and dropping down any possible harmful side effects in both the cases. It is important to note that, risk evaluations are required before new nano based products are approved for commercial use to minimise any potential hazards to human health and the environment.

9. Source of Funding

None.

10. Conflict of Interest

None.

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